Effects of Exercise, Clenbuterol, Carvedilol, Dobutamine, and Sedentary Existence in Acute Imipramine-Induced Heart Failure in Rat

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Saikaew Sutayatram, DVM

Graduate Program in Comparative & Veterinary Medicine

The Ohio State University
2014

Dissertation Committee:

Dr. Robert L. Hamlin, DVM, PhD Advisor

Dr. Carl V. Leier, MD

Dr. Mark Ziolo, PhD

Dr. Steven T. Devor, PhD

Abstract

Goal: The primary goal of this study was to determine if exercise training or exposure to drugs would protect rats from heart failure produced, acutely, by IV imipramine. Imipramine was selected because it produces a failing heart acutely and reversibly, (but it may mediate failure over mechanisms different from other etiologies), and because its analogues are used commonly in the human population. Rats were selected because of reasonable cost, enormous literature on their use for cardiovascular studies, minimal training required for performing exercise (6 at a time), and their homogenous population.

Methods: Fifty-four, young-mature, male, Sprague Dawley rats were allocated randomly with 10 rats per each of 5 intervention groups in which 6 were exposed to and 4 not exposed to imipramine: (1) 6 weeks of sedentary, (2) 6 weeks of exercise (~1900 minutes of aerobic interval training totally), (3) 2 weeks of 3 mg/kg SC bid carvedilol, (4) 2 weeks of 2 mg/kg SC qd clenbuterol, and (5) 2 weeks of 0.75 mg/kg SC tid dobutamine. A 6^{th} group of 4 rats was sedentary for 6 weeks and received only a matched-volume of water as a vehicle. The following physiological measurements were made: orthogonal lead ECGs, systemic arterial and left ventricular pressures, and maximal rates of rise and fall of left ventricular pressure. The following anatomical/structural measurements were made: left ventricular end-diastolic and end-systolic volumes, body weight, and weights of brain, heart, and adrenal. Values were expressed as means ± SE of each group. ECGs

were obtained (1), initially, after rats had received interventions (i.e., exercise or drugs) and while in a Faraday cage anesthetized with pentobarbital (termed **baseline pre-surgery**), then both ECGs and hemodynamics were recorded (2) before they received imipramine or vehicle infusion (termed **baseline instrumentation**), (3) at the midpoint of infusion (termed **mid-dose**), (4) at the end-point of infusion (termed **end-dose**), and (5) 1 hour after cessation of infusion (termed **end recovery**). Each intervention was selected for its novel pharmacology that has been suggested may be effective at treating/preventing heart failure: carvedilol is a β_1-, β_2-, and α-blocker and a potent scavenger of free radical of oxygen, clenbuterol is a β_2 agonist, and dobutamine is a β_1 agonist and has been shown to produce sustained benefit in treating heart failure even after cessation of its use. Differences of statistical significance in means for all parameters measured during imipramine challenge were sought among groups using 2-way ANOVA with repeated measures design on group and time. Although not included in this document, data will be reanalyzed comparing, each intervention, against no intervention (i.e., sedentary). This will increase power, dramatically, to identify a potential benefit (should there be one) for preventing/blunting reduction in cardiac function induced by imipramine.

Results and Discussion: Exercise, carvedilol, clenbuterol, and dobutamine produced physiological effects in these rats consistent with their known properties. All rats survived all imipramine challenges with hemodynamic and ECG changes typical of acute imipramine exposure, i.e., an initial decrease in function with or without spontaneous recovery during infusion, and then recovery nearly complete within 1 hour after cessation

of infusion. No intervention (exercise or pharmacological) altered statistically (i.e., blunted or exaggerated) hemodynamic responses to imipramine; however various interventions produced differences in responses to imipramine from those produced by other interventions. The single exception is that all interventions, except carvedilol, lengthened, significantly, QA—the interval between onset of QRS and onset of the aortic pressure pulse. Such lengthening could be caused by: (1) reduction in myocardial contractility, (2) decreased elasticity modulus of the aorta (i.e., increased compliance), and (3) prolongation of QRS and/or electromechanical coupling. The lack of protection of hemodynamic effects constituting a failing heart in this study may be due to: (1) inability to measure differences, (2) the interventions are truly ineffective in this model, and (3) results from a failing heart produced by imipramine may not be applicable to a failing heart occurring naturally.

However significant and potentially important changes occurred to the ECG in response to imipramine. Prolongations of QT, QTc, and T wave duration by imipramine were blunted equally by exercise and carvedilol when compared with dobutamine, but trended to be blunted when compared to sedentary rats. Clenbuterol trended to further prolong PR interval. Dobutamine prolonged QT, QTc, and duration of the T wave compared to rats (only) that were exercised or received carvedilol. Dobutamine produced the greatest change in QT in response to imipramine compared to all other groups, and also the greatest changes of QTc and T duration compared with those of exercise and carvedilol.

Imipramine decreased the height of the R wave in all groups. However, R wave amplitiude in AVF remained depressed after cessation of imipramine longer for clenbuterol than for other interventions. There are no other significant differences among groups/interventions in parameters of recovery, i.e., after cessation of infusion.

It is important to understand that failure to identify protection against adverse imipramine-produced hemodynamic effects does not imply that there might not be value of an intervention in a head to head evaluation comparing each intervention with nothing. This study used 2-way ANOVA with repeated measure design to compare all interventions; whereas head to head comparisons of each intervention against nothing could have use the much more robust *t*-test. However, comparing each intervention against only nothing was not the goal of this study.

Dedication

DEDICATED TO HIS MAJESTY KING BHUMIPOL ADULYADEJ,

THE KING OF THAILAND

Acknowledgements

I would like to sincerily thank my advisor, Dr. Robert L. Hamlin who has always helped and guided me througout my graduate program, and all of my committee members, Dr. Carl V. Leier, Dr. Mark Ziolo, and Dr. Steven T. Devor, who all gave me important advice and suggestions. Also, I want to thank QTest Labs and staff, especially Mr. David M. Hamlin, Dr. Carlos del Rio, Dr. Steve Roof, Dr. Yukie Ueyama, Dr. Brad Youngblood, and Mrs. Laurie Shellhammer, who have been funded, helped, trained, and provided assistance in all parts of my research project requirements. Moreover, I would like to thank the department of Physiology & Cellbiology, The OSU, for lending me the equipment that was used in my study, and Mr. Daniel Galano who created the data input program for my study.

A special thanks goes to The Anada Mahidol Foundation, who provided a comprehensive scholarship, as well as the foundation's staff, who facilitated my opportunity beginning with the preparation period, prior to starting my graduate program, and continued until graduation.

And my most important thanks goes to my mother and my brother, who have raised and guided me into an education-oriented person, as well as taken good care of me and loved me more than I could have imagined.

Vita

October 19th, 1981. ……....Born, Nakhon Sawan Province, Thailand

2000-2006...……..…...……....DVM, Veterinary medicine, Chulalongkorn University

2006……...…Jaras Suebsang award for top clinical practice score of last year Veterinary student, The Veterinary Practitioner Association of Thailand (VPAT)

2009-2014……..Graduate student, Department of Veterinary Biosciences, The Ohio State University

Publications

1. **Sutayatram S**, Boonsri D, Pipatanatanakij P, Techangamsuwam S, Whananaitham S, Rungsipipat A. Hemopathology and coagulation induced by canine monocytic ehrlichiosis. *J NRCT (Sci).* 2008; 40(2): 63-82.
2. Sithanukul S, Shayarattanasin P, Hiranpradith V, Chansaisakorn W, Trisiriroj M, Komolvanich S, **Sutayatram S**, Buranakarl C. Blood Pressure, Urinary Protein Creatinine Ratio and Oxidative Stress in Dogs with Urolithiasis. *Thai J Vet Med*. 2010; 40(3): 323-330.
3. Ritthikulprasert S, Rodphol M, Nimrotham A, **Sutayatram S**, Komolvanich S, Trisiroj M, Buranakarl C. Effects of Erythropoietin om Blood Pressure, Renal Function and Red Blood Cell Production in Dogs with Chronic Kidney Disease with and without Angiotensin Converting Enzyme Inhibitor. Thai J Vet Med. 2011; 41(2): 227-234.
4. Galvo JFD, Kisseberth WC, Murahari S, **Sutayatram S**, Chew DJ, Inpanbutr N. Effect of gemcitabine and gemcitabine in combination with carboplatin on five canine transitional cell carcinoma cell lines. *Am J Vet Res.* 2012; 73(8):1262-1272.

Field of study

Major Field: Comparative & Veterinary Medicine

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

1.1 General Introduction

Heart disease is one of the most important diseases in both human and animals. According to the World Health Organization (WHO), cardiovascular diseases (CVDs), especially, heart attack and stroke are the cause of death in approximately 17 million persons each year, worldwide. Heart diseases may kill more persons than all of the other diseases together. Besides the mortality, costs of treatment, rehabilitation, and inability to work are enormous. Data from the American Heart Association (AHA), only in the US, shows direct cost of therapy and indirect losses from reduction in productivity can equal up to $53.6 million USD in 2004. Likewise, in developing areas where vaccination and veterinary care are sufficient, CVDs, particularly heart failure, and other degenerative diseases such as cancer and renal failure, become important causes of death in companion animals. Although, CVDs might not be the most important diseases in dogs and cats, ~11 to 42% of the dogs in the US have some form of heart disease [1]. In some breeds it is even more significant (i.e. Doberman pinscher, Fox terrier, and Newfoundland) [2]. Moreover, CVDs affect quality of life (QoL) and result in high veterinary costs due to the chronicity and natural progression.

There are several subsets of CVDs: coronary heart disease, stroke, congenital heart diseases, valvular heart diseases, peripheral vascular diseases. In most human and animal cases, patients who recover from those acute CVDs often develop heart failure (HF). According to AHA, HF is a chronic, progressive condition in which the heart cannot pump enough blood or distribute blood to meet the body‘s oxygen and nutrient requirements. HF can result from abnormal systolic function (a weak force of contraction), abnormal diastolic function (impaired filling), or from both. Abnormal systolic function may be caused by degenerative or injury to myocardial tissue, valvular diseases, as well as to chronic increased afterload (hindrance to ejection). Impaired relaxation may result from increased LV stiffness, pericardial effusion, or from constrictive pericarditis. When impaired diastolic filling occurs, impaired systolic ejection also occurs according to the Cyon-Frank-Starling law of the heart that states systolic function depends upon preload (the volume of blood in the heart just before it contracts). HF is classified as left-sided, right-sided, or combined, based upon where the predominant lesion is, and results in backing up of blood into the lungs (left-side), the system (right-side), or both (right- and left-side). It is important to make a distinction among a failing heart (in which contractility is impaired), heart failure (in which signs and symptoms result from inadequate cardiac output), and congestive heart failure (in which signs and symptoms result from the backing up of blood into a capillary bed). Left sided congestive HF is most important since signs and symptoms (i.e., asphyxia) are more life-threatening.

Myocardial function, the ability of the heart to transfer blood from veins to arteries, depends upon contractility (the inotropic state) and loading conditions (preload and afterload) in both health and disease. Reduced function often manifest as heart failure characterized by signs and symptoms and reduced life span.

There are two ways to study the alterations of the myocardium: *in vitro* (e.g., cell culture, Langendorff preparation, and papillary muscle chamber), *in vivo* (e.g., intact, anesthetized animals, intact awake animals, with various degrees of instrumentation). A popular *in vitro* model to study heart function is the Langendorff preparation or the isolated, perfused heart. A popular *in vivo* animal model to study HF is myocardial infarction (MI) in rats, because this model mimics clinical appearances and pathophysiology observed in patients. However, the MI rat model, which is a good model to study post-MI cardiac remodeling [3], might not be an ideal model to study acute recovery properties of HF treatment or interventions, due to it progressive nature and slower recovery of the model. Thus, a reversible HF model might be a better option to study the recovery resulting from treatment. The study can be done in shorter periods of study.

There are several drug-induced HF models in rats that have been developed, such as doxorubicin-induced cardiomyopathy, homocysteine-induced ventricular dysfunction, and isoproterenol-induced myocardial damages [3]. However, these well-known HF-inducing drugs need to be chronically administered (usually) to rodents and may not be fully reversible or may take months to reverse. Therefore, imipramine, a tricyclic antidepressant that can cause a short-term and partially reversible HF [4], appears to be

preferable to other models, and was chosen to illustrate the potential for cardiovascular protection and recovery from exercise or drugs in anesthetized rats.

Several treatments and interventions have been studied and applied to HF patients. These include drugs, devices, and behavioral managements-- most important of which is exercise. Aerobic or endurance exercise training (ET) has been well documented to improve aerobic capacity and QoL, as well as to reduce attenuation of cardiovascular function and remodeling in cardiovascular diseases. This often translates to reduced cardiovascular morbidity and mortality. Thus, ET has become an important part of HF management and many health organizations support the physical activity guidelines to prevent and slow the progression of cardiovascular disease in humans. Also, in post-MI HF rats, 8 weeks of ET can partially, but nevertheless significantly, reverse ventricular and myocardial hypertrophy, attenuate the decline in contractile function and Ca^{2+} handling, improve positive lusitropy, and reduce the time to peak shortening [5]. However, a considerable number of patients with heart disease are unable to perform exercise due to aging, to severe concurrent systemic disease, or to other musculoskeletal problems. Thus, using drugs, such as dobutamine (a β_1-sympathomimetic drug) and clenbuterol (a β_2-sympathomimetic drug), that potentially mimic cardiovascular and hemodynamic changes that occur during exercise, or carvedilol (a mixed β and an α-blocking drug that also is a scavenger of free radicals of oxygen) that has been used extensively in HF management, may be beneficial to these patients.

1.2 Cardiovascular function and cardiovascular research: Pressure volume loop (PVL) and electrocardiogram (ECG)

The cardiovascular system (CVS) is one of the most complicated but well-organized systems in the body. It consists of an integrator, controllers (e.g., heart, blood vessels, the kidneys, the gastrointestinal system), and level detectors that monitor ther levels of important controlled variables (e.g., pressures, CO, SV, BV). In order to achieve the most effective circulation to each of the trillions of cells comprsing the body, levels of all controlled variables must, in fact, be controlled to within rather narrow limits. Neurohumoral communication among components of the biological control system permit the "error" signal between the set point and actual level of the variable to be "adjusted" toward zero, (i.e., no "error") or set points and levels are equal.

The medulla oblongata, in the brainstem, is the primary site receiving and integrating (actually subtracting) synaptic inputs from the hypothalamus that provides information on the desired set points (i.e., ideal values for controlled variables), and local detectors (e.g., baroreceptor at high-pressure side of CVS (HPBR), low-pressure baroreceptor (LPBR) at low-pressure side of CVS, and juxtaglomerular apparatus (JGA) at kidney) for each variable which provide actual values [e.g., stroke volume (SV), systemic arterial pressure (SAP), and blood volume (BV)]. After the integrator compares inputs from both sites, it sends tne error signal to cardiovascular controllers (i.e., the heart and vessels, the kidneys, the GI tract). The cardiovascular controllers adjust their functions through 2 types of modulators: extrinsic and intrinsic modulators. The extrinsic cardiovascular modulators consist of (1) the autonomic nervous system (ANS), higher

brain (cerebral) activity, the respiratory system, all integrated at the medullary level and communicated by neurohumoral factors [e.g., cathecholamines from adrenal medulla, renin-angiotensin-aldosterone (RAA) system, cortisol, atrial natriuretic peptide (ANP) and brain-type natriuretic peptide (BNP), and antidiuretic hormone (ADH)]. Further adjustments result, locally, from modulation due to metabolites and changes in ionic equilibrium. Critical parameters of function are modulated by plexuses of nerves and pacemaker cell in the heart. Although the intrinsic modulators [i.e., sinoatrial (SA) node and myocardium] can regulate cardiovascular functions by themselves, normally they are under the influences of one or more extrinsic factor to provide the ranges of cardiovasdcular function that constitute homeostatic constancy of the internal milieu.

Important cardiovascular variables that need to be regulated within suitable level at all the time are heart rate (HR) and rhythm, cardiac output (CO), stroke volume (SV), blood volume (BV), blood pressure (BP), and blood gas variables. In order to control BP, its determinants, CO and hindrance to ejection, must be controlled since BP=CO• hindrance (total peripheral resistance, TPR). Of course CO is the product of HR and SV, both of which are controlled by autonomic efferent activity and humoral factors (e.g., catecholamines, angiotensin, atriopeptins, and ADH).

This system for determining BP is shown shematically in figure 1.

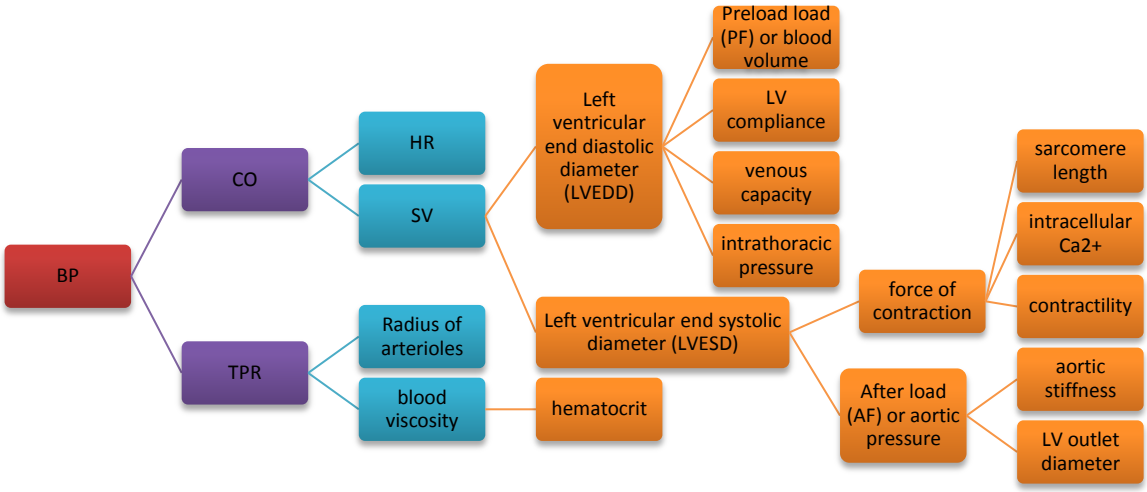

Figure 1: Control of systemic arterial blood pressure.

1.2.1 Pressure volume loop (PVL) study

LV is one of the most important controllers of CVS, since its contraction is a prime in determining the quality of pump function. Of course this is affected by venous return that, along with pleural pressure, determines filling. It is essential that studies on the CVS and its pathophysiology must focus on both myocardial contractility and ventricular filling (preload).

The rat is/has been used very commonly in studies on cardiovascular function. Although tiny compared to man, its function has many features in common with human (However there are also many differences), they are inexpensive and easy to house, they

require only small amounts of (often-times) very expensive test articles, and animal rights' activists are less concerned about their use. They may be modified and standardized genetically [6]. There are many rat models to study LV function: (1) *in vitro* study: isolated heart preparation as aortic perfusion technique known as Langendorff preparation [7], isolated perfusion heart preparation as working heart preparation [8], and (2) *in vivo* study: pressure-volume-loop (PVL) anesthetized rat model using pressure-volume conductance catheter technique [9], and conscious instrumental radio-telemetry rat model [10]. Unlike LV *in vivo* studies, LV *in vitro* studies have the advantages of beter control neurohormonal influences [6]; therefore, they can provide more accurate and insightful information on direct effects of test stimuli on LV function. However, the intact neurohormonal system of *in vivo* LV studies allows them to explore more comprehensive pathophysiology and to quantify data on overall heart and cardiovascular performance, resulting in better/more apropriate extrapolations to more real life clinical situations in human.

Data obtained from unrestrained conscious rats can be recorded using radiotelemetry. Recently left ventricular pressure-volume relationships have been explored using either impedance (or conductance) catheters advanced into the LV from a carotid artery, or from signals generated by sonomicrometer crystals. This model/technology has an advantage over (clinical) noninvasive cardiovascular examination methods such as echocardiography and MRI, in term of data accuracy and specificity to quantify LV performance. Most importantly, this method permits the most accurate assessment of load-independent functions of LV performance, and dose not

depent on the motion pictures, compared with those noninvasive cardiovascular examinations [11].

As described by Peacher and colleague (2008) [11], PVLs from anesthetized small animal models revealed correlation of changing in LV pressure and its concomitant volume by combining information received from a conductance catheter and a micromanometer pressure transducer. The conductance catheter generates an electric field, passing through blood and LV muscle that creates measureable differences in voltage depending on surrounding conductances and volumes. It analyzed and translated voltage differences into a time-varying signal of blood volume, while the micromanometer pressure transducer concomitantly receives real-time LV pressure changes and depicts those changes in form of LV pressure wave form. In these studies, animals must be anesthetized, body temperature controlled, and they must be intubulated, before the catheters can be inserted into LV and abdominal aorta from right carotid artery and femoral artery, respectively. Surgical LV catheterization may be peformed with an open or closed chest, and the difference—that may be quite important— may reflect the role of denervation with an open-chest approach. The close-chest approach has several benefits over the invasive method allowing a more prolong study time and more stable physiology of the testing animal. After placing catheters in the right positions, and allowing PV signals to be stable during baseline, infusion of test agents through the venous catheter can be performed.

Beside surgical preparation, data acquisition and data analysis are also critical to accurate interrogation of the parameters. There are several important hemodynamic

parameters and indices of both systolic and diastolic function that can be acquired from the PVL study without using vascular balloon occlusion to generate effects of variation of preload on load-dependent physioloigy [e.g., HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), mean blood pressure (MBP), end systolic pressure of LV (LVESP), end diastolic pressure of LV (LVEDP), SV, CO, +d*P*/d*t* or peak of LV pressure rise, -d*P*/d*t* or peak of LV pressure decline, LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), ejection fraction (EF) as SV/EDV ratio, tau or relaxation time constant, and contractility index (CI) or +d*P*/d*t* divided by pressure at this point].

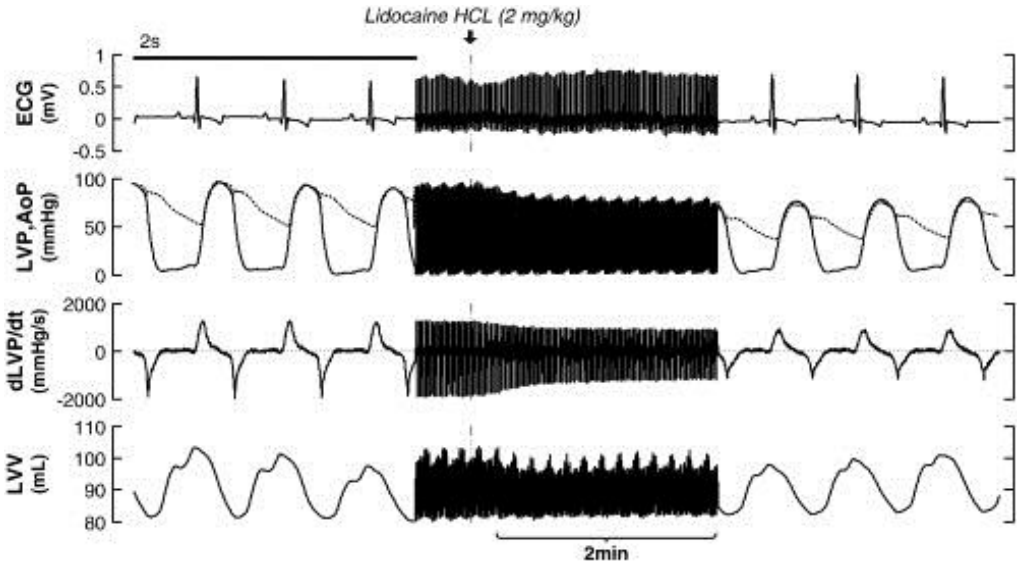

Figure 2. ECG, AoP, LVP, d*P*/d*t* of the left ventricular pressure, and LVV at rapid paper speed (left) during infusion of a drug (slow paper speed, center) and after infusion of the drug (right, rapid paper) [12].

As can be seen in Figure 2, data from a PVL study can show continuously on the LV pressure (LVP), aortic pressure (AoP), LV pressure rise and decline (dLVP/d*t*), and LV volume (LVV) at each time point of cardiac cycle as compared timed by the ECG recorded at both high and low speeds [12].

Many physiological parameters can predict or transfer into clinical outcomes. Of course HR is a strong predictor of mortality and cardiovascular outcome. Other peredictors include: LVEDV, termed preload, that determines avidity of binding of Ca^{2+} to tropoin-C; end diastolic pressure volume relationship (EDPVR) obtained from PV loops, ratio of EDP to EDV; -d*P*/d*t*; tau; +d*P*/d*t*; prelolad recruitable stroke work (PRSW); end-systolic pessure volume relationship (ESPVR) during brief periods of heterometric autoregulation; ejection fraction (EF = SV/EDV); afterload or peak myocardial tension ($=[(P \bullet r/WT)]_{max}$); cardiac index (CI). These indeces are a combination of load-indepdnent and dependent parameters.

Examples of correlations among parameters of function and clinical findings of those parameters may be reported with respect to the following 8 parmeters. HR is a strong predictor of mortality and cardiovascular outcome in the study of patients with stable HF [13]. Increase in EDP, and decrease in +d*P*/d*t*, -d*P*/d*t*, and peak LV systolic pressure are associated with myocardial infarction (MI) in rats [14]. LVEDV is associated with risk of cardiac hospitalization in a study of patients with chronic HF [15]. EF is a strong predictor of cardiovascular outcome in a study of patients with HF due to a broad spectum of etiologies [16]. Tau was considered as a "gold standard" to quanlify active relaxation [17]. PRSW and tau can be used to detect improvements of cardiac

performances concomitant with improvements on cardiac remodeling in diabetic mellitus rat study [18].

It must be known however, which parameters are so-called load-dependent (e.g., EF, dP/dt, and tau), and which are load-independent (the "gold standards" like load-independent ESPVR and PRSW) measures of inotropy (contractility) or lusitropy (compliance). They must never be confused or used interchangeably. +dP/dt, dependent upon both contractility and loading conditions [12], has been used to develop several contractility indeces (e.g., duration from onset of dP/dt to peak dP/dt [19], peak of first deviation of dP/dt or d^2P/dt^2 [20], +dP/dt divide by EDP [21], dP/dt_{30} or dP/dt value at pressure from 13-30 mmHg [22], and V_{max} calculated of dP/dt and LVP curve extrapolated to zero pressure [23]) that can reduce effects from factors other than contractility.

With increase of demand for computerized programs in research setting, biomedical companies are developing detailed programs for obtaining and measuring/calculating PVL data. EMKA technologies provide cardiac index (CI) as +dP/dt divide by LVP; this is a relatively—but not a completely—load independent index of contractility, but it has gained acceptance in the Safety Pharmacology community and with drug regulatory agencies [24].

1.2.2 Electrocardiogram (ECG) study

Besides LV performance, electrical activity of the heart is also vulnerable to adverse effects from many cardiovascular diseases, drugs, and intoxicants. In fact, the cardiac electrical activity, measured best (quickly, safely, and inexpensively) by ECG,

has been studied since the nineteenth century, originated by Waller (1887) [25]. It has become a "gold standard" for clinical screening of cardiovascular health, monitoring progression of CVDs, and cardiotoxicology studies. ECG study provides insightful information on cardiac automaticity and conductivity, as well as, detecting alterations in cardiac rhythm and autonomic regulation. In the field of cardiotoxicology, small animals especially mice and rat, are major study models due to their low cost, genetic homogeneity, ability to genetically enghineer, and necessity for use of only minute quantities of test articles. More importantly, according to Food and Drug administration (FDA), cardiotoxicity of new can be detected reliably in ECG studies. In particular they focus on QT instability and QTc of the ECG that have been proven reliable for predicting adverse event in humans. Studies in animals are expected before first in human trials. The FDA has created many guild line and standards on how to ECGs are obtained and interpreted [26].

ECG waveforms can depict physiological and pathological electrical activity of the heart. As shown in figure 3, arsenic trioxide (AS_2O_3) lengthened QT duration in rat ECGs due to alteration in transmembrane current balance of L-type-Ca current ($I_{Ca,\,L}$) and inward rectifier K^+ current (I_{Kr}) [27]. At each phase of electrical activity, there are varieties of ion channels that respond differently with specific ionic flows (see figure 4). Also, there are some species with specific differences in conductances throuth various ion-specific channels; these differences must be known, and specific species and/or strains must be selected for their polymorphisms in these channels. In particular, structures and physiologies of I_{Kr} (hERG), I_{to} (transient outward K^+ current), $I_{Ca,\,L}$, I_{Na}

(inward Na^+ current), I_f (funny current) channels need to be considered before data from a species is interpreted for extrapolation to humans. Of importance to this study, the rat lacks an I_{Kr} channel [28], but has particularly robust I_{Ks}, I_{to}, and (the ultra-rapid acting K^+ channel) I_{KUR} channels.

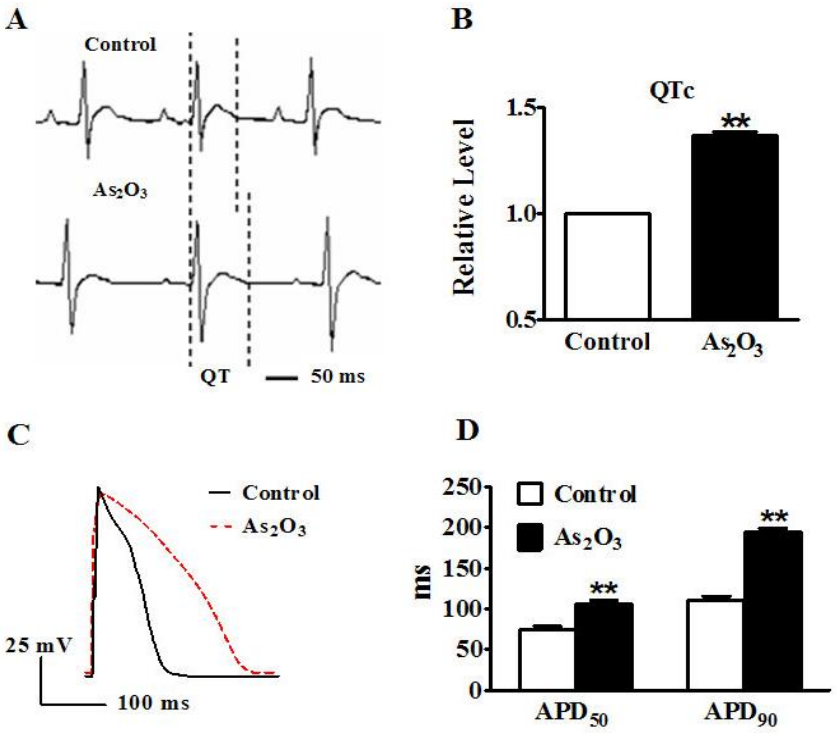

Figure 3. effect of AS_2O_3 on QT duration in rat. (A) ECG tracing of control rat and AS_2O_3 treated rat. (B) Relative level of QTc in both groups. (C) Action potential tracing of control rat and AS_2O_3 treated rat. (D) Action potential duration in both groups [27].

As describe by Driscoll (1981) [29], the rat ECG is unique with a short QT, equivocal Q waves in many leads, and no discernible isoelectric line among P, QRS, and T waves. To permit rapid ventriclar repolarization, the rat myocardium possesses large

amounts of I_{to} and I_{KUR} which causes repolarization to occur well before depolarization ends, thus obfuscating separation of depolarization and repolarization, and production of J point deviatons of injury or hypertrophy. The J wave is in fact not due to depolartization but is in fact a wave produced by differences in early repolarization among various ventricular regions (principally endocardial and epicardial). Merging of ST portion in rats (i.e., J wave), is a result of heterogenity of I_{to} physiology among cardiac structures [30]. Owing to these differences, analysis of the rat ECG is more difficult [6], and may create greater variations among studies.

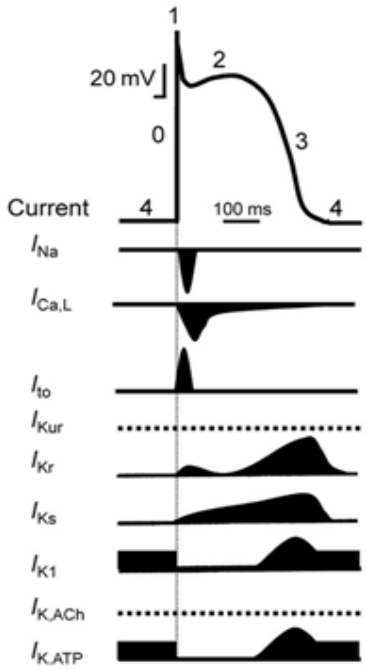

Figure 4. Human ventricular action potential curve and its correlated ion currents. Phase 0, rapid depolarization phase: I_{Na}; Phase 1, rapid early repolarization phase: I_{to}; Phase 2, slow (plateau) repolarization phase: $I_{Ca,\ L}$, I_{Kr}, and I_{Ks} ; Phase 3, rapid repolarization phase due to I_{Kr}, and I_{Ks}; Phase 4, resting membrane potential due to predominantly I_{K1} and/or combine with I_{KATP} during ischemia episode [31].

Nevertheless, the rat ECG still has been widely used to monitor both clinical and research events, for alteration in electrophysiology induced by many changing ion concentrations and ion channel physiologies produced by diseases, drugs, or toxins. For instance, Sorodoc's et al. (2013) study [32] showed that amitriptyline-induced sublethal cardiotoxicity was associated with prolonged QRS and QT in rats. Also, lengthening of QT and flattening of T wave are found commonly in rats that received doxorubicin, a copmmomly-used antineo-plastic with severe cardiotoxicity [33]. Moreover, high concentrations of ozone in the environment have produced alterations in the ECG (i.e. PR prolongation, QTc shortening, and ST depression), and both morbidity and mortality from cardiovascular effects [34].

The QA interval, duration from the beginning of the Q wave in ECG (Q) to the beginning of upstroke of aortic pressure (point A), is considered an indirect measure of cardiac contractility. QA relates inversely with cardiac contractility, but is also affected by arterial modulus of elasticity, electropressor, and ED coupling. QA is flawed similarly with +dP/d*t*. There are several studies that used QA interval such as Adeyemi's et al. (2009) rat study [35], in which the negative inotrope (verapamil) decreased +dP/d*t* but increased QA interval, while positive inotrope (salmeterol) increased +dP/d*t* but decreased QA interval. Moreover, in conscious telemeterede dog model, atenolol (a β_1-adrenergic blocker) decreased +dP/d*t* but also increasd QA interval, with small effects on systemic blood pressure and HR, while AH-1058, a novel Ca^{2+} channel blocker with negative inotropic, chronotropic, and dromotropic effects reduced SBP, +dP/d*t*, and HR,

and prolonged QA interval [36]. Therefore, examination of drugs effects on QA may provide additional information on cardiovascular performances.

1.3 Heart Failure models in rats

HF has resulted in an enormous economic burden globally due to loss of life and productivity, billions of dollars of health care, billions of dollars for research to prevent and combat it, especially in western countries. In terms of management, HF prevention and control are not only costly, but also very complex, must be persistant, and often are difficult to obtain. All of these reasons have propelled academia, the pharmaceutical industry, contract research organizations, and federal regulatory agencies to study all aspects (e.g., risk factors, pathophysiology, and treatment including rehabilitation).

For various reasons, invasive studies may be conducted with great restrictions in humans. Therefore, in the past decades researchers have developed and exploited animal models that mimic (sometimes inadequately) each specific type of HF, mainly (in the past) systolic HF due to its less problematic method compared with diastolic HF [3], but now with emphasis on diastolic HF. Each species and models has its own unique advantages and disadvantages. However, rodent moldels seem to be the most popular since they are more homogenous, can be genetically customized, are inexpensive and manageable, and have yielded useful information extrapolatable to humans.

1.3.1 Pressure overload induced HF

Chronic pressure overload resulting from systemic arterial hypertension is a well-known cause of cardiac hypertrophy, vascular remodeling, and HF. Pressure-overload

may be produced by supravalular aortic [37] or abdominal aortic [38] restriction using surgical banding to a 50% stenosis resulting in a 50-60 mmHg pressure gradients between aorta and LV [4]. Gradually, rats with aortic banding (AB) will develop alterations in cardiac performances (e.g., LV hypertrophy, increase in LVV and left atrial pressure, and decline in EF), clinical signs of HF (e.g., exercise intolerance and respiratory distress), together with cardiac cellular and molecular changes such as, T-tubule remodeling [39], and alterations of myocardial proteases, TNF-α, IL-1β [40], and cardiac sarcoplasmic reticular (SR) Ca^{2+} ATPase 2a (SERCA-2a) [41]. Sometimes anatomical remodeling correlates well with altered physiological function (e.g., CO); other times the 2 consequences are disjoint. This model correlates with LV remodeling more than reductions in LV functions [42]. This model has the important advantage/disadvantage: slow progression (up to months) allows time for intervention and ability to evaluate at finite stages, but adds cost of housing and impacts of ageing must factored into the responces. Furthermore great variabilities in findings and surgical complications may exist [3].

1.3.2 Volume overload induced HF

When the heart is forced (due to mitral regurgitation, aortic regurgitation, left to right shunt, dilated cardiomyopathy) to pump abnormally large volumes of blood, the volume overload produces dramatic structural, electrophysiological, biochemical, and energetic changes leading to HF. There are several experimental extra- or intra-cardiac AV shunts (e.g., infrarenal aorta-to-vena cava fistula [43], femoral artery to femoral vein [44], and aortic valve cups puncture [45]) leading to HF characterized by elevated filling

pressures, arrhythmia, high venous return, and reduction in CO. Moreover, arterial-venous fistulae in the thorax, abdomen, or between femoral artery and vein produce a standardized increase in preload. Dilatation of the left ventricle—from any source—mimics idiopathic dilated cardiomyopathy with increased afterload, elavation of atriopeptins, and impaired coronary blood flow, leading to myocardial necrosis, inflammation, fibrosis, collagen disorder, and LV dysfunction [46]. Decreased LV performance may lead to compensatory hypertrophy and decrease in diastolic function [3]. The cardiac hypertrophy in AV shunt is most likely due to stretch of myocardial fibers. Iron deficiency anemia in weaning rats is an interesting and different form of HF. It is phenotypically like dilated cardiomyopathy [47] but the pathogenesis is dissimilar. Similar to models with pressure overload, HF models due to volume overload require rather long time to develop, and require skillful invasive surgical manipulation, but they are more controllable in severity.

1.3.3 Myocardial infraction-induced HF

Myocardial infraction (MI) due, in most cases, to coronary occlusion is the leading cause of HF and mortality in humans; animal models with MI produced by coronary occlusion are used commonly to study HF. To mimic coronary occlusion in the clinical setting, a major coronary artery in an infrahuman mammal—usaully rat or dog—is either ligated or infused/embolized with microspheres. When the infarct is large enough, ischemia leading to HF develops. The rat model of MI has been used to evaluate both acute and chronic HF, as well as to study ventricular mechanics, changes in hindrance to ejection, arrhythmia, remodeling of myocardium and blood vessels,

responses to therapy, and mortality. In post-MI HF rats, with significant infarcts size, rats showed substantial alterations, at 6 weeks, in structure and function, compensatory cardiac hypertrophy (i.e., increased heart weight as well as length and width of myocytes), with decline in force of contraction and rate of relaxation [48]. Moreover, these rats had reduction in intracellular pH (pHi), which can reduce myofilament Ca^{2+} sensitivity, and alter electrical activity and Ca^{2+} handling. In this MI rat model, there is a decline in FS and Ca^{2+} sensitivity, increase Ca^{2+} transients, reduction of SERCA and Na^{+}/Ca^{2+} exchanger (NCX) protein causing Ca^{2+} overload; therefore, depression of contractility. This Ca^{2+} overload can also lead to energy deficit, cardiac remodeling, and apoptosis [5]. Study in rats with myocardial infarction, showed that myocardial contractility is more depressed in regions adjacent to the ligated coronary artery compared with remote areas [49]. However, the MI-HF rat model is the result of sudden occlusion of a healthy coronary artery in an otherwise heathy rat; this is less likely to happen in a "real" clinical setting, and may limit the ability to extrapolate from rat to human. Other disadvantages of this model include variation of HF onset, high mortality rate, and variation between rats [6].

1.3.4 Pharmacologically-induced HF

There are several drug-induced HF rat models that have been used and developed in CDVs research area. First of all, **doxorubicin** (Adriamycin) is known to be cardiotoxic chemotherapy in both humans and animals, and is well-known to produce (drug-induced) HF. Pathophysiology of doxorubicin-induced HF includes oxidative stress due to free radical formation, leading to oxidized macromolecules, lipid peroxidation, and

myocardial death [50]. In an acute, single dose, doxorubicin-induced HF, cardiotoxicity is associated with oxidative damage indicated by DNA damage and by changes in cardiac morphology and antioxidant functions [51]. Doxorubicin-induced cardiomyopathy does not only act in a dose-dependent manner, but also in a time-dependent (cumulative) manner [52]. Multiple doxorubicin administration in rats showed that doxorubicin had high affinity to heart tissue, and caused alterations in myocardial structures as well as depressed LV EF [53]. Doxorubicin treatment also produced dilatation and thinning of the ventricular free-wall, together with reduction in systolic and diastolic function [3]. Thus, chronic doxorubicin treatment can potentially result in irreversible cardiomyopathy and chronic HF. Doxorubicin- induced HF is a prominent model in term of rapidity of onset, requiring no surgery, and being relatively inexpensive. However, it contains high variability, is not controllable, is irreversible, and may be insidoious in onset (i.e., occurring in human decades after termination of therapy).

Similarly, some drugs that induce **hyperhomocysteinemia** (HHcy: abnormally high homocystein, sulfur amino acid, in blood circulation), such as homocysteine or methionine, can increase reactive oxygen species leading to oxidative stress and dysfunction of the heart, together with autonomic dysfunction and hepatic oxidative stress [54]. Methionine is commonly added into the rat diet, and at approximately 10 weeks, rats will show evidences of oxidative stress-induced cardiotoxicity, especially glutathione peroxidase enzyme activity [55]. Although producing hyperhomocysteinemia cardiotoxicity is simple, it is permanent, lengthy to produce, and expensive.

Isoproterenol, a non-selective β-adrenergic agonist, acts as positive inotropic and chronotropic via stimulating both β_1- and β_2-adrenergic receptors. It results in pharmacologically-induced myocardial ischemic/injury, and alters—predominantly—diastolic function (a negative lusitrope). Negative lusitropy plus myocardial fibrosis lead to both systolic and diastolic HF with ECG alterations (e.g., prolong QTc, ST depression, pathological Q waves and inverted T waves), as well as elevation of troponin, and significant infraction area [56] predominantly of the subendocardium and papillary muscles, at which oxygen demand/consumption are high. Within 24 hours after a single high dose, it provokes acute cardiotoxicity mediated by accelerated HR and positive inotropy, leading to vastly increased myocardial oxygen consumption and ultimate reduction in systolic and diastolic dysfunction, ECG alterations, and histological abnormality (e.g., inflammatory infiltration, myocardial necrosis) [57]. Moreover, after a day or 2, isoproterenol depresses +dP/d*t* and -dP/d*t* [58]. Its pathophysiology involves mitochondrial-dependent apoptotic damage, as well as myocardial lipid peroxidation [59]. Isoproterenol induces controlled and irreversible HF. Therefore, it is not a preferred HF model to be used in an acute study aiming to investigate recovery properties or prophylactic measures.

Imipramine is a prototypical, common-used tricyclic antidepressant drug (TCA). TCAs include amitriptyline, nortriptyrine, and imipramine. Imipramine had hypothesized mechanisms of actions of blocking serotonin and norepinephrine reuptake [60, 61] at CNS nerve endings, and hindering mitochondrial function in the CNS. [62]. It has large volume distribution up to 60 L/kg in human, and develops much concentration in brain,

liver, and myocardium, than in plasma. It is mainly metabolized by the liver and thus can be altered by and co-administration drugs that either activate or block hepatic microsomes [63].

Imipramine acts as an antidepressant in both humans and infrahuman animals (i.e., rodents) [64]; it possesses antinociceptive behavior in rats [61]. The FDA contraindicates use in patients with myocardial infraction, and recommends caution in combination with many other drugs that might affect cytochrome P540 2D6, or that might posses anticholinergic or catecholaminergic properties. Overdose of imipramine results in cardiac toxicity, and mortality in patients [65, 66]. Severe TCA-intoxication can also lead to ventricular fibrillation, torsades des pointes, or asystole, and can produce dramatic hypotension, seizures, and cardiac arrest [67]. These same adverse properties occurred in animals [68] have made imipramine ideal for drug-induced HF animal model.

At high intravenous infusion doses (1mg/kg/min), it creates acute HF characterized by progressive hypotension, initial tachycardia followed by rapid onset bradycardia, and ECG alterations (prolong PR, ST, and QT, together with ventricular arrhythmia or AV block). It produces cardiovascular collapse approximately 20 min after infusion to these anesthetized rats [69]. In Langendorff-perfused intact rat hearts, imipramine perfusion depresses LV function including HR and velocity of LV pressure change ($dLVP/dt_{max}$) [70]. Imipramine affects ion channels (i.e., $I_{Ca,\,L}$, I_{Na}, and I_{to}), ANS control, and myocyte function in a reversible fashion. For instance, it causes I_{Na} inhibition in concentration-dependent manner [71]. It also inhibits $I_{Ca,\,L}$ [72], but does not appear to

alter SR Ca^{2+} [73]. It increases intracellular Mg^{2+} and activates extracellular signal-regulated kinase 1/2 (ERK ½) [70]. It is also an α_1-adrenoceptor antagonist [61].

Besides its simplicity for use, imipramine is inexpensive, acts rapidly, is safe to handel, works in all species independent of anesthesia, and is reproducible [68]. It is compatible with preconditioning to achieve cardioprotection [69, 74]. Therefore, imipramine-induced reversible HF model seemed to be ideal for this study.

1.5 Effects of endurance exercise training on cardiovascular functions

It is well-known that exercise training (ET) is beneficial to body functions (e.g. glucose metabolism [75], skeletal muscle function, cardiovascular function, and psychological function), aerobic capacity and QoL, as well as, to reduce attenuation of cardiovascular function and remodeling in cardiovascular diseases. It is known to reduce cardiovascular morbidity and mortality. According to the CDC, inadequate physical activity or sedentary lifestyle is one of the important behavioral risk factors for CDVs since it can also result in other risk factors: obesity, high blood pressure, high triglyceride-low HDL cholesterol, and diabetics. Thus, ET has become an important program in both prevention and management of HF; many health organizations support physical activity guidelines to prevent and slow the progression of cardiovascular disease in humans.

There are many important improvements from ET in both extrinsic and intrinsic cardiac adaptation; e.g., molecular, histological, gross structural, electrophysiological, biochecmical, hemodynamic.

1.5.1 Effects of ET on extrinsic cardiac adaptation: Blood volume

ET may increase blood volume mainly by increasing plasma protein synthesis [76, 77] and of course increase in BV increases venous return augmenting force of contraction via the Cyon-Frank-Starling law-of-the-heart (heterometric storegulation). Short-term ET (6 days) can cause plasma volume expansion leading to increase LVEDV, LV ejection fraction, SV, and CO during exercise [78]. Beside plasma volume expansion, although PCV may decrease, ET also increases RBC mass. The study in elite endurance-trained adolescent subjects, showed that these subjects had significantly greater total hemoglobin (tHb) mass compared with non-endurance-train (nEND) adolescent (both male and female) subjects, with no significant difference in mean hematocrit (Hct) between these groups [79]. Cardiovascular function can be improved from expansion of both plasma volume (higher CO) and higher tHb (O_2-carrying capacity).

1.5.2 Effects of ET on extrinsic cardiac adaptation: Cardiac autonomic regulation

Alteration of sympatho-vagal balance by ET is a well-known consequence of exercise training. ET can reduce sympathetic activation, but increase vagal tone leading to a lower HR and increased cardiac reserve during resting. As can be seen in short-term ET of untrained individuals, ET can reduce both resting and submaximal HR, together with an increase in SV due to plasma expansion and the enhance Cyon-Frank-Starling effect; therefore, CO can be enhanced and meets the increased metabolic demands during exercise [78]. Likewise, animals exhibit ANS alterations due to ET. After the 2^{nd} week of ET in spontaneous hypertensive rats, low-intensity treadmill training could improve baroreflex response, and minimize oxidative stress and pro-inflammatory cytokines

secretion within the hypothalamic paraventricular nucleus. It also restored HR variability and reduced resting HR via contributing a vagal component to SA nodal function by the 4^{th} week of ET [80]. Of course ET-induced bradycardia increased coronary blood flow and ventricular filling time, decreased myocardial oxygen demand (MVO_2) and reduced risk of arrhythmia.

1.5.3 Effects of ET on intrinsic cardiac adaptation: LV mass and internal dimension

Many studies have focused on alterations of LV myocardial plasticity modified by physical activity. People with extreme sedentary lifestyles, i.e. bed rest or spinal cord injury (SCI), LV mass index was lower than able-bodies subjects and SCI athletes; indeed, SCI athletes had LV mass index equal to able-bodies group [81]. The same findings on reduction in LV mass or cardiac atrophy occurred in a study of 6 week bed rest and after 10 days of spaceflight, indicating that reduced myocardial load can cause physiological adaptation on LV mass [82]. In high endurance activity (elite ET athletes), absolute and scaled LVEDV, together with LV mass are significantly higher than in resistance-trained athletes and sedentary controls [83]. Likewise, Kisvistö and colleagues (2006) [84] found that 3-month ET in healthy sedentary subjects can cause physiological LV hypertrophy (increase LV mass without a decrease in chamber size), or eccentric hypertrophy. In rats, with higher physical activity as in low-intensity ET by treadmill for 8 weeks, ET also showed structural change of LV myocardium (increased in cell length and volume) [85].

ET-induced eccentric hypertrophy is a “favorable” contrary to hypertrophy from cardiovascular disease. This eccentric hypertrophy mainly results from plasma volume

expansion in the induction stage, follow by genomic-change in myocardial structural and function specific to volume overload. Some studies provide evidence in which ET-induced eccentric hypertrophy leading to enhanced myocardial systolic function, increased in SV and CO. In the study of Fujimoto and colleagues (2010) [86], 1-year ET in sedentary seniors showed a 10% increase in LV mass index without change in LV mass-volume ratio. This was accompanied by increase SV and stroke work. In a cross-sectional analysis when comparing elite male endurance athletes (EG) who had more than 10 years of regular ET with control individuals, the EG group had 80% more LV mass, with 37% more LVEDV and larger SV. During high intensity exercise, there is a significant correlation with the increase LV mass index and increase peak systolic contraction velocity, reflections of enhanced inotropy. Thus, ET improves cardiac systolic function during exercise [87]. In another rat study, Kemi and colleagues (2004) [88] showed that 10-week high-intensity ET caused higher ventricular weight, cardiomyocyte dimensions, and improved contractility and Ca^{2+} handling.

1.5.4 Effects of ET on intrinsic cardiac adaptation: LV compliance

Ventricular compliance refers to ease of filling (lusitropy). There are 2 components to lusitropy. The 1^{st} occurs before there is any filling as LVP plummets during early relaxation when Ca^{2+} is driven off of troponin-C and sequestered into the sarcoplasmic retiruclum (SR) through the SERCA channel, an active, energy using reaction. The 2^{nd} occurs as the ventricle actually fills, passively from the pressure gradient between atrium and ventricle. Lusitropy can be studied by a combination ventricular manometry (i.e., -dP/d*t* and Tau) for phase 1, and (phase 2) pressure-volume

loops from which the filling slope between opening the AV valve to atrial systole. The ventricular filling force is, in fact, the pressure difference between that in the ventricle (LVEDP) and that in the pleural space (Ppl). However the final EDV—presuming enough time has elapsed for filling—is expressed as: EDV = (LVEDP-Ppl)/E_V, where E_V stands for the elasticity modulus, or stiffness of the wall. Ventricular compliance is determined by the physical properties of the ventricular wall: muscular, fibrosis, and edema. Diseases and ageing alter lusitropy as, of course, does pathology.

There is some evidence that ET can increase ventricular compliance, i.e., render the chamber more easaily filled. For example, 12 weeks of ET in rats showed significant decrease in LV myocardial stiffness compared with hearts from, age-matched untrained rats. This occurred without changes in collagen, and resulted in higher CO [89]. They also found that ET improved cardiac cell metabolism. These findings were likely to have resulted from exercise-induced increase in coronary shear stress secondary to increased nitric oxide (NO) release. NO is important in regulating blood flow to all vascular beds, resulting to balance oxygen delivery with demand. These ET-induced cardiac adaptations in rats are also mimicked in humans, especially shown in with lifelong, high-frequency ET [90].

ET-induced LV remodeling salvages function, whereas maladaptive remodeling causes collagen deposition and other structural and biochemical changes that result in diastolic stiffness and and impaired diastolic function. As presented in a 3-month ET study in healthy sedentary subjects by Kisvistö and colleagues (2006) [84], ET can

enhance global early diastolic LV myocardial relaxation, concomitant with physiological LV adaptation. This beneficial adaptation includes accelerated Ca^{2+} resequestration.

1.5.5 Effects of ET on intrinsic cardiac adaptation: LV contractility

Improved inotropy is another ET-induced cardiac alteration. This improvement in contractility can rersult from accelerated/more efficient excitation-contraction coupling mediated by improved Ca^{2+} kinetics increased myofilament Ca^{2+} sensitivity. There are several experiments that studied Ca^{2+} handling and found that improvement of contractility is linked to increase in activity of SERCA-2a in rats. This step is vital to both the pathogenesis of HF and to response to therapeutic interventions. SERCA physiology is controlled by phospholamban (PLB), which the unphosphorylated form can bind to and inhibits SERCA. Phosphorylation of PLB is controlled by cAMP-dependent protein kinase A (PKA) and Ca^{2+}/calmodulin-dependent kinase II (CaMK II), both of which can phosphorylate PLB and reduce its inhibition on SERCA (see figure 5).

Correspondingly, Kemi and colleagues (2007) [92] evaluated the effects of 6-weeks of aerobic interval training (AIT) on rat cardiac contractility and Ca^{2+}cycling, and found that ET increased phosphorylation of PLB, causing elevate SERCA-2a activity, leading to an increase in amplituider Ca^{2+} transients and fractional shortening. This training also increased activation of CaMK II function, which increases cardiac Ca^{2+} sensitivity, inotropy (manifested as increase in fractional shortening) and lusitropy (manifested increased rate of relaxation).

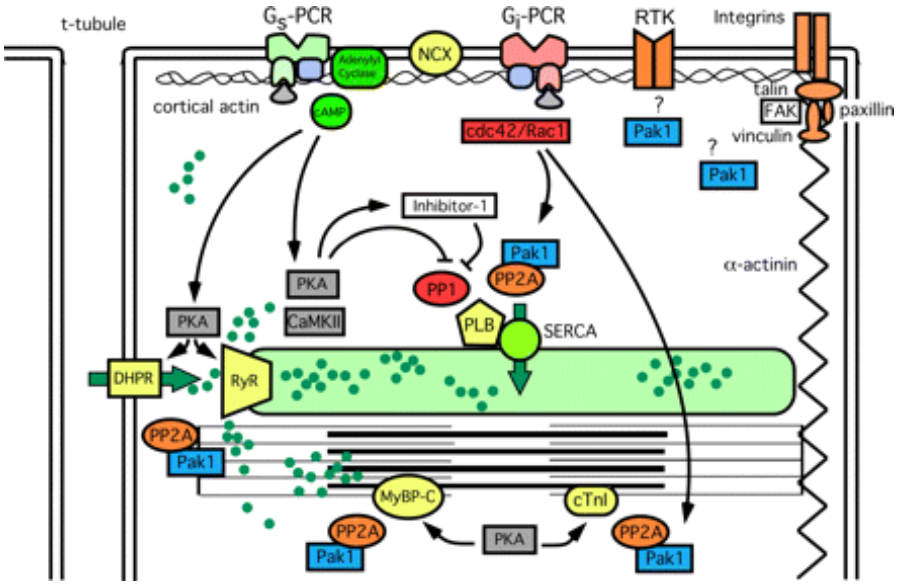

Figure 5. Unphosphorylated PLB binds to and inhibits activity of SERCA, until PKA or CaMK II phosphorylates PLB, allowing PLB to detach from SERCA [91].

Another molecular pathway that is improved by exercise invovles nitric oxide synthase (NOS). The neuronal isoform NOS (NOS-1) is a modulator of myocardial contractility and Ca^{2+} handling by producing NO that stimulates release of Ca^{2+} from the SR through ryanodine receptor (RyR2) S-nitrosylation [93] during excitation-contraction coupling, and facilitates Ca^{2+} reuptake by SR [94] during diastole. Of course, SR release Ca^{2+} through RyR2 depends upon normal SR Ca^{2+}. A study, reporting effects of NOS-1 on myocardial contractility, showed that 8-weeks of high-intensity interval training in rats improved cardiac contractility (as fractional shortening), increased amplitudes of Ca^{2+} transients, and improved both inotropy and lusitropy. Also, inhibition of NOS-1 in this study caused reduction in maximal SR Ca^{2+} reuptake via SERCA [95].

1.5.6 Effects of ET on intrinsic cardiac adaptation: LV oxidative status

Oxidative stress results from an imbalance between production and scavanging of free radicals of reactive oxygen species (ROS) produced. Scavenging depends upon amount and activity of scavenging antioxidative enzymes such as superoxide dismutase (SOD), glutathione, and catalase. Injury from free radical results, principally, from lipid peroxidation of cell membanes and injuiry to nuclear DNA. This, of course, disturbs normal cellular signaling.

Several severe diseases are associated with oxidative stress: cancer and adverse responses to antineoplastics, atherosclerosis, Parkinson's, and HF. In CVDs, aging and ischemia/reperfusion injury (IR) may reslt from high amounts/activity of ROS. Several studies suggest that ET can improve free radical scavenging. For rats exposed to small concentrations of carbon monoxide, 8 weeks of moderate ET (5day/week for 4 weeks and 2 days/week for a 2^{nd} 4 weeks) can reduce toxicity from free-radical, leading to lower cardiac vulnerability to arrhythmia, and reduced area of infraction [96]. Rats exposed to ET for shorter periods (2 weeks) following coronary ligation-induced IR, have significant increases in manganese SOD levels resulting in attenuation the magnitude of IR-induced oxidative stress, and improved Ca^{2+} handling protein, and less apoptosis and necrosis [97]. Improvement of antioxidative status in the heart by ET also could partially prevent arrhythmia and cardiac necrosis due to IR in rat [98]. Similarly, ET-induced cardioprotective effect improves oxidative status (increased SOD level) that occurrs in age-related cardiovascular changes in rats [99], and in ovariectomized-induced menopause rat model [100].

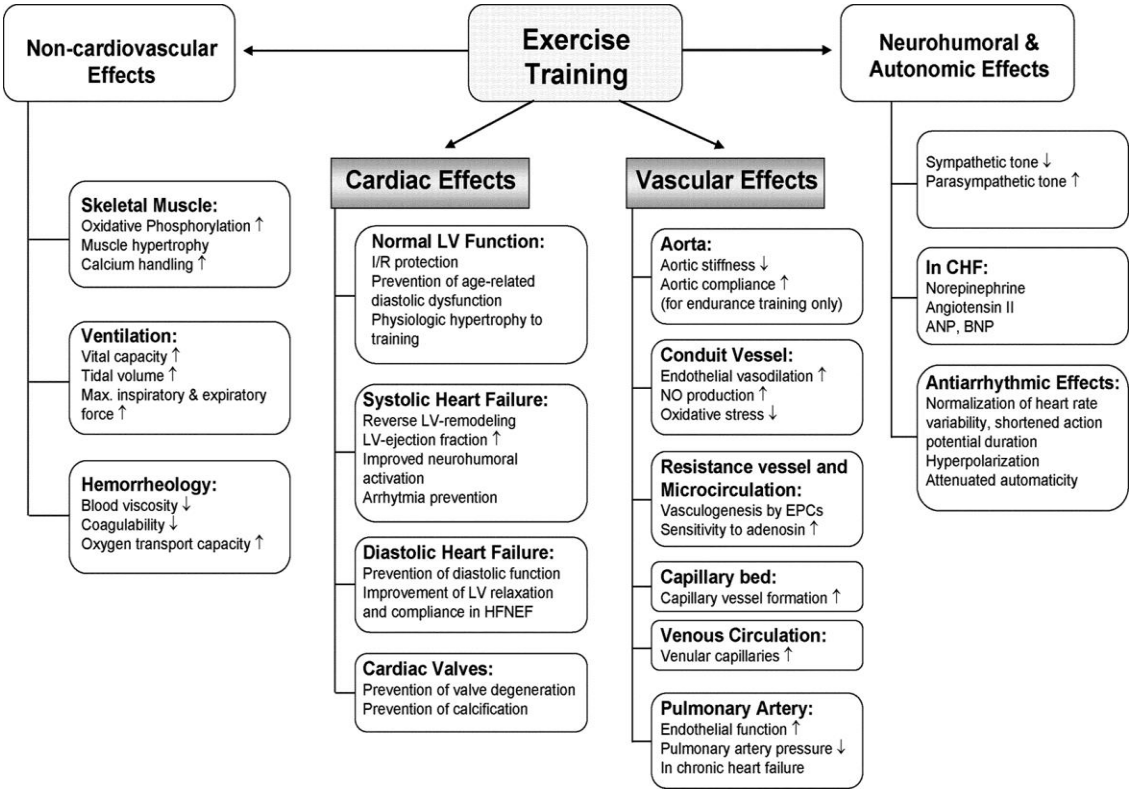

Figure 6. Summary of ET-induced cardio protective effects via different body systems. Max, maximum; HFNEF, HF with normal EF; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide [101].

Aside from above effects of ET on cardiovascular function, ET has other beneficial effects in both physiological and pathological situations (i.e., systolic HF, and congestive HF). Mechanisms of favorable effects of ET on cardiovascular function and other systems are listed in figure 5. From all of the above beneficial effects of ET descrived in many rat models [92, 97, 100, 102], moderate periods (6 weeks) of high

intensity ET as AIT via motor-driven treadmill should provide sufficient preconditioning to protect the heart during experimentally-induced acute HF by imipramine challenge.

1.6 Pharmacological preconditioning

In the areas of cardiovascular research enormous efforts and amounts of money have been expended to prevent and manage adverse consequences of oxidative stress in particular as relatged to ischemia/reperfusion (IR) and other cardiotoxic substances. Many drugs and methods have been evaluated to effect preconditioning, an effort to prevent or modify pathophysiology. Several pharmacological substances have been selected and used in preconditioning trials [50, 103, 104, 105] both to prevent and modify effects of aversive stimuli, principally free radicals of oxygen that produce life-threatening, often irreversible, pathology. Pharmacological substances that can augment the cellular antioxidative functions are at the fore front. They are directed at protecting ANS dysregulation, myocardial energetics, and other maladaptive consequences. Preconditioning is intended to enhance beneficial adaptive functions. In this study, the main focus is on pharmacological conditioning agents that may attenuate the effects of imipramine-induced HF in rats and their hypothesized mechanisms are presented below.

1.6.1 Effects of carvedilol on cardiovascular functions

Carvedilol is a third-generation β-blockers that has non-selective β- and α_1-adrenergic receptor antagonism without intrinsic sympathomimetic activity or membrane stabilizing activity. It can block norepinephrine (NE) effects on β_1- and β_2-adrenergic receptors leading to reduction of HR and force of contraction, together with blocking

effects of on α_1-adrenergic receptors of arterial and venous blood vessels causing lowering in blood pressure. Venodilation also reduces preload or heart load. Most effects of carvedilol, then, are cardioprotective. Even though a primary effect may be to reduce contractility, when given chronically to patients with HF, contractility actually increases; this along with cardio deceleration slows progression of heart disease. In addition to reduced work load and improving myocardial energetics, carvedilol is also a potent scavanger of free radical of oxygen, and this antioxidant property protects the heart.

This antioxidative property of carvedilol is particularly favorable in protecting the IR myocardium of any origin, but also during ROS of ageing or cell injury of other causes exploiting other pathways. Antioxidative property of carvedilol can be direct effect [106], or indirect effect (i.e., reduced ROS production). ROS production and cardiac hypertrophy are also mediated by α_1-adrenergic receptor (as shown in isolated adult rat myocardial cell culture) [107], thus it is clear why the α_1-blocker property of carvedilol can atenuate this pathology. Moreover, NE is elevated in HF and mobidity and mortality relate stongly with NE plasma/tissue levels, therefore it is obvious why carvedilol should be so helpful. Monteiro and colleagues (2003) [108] found that the ischemic rat heart perfused with Langendorff technology mainfests less mitochondrial damage from oxidative stress, and restored mitochondrial energy production when treated solution with carvedilol.

In intact animal studies, carvedilol prevented oxidative stress via adenosine (ADO)-dependent pathways [109, 110]. Asanuma and colleagues (2000) in an open-chest canine study [111], demonstrated carvedilol preconditioning mimimized infract size

but the protection was diminished with ADO receptor antagonist, confirming that benefit from carvedilol resulted, no doubt at least in part, from energetic changes (i.e., HR reduction). Of course decreased afterload and heart rate are properties shared between carvedilol and ADO, and both produce a more favorable energetic balance. Chronic administration of carvedilol (10 mg/kg/d for 14 days), also protected mice from myocardial inflammation and necrosis due to viral myocarditis, via increase antioxidative function (i.e., increase SOD and decrease malondildehyde), up-regulation of anti-inflammatory cytokine (i.e., increase interferon-γ and interleukin-12) [112]. Of interest, when treating with interferon-γ and interleukin-12, mice with viral myocarditis had better survival, fewer myocardial lesions, and less viral replication [113, 114].

In rats treated with carvedilol (80mg/kg/day PO for 5day) for preconditioning sizes of infarcts, following coronary occlusion in isolated perfused hearts [104], were greatly reduced. Structural and functional changes produced by chronic daunorubicin (anticancer drug with oxidative stress cardiotoxicity), were greatly minimized by treatment with carvedilol (30 mg/kg/d for 6 weeks). Carvedilol also improved survival rate and systolic and diastolic functions, as well as reduced both myocardial fibrosis and hypertrophy due to daunorubicin [115]. Likewise, 6-month oral carvedilol (30 mg/kg/d) minimized both LV hypertrophy and dilatation, and increased EF in volume-overloaded cardiomyopathy in rats [116]. Carvedilol can also prevent and reverse hypertrophy in spontaneously hypertensive, stroke-prone rats fed a high-fat/high-salt diet. In these rats, carvedilol decreased LVEDV, but increased SV, EF, and CO, as well as attenuated cardiac remodeling (i.e., prevented increase in LV wall thickness), without reduction in

blood pressure. This indicates that the principal mode of action was related to carvedilol's antioxidant property and not that in merely slows heart rate or improves energetics [117]. Still, although a fundamental negative inotrope when given to a normal animal, carvedilol improves contractility after aversive stimuli may provoke molecular mechanisms (e.g., augmentation of inflammation-related gene and cytokines [118]). The role of carvedilol to improve SERCA cannot be understated, since current wisdom indicates that this channel is probably proximate to development of HF. However, carvedilol administration could restore the low SERCA expression in post infraction rat model [119].

Another interesting cardioprotective mechanism of carvedilol is mediated via a NO-dependent pathway. Chen and colleagues (2012) [120], studying unilateral renal clip-induced hypertension in rats, exposed them by gavage to carvedilol (20 mg/kg/d for 8 weeks), and found a dramatic decrease in myocardial fibrosis (i.e., collagen volume fraction, and perivascular collagen area) that was diminished by blocking NO with concomitant gavage L-NAME. Of course, NO exerts many important effects including vasodilation and anti-proliferation. These NO modulating effects, especially vasodilation, may explain many favorable clinical results (reverse LV remodeling and improvement of coronary flow reserve) in patients with dilated cardiomyopathy who received carvedilol treatment [121]. Shashurin and colleagues (2010) showed the level of NO correlated with severity of the cardiac dysfunction in rats with congestive HF [122], and rats receiving carvedilol or proxodolol had lower myocardial NO concentration than untreated-rats.

In clinical settings, carvedilol has been widely used for treatment of hypertension, ischemic heart disease, and congestive HF. However, recent studies suggest that β-

blockers do not provide more benefit than other antihypertensive medication or, in fact, placebo; therefore, the AHA and other medical health institutes do not recommended β-blockers as a first-line of treatment for primary hypertension[123]. Nevertheless, in more complex situations such as ischemic and congestive HF, β-blockers, together with other conventional hypertensive medications such as angiotensin converting enzyme (ACE) inhibitor, calcium channel blocker, and/or diuretic, seem to provide more benefits to patients. Indeed, in the Heart and Soul Study, HF patients with diastolic dysfunction and stable coronary heart disease who received β-blockers had lower risk of hospitalization than those who did not received β-blockers [124].

When compared with other β-blockers (i.e. atenolol, bisoprolol, metroprolol, and nebivolo), carvedilol has fewer adverse effects due to lacking intrinsic sympathetic activity [123]. Carvedilol seems to have a lower risk of worsening symptoms. Also, in retrospective nationwide cohort study, HF patients who receive carvedilol had significantly lower all-cause mortality and hospitalization risk, compared with other β-blockers (i.e., metoprolol and bisoprolol) [125]. However, there was a controversial that carvedilol may be better than metoprolol in improving vascular outcomes in ischemic HF or idiopathic cardiomyopathy patients [126]. With fewer adverse effects of carvedilol and the antioxidant property, carvedilol is preferred over other β-blockers or cardiovascular medications [112, 119, 126, 127, 128, 129]. In fact, carvedilol, spironolactone, and ACE inhibitors are unique in their approval by the FDA.

All of the above carvedilol cardioprotective findings, indicates that carvedilol has more potency in cardio-protection than other β-blockers. Moreover, carvedilol seems to

be safe and well-tolerated for chronic pharmacological preconditioning in rat models. Even in a low dose, chronic carvedilol administration (2 mg/kg/d for 8 weeks) cardioprotections by carvedilol is effective [130]. Therefore, low dose-chronic administration of carvedilol at 3 mg/kg SC BID 5 day/w for 2 weeks may provide cardioprotection against imipramine-induced acute HF in rats in this study.

1.6.2 Effects of clenbuterol on cardiovascular functions

Clenbuterol, a selective long-acting β_2-adrenergic receptor agonist, has some similarity in structure and pharmacology with epinephrine. As a β_2-adrenergic agonist, clenbuterol is able to activate adenylyl cyclase leading to increase production of cyclic AMP (cAMP). Effects of clenbuterol rely mainly on its β_2-sympathomimetic properties. They are smooth muscle relaxation due to β_2-agonist induced production of cAMP, increase hepatic glycogenolysis, increased pancreatic glucagon releasing. It also shows anabolic effects on skeletal muscle and increased lipolysis via activation of β_3-adrenergic receptors leading to drug abuse in body builder and weight loss control [131]. Clenbuterol may also produce other favorable effects by producing increased aerobic capacity, stimulation of CNS, and increasing blood pressure and oxygen transportation.

For humans, clenbuterol is commonly used in chronic breathing disorders induced by airway smooth muscle spasm (asthma), for its bronchodilator effect. However, according to the FDA, clenbuterol is not yet approved for use in any prescription medication in the US, and it is prohibited for use in any food producing animals due to its possible residual/persistant adverse effects on consumers. For instance, Daubert and colleagues (2007) [131] reported that acute clenbuterol overdose in a 31-year-old male

patient caused supraventricular tachycardia, atrial fibrillation, and hyperglycemia, all of which could result from the β_1-adrenergic (cross-over) property with high doses of clenbuterol. Retrospective reviews from poison control centers reveals that patients with clenbuterol exposure (most of the patients are body builders or people on weight-reduction programs), often manifest adverse effects: tachycardia, widen pulse pressure, tachypnea, hypokalemia, hyperglycemia, ST alterations, elevated troponin, increased creatinine phosphokinase, palpitations, chest pain, myocardial injury, and tremor [132]. Beside muscle mass enhancement and weight loss, clenbuterol is also used, illegally, as a performance- enhancing drug for athletes; it is banned as a growth promoter for livestock. In the US, clenbuterol is used widely to treat horses with chronic obstructive pulmonary disease (COPD) for its bronchodilator effect.

Interestingly, even with reports of adverse side effects, some researchers and physicians believed that clenbuterol may provide benefits (i.e., cardiac restoration and/or preconditioning effects on CVS) to patients with end stage HF who are implanted with LV assist devices (LVAD) [133, 134, 135, 136, 137, 138, 139].

After dosing horses, with recurrent airway obstruction, with 0.8 μg/kg BID clenbuterol for 14 days, cardiac function improved (e.g., increase in early and late diastolic velocity and isovolumic contractility, with decrease QA duration and global ventricular function index or Tei index), indicating clenbuterol restored, at least partially, myocardial function [140]. Similarly, in the post-MI rat model, 7 days of treatment with clenbuterol, 2 mg/kg/day, increased SR Ca^{2+} transients, improved EF, and increased HR, concomitant with cardiac hypertrophy [141]. Also, 0.5 mg/kg clenbuterol given

intraperitonially 1 hour before induced IR in anesthetized rats, reduced infract size, improved diastolic function and SERCA activity, increased SOD, and reduced MDA, LDH and CK. The reduction in apoptosis may mediate possibly by augmentation of ERK 1/2 phosphorylation. When clenbuterol was blocked with a selective β_2-antagonist or G_i-protein inhibitor, those effects were blunted. Therefore, clenbuterol is likely to have cardio-protective actions against IR mediated by β_2-adrenoceptor-G_i-protein signaling [142]. In the IR Langendorff rat heart model, pretreatment with clenbuterol also (1) improved diastolic function (LVEDP), (2) increased coronary flow, (3) increased Ca^{2+}-ATPase activity, (4) improved oxidative status (increased SOD and decreased MDA). In the same study, cultures of newborn rat myocardium exposed to clenbuterol developed less apoptosis when challenged with hydrogen peroxide [143].

On the other hand, chronic 2.4 µg/kg BID clenbuterol treatment [(5 day/week) for 8 weeks in mares, with- or without-treadmill ET], attenuated cardiovascular function, measured by increased LV diameters, thicken interventricular septal wall, and dilated aortic root dimension (which could lead to aortic rupture) [144]. Likewise, when given 2.4 µg/kg/day of clenbuterol in drinking water for 7 days, mice developed augmented cardiac extracellular matrix leading to attenuation of diastolic function as increase isovolumic relaxation time and left atrial dimensions, together with decreased LV free wall tissue Doppler ratio, without alterations in EF, HR, and CO [135]. Also, in a normal rat study, clenbuterol produced dose-dependent cardiotoxicity, and caused higher HR and apoptosis in caspace 3 immunohistochemistry at higher doses. This apoptosis was prevented by a β_2-antagonist. However, both low (0.3 mmol/kg) and high dose (3

mmol/kg) of clenbuterol decreased DBP and SBP [145]. Likewise, a single SC clenbuterol injection of t 1 μg/kg produced significant apoptosis peaking at dose of 5 mg/kg (maximum tested dose). This apoptosis was diminished when using β-blockers concomitantly, indicating that neuromodulation of clenbuterol via β_1-adrenergic receptors plays an important role in myocardial apoptosis [146]. These findings were consistent with the results of Zaugg and colleagues (2000) [147], in which the β_2-adrenergic receptor agonist (albuterol) created myocardial apoptosis less than NE, and β_1-adrenergic antagonist (atenolol) could prevent apoptosis-induced by albuterol or NE.

Other cardiovascular effects of clenbuterol were altered using β-adrenergic blockers for varying receptor types. As can be seen in β_2-adrenergic receptor knockout mice, chronic treatment with clenbuterol at 2 mg/kg/day for 7 days had a lesser effect on increasing LV posterior wall thickness, EF, and myocardial size. However, the hearts from knockout and control rats showed similar contractility and Ca^{2+} handling, all of which suggest that the cardiac hypertrophy of clenbuterol depend principally on β_2-adrenergic receptors but not on contractility [138].

In an *in vitro* cardiomyocytes (e.g. myocardium, and cardiac fibroblast) culture, cardiac hypertrophic produced by clenbuterol relied on paracrine signaling, since cells exposed to clenbuterol had higher expressions of ANP, BNP, and insulin-like growth factor I (IGF-1) mRNA, without alteration in α-skeletal muscle actin mRNA expression indicating physiological hypertrophy. More importantly, with blocking IGF-1, the hypertrophic effect was diminished [137]. Furthermore, this myocardial gene expression by clenbuterol also occurred in an *in vivo* rat study, in which rats were implanted with

mini-osmotic pumps in order to continuously infuse clenbuterol at 2 mg/kg for 28 day. In this experiment, clenbuterol treated rats developed cardiac hypertrophy with increased muscle mass, higher HR, prolong QT interval, and up-regulation of angiogenesis and integrin signaling genes [134].

From some rat HF models, chronic clenbuterol treatment seems to be safe and effective. Clenbuterol preconditioning showed both cardiotoxic and cardioprotective effects. Therefore, chronic clenbuterol preconditioning using the 2mg/kg SC SID 5 day/week for 2 weeks (dose suggestged by Siedlecka et al. (2011) [138]), before challenge with imipramine, may alter cardiovascular effects of imipramine in this study.

1.6.3 Effects of dobutamine on cardiovascular functions

Dobutamine is a synthetic catecholamine that must be administered intravenously, and increases myocardial contractility and CO, produces mild elevation of HR, but without significant increase in peripheral arterial resistance [148]. These cardiovascular effects are attributable to a more dominant β_1-adrenergic receptor effect than β_2- and α_1-adrenergic receptor effects, thus it can augment myocardial contractility and CO, with less alteration in TPR [149]. Futhermore, dobutamine appears to activate β_1-adrenergic inotropic receptors than chronotropic receptors, and has less arrhythmogenic effect even in HF patients. [148]. It had been used in the US since 1978, preferably, acute HF with reduction in CO and elevation of diastolic filling pressure [150].

However, there were several studies that report increased risk of death in HF patients receiving dobutamine. The Flolan International Randomized Survival Trial (FIRST) showed that patients who received continuous intravenous dobutamine (n=8),

had worst first outcomes and 6-month mortality rate than those who did not (n=391) [151]. The Evaluation Study of Congestive heart failure And Pulmonary artery Catheterization Effectiveness (ESCAPE) trial also demonstrated that most inotropes, including dobutamine, were associated with adverse outcomes, as overall 6-month mortality, compared with vasodilators treatment [152]. The retrospective cohort study of Cardoso and colleagues (2014) [153] found that patients who received inotropic drugs (as dobutamine) in the group of 1992-1999 had lower first year survival rate compared with patients who did not received inotropes. Patients receiving inotropic support in 2005-2006 (in which HF severity was worse than those in 1992-1999) showed no difference in survival rate compared with patients who did not use inotropes. Association between the dobutamine treatment and higher risk of death in other studies may depend on lack of randomization, as well as differences in severity at baseline.

In control clinical studies, dobutamine produced beneficial cardiovascular effects. For example, after patients with chronic congestive HF received continuous intravenous infusion of dobutamine at 2.5, 5, and 10 μg/kg/min for 30 minute at each dose, there were increases in CO (82% increase) and SV (39% increase), without clinically significant alterations in HR or rhythm, or in mean aortic or pulmonary arterial pressures. Also, these patients were well-tolerated to the drug [148]. In patients with (non-ischemic) dilated cardiomyopathy, when duration of dobutamine infusion was lengthened to 3 days with gradually incremental dose from 2.5 μg/kg/min up to 15 μg/kg/min, several advantages occured to both hemodynamic and metabolic properties, i.e., CO and coronary blood flow, ATP/creatine ratio, and reduction in BUN. These improvements

may explain clinical improvement from 3 days dobutamine infusion [154]. In another dobutamine infusion study in which patients with moderate to severe congestive HF completed 24 weeks of short period of dobutamine infusion, weekly 4 hour-infusion of escalating doses from 2.5 µg/kg/min to 10 µg/kg/min or to the dose that not increase HR more than 40%, over the first 30 min, there were significant improvements in clinical status and exercise performance (e.g., velocity of circumferential fiber shortening, percent change of the minor axis of LV during systole, exercise tolerance, and functional classification of HF) [155].

Reports from animal studies testing dobutamine on cardiovascular function, showed consistency of cardiovascular benefits shared with human clinical trials. Mielgo and colleagues' (2014) review article on dobutamine given to "pediatric" animals (such as piglets, lambs, puppies, and foals) concluded that dobutamine infusion improved CO in a dose-dependent manner, together with increase in: HR, SV, and MAP. However, there were variations in dobutamine responses which may depend on animal age, as well as dose level and infusion duration [156]. Normal rats given a single, IP dose of 4 µg/kg dobutamine, developed greater augmentation in systolic and diastolic cardiovascular function than rats with streptozotocin-induced diabetes. Although magnitude of cardiovascular improvement was lower in diabetic rats, dobutamine still showed efficacy to preserve lusitropy, regardless of the alteration in β_3-adrenergic receptor over-expression [157].

Dobutamine improved cardiovascular performance depends on its stimulation on β_1-adrenergic receptor, predominantly on positive inotropic with lesser on positive

chronotropy. Fink and colleagues (2013) [158] confirmed that β_1-adrenergic receptor stimulation is imperative for the beneficial actions of dobutamine, since co-administration of esmolol (β_1-adrenergic receptor antagonist) diminished positive effects of pretreatment before induction of sepsis. This was confirmed by measaurements of total hepatic flow, hepatic microcirculation, hepatocellular injury, and survival time. In another septic rat study, perfusion of isolated rat hearts with dobutamine resulted in dose-dependent cardiovascular responses: positive inotropy, chronotropy, and lusitropy, in both the septic group and sham group. Dobutamine also proportionally decreased myocardial oxygen supply-demand ratio in another preconditioning septic rat model [159]. Likewise, in experimental bupivacaine-induced cardiotoxicity a rat model, dobutamine 3 μg/kg/min infusion preserved several beneficial β_1-adrenergic effects: (1) increased survival time, (2) slowed the progression of cardiotoxicity, (3) prolong time from start bupivacaine intravenous injection to time at 50% and 70% HR reduction, time at 50% and 70% MAP reduction, and (4) prolonged time to cardiac arrest [160].

Another study (Chou and colleagues (2012) [161]) showed the association between dobutamine action and cardiac receptor expression. They examined dobutamine effects on expression of peroxisome proliferation-activated receptor delta (PPAR δ), a nuclear hormone receptor that regulates myocardial contraction and is down-regulated in cardiomyopathy situation, in neonatal rat cardiomyocytes. They found that dobutamine increases expression of PPAR δ and cardiac troponin I phosphorylation (in a time- and dose-dependent manner) only when there was no β_1-adrenergic antagonist co-administration.

Dobutamine can preserve cardiovascular mechanical performances by other methods. As discussed by Wang and colleagues (2013) [162] on an IR rat model, dobutamine preconditioning significantly alleviated IR-induced myocardial injury and oxidative stress in dose-dependent manner. The mechanism of this cardioprotection was also attributed to β_1-adrenergic receptor stimulation-induced production of heme oxygenase-1 (OH-1) [an anti-inflammatory, anti-apoptotic, and anti-proliferating enzyme], mediated via phosphatidylinositol 3-kinase (PI3K), and P38 mitogen-activating protein kinase (p38 MAPK). OH-1 can inhibit high mobility group box 1 protein (HMGB1) that has late inflammatory cytokine effects leading to progression of IR-induced myocardium injury. Effects of dobutamine may be mediated by induction of heat shock protein 70 (Hsp 70), as show in dobutamine preconditioning in Jurkat T lymphocyte cell culture, in which apoptosis is modified by dobutamine-induced increase in Hsp 70 [163].

Besides using dobutamine or other inotropic drugs in HF and septic cardiomyopathy, dobutamine can be safely applied for hemodynamic support before initiation of epoprostenol (first-line drug for pulmonary arterial hypertension that has hemodynamic suppression) [164], and for application of dobutamine stress test in evaluation cardiovascular performances. Dobutamine stress tests are important diagnostic tests that impose stress on the cardiovascular system and may uncover impaired cardiovascular reserve. This test is very useful to detect subtle global myocardial dysfunction often present with coronary insufficiency or ischemia that may be not present during rest. Dobutamine has advantage over exercise stress in treadmills are not required,

and that it simulates exercise in patients who are unable to perform exercise and it allows stress echocardiography (DSE) and/or stress during MRI or x-ray. DSE is safe for use in persons of all ages [165], in the morbidly obesity [166], as well as in animals (e.g., pulmonary embolism lambs [167], rats [168], aging-naked mole rats [169], and spontaneous hypertensive rats [170]). DSE is very sensitive [171] and accurate for detecting cardiac functional impairment, and it is considered a gold standard for evaluating patients with after myocardial infarction.

Dobutamine is not used only for brief stimulation to mimic exercise, but also for pharmacologically-induced physical conditioning as by Sullivan and colleagues (1985) [172], in which healthy young men were given, daily for 2-hour/dayh for 3 weeks, 7.9-15 μg/kg/min dobutamine infused during bed rest-induced physical deconditioning, to restore physical capacity (e.g., maximal exercise duration, oxygen consumption, and work load), exercise hemodynamics (e.g., HR, SV, and CO), and lactate levels during exercise. Persons receiving dobutamine infusion had those variables similar to those of persons who received ET, and superior to those who receiving saline. As showed by Grimes and colleagues (2014), 3 mg/kg of dobutamine given IP can simulate cardiac stress mimicking exercise [169]. Therefore, using chronic dobutamine preconditioning at 0.75 mg/kg SC three times a day (to counterbalance its brief action) 5 day/week for 2 weeks, may provide the same positive cardiac adaptations as exercise trained rats and protect cardiovascular functions during imipramine challenge.

1.7 Study Aims and Hypotheses

1.7.1 Quantify, and compare, CV physiology of normal, anesthetized rats that have been exposed, chronically to sedentary existence or to aerobic interval exercise, carvedilol, clenbuterol, and dobutamine

Hypothesis I: Rats have definitive but different CV responses to exercise training or drugs based upon different and well-known pharmacological properties.

1.7.2 Compare non-electrophysiological CV responses of all rats (i.e., sedentary, exercised, carvedilol, clenbuterol, and dobutamine) to onset and termination of exposure to imipramine.

Hypothesis II: Rats conditioned with exercise, carvedilol, clenbuterol, or dobutamine are more resistant to effects on mechanical properties affected by imipramine compared with sedentary existence.

1.7.3 Quantify ECG changes in the above rats exposed to and recovering from an imipramine challenge

Hypothesis III: Rats conditioned with exercise, carvedilol, clenbuterol, or dobutamine are resistant to electrophysiological effects of imipramine-induced HF.

Chapter 2: Material, methods, and studies

2.1 Materials and Methods

The procedures used in this protocol were reviewed and approved by QTest Labs' Institutional Animal Care and Use Committee (IACUC) for compliance with regulations and current accepted practices. This study does not duplicate previous work. The number of animals used in this study is the minimum number necessary for the evaluation of the results. Procedures involving the animals are addressed either in the protocol or in QTest Labs' Standard Operating Procedures (SOPs). These procedures are meant to ensure that the animals' exposure to pain and distress are minimized.

All animals (with the exception of any surviving spare animals) were euthanatized (while fully anesthetized) in accordance with accepted American Veterinary Medical Association (AVMA) guidelines (AVMA Guidelines for the Euthanasia of Animals: 2013 Edition).

2.1.1 Animals, Animal care, Housing, and environment conditions

Male Sprague-Dawley rats, 6 weeks old and weighing 150-300 g, were obtained from a USDA-approved vender. Ten rats were allocated to each of five intervention groups, and four rats were assigned to one vehicle group. The number of animals was

determined to meet the study objectives and was chosen based upon studies of similar design performed at OSU Department of Physiology [173].

The animal care and housing environments were maintained according to facility SOP 500 (Receipt, Care, Identification, and Housing of All Laboratory Animals). In short, automated light/dark cycle was set at 12 hours; room temperature and relative humidity were set at 68-79°F and 30-70 %, respectively. These numbers were monitored daily and were recorded in each animal's room logbook. In cases of deviation of these environment parameters, the source was noted and corrected promptly. All rat cages were rotated bi-weekly in order to prevent phototoxic retinopathy.

2.1.2 Test compounds: carvedilol

Carvedilol (C3993 Sigma) was dissolved in Di-methyl sulfoxide (DMSO) to 18 mg/mL, and then the solution was filtered to exclused microorganisms before storage in sterile plastic tubes or in tuberculin syringes covered with aluminum foil. Diluted solutions were used within 7 days after being prepared and stored in refrigerator.

2.1.3 Test compounds: clenbuterol

Clenbuterol hydrochloride (C5423 Sigma) was dissolved in sterile water to 1.25 mg/mL, and the solution was filtered to exclused microorganisms before storage in sterile plastic tubes or tuberculin syringes covered with aluminum foil. Diluted solutions were used within 7 days after being prepared and stored in a refrigerator.

2.1.4 Test compounds: dobutamine

The beta-adrenergic agonist, dobutamine hydrochloride 12.5 mg/mL (562998 Makesson), was dissolved in sterile water to 1.25 mg/mL, filtered to exclused microorganisms, and the solution was stored in sterile plastic syringes covered with aluminum foil. Diluted solutions were used within 24 hours after being prepared and stored in refrigerator.

2.1.5 Test compounds: imipramine

Imipramine hydrochloride-BioXtra, ≥99% TLC (I8099 Sigma) was dissolved in sterile water to 8 mg/mL, and the solution was filtered to exclused microorganisms, filtered before being stored in sterile plastic tubes covered with aluminum foil. Diluted solutions were used within 3 days after prepared and stored in freezer.

2.2 Study design

Fifty four (54) active rats were randomly assigned to one of six groups: (1) sedentary, (2) exercised, (3) carvedilol, (4) clenbuterol, (5) dobutamine, (6) sedentary vehicle (see table 1). Animals were clinically evaluated for general health or injury (daily) prior to intervention and throughout the intervention period. Subsequently, the animals were studied terminally within 5 days after completing 6 weeks of exercise or sedentary lifestyle, and within 24 hours after last dosing of carvedilol, clenbuterol, or dobutamine.

Group	Target Dose Level	Target Dose Volume (mL)	Duration of Treatment (week)	Number of Animals (n)
Sedentary	0	0	6	10
Exercised	80 min/day 5 days/week	0	6	10
carvedilol	3 mg/kg SC BID 5 days/week	0.05	2	10
clenbuterol	2 mg/kg SC SID 5 days/week	0.6	2	10
dobutamine	0.75 mg/kg SC TID 5 days/week	0.2	2	10
Sedentary vehicle	0	0	6	4

Table 1. Study groups and treatments. SC, subcutaneous injection; BID, twice a day; SID, once a day; TID, three times a day.

2.3 Exercise regiment

A rat treadmill, 6 individual lanes (Model Exer-6M Treadmill, Columbus Instruments) was used in this study. It had speed adjustable from 0 to 99 m/min, and inclines from 0° to 25°. Electrical stimulation could be adjusted for both repetition rate and intensity. The treadmill was placed in a temperature and humidity controlled room. The treadmill was cleaned with a mild solution of detergent and water, then sanitized with Pro-tech RTU disinfectant cleaner (McKesson®) before first use. During the study period, disposable absorbent paddings was placed underneath the treadmill to collect feces and urine and change daily; the treadmill running rubber belt, shock grid, plastic

partition walls, as well as plastic roof were cleaned with Pro-tech RTU disinfectant cleaner (McKesson®) every day after being used.

2.3.1 Acclimatization

Three days before starting the exercise period, rats were acclimatized to the treadmill by placing each rat on an individual lane of the treadmill with the belt stationary and shock grids off, but with the belt motor on for 15 minutes on the first day, in order to allow rats to acclimatize with the treadmill lane and the sound of motor, as well as, the exercise room environment. On the second day, each rat was placed on the same individual lane but with the shock grids on and the belt moving at several settings of incrementally slow speed (0-7 m/min) for 5 min to serve as a warm up period, then the speed was slowly ramped up at 1 m/min increments and individually adjusted to match the comfort level of each rat with a maximal speed of 14 m/min, and total exercise duration of 25 minutes on the second day. On the third day, all rats were treated the same as the second day, but the inclination was increased to 5°, the maximal speed was 18 m/min, and total exercise duration were 30 min. During the experiment, if a rat was exhausted, the shock grid was turned off and the rat was allowed to rest.

Criteria for exhaustion include, but was not limited to: (a) rats show no attempt to escape from the shocker over more than 5 consecutive seconds; (b) rats spend greater than 50% of exercise time on the shock grid, (c) rats are willing to sustain >2 seconds for the 3rd shock rather than return to running on the treadmill, (d) other signs indicating physical exhaustion.

Also, in case of exercise related injury such as lameness and/or detachment of a nail, the animals were allowed to rest in the cage until a veterinarian made a decision that those rats could run on the treadmill again.

2.3.2 Exercise protocol

Rats received aerobic interval training (AIT) 5 days/week for 6 consecutive weeks, starting at an exercise time of 50 min/day at week 1 and gradually increased to 80 min/day at week 6. After rats had adequately warmed up for ~10 min by repeating several sets of short sprint at slow speed, they ran several sets of AIT on the treadmill (a set of AIT is one round of a constantly high intensity fast pace for ~4 min followed by ~1 min of low intensity recovery pace), and then they had cool down running for ~5 min. For warm up, rats ran several short sprint sets starting at 7 m/min and gradually increasing the speed up to the fast speed pace of that day, (e.g. gradually increased speed from 0 to 7 m/min and maintained for 1 min then reduced speed down to 5 m/min for 30 s. then gradually increased speed back up again until reach 12 m/min and maintain for 1 min, these sets of short sprint were repeated until reach fast pace speed of each day). During actual AIT, the incline and speed of the treadmill were gradually increased, as well as number of running sets (see table 2). During 5 min cool down, the rat ran at ~50% of the fast pace speed with lower degree of electric stimulation or turn off shock grids.

If a rat shows signs of exhaustion or injury, the shock grid was turned off and the rat was allowed to rest.

Week	Incline (°)	Total AIT Time (min)	Number of AIT Set (set/day)	Fast Pace (m/min)	Recovery Pace (m/min)
1	5	40	8	18	10
2	10	50	10	22	11
3	15	60	12	26	12
4	20	70	14	30	13
5	20	80	16	30	14
6	20	80	16	30	15

Table 2. Exercise training regimen. AIT, aerobic interval training.

To prevent heat exhaustion or early exercise exhaustion, temperature in the exercise room was set to 65-70ºF, and relative humidity was also set at 30-40%. In addition to the air conditioner, a fan and de-humidifier were used to maintain desired environmental conditions in the room. This exercise room environment was maintained throughout the exercise period.

A veterinarian or trained animal technician observed each rat all the time that the animal was on the treadmill to ensure safety of the rat. Each rat was scored for his exercise performance daily (score 0-5), regarding the percentage of the time spent on the shock grid or cessation of running, and % of the time spent running (see table 3). These scores were graded by one person throughout the experiment for consistency, and were recorded in each rat's individual file, in addition to other abnormal physical observations (such as abnormal breathing patterns, stress-induced porphyrin discharge, or other

injuries) after exercise. The rats that had average performance scores below 4 were excluded from the exercise group.

Score	Time spent on shock grid or stop running during AIT (%)	Time spend running during AIT (%)
0	≥50	≤50
1	40-50	50-60
2	30-40	60-70
3	20-30	70-80
4	10-20	80-90
5	0-10	90-100

Table 3. Exercise performance score. AIT, aerobic interval training.

2.4 data collection at the terminal experiment

2.4.1 ECG collection before pressure-volume implantation surgery

At the terminal study day, rats were anesthetized with sodium pentobarbital (80 to 100 mg/kg) intraperitoneally (IP). After rats were in an adequate anesthetic plane/depth (i.e., no pedal reflex or muscle tone, and good breathing pattern), alligator clamp ECG leads were directly attached to the SC layer through small skin incisions, at positioning for leads I, AVF, and V3 in the Faraday cage. ECGs were recorded (EMKA) for a minimum of 3 min after a steady baseline was achieved to serve as the pre-surgery (after

complete course of intervention) interrogation. ECG data was analyzed for durations and amplitudes of conventional components.

2.4.2 ECG and hemodynamic variables collection during pressure-volume study

In rats that were assigned to be dosed with imipramine (n=6 in sedentary, exercise, carvedilol, clenbuterol, and dobutamine group) or vehicle (sterile water) (n=4 in sedentary vehicle group) in order to investigate cardiovascular effects, after pre-surgery ECG data was collected, rats were shaved and positioned in dorsal recumbence on a temperature controlled table, endotracheally intubated, and mechanically ventilated (~90 breaths/min, ~2.5 mL tidal volume with 100% O_2 using an adjustable small animal ventilator [Harvard Apparatus]). Anesthesia was maintained to effect with continuous sodium pentobarbital IV infusion (3 to 5 mg/kg/hr). For LV mechano-energetic evaluations, the right carotid artery was isolated, dissected free from its surrounding tissue, and was cannulated with a 2F high-fidelity conductance/micromanometer catheter (Millar Instruments). This catheter was advanced retrogradely across the aortic valve and into the LV chamber in order to determine, simultaneously, left-ventricular pressure and volume (via conductivity). In order to record arterial pressures, a 2F high-fidelity micromanometer catheter (Millar Instruments) was inserted into a femoral artery and advanced towards the abdominal aorta. Left ventricular (LV) pressure volume (PV) loops during heterometric autoregulation were measured for: end diastolic pressure (EDP), peak left ventricular pressure (LVP), rate of change intraventricular pressure (+dP/d*t* and -dP/d*t*), QA interval, and time constant (tau) of the rate of fall of LVP. Ventricular function was assessed as developed pressure, LVEDP, +dP/d*t* and -dP/d*t*, and

tau. An in-dwelling catheter was placed into a vein for continuous administration for 1 hour of imipramine (8 mg/mL) 20 mg/kg/hr or volume-matched sterile water in the vehicle group.

The ECG and hemodynamic parameters were continuously collected and recorded (1) before dosing imipramine or sterile water (termed baseline instrumentation data), (2) during dosing (termed imipramine or vehicle data), and (3) after cessation of dosing (termed recovery period data). Noted, baseline instrumentation data was obtained at the time point just before intiation of dosing (when cardiovascular function was stable after rats had received all instrumentation and heparin). Data were collected continuously during the entire dosing period and during one hour of the recovery for imipramine or vehicle infusion period. Following the completion of each animal's experiment, the animals were euthanized by exsanguination (i.e., removal of the heart) and decapitation while the animals were already under general anesthesia (an overdose of pentobarbital IP was used to ensure the desired anesthesia), as per facility SOP 503 (Euthanasia and Disposal) and in accordance with accepted American Veterinary Medical Association (AVMA) guidelines (AVMA Guideline for the Euthanasia of Animals: 2013 Edition).

2.4.3 Tissue collection and weight

In all animals, the heart and brain were weighed by a four digit digital scale (Denver instrument) in order to measure the following parameters: heart weight (hW), hW: body weight (BW) ratio, and hW: brain weight (bW) ratio. In addition, for a minimum of 4 rats from sedentary, exercise, and pharmacological preconditioning

groups, left and right adrenal glands were also collected and weighted to obtain adrenal gland weight (aW), and aW: BW ratio serving as a stress indicator [174].

2.5 data analysis

Measurements for all physiological parameters were made manually and automatically from collected waveforms, e.g., ECG, Aortic blood pressure (AoP), LV volume (LVV), and all values were averaged over 60 seconds (if possible/relevant) by IOX and ECG Auto program version 3.3.0.15 (EMKA).

Specifically, times for interrogations are:

1. Baseline presurgery—rats were anesthetized and records were taken in Faraday cage before surgical interventions.

2. Baseline instrumentation—rats were anesthetized and catheters were placed, and physiological variables were stable.

3. Imipramine/vehicle—Rats were anesthetized, and were receiving either imipramine or vehicle; records were analyzed every 5 minutes; stats conducted only at mid-dose and at end-dose.

4. Recovery period—Rats were anesthetized and infusions had been terminated; records were analyzed every 5 minutes; stats measured only at the end of recovery.

Imipramine or vehicle data, and recovery period data were analyzed every 5 minutes for both ECG and hemodynamic parameters. In all of these time points, data were averaged from the last one minute of each time point. Data from 30 to 40 minutes during dosing of imipramine or vehicle were averaged to serve as mid-dose values; data

at 60 minutes of dosing were used as end-dose values, and data at the end of recovery period were used as recovery-60 for statistical analysis.

ECG wave form markers for ECG analysis were agreed upon by consultation with an experienced veterinary cardiologist and physiologist. In case of electrical noise (60 Hz or muscle tremor), simultaneous comparison of multiple leads was used to determine the most accurate markers for each individual ECG wave (see figure 7). That is the end of QRS was clear in one lead, whereas in another lead a rounded, low-amlplitude deflection obfuscated the end of QRS. Measurements of ECGs, AoPs, LVVs, and tissue weights were done by one person for consistency. Search for intraobserver reliability was done for ECG wave forms, by re-measuring the same ECG wave form 10 times on 10 different days, then calculating means and standard errors (SEM) and expressing reliability as C (coefficient of variation).

Measurements for all physiological parameters were made manually and automatically from collected waveforms, e.g., ECG, Aortic blood pressure (AoP), LV volume (LVV), and all values were averaged over 60 seconds (if possible/relevant) by IOX and ECG Auto program version 3.3.0.15 (EMKA). Imipramine or vehicle data, and recovery period data were analyzed every 5 minutes for both ECG and hemodynamic parameters. In all of these time points, data were averaged from the last one minute of each time point. Data from 30 to 40 min during dosing imipramine or vehicle were average to serve as mid-dose values, data at 60 min of dosing were used as end-dose values, and data at the end of recovery period were used as recovery-60 for statistical analysis.

ECG wave form markers for ECG analysis were consulted with experienced veterinarian cardiologist and physiologist. In case of electrical noise, simultaneous comparison of multiple leads were used to determine the most accurate markers in each individual wave of ECG (see figure 7). All ECG, AoP, LVV, and tissue collection weight were done by one person for consistency. Intrapersonal measurement variation were done in ECG wave form marker, by re-measurement same ECG wave form duration 10 time in 10 different days, then all duration data were analyzed for mean, standard errors (SE), and coefficient of variation (C_V = standard deviation/mean), see table 38 in appendix A.

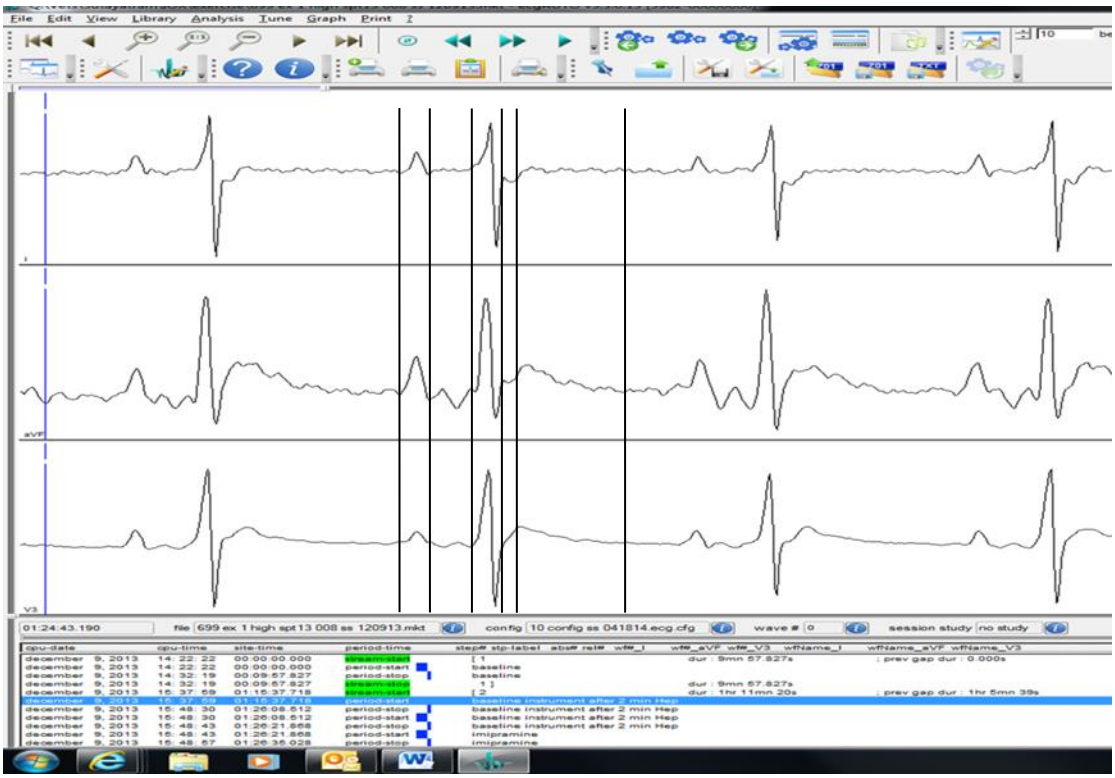

Figure 7. Multiple lead ECG line markers for approximating lead AVF ECG wave form markers.

Data at each time point were presented as means with standard errors (mean ± SE) and are summarized in tables as well as with graphical representations.

2.6 Measurement parameters

There were three main groups of variables in this study: (1) body weight and tissue weight, (2) hemodynamic parameters, (3) ECG variables. Details and abbrevations of each parameter are listed in table 4.

2.7 Statistical analysis

Results of parameters are presented as mean ± SE. Data were analyzed statistically (1) at baseline pre-surgery (e.g., body weight, surface ECG values during baseline collection inside Faraday cage), (2) at baseline-instrumentation (e.g., surface ECG and hemodynamic variables obtained from Millar catheters at right before start infusion of imipramine or volume-matched vehicle), (3) mid-dose (average of values from 30-40 min after infusion with imipramine or volume-matched vehicle), (4) end-dose (values at 60 min after infusion), and (5) end recovery (values at 60 min after cessation of infusion) periods. Comparisons were made using one-way analysis of variance for parameters measured only once (e.g., weights, pre-surgery ECG, baseline hemodynamics), and using two-way analysis of variance with repeated measures design on both group and time, and when indicated by a significant F-statistic, followed by a pairwise multiple comparison test (Tukey test) to identify effects on group and time. A $P < 0.05$ is considered statistically significant.

Abbreviations	Parameters
Weight	
BW	Body weight (g)
hW	Heart weight (g)
bW	Brain weight (g)
aW	Adrenal gland weight (g)
Hemodynamics	
SBP	Systolic blood pressure (mmHg)
DBP	Diastolic blood pressure (mmHg)
PP	Pulse pressure (mmHg)
MBP	Mean blood pressure (mmHg)
HR	Heart rate (bpm)
LVEDP	Left ventricular end-diastolic pressure (mmHg)
LVESP	Left ventricular end-systolic pressure (mmHg)
+dP/d*t*	Maximum rate of increase in pressure during contraction (mmHg/s)
-dP/d*t*	Minimum rate of increase in pressure during contraction (mmHg/s)
CI	Contractility index (s^{-1}), the +dP/d*t* divided by pressure at this point
tau	Time constant of relaxation (s)
LVEDV	Left venticular end-diastolic volume (RVU or relative volume unit)
LVESV	Left venticular end-diastolic volume (RVU)
SV	Stroke volume (RVU)
CO	Cardiac output (RVU/min)
(+dP/d*t*)/EDV	maximum rate of increase in pressure during contraction divided by LV end-diastolic volume (mmHg/s*RVU)
ECG	
R_a	R wave amplitude (mV)
T_a	T wave amplitude (mV)
P_a	P wave amplitude (mV)
Q_a	Q wave amplitude (mV)
S_a	S wave amplitude (mV)
P_d	P wave duration (ms)
PR	Duration from beginning P wave to beginning of Q wave (ms)
PR_{sect}	Duration from end of P wave to beginning of Q wave (ms)
QRS	Duration from beginning of Q wave to end of S wave (ms)
QT	Duration from beginning of Q wave to end of T wave (ms)
QTcB	Corrected QT by Bazett ‘s formula (ms)
QTcF	Corrected QT by Fridericia ‘s formula (ms)
QT_1	Duration from end of S wave to beginning of T wave (ms)
QA	Duration from beginning of Q to point of aortic pressure upstroke (ms)
T_d	Duration of T wave (ms)

Table 4. Abbreviations of all parameters.

Chapter 3: Effects of interventions on organ weight, hemodynamic values, and ECGs

3.1 Effects of interventions on body weight and tissue weights

3.1.1 Effects of interventions on body weight, heart weight, brain weight, and their ratios

When rats were studied after the completion of exposures to interventions, because they all could not be studied simultaneously, interventions began at different ages so that at the time of physiological evaluation, their ages were comparable but may have differed by 4 weeks. This accounts for the relatively large SE in all intevention groups except exercise. Body weights, tissue weights, and their ratios are presented in Table 5.

Group	Sedentary n = 10	Exercise n = 10	Carvedilol n = 10	Clenbuterol n = 10	Dobutamine n = 10
BW (g)	386.4 ± 11.6	421.5 ± 5.4[d]	397.6 ± 9.4	412.8 ± 14.0	381.1 ± 7.3
hW (g)	1.208 ± 0.040	1.285 ± 0.013	1.297 ± 0.028	1.343 ± 0.044	1.259 ± 0.021
bW (g)	1.837 ± 0.017	1.901 ± 0.016	1.856 ± 0.018	1.842 ± 0.014	1.860 ± 0.017
hW/bW	0.657 ± 0.019 [cl]	0.676 ± 0.007	0.699 ± 0.015	0.729 ± 0.021	0.677 ± 0.013
hW/BW (%)	0.313 ± 0.006	0.326 ± 0.003[d]	0.326 ± 0.006	0.331 ± 0.006	0.305 ± 0.004

Table 5. Body weight, tissue weight, and their ratios. Values are means ± SE; n = 10; [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine.

Exercise-trained rats and rats receiving clenbuterol trended to have higher body weight. There were no (significant) differences in hW or bW among groups. However both BW and hW/BW (as %) of the exercise group were significantly higher than those of dobutamine group ($P < 0.05$). hW/bW in the sedentary group was significantly lower than that in the clenbuterol group ($P < 0.05$).

3.1.2 Effects of interventions on adrenal gland weight and their ratios to BW

Table 6 shows aW and the ratio, aW/BW. Rats exposed to drugs ("pharmacological training") and exercise-trained trended to have higher aW and aW/BW. However these differences did not achieve (statistical) signifcance.

Group	**Sedentary n = 5**	**pharmacological training n = 8**	**Exercise n = 10**
Left aW (mg)	22.04 ± 0.56	23.98 ± 1.09	23.81 ± 1.61
Right aW (mg)	22.48 ± 1.08	24.42 ± 1.37	24.61 ± 1.79
Both aW (mg)	44.52 ± 1.21	48.40 ± 1.98	48.42 ± 3.00
Left aW/BW (%)	0.00515 ± 0.00019	0.00595 ± 0.00041	0.00564 ± 0.00043
Right aW/BW (%)	0.00524 ± 0.00018	0.00603 ± 0.00040	0.00583 ± 0.00045
Both aW/BW (%)	0.01039 ± 0.00025	0.01198 ± 0.00073	0.01147 ± 0.00080

Table 6. Adrenal gland weight in sedentary, pharmacological training (i.e., carvedilol, clenbuterol, and dobutamine), and exercise group. Values are means ± SE.

3.2 Effects of interventions on hemodynamics

Pressures, recorded in the abdominal aorta and left ventricle, and volume recorded from the left ventricle, are shown in Table 7. The dobutamine group had statistically lower SBP compared with the clenbuterol group ($P < 0.05$). In the dobutamine group, PP, LVESP, and CI were lower significantly than in either the clenbuterol or the exercise group ($P < 0.05$). +dP/d*t* in the dobutamine group were lower than in the clenbuterol group ($P < 0.05$). Finally, LVESP in the carvedilol group was significantly lower than in the clenbuterol group ($P < 0.05$).

Group	**Sedentary n = 6**	**Exercise n = 6**	**Carvedilol n = 6**	**Clenbuterol n = 6**	**Dobutamine n = 6**
SBP (mmHg)	165.6 ± 8.5	172.8 ± 2.5	160.4 ± 4.3	179.1 ± 8.3[d]	149.4 ± 6.2
DBP (mmHg)	123.8 ± 7.5	121.4 ± 2.3	119.7 ± 1.8	129.4 ± 5.8	116.8 ± 4.9
PP (mmHg)	41.8 ± 4.7	51.4 ± 2.9[d]	40.8 ± 4.4	49.7 ± 4.9[d]	32.6 ± 2.6
MBP (mmHg)	140.4 ± 7.7	143.4 ± 1.5	135.9 ± 2.4	149.8 ± 6.3	129.3 ± 5.5
HR (bpm)	412.5 ± 21.2	388.9 ± 12.9	380.1 ± 11.0	412.2 ± 9.9	415.4 ± 14.4
LVEDP (mmHg)	7.0 ± 1.8	5.5 ± 1.5	4.7 ± 0.8	2.8 ± 0.5	5.5 ± 1.6
LVESP (mmHg)	158.7 ± 7.3	165.2 ± 1.6[d]	147.9 ± 4.1[cl]	171.5 ± 7.4[d]	141.0 ± 5.7
+dP/d*t* (mmHg/s)	6,627 ± 191	6,560 ± 86	6,180 ± 385	7,471 ± 622[d]	5,286 ± 317
-dP/d*t* (mmHg/s)	-6,821 ± 399	-6,372 ± 171	-6,334 ± 637	-6,316 ± 287	-5,237 ± 344
CI (s^{-1})	89.5 ± 3.4	95.6 ± 1.0[d]	89.0 ± 2.6	96.0 ± 3.5[d]	83.2 ± 2.4
tau (ms)	7.7 ± 0.9	7.8 ± 0.3	8.3 ± 0.8	9.3 ± 0.8	7.8 ± 0.4
LVEDV (RVU)	20.4 ± 1.2	19.9 ± 0.4	20.0 ± 1.0	22.1 ± 1.5	19.8 ± 1.6
LVESV (RVU)	18.9 ± 1.3	18.3 ± 0.6	17.9 ± 1.1	21.0 ± 1.4	18.5 ± 1.4
SV (RVU)	1.5 ± 0.3	1.6 ± 0.3	2.1 ± 0.5	1.0 ± 0.2	1.3 ± 0.3
CO (RVU /min)	605 ± 111	613 ± 118	805 ± 215	407 ± 91	509 ± 122
(+dP/d*t*)/LVEDV (mmHg/s* RVU)	332.4 ± 27.0	330.8 ± 10.0	310.5 ± 17.9	353.5 ± 50.5	278.3 ± 32.5

Table 7. Hemodynamic parameters in each intervention at baseline-instrumentation measured by the Millar pressure-volume conductance catheter system. Values are means ± SE; n = 6. [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine.

3.3 Effects of interventions on ECGs recorded in the Faraday cage at pre-surgery period

3.3.1 Effects of interventions on lead I

Group	Sedentary n = 10	Exercise n = 10	Carvedilol n = 10	Clenbuterol n = 10	Dobutamine n = 10
HR (bpm)	353 ± 9	320 ± 6[cl]	330 ± 9	360 ± 8	347 ± 9
R_a (mV)	0.264 ± 0.057	0.132 ± 0.032	0.206 ± 0.053	0.318 ± 0.036	0.254 ± 0.071
T_a (mV)	-0.014 ± 0.003	-0.021 ± 0.003[cl]	-0.012 ± 0.011	0.007 ± 0.005[d]	-0.019 ± 0.003
P_a (mV)	0.029 ± 0.007	0.017 ± 0.005	0.013 ± 0.006[cl]	0.042 ± 0.006[d]	0.015 ± 0.008
Q_a (mV)	-0.0161 ± 0.0116	-0.0100 ± 0.0085	-0.0585 ± 0.0238	-0.0129 ± 0.0050	-0.0646 ± 0.0352
S_a (mV)	-0.230 ± 0.029	-0.306 ± 0.045[cl]	-0.179 ± 0.039	-0.131 ± 0.022	-0.176 ± 0.025

Table 8. ECG variables from lead I after rats completed intervention. Values are means ± SE; [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine.

Table 8 shows values of wave forms from lead I ECGs after rats completed interventions. Clenbuterol had significantly higher HR than that of the exercise group. HR in the exercise group tended to be lowest. The clenbuterol group had T wave amplitudes significantly higher than either the dobutamine or exercise groups ($P < 0.05$). P_a in the clenbuterol group was significantly higher than those of either the carvedilol or dobutamine groups ($P < 0.05$). S waves in the clenbuterol group were significantly less negative than S waves in the exercise group ($P < 0.05$).

3.3.2 Effects of interventions on lead AVF

Table 9 shows values of wave forms in lead AVF. Clenbuterol intervention increased HR (compared with exercise; $P < 0.05$) and decreased R amplitude (compared with dobutamine group; $P < 0.05$).

Group	Sedentaery n = 10	Exercise n = 10	Carvedilol n = 10	Clenbuterol n = 10	Dobutamine n = 10
HR (bpm)	353 ± 9	321 ± 6[cl]	330 ± 9	360 ± 8	347 ± 9
R_a (mV)	0.342 ± 0.034	0.272 ± 0.034	0.289 ± 0.036	0.221 ± 0.020[d]	0.381 ± 0.041
T_a (mV)	0.082 ± 0.012	0.072 ± 0.007	0.070 ± 0.006	0.090 ± 0.009	0.074 ± 0.007
P_a (mV)	0.084 ± 0.009	0.071 ± 0.005	0.070 ± 0.007	0.081 ± 0.007	0.088 ± 0.009
Q_a (mV)	-0.0054 ± 0.0026	-0.0013 ± 0.0014	-0.0023 ± 0.0015	-0.0046 ± 0.0010	-0.0051 ± 0.0024
S_a (mV)	-0.172 ± 0.037	-0.184 ± 0.037	-0.240 ± 0.048	-0.203 ± 0.041	-0.144 ± 0.044

Table 9. ECG variables from lead AVF after rats completed intervention. Values are means ± SE; [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine.

3.3.3 Effects of interventions on lead V3

Durations of wave forms from lead V3 (an anterior precordial lead with proximity to the left ventricle) are presented in table 10. Wave forms from this lead contained fewer artifacts and are, of course, "biased by proximity". Exercise training had produced signficantly longer RR intervals (i.e., lower in HRs) compared with those of the clenbuterol group ($P < 0.05$). PR was more prolonged in the exercise group than in the dobutamine group ($P < 0.05$). It is well-known that PR and HR are related inversely. Also, exercise training shortened QTcB, QTcF, and T duration compared to those in the sedentary group ($P < 0.001$, $P < 0.05$, and $P < 0.05$, respectively).

Likewise, carvedilol intervention also shortened QTcB, QTcF, and T duration compared with sedentary group ($P < 0.05$). Clenbuterol intervention led to significantly shorter T duration compared with that of the sedentary group ($P < 0.05$). On the other hand, chronic dobutamine administration significantly lengthened QT, QTcB, and QTcF compared with those in the exercise, carvedilol, and clenbuterol groups. The dobutamine intervention also prolonged T duration (compared with those of exercise, carvedilol, and clenbuterol groups; $P < 0.05$).

Group	**Sedentaery n = 10**	**Exercise n = 10**	**Carvedilol n = 10**	**Clenbuterol n = 10**	**Dobutamine n = 10**
RR (ms)	171 ± 4	188 ± 4[cl]	183 ± 5	168 ± 4	174 ± 5
HR (bpm)	353 ± 9	321 ± 6[cl]	330 ± 9	360 ± 7	347 ± 9
PR (ms)	45.8 ± 0.8	48.0 ± 1.3[d]	45.0 ± 0.7	46.3 ± 1.4	42.9 ± 0.9
P_d (ms)	18.4 ± 0.6	18.3 ± 0.4	17.8 ± 0.7	17.9 ± 0.6	16.9 ± 0.6
QRS (ms)	20.2 ± 0.4	21.6 ± 0.5	19.9 ± 0.7	20.4 ± 0.4	20.7 ± 0.5
QT (ms)	73.9 ± 1.7	68.3 ± 0.8[d]	68.6 ± 1.4[d]	70.0 ± 1.5[d]	77.0 ± 1.3
QTcB (ms_c)	178.7 ± 3.7	157.8 ± 2.2[D, S]	160.7 ± 3.6 [D, s]	171.3 ± 4.3 [d]	184.9 ± 2.7
QTcF (ms_c)	133.1 ± 2.7	119.4 ± 1.5 [D, s]	121.0 ± 2.5 [D, s]	127.1 ± 3.0 [D]	138.1 ± 2.0
PR_{sect} (ms)	27.5 ± 0.6	29.7 ± 1.1	27.2 ± 1.0	28.4 ± 0.9	26.1 ± 0.9
QT_1 (m_c)	9.1 ± 0.6	9.1 ± 0.4	10.6 ± 1.3	11.5 ± 0.8	11.2 ± 0.5
T_d (ms)	44.6 ± 1.5	37.7 ± 0.8 [s, d]	38.2 ± 1.9 [s, d]	38.2 ± 1.9 [s, d]	45.2 ± 1.0

Table 10. ECG variables from lead V3 after rats completed intervention. Values are means ± SE; [S]$P <$ 0.001 vs. sedentary; [D]$P < 0.001$ vs. dobutamine; [d]$P < 0.05$ vs. dobutamine; [s]$P < 0.05$ vs. sedentary; [cl]$P <$ 0.05 vs. clenbuterol.

Figures 8 to 12 show examples of lead V3 ECG wave forms with 5 ms time lines. These ECGs were collected inside Faraday cage during the pre-surgery period.

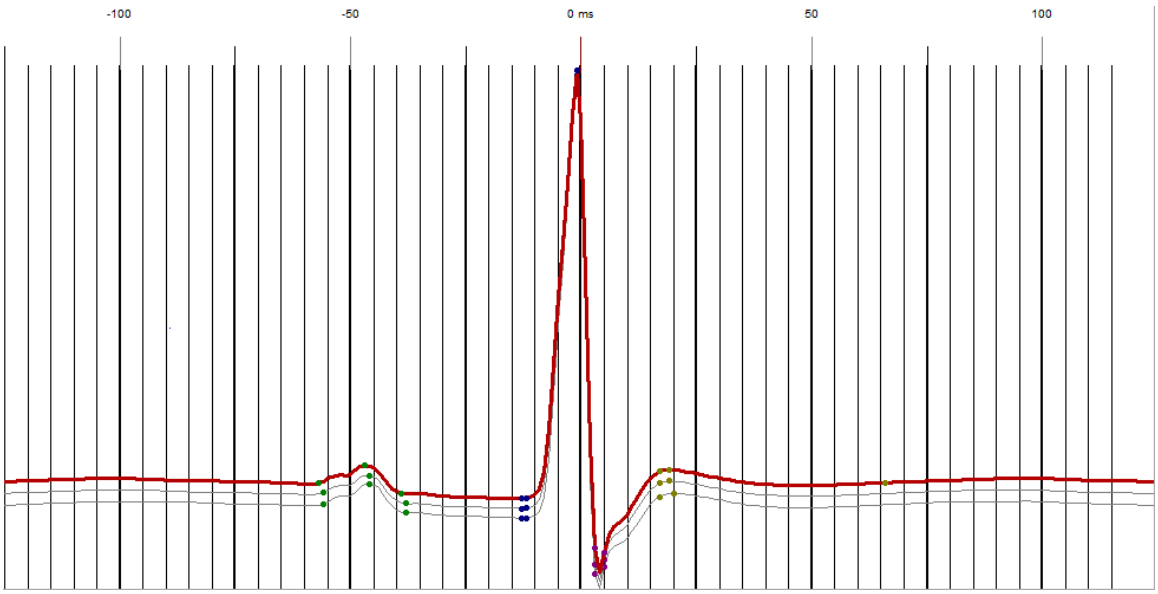

Figure 8. ECG from lead V3 of rat in the sedentary group after completing 6 weeks of sedentary existence.

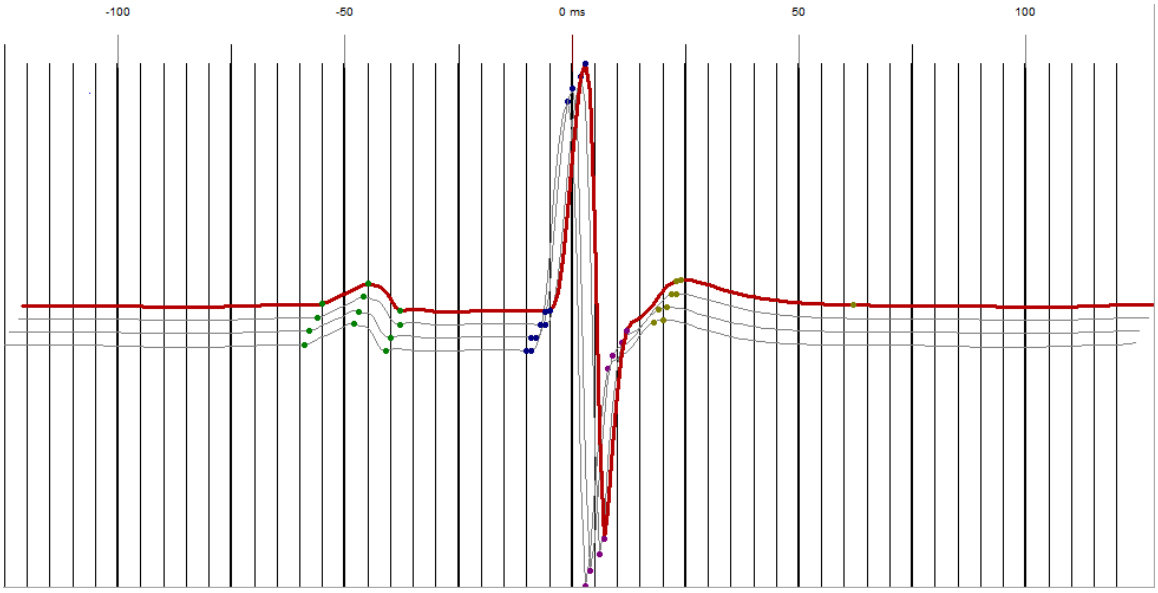

Figure 9. ECG from lead V3 of rat in the exercise group after after completing 6 weeks of exercise training.

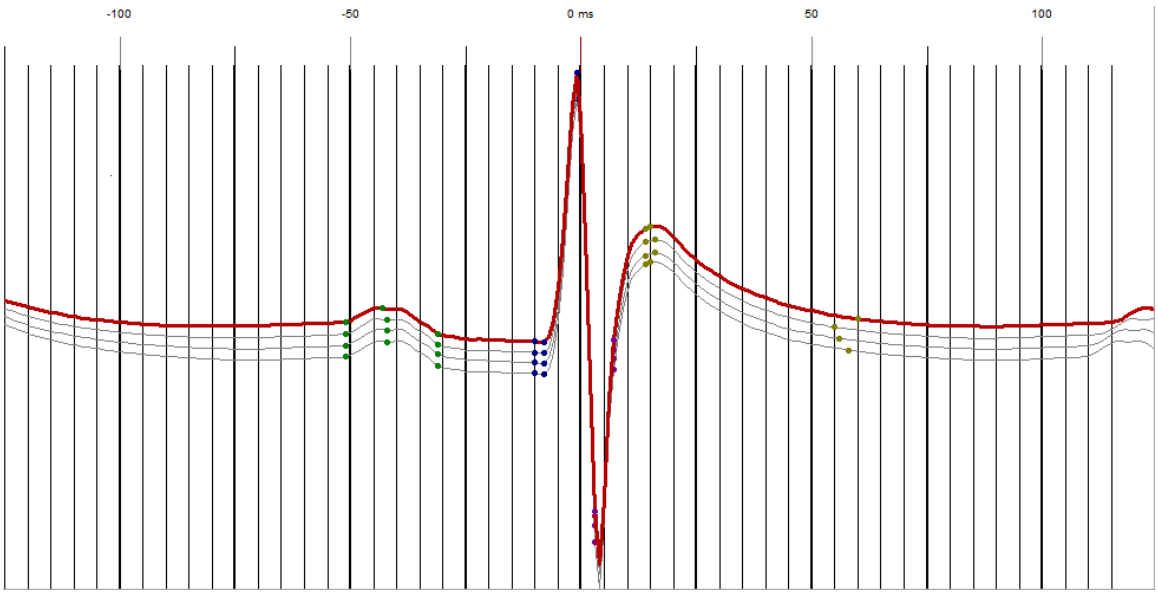

Figure 10. ECG from lead V3 of rat in the carvedilol group after after completing 2 weeks of intervention.

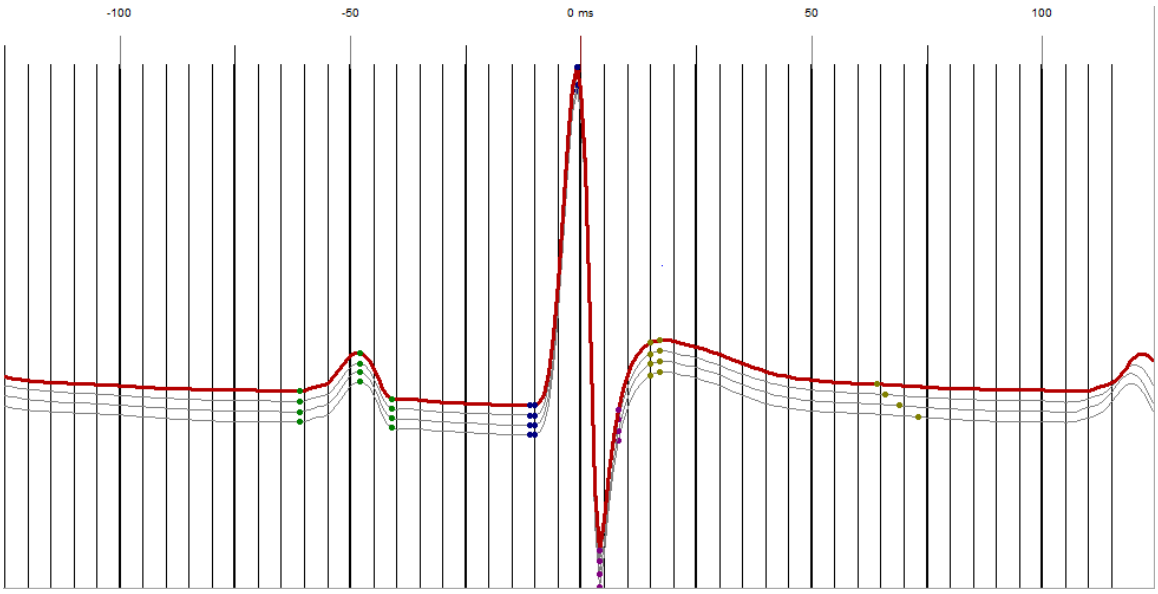

Figure 11. ECG from lead V3 of rat in the clenbuterol group after after completing 2 weeks of intervention.

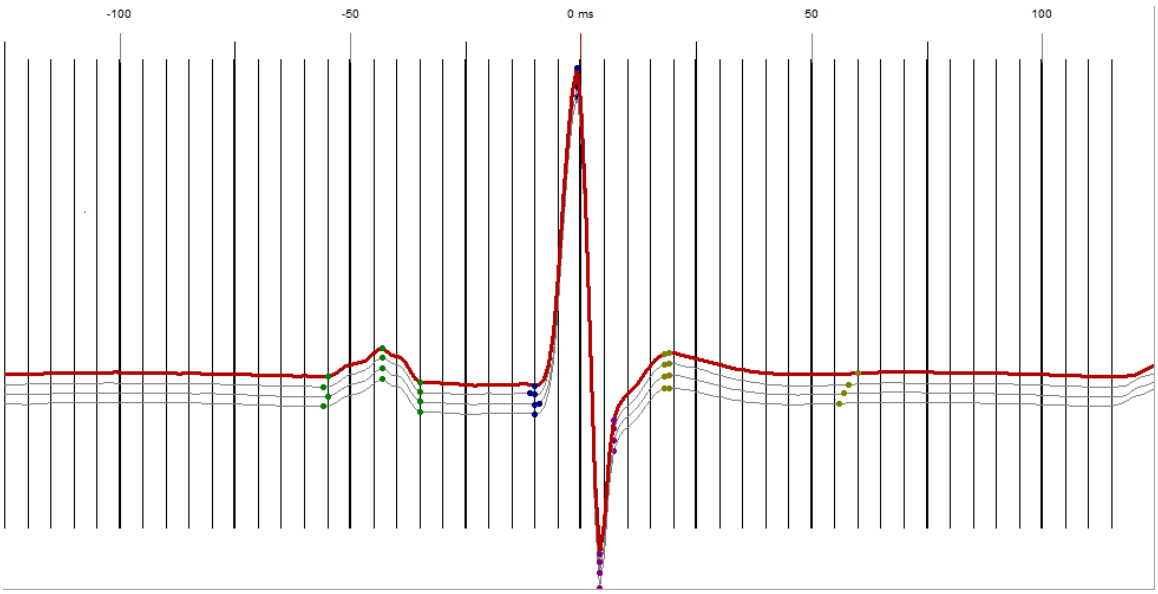

Figure 12. ECG from lead V3 of rat in the dobutamine group after after completing 2 weeks of intervention.

Chapter 4: Effects of imipramine on hemodynamics and ECGs in sedentary rats

4.1 Effects of imipramine on hemodynamics in sedentary rats

4.1.1 Effects of imipramine on aortic pressures

Table 11 shows the hemodynamic parameters, resulting from imipramine infusion, compared with matched-volume vehicle infusion in sedentary rats measured by the Millar pressure catheter system in the abdominal aorta. Continuous infusion of imipramine, 20 mg/kg/hr, resulted in reduction in all arterial pressures ($P < 0.001$) at mid-dose, end-dose, and end recovery (PP only at mid-dose) compared with values at their baseline-instrumentation. HR decreased significantly, compared with baseline-instrumentation at mid-dose, end-dose period, and end-recovery period.

Spontaneous recovery was inidcated by all pressures except PP increasing significantly and gradually from mid-dose to the end-dose period. After cessation of imipramine infusion, all pressures, but DBP, recovered gradually and significantly from the end-dose period to the end recovery period. However, all of those pressures remained significantly lower than baseline-instrumentation values. HR trended to increase between mid-dose and end-dose period. However, at end of recovery HR was significantly higher than at mid-dose and end-dose periods but was lower than at baseline.

In the volume-matched vehicle infusion group, there were no significant differences among periods (i.e. baseline-instrument, mid-dose, end-dose, and end

recovery periods). As expected, compared with the imipramine group, rats given vehicle infusion had statistically higher values of SBP ($P < 0.05$), DBP, and MBP ($P < 0.001$) at mid-dose and end-dose periods. The vehicle infusion group had statistically higher values of DBP and MBP values at end recovery period than the imipramine group ($P < 0.05$).

Expressed as % change from its baseline-instrumentation values-induced by infusion (table 12), the same alterations occurred in aortic pressures in both imipramine and volume-matched vehicle infusion groups. Differences in SBP, DBP, and MBP between imipramine and vehicle were significant at mid-dose, end-dose, and end-recovery. Differences in PP, between imipramine and vehicle, were significant at mid-dose and end-dose. Differences in HR, between imipramine and vehicle, achieved significane at mid-dose, end-dose, and end recovery period.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
Imipramine	Baseline	165.6 ± 8.5	123.8 ± 7.5	41.8 ± 4.7	140.4 ± 7.7	412.5 ± 21.2
	Mid-dose	82.7 ± 12.1 [Bi, ed, R, v]	54.7 ± 10.1 [Bi, ed, R, V]	28.0 ± 4.2 [bi, R]	65.8 ± 11.1 [Bi, ed, R, V]	323.9 ± 21.4 [Bi, r]
	End-dose	104.8 ± 14.9 [Bi, r, v]	70.9 ± 8.3 [Bi, V]	33.9 ± 8.0 [r]	84.2 ± 10.9 [Bi, r, V]	332.6 ± 26.6 [Bi, r]
	End recovery	129.3 ± 10.3 [Bi]	84.0 ± 6.8 [Bi, v]	45.3 ± 6.7	102.0 ± 8.1 [Bi, v]	371.1 ± 35.2 [bi]
Vehicle	Baseline	145.5 ± 9.7	110.6 ± 5.9	34.9 ± 6.6	126.9 ± 7.1	360.2 ± 11.1
	Mid-dose	152.1 ± 7.8	113.6 ± 2.7	38.6 ± 7.1	131.2 ± 4.0	366.5 ± 12.0
	End-dose	164.0 ± 7.8	122.0 ± 4.2	42.0 ± 6.6	140.8 ± 5.0	369.0 ± 12.1
	End recovery	153.4 ± 7.5	114.1 ± 5.4	39.3 ± 7.7	132.4 ± 5.1	369.3 ± 11.6

Table 11. Hemodynamic effects of imipramine or vehicle infusion in sedentary rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [ed]$P < 0.05$ vs. its end dose; [V]$P < 0.001$ vs. vehicle; [v]$P < 0.05$ vs. vehicle.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-50.7 ± 5.2 $^{Bi, ed, R, V}$	-56.9 ± 6.2 $^{Bi, ed, R, V}$	-33.4 ± 5.3 $^{bi, R, V}$	-54.0 ± 5.7 $^{Bi, ed, R, V}$	-21.5 ± 3.3 $^{Bi, r, V}$
	End-dose	-37.5 ± 6.5 $^{Bi, r, V}$	-42.7 ± 5.4 $^{Bi, V}$	-22.9 ± 11.3 $^{r, V}$	-40.4 ± 5.9 $^{Bi, r, V}$	-19.5 ± 4.3 $^{Bi, r, V}$
	End recovery	-22.4 ± 2.4 $^{Bi, V}$	-32.4 ± 2.6 $^{Bi, V}$	8.2 ± 11.1	-27.7 ± 2.2 $^{Bi, V}$	-10.5 ± 6.2 $^{bi, V}$
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	5.0 ± 3.0	3.2 ± 3.1	11.4 ± 3.9	3.9 ± 3.1	1.8 ± 1.6
	End-dose	13.2 ± 3.3	10.8 ± 3.8	22.6 ± 4.0	11.4 ± 3.5	2.5 ± 1.1
	End recovery	6.1 ± 4.5	3.7 ± 5.4	14.3 ± 9.9	4.9 ± 4.6	2.6 ± 1.5

Table 12. Hemodynamic effects of imipramine or vehicle infusion in sedentary rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{ed}P < 0.05$ vs. its end dose; $^{V}P < 0.001$ vs. vehicle.

4.1.2 Effects of imipramine on LV hemodynamics

Table 13 shows hemodynamic effects of imipramine or volume-matched vehicle infusion on sedentary. Beside reduction of the systemic hemodynamic values, imipramine infusion also produced gradually-decreases in LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV at mid-dose, end-dose, and end recovery periods when compared with their baseline-instrumentation values. There were trends for spontaneous recovery during imipramine infusion between mid-dose and end-dose period. By 1 hour after end of infusion, LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV recovered. Imipramine tended to depress CI compared with baseline-instrument values; however, there were no significanct differences in CI among time points.

Matched-volume, vehicle-infusion tended to increase LVESP, +dP/d*t*, -dP/d*t*, CI, and (+dP/d*t*)/EDV. However, significances existed only in the LVESP between baseline-instrument and end recovery periods ($P < 0.05$).

When compared with imipramine, vehicle infusion had statistically higher values of LVESP, +dP/d*t*, -dP/d*t*, SV, CO, and (+dP/d*t*)/EDV. Vehicle infusion also had statistically higher values of LVESP and +dP/d*t* than those of the imipramine group at mid-dose and end-dose ($P < 0.001$), and at end recovery period ($P < 0.05$). Values of -dP/d*t* of vehicle rats were more negative than those of the imipramine group at mid-dose ($P < 0.001$), end-dose, and end recovery periods ($P < 0.05$). (+dP/d*t*)/EDV in the imipramine group were significantly lower than those of the vehicle group at mid-dose and end-dose periods ($P < 0.05$). Values for SV and CO for the vehicle group

were significantly higher at baseline-instrument and mid-dose periods compared with the imipramine infusion rats ($P < 0.05$).

When expressed as % change from their baseline-instrumentation values, the same trends occurred as in the raw data of LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV (see table 14). There were significant differences for CI between % reduction between vehicle and imipramine infusion at mid-dose, end-dose, and end recovery periods ($P < 0.05$).

Vehicle infusion produced differences in % change, from end-dose to recovery period, in reduction values of LVEDP. Vehicle infusion significantly increased LVESP at end-dose compared with baseline-instrumentation values ($P < 0.05$). Vehicle infusion produced significant reduction in -dP/d*t* at end recovery compared with its baseline-instrument values, and increased (+dP/d*t*)/EDV at end recovery period compared with its baseline-instrumentation values.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
Imipramine	Baseline	7.0 ± 1.8	158.7 ± 7.3	6,627 ± 191	-6,821 ± 399	89.5 ± 3.4	7.7 ± 0.9
	Mid-dose	7.3 ± 1.6	86.2 ± 8.3$^{Bi, R, V}$	3,124 ± 427$^{Bi, R, V}$	-3,099 ± 419$^{Bi, R, V}$	83.9 ± 3.6	8.1 ± 0.9
	End-dose	7.1 ± 1.7	102.2 ± 10.6$^{Bi, r, V}$	3,859 ± 626$^{Bi, r, V}$	-3,924 ± 610$^{Bi, r, v}$	83.5 ± 6.0	8.2 ± 1.1
	End recovery	5.4 ± 1.8	122.6 ± 8.3$^{Bi, v}$	5,020 ± 454$^{Bi, v}$	-5,207 ± 537$^{Bi, v}$	86.0 ± 5.3	7.6 ± 1.0
Vehicle	Baseline	5.3 ± 1.3	139.8 ± 7.6	5,996 ± 546	-6,446 ± 819	83.3 ± 4.5	9.5 ± 0.9
	Mid-dose	6.0 ± 1.8	150.1 ± 8.9	6,503 ± 349	-7,047 ± 644	85.5 ± 4.2	9.1 ± 0.9
	End-dose	5.6 ± 2.3	160.5 ± 9.5	6,938 ± 529	-7,495 ± 802	87.0 ± 4.1	9.3 ± 1.0
	End recovery	3.5 ± 1.8	152.7 ± 8.1^{bi}	6,918 ± 442	-7,624 ± 688	88.5 ± 5.6	8.5 ± 0.7

Continued

Table 13. Hemodynamic effects of imipramine or vehicle infusion in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle.

Table 13. Continued

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/dt)/EDV (mmHg/s* RVU)
Imipramine	Baseline	20.4 ± 1.2	18.9 ± 1.3	1.5 ± 0.3^{v}	605 ± 111^{v}	332.4 ± 27.0
	Mid-dose	20.6 ± 1.7	19.1 ± 1.7	1.5 ± 0.4^{v}	474 ± 132^{v}	160.6 ± 32.9$^{Bi, R, v}$
	End-dose	20.8 ± 1.7	19.1 ± 1.7	1.7 ± 0.5	570 ± 196	195.8 ± 42.3$^{Bi, r, v}$
	End recovery	20.3 ± 1.4	18.5 ± 1.5	1.8 ± 0.4	652 ± 181	256.8 ± 35.6^{Bi}
Vehicle	Baseline	21.4 ± 0.6	18.3 ± 0.7	3.4 ± 0.6	1,252 ± 254	280.3 ± 26.5
	Mid-dose	21.4 ± 0.6	18.6 ± 0.5	3.0 ± 0.5	1,135 ± 223	305.0 ± 18.4
	End-dose	21.8 ± 0.8	19.2 ± 0.4	2.9 ± 0.5	1,035 ± 184	318.1 ± 22.3
	End recovery	20.9 ± 0.5	18.2 ± 0.6	3.3 ± 0.6	1,242 ± 267	331.6 ± 18.5

Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	20.0 ± 20.1	-45.9 ± 3.6$^{Bi, R, V}$	-53.4 ± 5.0$^{Bi, R, V}$	54.6 ± 5.4$^{Bi, R, V}$	-6.1 ± 3.5^{v}	6.2 ± 5.7
	End-dose	14.9 ± 21.1	-35.7 ± 5.4$^{Bi, r, V}$	-42.5 ± 8.1$^{Bi, r, V}$	43.0 ± 7.8$^{Bi, r, V}$	-7.1 ± 3.7^{v}	6.3 ± 5.5
	End recovery	-14.6 ± 19.8	-22.8 ± 3.5$^{Bi, V}$	-24.7 ± 5.1$^{Bi, V}$	24.4 ± 4.6$^{Bi, V}$	-4.3 ± 2.5^{v}	-2.6 ± 4.0
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	8.0 ± 11.6	7.3 ± 2.1	9.7 ± 5.3	-11.0 ± 5.0	2.8 ± 2.6	-4.5 ± 2.7
	End-dose	-6.3 ± 24.2^{r}	14.7 ± 0.8^{bi}	16.2 ± 2.0	-17.3 ± 3.2	4.6 ± 1.8	-2.5 ± 4.7
	End recovery	-47.8 ± 21.6	9.4 ± 3.4	16.4 ± 4.4	-20.2 ± 5.9^{bi}	6.4 ± 4.2	-9.9 ± 3.5

Continued

Table 14. Hemodynamic effects of imipramine or vehicle infusion in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle.

Table 14. Continued

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
Imipramin	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	0.3 ± 3.1	0.6 ± 3.8	0.6 ± 18.1	-18.2 ± 17.1	-53.3 ± 5.5$^{Bi, R, V}$
	End-dose	1.2 ± 3.3	0.2 ± 4.1	9.3 ± 18.9	-8.6 ± 18.7	-42.8 ± 8.4$^{Bi, r, V}$
	End recovery	-0.7 ± 2.8	-2.2 ± 3.7	22.6 ± 20.6	14.5 ± 25.4	-23.4 ± 6.6$^{bi, V}$
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-0.3 ± 0.5	1.9 ± 2.7	-6.2 ± 9.8	-5.3 ± 10.3	10.1 ± 5.7
	End-dose	1.8 ± 1.8	5.1 ± 3.8	-9.9 ± 11.8	-11.6 ± 11.7	14.3 ± 3.0
	End recovery	-2.7 ± 1.3	-0.9 ± 1.2	-2.2 ± 4.6	-0.5 ± 5.4	19.6 ± 5.0^{Bi}

Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle.

4.2 Effects of imipramine on ECGs in sedentary rats

4.2.1 Effects of imipramine on ECG from lead I in sedentary rats

Table 15 shows amplitudes of ECG wave forms in lead I. Imipramine infusion resulted in decrease amplituee of R waves but increase depth of S waves during both mid-dose and end-dose periods compared with their baseline-instrumentation values ($P < 0.001$). There was no spontaneous recovery in either R or S amplitudes from mid-dose to end-dose. There were significant returns toward baseline from mid-dose to end recovery period, and from end-dose to end recovery period. At the end recovery period, R amplitiude and S depth return to their baseline-instrumentation values. Vehicle infusion resulted in slight increases in R amplitude, but without significance. At mid-dose and end-dose periods, depth of negative S waves in the vehicle group was significantly less for the imipramine group.

Infusion of vehicle (table 16) led to mild (i.e. insignificant) increases in R, T and S amplitudes/depths, while imipramine infusion caused obvious and significant reductions in % change from the baseline-instrument values in R and S amplitudes/depths at mid-dose and end-dose periods compared with their baseline-instrument values ($P < 0.05$). There was a significant recovery in depth of S waves between mid-dose and end-dose periods compared with the end recovery period. Both R and S amplitudes/depths of imipramine group at mid-dose and end-dose periods were significantly lower in % change compared with those of the vehicle infusion ($P < 0.05$).

There was no statistically significant alteration in T, P, and Q amplitudes from either imipramine or vehicle infusion, in either raw data (mV) or % change.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Imipramine	Baseline	0.254 ± 0.066	0.0063 ± 0.0036	0.0390 ± 0.0041	-0.0028 ± 0.0027	-0.128 ± 0.035
	Mid-dose	0.070 ± 0.018$^{Bi, r}$	0.0101 ± 0.0122	0.0374 ± 0.0058	0.0001 ± 0.0041	-0.343 ± 0.094$^{Bi, r, v}$
	End-dose	0.063 ± 0.014$^{Bi, r}$	0.0112 ± 0.0115	0.0352 ± 0.0073	-0.0030 ± 0.0065	-0.338 ± 0.093$^{Bi, r, v}$
	End recovery	0.181 ± 0.054	0.0055 ± 0.0065	0.0370 ± 0.0071	-0.0092 ± 0.0080	-0.180 ± 0.057
Vehicle	Baseline	0.176 ± 0.049	0.012 ± 0.014	0.043 ± 0.009	-0.0030 ± 0.0049	-0.097 ± 0.024
	Mid-dose	0.194 ± 0.050	0.013 ± 0.015	0.037 ± 0.012	-0.0074 ± 0.0039	-0.083 ± 0.024
	End-dose	0.199 ± 0.046	0.014 ± 0.015	0.036 ± 0.013	-0.0060 ± 0.0034	-0.083 ± 0.020
	End recovery	0.182 ± 0.037	0.014 ± 0.016	0.033 ± 0.009	-0.0015 ± 0.0036	-0.099 ± 0.031

Table 15. Effects of imipramine or vehicle infusion on ECG from lead I in sedentary rats. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. P_a, P wave amplitude; Q_a, Q wave amplitude; S_a, S wave amplitude. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-52.1 ± 20.7[bi, v]	-111.5 ± 97.3	-4.5 ± 8.1	-27.7 ± 364.4	-208.8 ± 86.2[bi, r, v]
	End-dose	-48.0 ± 26.9[bi, v]	-70.9 ± 126.2	-7.3 ± 16.6	-209.2 ± 540.5	-197.6 ± 73.7[bi, r, v]
	End recovery	-15.1 ± 18.8	-106.6 ± 99.9	-5.9 ± 12.7	-924.9 ± 706.4	-32.0 ± 15.2
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	11.5 ± 4.7	10.7 ± 22.7	-13.6 ± 18.8	-88.6 ± 71.1	15.6 ± 6.0
	End-dose	17.5 ± 7.8	16.2 ± 19.0	-18.3 ± 19.1	-67.2 ± 62.5	11.6 ± 8.9
	End recovery	12.3 ± 11.3	11.4 ± 3.8	-16.2 ± 22.5	15.0 ± 31.6	-1.1 ± 13.1

Table 16. Effects of imipramine or vehicle infusion on ECG from lead I in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle.

4.2.2 Effects of imipramine on ECG from lead AVF in sedentary rats

Table 17 shows values of wave form amplitudes of ECG variables from lead AVF in terms of alterations during infusion of imipramine or vehicle. Only R amplitude had significant alteration due to imipramine infusion, and it became significantly reduced from baseline-instrumentation values to mid-dose values ($P < 0.05$) with a gradual recovery (i.e. increase in values) from both mid-dose and end-dose periods to the end recovery period, $P < 0.001$ and $P < 0.05$, respectively. R amplitudes of the imipramine group were statistically higher than for the vehicle group at baseline-instrumentaton and end recovery periods ($P < 0.05$). There was no significant alteration in other variables in either imipramine or vehicle infusion group.

Table 18 shows effects of imipramine or vehicle infusion on ECG from lead AVF in sedentary rats (as % change from baseline-instrumentation values). Imipramine infusion trended to reduce R amplitude while vehicle trended to increased R amplitude. R amplitudes decreased from, baseline to midose. The amplitude returned at the end of recovery to a value not different from that at baseline. Imipramine produiced a % reduction of R amplitude that was statistically greater at mid-dose and end-dose periods compared with those of vehicle group ($P < 0.05$), in which R amplitude only trended to increase.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Imipramine	Baseline	0.313 ± 0.025[v]	0.099 ± 0.016	0.113 ± 0.007	-0.0053 ± 0.0058	-0.101 ± 0.043
	Mid-dose	0.247 ± 0.019[bi, R]	0.099 ± 0.015	0.083 ± 0.018	-0.0041 ± 0.0018	-0.162 ± 0.050
	End-dose	0.282 ± 0.017[r]	0.101 ± 0.015	0.093 ± 0.020	-0.0038 ± 0.0035	-0.193 ± 0.084
	End recovery	0.352 ± 0.020[v]	0.100 ± 0.017	0.109 ± 0.022	-0.0052 ± 0.0053	-0.101 ± 0.032
Vehicle	Baseline	0.222 ± 0.041	0.088 ± 0.012	0.052 ± 0.042	-0.0075 ± 0.0018	-0.311 ± 0.116
	Mid-dose	0.239 ± 0.037	0.085 ± 0.009	0.051 ± 0.047	-0.0088 ± 0.0029	-0.302 ± 0.112
	End-dose	0.253 ± 0.033	0.087 ± 0.010	0.059 ± 0.049	-0.0100 ± 0.0034	-0.306 ± 0.113
	End recovery	0.262 ± 0.033	0.096 ± 0.010	0.054 ± 0.045	-0.0045 ± 0.0027	-0.328 ± 0.124

Table 17. Effects of imipramine or vehicle infusion on ECG from lead AVF in sedentary rats. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. [bi]$P <$ 0.05 vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-20.0 ± 5.4$^{R, v}$	1.9 ± 7.6	-25.0 ± 16.9	-2.3 ± 44.4	-113.6 ± 61.0
	End-dose	-7.8 ± 7.4$^{r, v}$	3.0 ± 5.9	-17.0 ± 18.5	-2.3 ± 60.1	-104.2 ± 45.1
	End recovery	16.0 ± 11.5	2.4 ± 7.9	-4.0 ± 18.5	-24.2 ± 39.9	-19.4 ± 17.1
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	10.9 ± 7.2	-1.5 ± 6.1	-1.4 ± 8.6	-20.9 ± 20.6	1.3 ± 3.1
	End-dose	20.0 ± 13.2	1.9 ± 8.7	8.1 ± 12.2	-24.0 ± 14.5	-0.7 ± 4.0
	End recovery	24.9 ± 14.5	11.1 ± 6.6	2.8 ± 11.8	55.2 ± 25.9	-8.4 ± 6.7

Table 18. Effects of imipramine or vehicle infusion on ECG from lead AVF in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle.

4.2.3 Effects of imipramine on ECG from lead V3 in sedentary rats

ECG variables from lead V3 and their alterations due to imipramine or vehicle infusion are presented in table 19. Imipramine infusion caused an initial increase in HR during the first 10 minutes (see table 88 in appendix C.), followed by a gradual decrease in HR (413 ± 21 at baseline-instrument vs. 324 ± 21 at mid-dose, $P < 0.001$). It then slowly spontaneous recovered toward baseline-instrument value (i.e., lower HR at mid-dose and end-dose periods compared with end recovery, $P < 0.05$), with a significantly lower HR at end-dose and end recovery periods compared with baseline-instrument, $P < 0.001$ and $P < 0.05$, respectively).

Imipramine also significantly lengthened P, PR, PR_{sect}, QRS, and QT durations, at mid-dose and end-dose, compared with their baseline-instrumentation values ($P < 0.001$). Imipramine infusion also significantly prolonged T duration at mid-dose and end-dose periods ($P < 0.05$). Spontaneous recovery was shown in some of the parameters [i.e., PR (46.3 ± 1.6 at mid-dose vs. 50.0 ± 1.3 at end-dose, $P < 0.05$), and PR_{sect} (29.0 ± 1.3 at mid-dose vs. 32.3 ± 0.9 at end-dose, $P < 0.05$)]. Some of the variables also recovered after cessation of infusion: P duration (17.7 ± 0.7 at end-dose vs. 16.5 ± 1.1 at end recovery, $P < 0.05$), PR (46.3 ± 1.6 at mid-dose, 50.0 ± 1.3 at end-dose vs. 43.2 ± 1.3 at end recovery, $P < 0.05$ and $P < 0.001$, respectively), PR_{sect} (32.3 ± 0.9 at end-dose vs. 26.8 ± 0.9 at end recovery, $P < 0.001$), QRS (23.4 ± 0.9 at mid-dose, 24.1 ± 1.1 at end-dose vs. 21.2 ± 0.7 at end recovery, $P < 0.05$), QT (81.8 ± 4.2 at mid-dose, 81.5 ± 4.6 at end-dose vs. 73.7 ± 3.2 at end recovery, $P < 0.05$), QTcF (142.9 ± 7.5 at mid-dose, 143.3 ± 7.4 at end-dose vs. 134.1 ± 5.4 at end recovery, $P < 0.05$), QA (55.4 ± 3.7 at mid-dose,

56.3 ± 4.5 at end-dose vs. 50.4 ± 3.0 at end recovery, $P < 0.05$) and T duration (50.0 ± 4.0 at mid-dose, 48.5 ± 4.8 at end-dose vs. 41.9 ± 4.2 at end recovery, $P < 0.05$). Recoveries in ECG/pressure durations were partial for RR, HR, and PR, while other variables showed no significance between their baseline-instrumentation and end recovery period values.

There were no significant changes in the vehicle group for any variable. However, in the vehicle group, PR, PR_{sect}, QRS, and QA at mid-dose and end-dose periods were lower significantly compared with imipramine group ($P < 0.05$).

Table 20 shows values indicating alterations of ECG variables, from lead V3, expressed as % change from their baseline-instrument values. There were the same trends and statistical significances of imipramine infusion consistant with table 19.

Figure 13 and 14 show samples of lead V3 ECG wave from rats receiving vehicle infusion. Note that there is no obvious change in durations of ECG wave forms. On the other hand, imipramine infusion led to statistical alterations in ECG durations and R amplitude, as can be seen in figure 15 and 16.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Imipramine	Baseline	147 ± 8	413 ± 21	15.3 ± 0.7	40.4 ± 1.2	25.0 ± 1.4	19.7 ± 0.7
	Mid-dose	190 ± 14$^{Bi, r}$	324 ± 21$^{Bi, r}$	17.3 ± 0.8^{Bi}	46.3 ± 1.6$^{Bi, ed, r, v}$	29.0 ± 1.3$^{Bi, ed, v}$	23.4 ± 0.9$^{Bi, r}$
	End-dose	186 ± 15 ^{Bi}	333 ± 27$^{Bi, r}$	17.7 ± 0.7$^{Bi, r}$	50.0 ± 1.3$^{Bi, R, v}$	32.3 ± 0.9$^{Bi, R, v}$	24.1 ± 1.1$^{Bi, r}$
	End recovery	170 ± 18^{bi}	371 ± 35^{bi}	16.5 ± 1.1	43.2 ± 1.3^{bi}	26.8 ± 0.9	21.2 ± 0.7
Vehicle	Baseline	166 ± 6	362 ± 12	16.5 ± 0.7	41.0 ± 2.7	24.5 ± 2.2	21.0 ± 1.3
	Mid-dose	164 ± 6	367 ± 12	16.1 ± 0.8	39.5 ± 3.1	23.4 ± 2.5	21.2 ± 1.0
	End-dose	163 ± 6	369 ± 12	16.1 ± 0.8	39.2 ± 3.1	23.1 ± 2.6	21.5 ± 1.0
	End recovery	161 ± 6	374 ± 13	16.4 ± 0.9	38.6 ± 3.3	22.2 ± 2.6	21.5 ± 1.2

Continued

Table 19. Effects of imipramine or vehicle infusion on ECG from lead V3 in sedentary rats. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{ed}P < 0.05$ vs. its end dose; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle.

Table 19. Continued

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Imipramine	Baseline	71.6 ± 2.5	187.1 ± 6.0	135.8 ± 4.2	9.06 ± 0.90	48.9 ± 1.7	42.5 ± 2.9
	Mid-dose	81.8 ± 4.2[Bi, r]	189.0 ± 10.5	142.9 ± 7.5[r]	8.27 ± 0.80	55.4 ± 3.7[bi, v]	50.0 ± 4.0[bi, r]
	End-dose	81.5 ± 4.6[Bi, r]	190.3 ± 10.1	143.3 ± 7.4[r]	9.52 ± 0.96	56.3 ± 4.5[Bi, r, v]	48.5 ± 4.8 [bi, r]
	End recovery	73.7 ± 3.2	181.2 ± 8.6	134.1 ± 5.4	9.63 ± 1.30	50.4 ± 3.0	41.9 ± 4.2
Vehicle	Baseline	71.5 ± 0.9	175.4 ± 3.0	130.0 ± 1.8	10.6 ± 1.2	44.8 ± 2.3	39.6 ± 2.1
	Mid-dose	72.8 ± 0.5	180.0 ± 3.6	133.1 ± 2.0	11.2 ± 1.4	44.0 ± 1.7	40.0 ± 2.6
	End-dose	73.1 ± 1.1	181.2 ± 5.1	133.9 ± 3.1	11.4 ± 1.3	43.7 ± 1.6	39.9 ± 3.0
	End recovery	72.7 ± 1.6	181.5 ± 3.7	133.8 ± 2.5	12.1 ± 1.7	43.4 ± 0.7	38.8 ± 1.6

Values are means ± SE. Imipramine n = 6 and vehicle n = 4. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	28.7 ± 5.6$^{Bi, r, v}$	-21.6 ± 3.3$^{Bi, r, V}$	13.0 ± 3.2$^{Bi, V}$	14.8 ± 2.3$^{Bi, ed, r, V}$	16.6 ± 4.5$^{bi, ed, V}$	19.5 ± 5.9$^{Bi, r, v}$
	End-dose	26.3 ± 6.8 $^{Bi, v}$	-19.7 ± 4.3$^{Bi, r, V}$	15.4 ± 2.3$^{Bi, r, V}$	24.1 ± 3.7$^{Bi, R, V}$	30.6 ± 6.1$^{Bi, R, V}$	23.5 ± 7.9$^{Bi, r, v}$
	End recovery	14.9 ± 8.6$^{bi, v}$	-10.7 ± 6.2$^{bi, v}$	7.0 ± 4.1	7.1 ± 1.7$^{bi, V}$	7.6 ± 2.8^{v}	8.4 ± 5.0
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-1.2 ± 1.1	1.3 ± 1.1	-2.3 ± 0.5	-3.9 ± 1.7	-5.0 ± 2.5	1.3 ± 1.2
	End-dose	-1.9 ± 0.6	2.0 ± 0.6	-2.3 ± 0.6	-4.5 ± 1.8	-6.1 ± 2.8	2.7 ± 1.4
	End recovery	-3.2 ± 0.1	3.3 ± 0.1	-0.4 ± 1.4	-6.0 ± 2.8	-10.0 ± 4.0	2.8 ± 0.7

Continued

Table 20. Effects of imipramine or vehicle infusion on ECG from lead V3 in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE. Imipramine n = 6 and vehicle n = 4. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{ed}P < 0.05$ vs. its end dose; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle.

Table 20. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Imipramine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	14.1 ± 4.0[Bi, r, v]	0.8 ± 3.0	5.0 ± 3.1[r]	-4.3 ± 12.2	12.8 ± 5.0[bi, v]	17.6 ± 6.1[bi, r, v]
	End-dose	13.7 ± 4.5[Bi, r, v]	1.4 ± 2.8	5.3 ± 3.1[r]	8.6 ± 11.0	14.4 ± 7.0[bi, r, v]	13.2 ± 7.6[r]
	End recovery	2.9 ± 2.0	-3.3 ± 2.4	-1.4 ± 1.6	6.8 ± 8.8	2.6 ± 3.7	-2.6 ± 4.5
Vehicle	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	2.0 ± 1.9	2.6 ± 1.7	2.4 ± 1.8	6.4 ± 6.1	-1.7 ± 1.4	1.1 ± 4.0
	End-dose	2.3 ± 2.0	3.3 ± 1.8	3.0 ± 1.9	8.3 ± 5.9	-2.3 ± 1.6	0.7 ± 4.6
	End recovery	1.7 ± 1.1	3.5 ± 1.0	2.9 ± 1.0	14.5 ± 8.1	-2.5 ± 4.0	-1.7 ± 2.1

Values are means ± SE. Imipramine n = 6 and vehicle n = 4. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle.

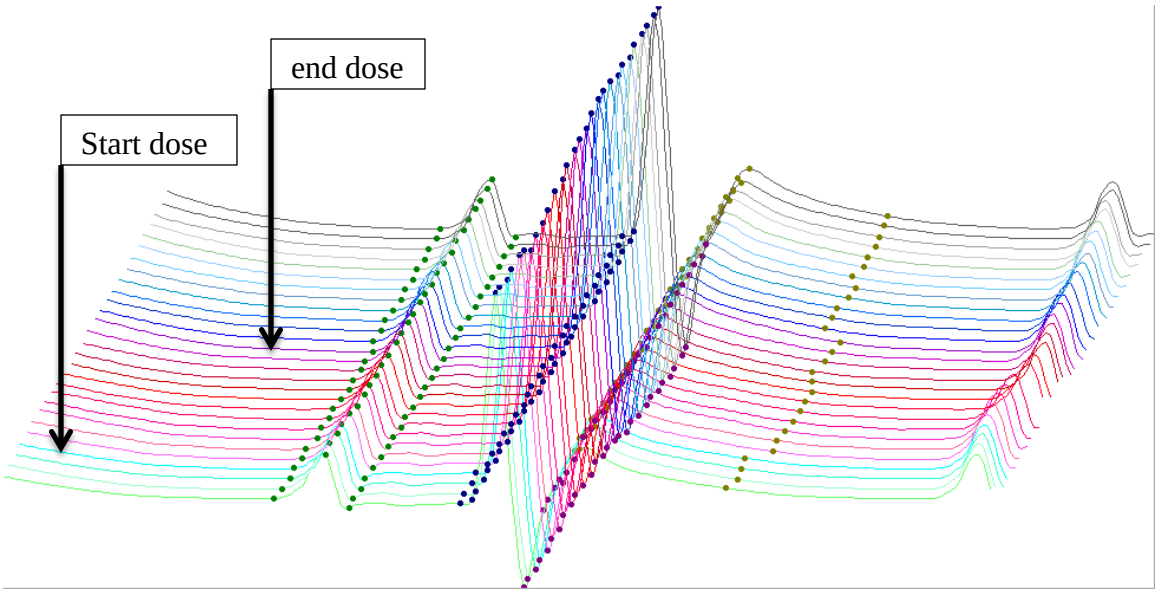

Figure 13. Effects of vehicle infusion on ECG from lead V3 in sedentary rat.

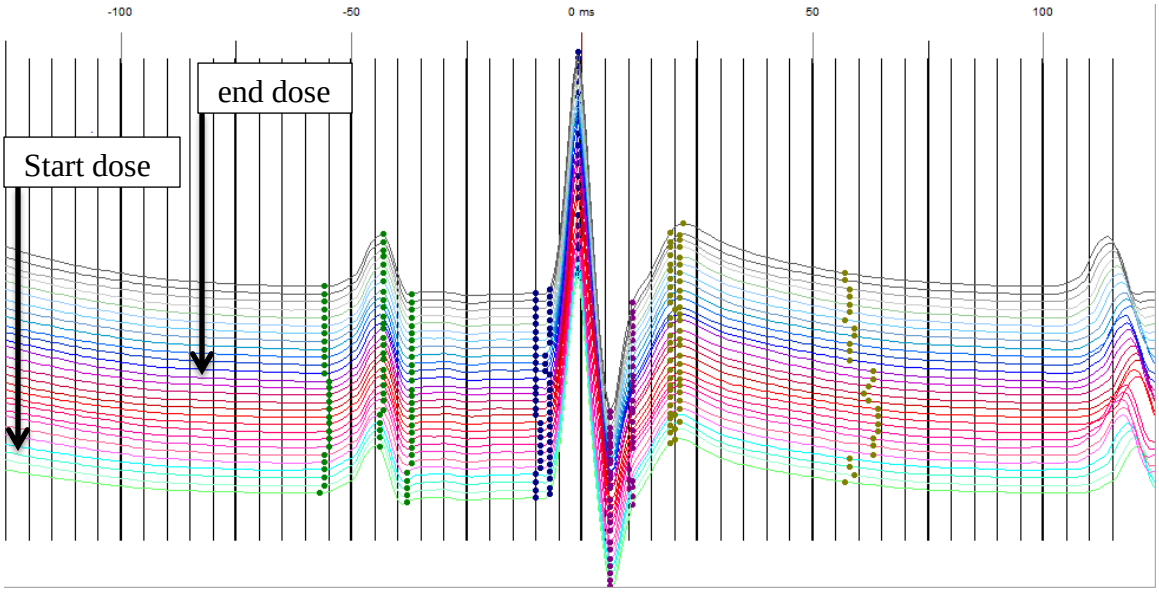

Figure 14. Effects of vehicle infusion on ECG durations from lead V3 in sedentary rat.

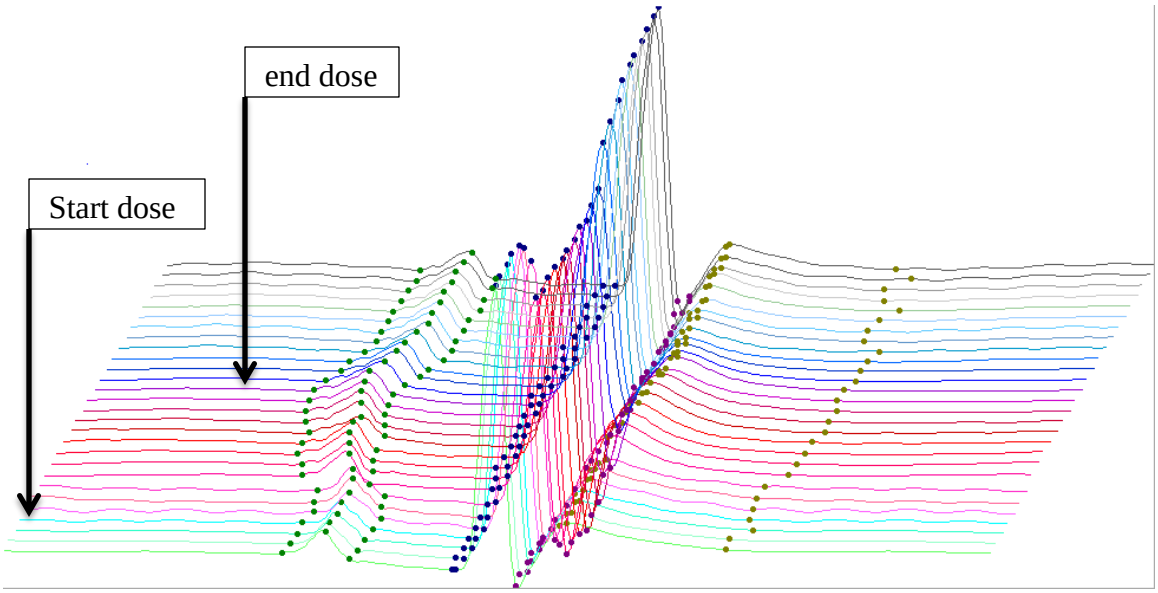

Figure 15. Effects of imipramine infusion on ECG from lead V3 in sedentary rat.

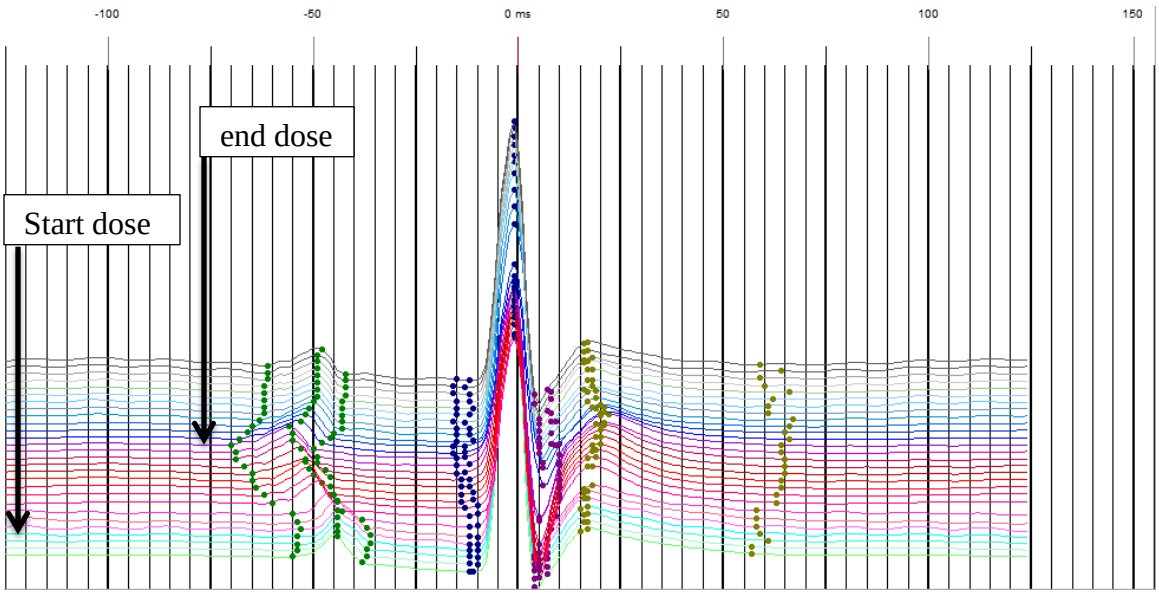

Figure 16. Effects of imipramine infusion on ECG durations from lead V3 in sedentary rat.

Chapter 5: Effects of imipramine on hemodynamics and ECGs in all interventions

5.1 Effects of imipramine on hemodynamics in all interventions

5.1.1 Effects of imipramine on aortic pressures in all interventions

Table 21 contains hemodynamic values affected during imipramine infusion to rats after each intervention. The exercise and carvedilol groups trended to have lower HR, while the dobutamine group trended toward having lower SBP and MBP at the baseline-instrumentation period. There were no differences in aortic pressures among interventions at baseline-instrumentation period.

IV infusion of imipramine (20 mg/kg/hr) significantly reduced SBP, DBP, MBP, and HR in all interventions, at mid-dose period compared with their baseline-instrumentation values. PP was decreased at mid-dose period compared with the baseline-instrumentation period, in the sedentary and the dobutamine groups ($P < 0.05$) as well as in the exercise and the clenbuterol groups ($P < 0.001$). At the end-dose period, most of the interventions trended to have spontaneous recovery of the SBP, DBP, PP, MBP, and HR, but these variables remained significantly different from their baseline-instrumentation values ($P < 0.001$ in SBP, DBP, MAP, and HR in all group; $P < 0.001$ in PP of exercise group; $P < 0.05$ in PP of clenbuterol group).

At the end recovery period, when compared with their baseline-instrumentation period, most of these rats partially recovery from imipramine effects with significant reductions in SBP, DBP, and MBP ($P < 0.001$) as well as in HR ($P < 0.05$), in the exercise and sedentary groups. Likewise, DBP and MBP of the exercise group partial recovered ($P < 0.001$). SBP and HR of the exercise group also partially recovered ($P < 0.05$). Carvedilol had significantly lower values of SBP, DBP, and MBP ($P < 0.001$), with no significant differences in PP and HR at the end recovery period compared with their baseline-instrumentation period. Clenbuterol groups showed the same recovery as the carvedilol group, with the exception of HR, in which it was significantly lower than baseline-instrumentation HR, $P < 0.001$. Only the dobutamine group could recover from the imipramine effects on both SBP and HR compared with their baseline-instrumentation values; however, DBP and MBP were still significantly lower than baseline-instrumentation values.

When compared with the vehicle group, there were significant differences in SBP, DBP and MBP during mid-dose and end-dose in all imipramine challenge/groups (table 21). Significant HR reduction was found only at the end-dose peroid of the exercise group compared with the vehicle group, $P < 0.05$. There was no significant effect of imipramine on PP in any imipramine challenge/groups compared with the vehicle group.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
Sedentary	Baseline	165.6 ± 8.5	123.8 ± 7.5	41.8 ± 4.7	140.4 ± 7.7	412.5 ± 21.2
	Mid-dose	82.7 ± 12.1 [Bi, R, V]	54.7 ± 10.1 [Bi, R, V]	28.0 ± 4.2 [bi, R]	65.8 ± 11.1 [Bi, R, V]	323.9 ± 21.4 [Bi, r]
	End-dose	104.8 ± 14.9 [Bi, r, v]	70.9 ± 8.3 [Bi, V]	33.9 ± 8.0 [r]	84.2 ± 10.9 [Bi, V]	332.6 ± 26.6 [Bi]
	End recovery	129.3 ± 10.3 [Bi]	84.0 ± 6.8 [Bi]	45.3 ± 6.7	102.0 ± 8.1 [Bi]	371.1 ± 35.2 [bi]
Exercise	Baseline	172.8 ± 2.5	121.4 ± 2.3	51.4 ± 2.9	143.4 ± 1.5	388.9 ± 12.9
	Mid-dose	79.8 ± 5.0 [Bi, R, V]	50.9 ± 4.4 [Bi, R, V]	28.9 ± 1.9 [Bi, R]	62.3 ± 4.5 [Bi, R, V]	294.7 ± 9.0 [Bi, r]
	End-dose	92.6 ± 6.5 [Bi, R, V]	61.0 ± 5.2 [Bi, R, V]	31.5 ± 2.1 [Bi, R]	73.0 ± 5.7 [Bi, R, V]	285.0 ± 10.5 [Bi, r, v]
	End recovery	140.5 ± 10.9 [bi]	93.1 ± 7.5 [Bi]	47.4 ± 4.4	113.0 ± 8.9 [Bi]	343.9 ± 17.4 [bi]
Carvedilol	Baseline	160.4 ± 4.3	119.7 ± 1.8	40.8 ± 4.4	135.9 ± 2.4	380.1 ± 11.0
	Mid-dose	101.6 ± 14.0 [Bi, V]	68.0 ± 9.0 [Bi, V]	33.6 ± 5.6 [R]	81.1 ± 10.5 [Bi, v]	328.5 ± 9.0 [bi]
	End-dose	109.4 ± 15.2 [Bi, v]	74.1 ± 11.3 [Bi, V]	35.3 ± 4.9	88.2 ± 12.8 [Bi, V]	302.2 ± 33.1 [Bi, r]
	End recovery	122.3 ± 9.1 [Bi]	78.5 ± 8.0 [Bi, v]	43.8 ± 4.6	96.3 ± 7.9 [Bi, v]	347.9 ± 13.0
Clenbuterol	Baseline	179.1 ± 8.3	129.4 ± 5.8	49.7 ± 4.9	149.8 ± 6.3	412.2 ± 9.9
	Mid-dose	89.0 ± 10.7 [Bi, r, V]	58.6 ± 8.2 [Bi, V]	30.4 ± 3.4 [Bi, R]	70.5 ± 9.2 [Bi, R, V]	314.6 ± 10.3 [Bi]
	End-dose	90.9 ± 9.4 [Bi, r, V]	55.1 ± 7.7 [Bi, V]	35.8 ± 2.8 [bi, R]	69.4 ± 8.1 [Bi, R, V]	305.5 ± 14.1 [Bi]
	End recovery	122.2 ± 7.4 [Bi]	70.7 ± 4.7 [Bi, v]	51.5 ± 5.9	91.0 ± 4.9 [Bi, v]	334.9 ± 12.9 [Bi]
Dobutamine	Baseline	149.4 ± 6.2	116.8 ± 4.9	32.6 ± 2.6	129.3 ± 5.5	415.4 ± 14.4
	Mid-dose	69.3 ± 5.3 [Bi, R, V]	48.5 ± 5.0 [Bi, R, V]	20.8 ± 2.0 [bi, R]	56.9 ± 5.1 [Bi, R, V]	330.4 ± 17.0 [Bi, R]
	End-dose	83.2 ± 11.0 [Bi, R, V]	60.2 ± 8.8 [Bi, R, V]	23.0 ± 3.2 [R]	69.0 ± 9.7 [Bi, R, V]	321.4 ± 15.4 [Bi, R]
	End recovery	126.0 ± 6.6	88.0 ± 4.1 [Bi]	38.0 ± 3.6	102.6 ± 4.9 [bi]	393.3 ± 23.2

Table 21. Hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [V]$P < 0.001$ vs. vehicle; [v]$P < 0.05$ vs. vehicle.

Table 22 shows systemic effects of imipramine expressed as % change from baseline-instrumentation values in all interventions. Imipramine produced significant depression of systemic hemodynamic variables compared with the matched-volume vehicle infusion. For example, at mid-dose, end-dose, and end recovery periods, the imipramine-challenged rats had significantly lower % change of SBP, DBP, and MBP. Values of PP of sedentary, exercise, clenbuterol, and dobutamine groups also showed significant depression expressed by % change at mid-dose and end-dose periods compared with those of vehicle group. On the other hand, values of PP of carvedilol were different from the vehicle group only at end-dose period. As for % reduction in HR, imipramine infusion led to a significant decrease in both mid-dose and end-dose periods of all imipramine challenge groups ($P < 0.001$, except for in HR at mid-dose of carvedilol, $P < 0.05$), and at end-recovery period of the clenbuterol group ($P < 0.05$) compared with the vehicle group.

There were some significant differences in effects of imipramine among interventions. For instance, % changes of DBP at end recovery period of exercise and dobutamine groups were significantly greater than in the clenbuterol group ($P < 0.05$). The dobutamine group had significantly greater % change of MBP than the clenbuterol group at end recovery period ($P < 0.05$).

Figure 17-24 show effects of imipramine on SBP, DBP, MBP, and HR from both raw data and in % change (i.e. BL-adjusted values) for each intervention with 5 minute time points from start dose to 1 hr after cessation of infusion.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-50.7 ± 5.2$^{Bi, R, V}$	-56.9 ± 6.2$^{Bi, R, V}$	-33.4 ± 5.3$^{Bi, R, v}$	-54.0 ± 5.7$^{Bi, R, V}$	-21.5 ± 3.3$^{Bi, r, V}$
	End-dose	-37.5 ± 6.5$^{Bi, r, V}$	-42.7 ± 5.4$^{Bi, V}$	-22.9 ± 11.3$^{r, v}$	-40.4 ± 5.9$^{Bi, V}$	-19.5 ± 4.3$^{Bi, V}$
	End recovery	-22.4 ± 2.4$^{Bi, v}$	-32.4 ± 2.6$^{Bi, V}$	8.2 ± 11.1^{bi}	-27.7 ± 2.2$^{Bi, V}$	-10.5 ± 6.2^{bi}
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-53.6 ± 3.4$^{Bi, R, V}$	-58.0 ± 3.9$^{Bi, R, V}$	-42.3 ± 6.0$^{Bi, R, V}$	-56.5 ± 3.4$^{Bi, R, V}$	-24.1 ± 1.8$^{Bi, r, V}$
	End-dose	-46.4 ± 4.0$^{Bi, R, V}$	-49.6 ± 4.7$^{Bi, R, V}$	-38.2 ± 4.0$^{Bi, r, V}$	-49.0 ± 4.2$^{Bi, R, V}$	-26.7 ± 0.7$^{Bi, R, V}$
	End recovery	-18.9 ± 5.8$^{bi, v}$	-23.0 ± 6.9$^{Bi, v, cl}$	-7.9 ± 5.5	-21.1 ± 6.3$^{Bi, v}$	-11.7 ± 2.9^{bi}
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-36.9 ± 7.9$^{Bi, V}$	-42.8 ± 8.0$^{Bi, V}$	-18.8 ± 6.9^{R}	-40.2 ± 7.8$^{Bi, V}$	-13.5 ± 2.1$^{bi, v}$
	End-dose	-31.9 ± 8.9$^{Bi, V}$	-37.8 ± 9.6$^{Bi, V}$	-11.7 ± 9.9^{v}	-35.0 ± 9.2$^{Bi, V}$	-20.7 ± 8.5$^{Bi, r, V}$
	End recovery	-23.8 ± 5.3$^{Bi, v}$	-34.1 ± 7.3$^{Bi, V}$	7.8 ± 4.6	-29.0 ± 6.1$^{Bi, V}$	-8.5 ± 1.6
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-50.7 ± 4.4$^{Bi, r, V}$	-55.6 ± 4.3$^{Bi, V}$	-36.1 ± 8.6$^{Bi, R, V}$	-53.7 ± 4.3$^{Bi, r, V}$	-23.5 ± 2.8$^{Bi, V}$
	End-dose	-49.2 ± 4.5$^{Bi, r, V}$	-57.6 ± 4.8$^{Bi, V}$	-24.2 ± 10.6$^{bi, R, V}$	-53.8 ± 4.4$^{Bi, r, V}$	-25.5 ± 4.4$^{Bi, V}$
	End recovery	-31.7 ± 2.9$^{Bi, V}$	-45.5 ± 1.8$^{Bi, V}$	7.6 ± 14.4	-39.3 ± 1.2$^{Bi, V, d}$	-18.8 ± 2.5$^{Bi, V}$
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-53.0 ± 4.3$^{Bi, R, V}$	-57.9 ± 4.9$^{Bi, R, V}$	-35.7 ± 4.9$^{Bi, R, V}$	-55.4 ± 4.6$^{Bi, R, V}$	-20.5 ± 2.7$^{Bi, R, V}$
	End-dose	-43.7 ± 7.8$^{Bi, R, V}$	-47.8 ± 8.0$^{Bi, R, V}$	-29.5 ± 7.7$^{bi, R, V}$	-46.0 ± 8.0$^{Bi, R, V}$	-22.5 ± 3.2$^{Bi, R, V}$
	End recovery	-15.3 ± 4.1$^{bi, v}$	-23.8 ± 5.2$^{Bi, v, cl}$	16.2 ± 3.2	-20.0 ± 4.7$^{bi, v}$	-5.5 ± 3.7

Table 22. Hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{cl}P < 0.05$ vs. clenbuterol; $^{d}P < 0.05$ vs. dobutamine.

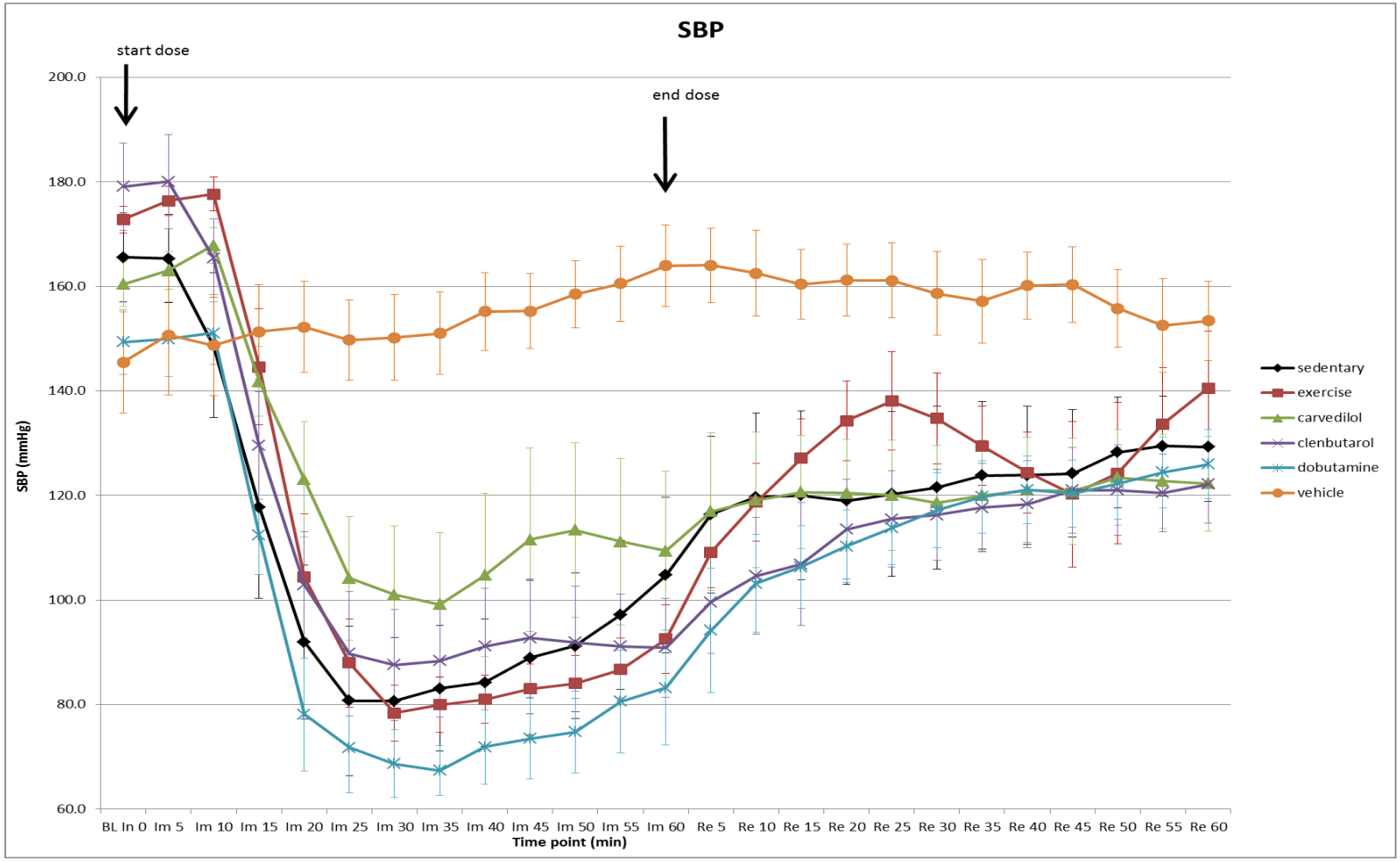

Figure 17. Effect of imipramine or vehicle infusion on SBP in all interventions. Values are means ± SE. SBP, systolic blood pressure.

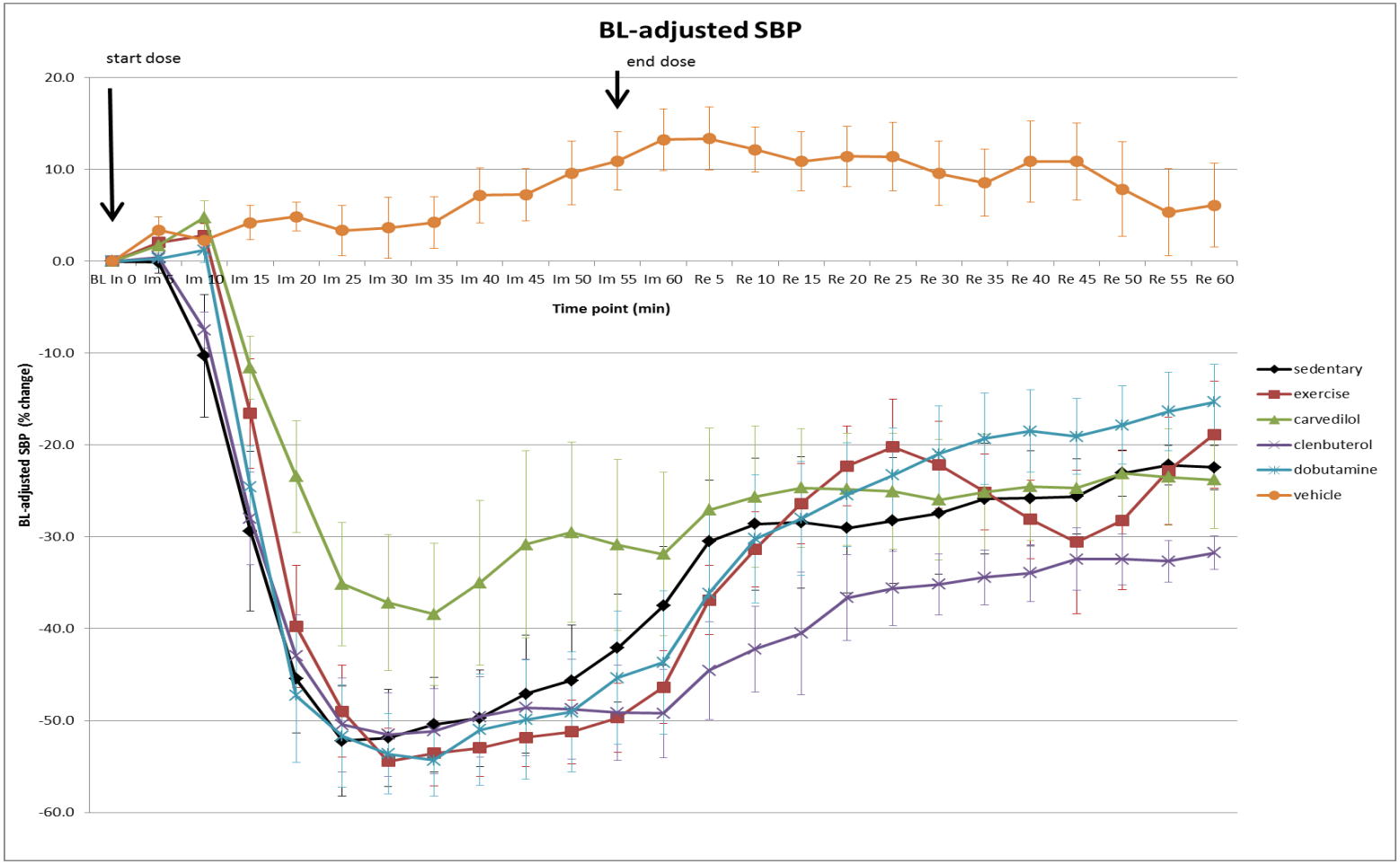

Figure 18. Effect of imipramine or vehicle infusion on BL-adjusted SBP in all interventions. Values are means ± SE. BL-adjusted SBP, % change from its baseline-instrumentation value of systolic blood pressure.

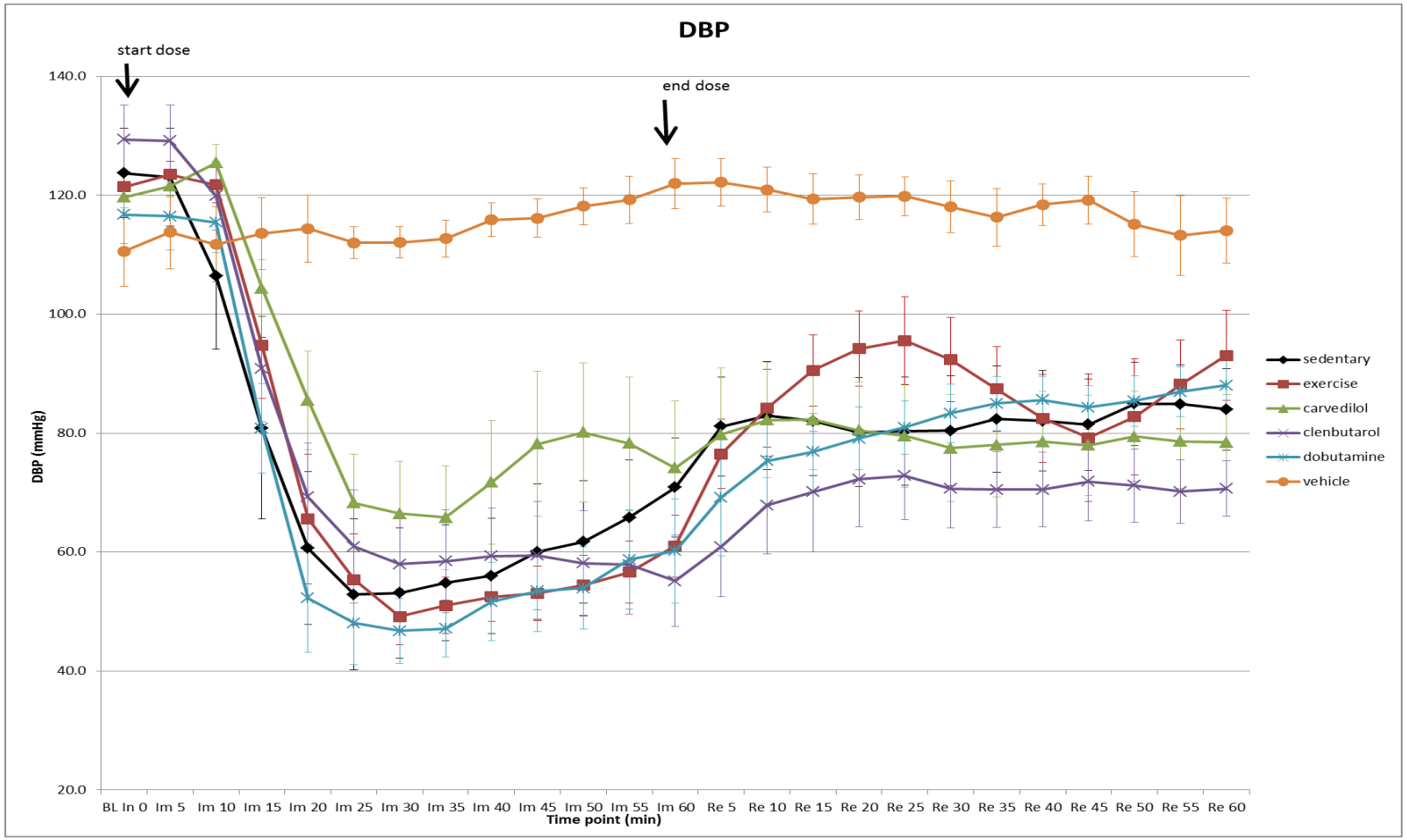

Figure 19. Effect of imipramine or vehicle infusion on DBP in all interventions. Values are means ± SE. DBP, diastolic blood pressure.

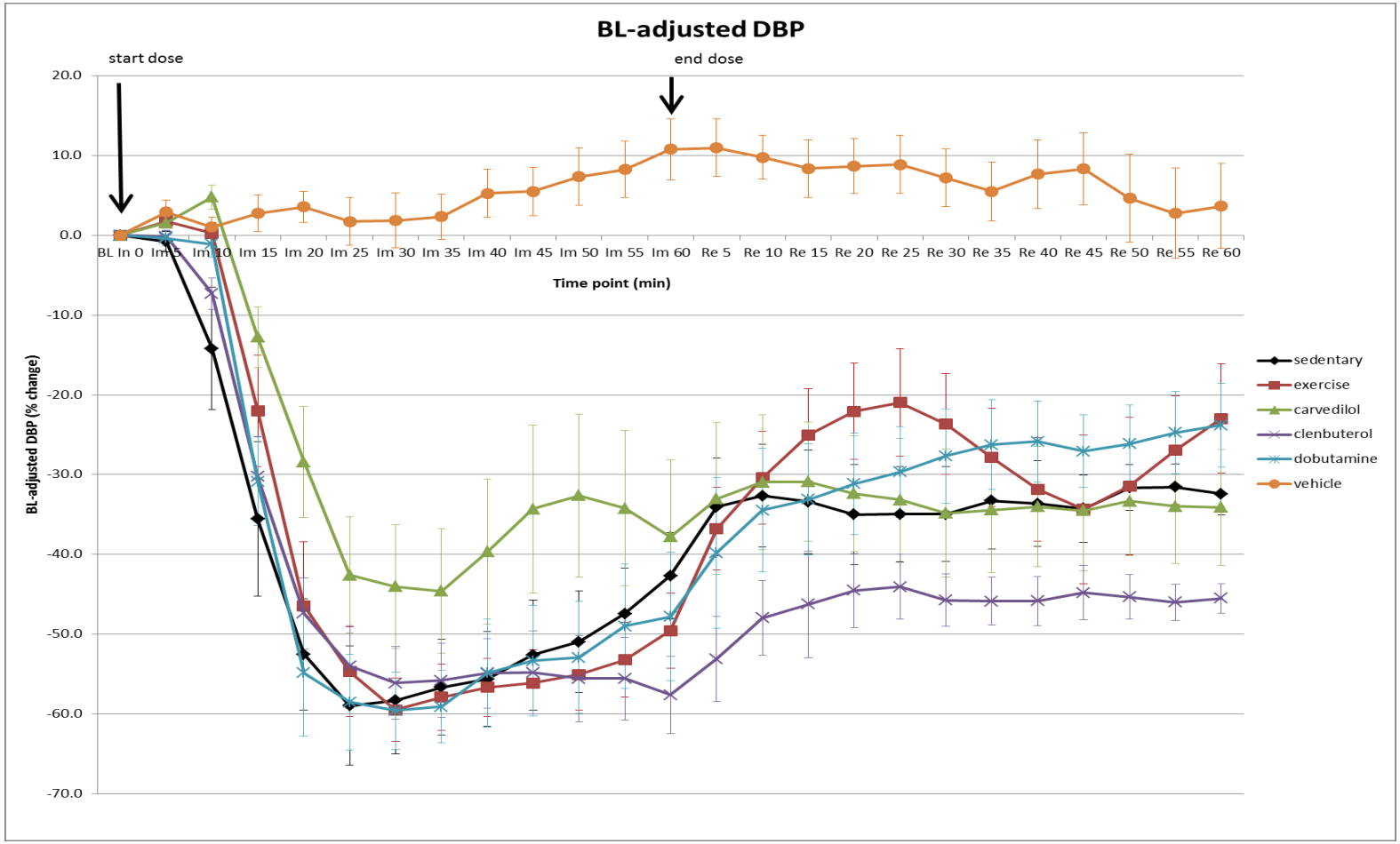

Figure 20. Effect of imipramine or vehicle infusion on BL-adjusted DBP in all interventions. Values are means ± SE. BL-adjusted DBP, % change from its baseline-instrumentation value of diastolic blood pressure.

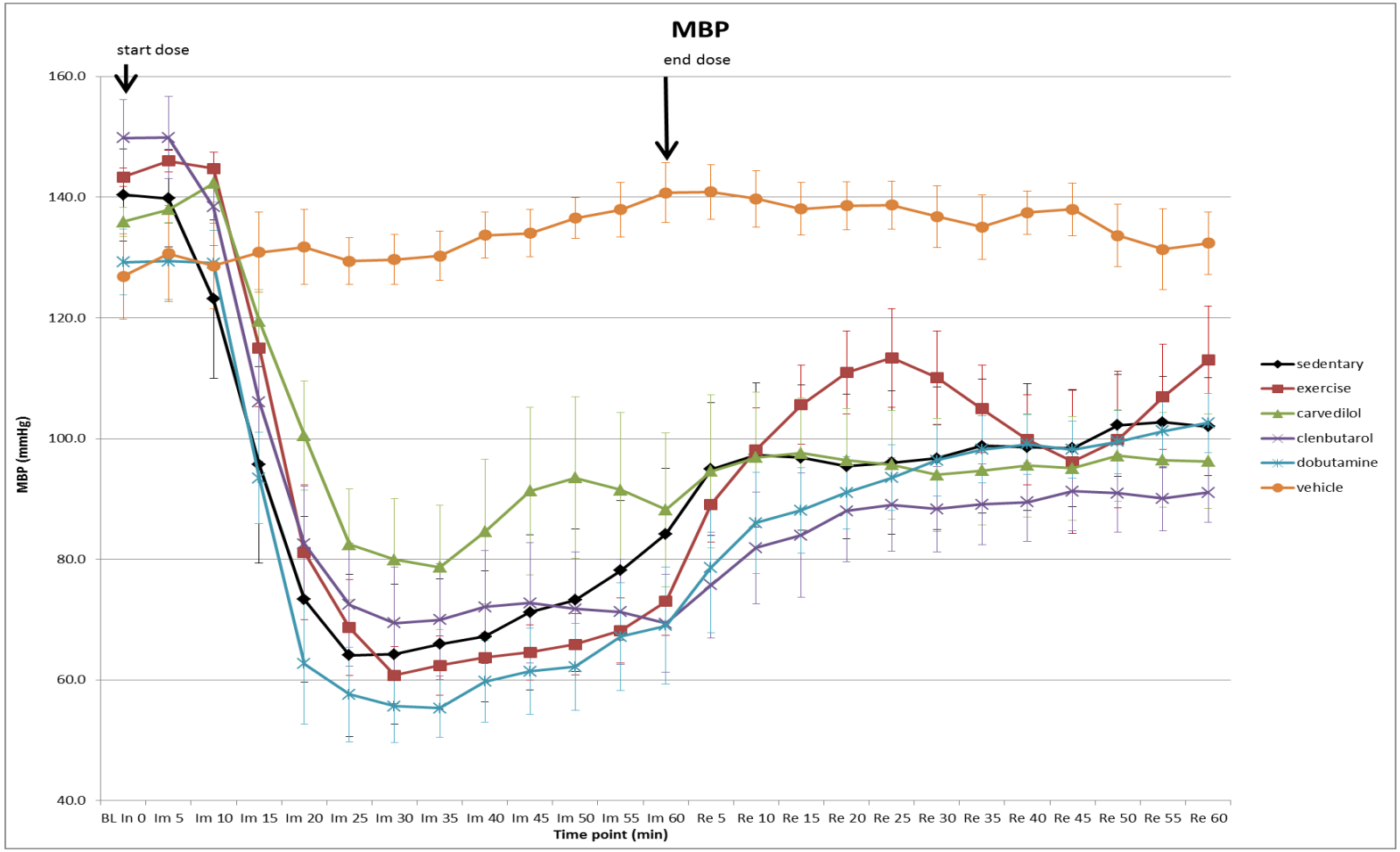

Figure21. Effect of imipramine or vehicle infusion on MBP in all intrventions. Values are means ± SE. MBP, Mean blood pressure.

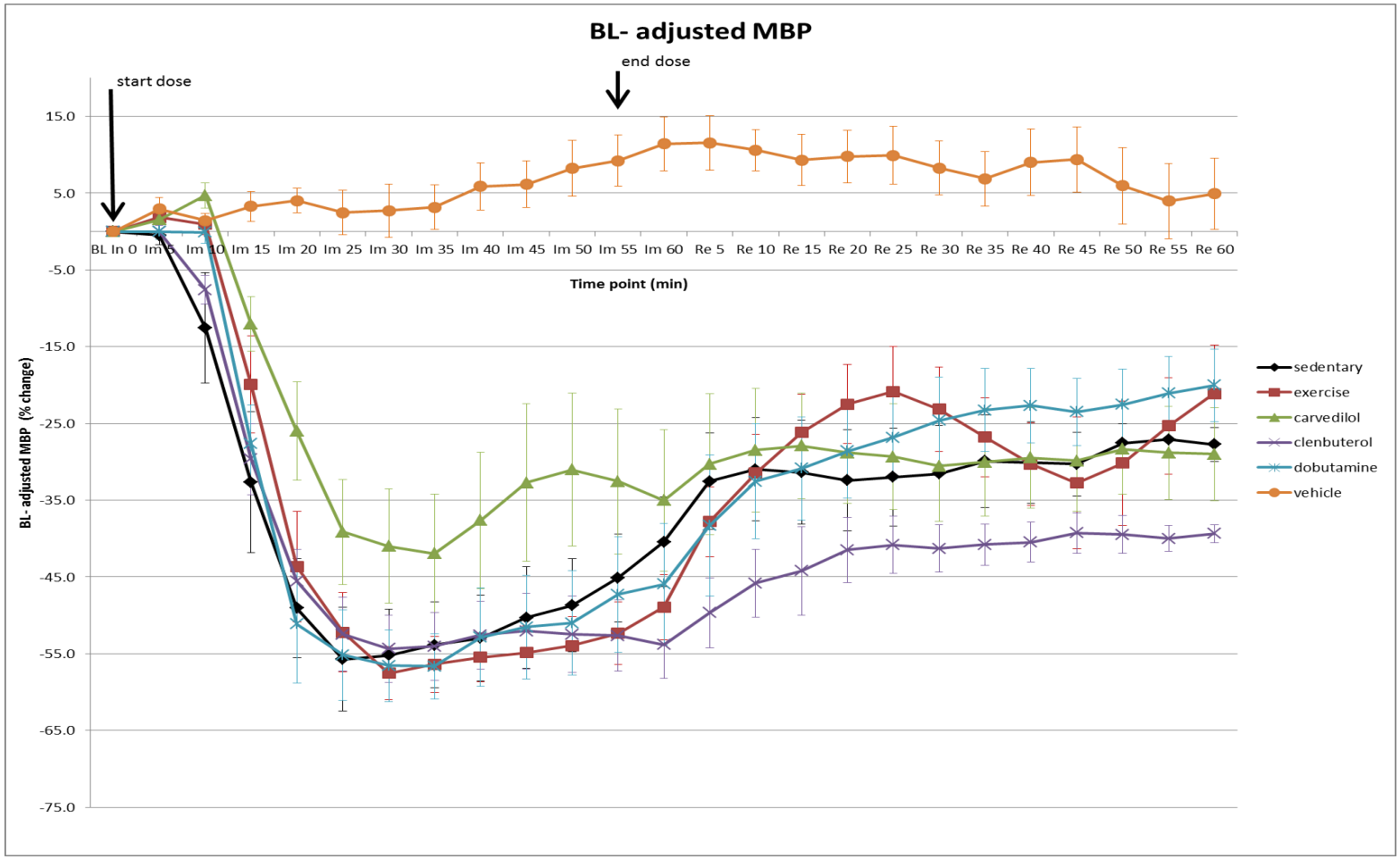

Figure 22. Effect of imipramine or vehicle infusion on BL-adjusted MBP in all interventions. Values are means ± SE. BL-adjusted MBP, % change from its baseline-instrumentation value of mean blood pressure.

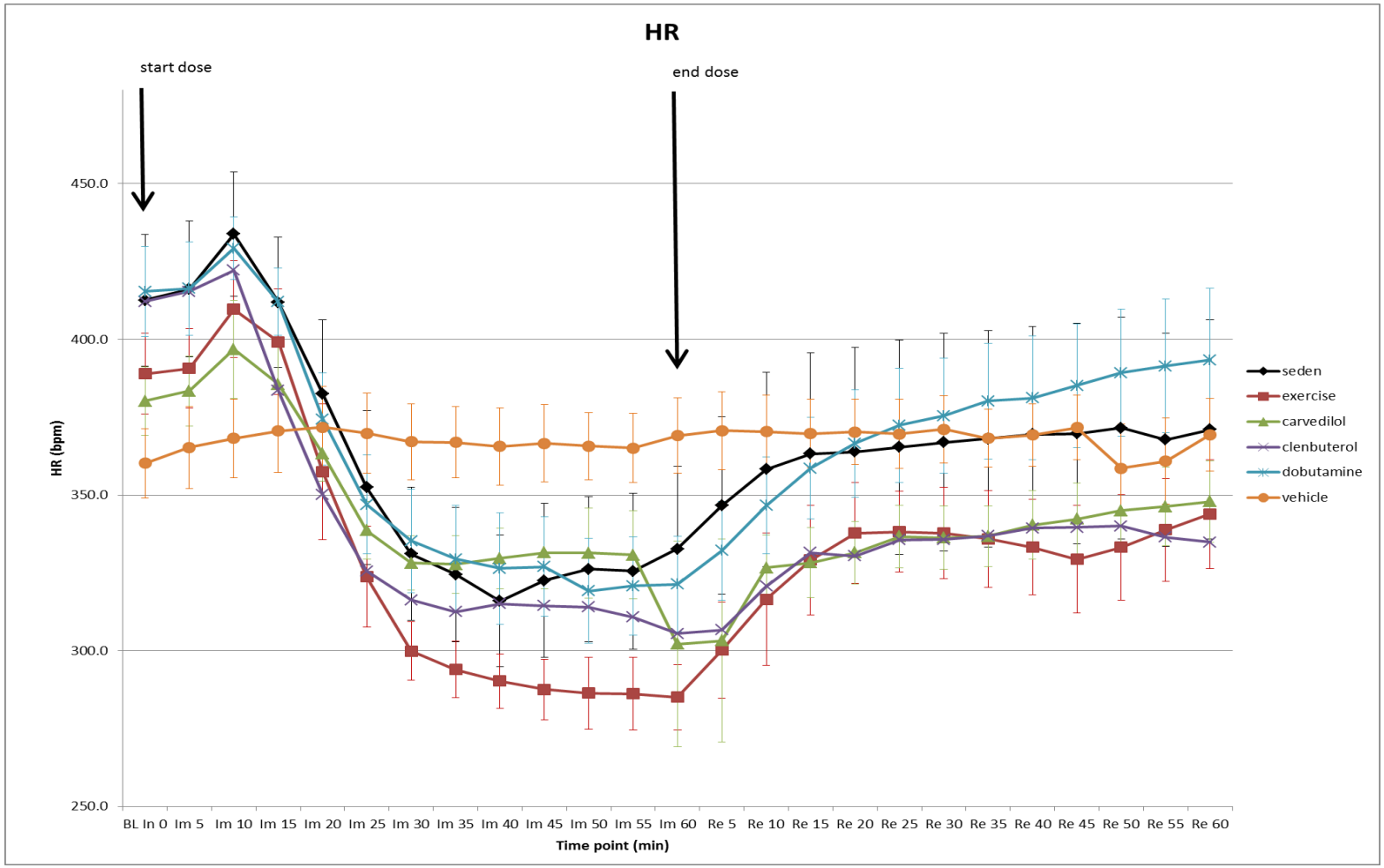

Figure 23. Effect of imipramine or vehicle infusion on HR in all interventions. Values are means ± SE. HR, heart rate.

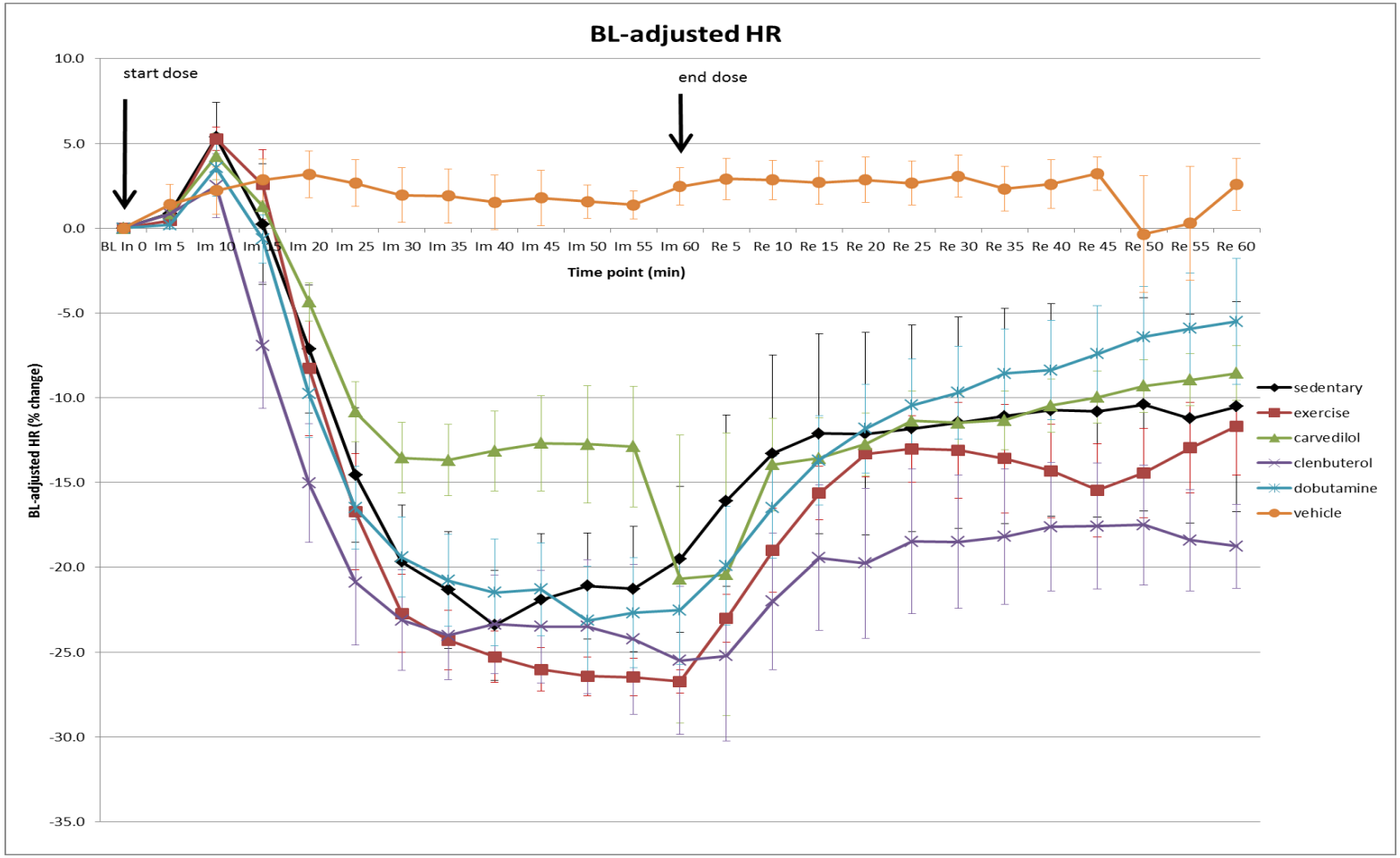

Figure 24. Effect of imipramine or vehicle infusion on BL-adjusted HR in all interventions. Values are means ± SE. BL-adjusted HR, % change from its baseline-instrumentation value of heart rate.

5.1.2 Effects of imipramine on LV hemodynamics in all interventions

Table 23 show effects of imipramine infusion on cardiac performances in all interventions and their comparisons among time points, and among groups including vehicle group. At baseline-instrumentation there were some significant differences among groups. For instance, the clenbuterol group had higher values of +dP/d*t* than the dobutamine group (7,471 ± 622 vs. 5,286 ± 317, $P < 0.05$), and values of SV and CO in the clenbuterol and the dobutamine groups were significant lower than the vehicle group ($P < 0.05$).

As indicated in this table, imipramine infusion caused significant reductions in LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV at mid-dose and end-dose periods compared with their baseline-instrumentation period in all groups ($P < 0.001$). There was no significant change in LVEDP in any period. Imipramine also depressed cardiac contractility (measured by CI) in the exercise group (82.4 ± 1.1 at mid-dose and 82.1 ± 1.8 at end-dose vs. 95.6 ± 1.0 at baseline-instrumentation, $P < 0.001$), in the carvedilol group (77.4 ± 2.3 at end-dose vs. 89.0 ± 2.6 at baseline-instrumentation, $P < 0.001$), and in the clenbuterol group (84.3 ± 4.2 at mid-dose and 84.8 ± 4.4 at end-dose vs. 96.0 ± 3.5 at baseline-instrumentation, $P < 0.001$). Moreover, imipramine could significantly lengthen tau at the mid-dose period in the dobutamine group (8.9 ± 0.4 at the mid-dose vs. 7.8 ± 0.4 at the baseline-instrumentation, $P < 0.05$).

As expected, there were trends towards spontaneous recovery from mid-dose to end-dose values in most of the interventions except the clenbuterol group. These recovery effects did not reach statistical difference. Even though, at the end recovery period, most

of the altered variables (e.g. LVESP, +dP/d*t*, and -dP/d*t* of all groups) significantly improved from the mid-dose and/or end-dose periods, they had only partially recovery when compared with their baseline-instrumentation values. Full recovery occurred in the +dP/d*t*, and -dP/d*t* for the dobutamine group. Values of (+dP/d*t*)/EDV also showed significant normalization from mid-dose and end-dose periods compared with end recovery period, with the exception in the carvedilol group. Tau improved significantly only in the dobutamine group ($P < 0.001$).

Clenbuterol intervention produced significant increase in values of LVEDV at mid-dose ($P < 0.05$), end-dose ($P < 0.001$), and end recovery periods ($P < 0.05$), compared with values during baseline-instrumentation. Likewise, significant increase in LVESV was also found in the exercise and the clenbuterol groups at end-dose period ($P < 0.05$), and mid-dose period of the dobutamine group ($P < 0.05$). Value of SV was significantly changed by imipramine only in the dobutamine group (1.9 ± 0.5 at mid-dose and 1.9 ± 0.5 at end-dose vs. 1.0 ± 0.2 at baseline-instrument, $P < 0.05$). There was no obvious change in the values of CO. There was no obvious indication of recovery in LV volumes in the clenbuterol group while, in the exercise and the dobutamine groups, LV volumes did recover.

Regarding differences among imipramine challanged groups and vehicle group, there were several differences in LV performance among groups. For example, at mid-dose of all imipramine challenged groups, values of LVESP, +dP/d*t*, -dP/d*t* in all interventions, and values of (+dP/d*t*)/EDV in most interventions, were significantly lower than those of the vehicle group ($P < 0.001$). The end-dose and end recovery values of

these parameters were also significantly lower than the vehicle group, with the exception of values of LVESP in the sedentary group at both time points, values of +dP/d*t* of exercise at end recovery, and values of (+dP/d*t*)/EDV at end recovery of sedentary, exercise, carvedilol, and dobutamine groups.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
Sedentary	Baseline	7.0 ± 1.8	158.7 ± 7.3	6,627 ± 191	-6,821 ± 399	89.5 ± 3.4	7.7 ± 0.9
	Mid-dose	7.3 ± 1.6	86.2 ± 8.3 $^{Bi, R, V}$	3,124 ± 427 $^{Bi, R, V}$	-3,099 ± 419 $^{Bi, R, V}$	83.9 ± 3.6	8.1 ± 0.9
	End-dose	7.1 ± 1.7	102.2 ± 10.6 $^{Bi, r}$	3,859 ± 626 $^{Bi, r, V}$	-3,924 ± 610 $^{Bi, r, V}$	83.5 ± 6.0	8.2 ± 1.1
	End recovery	5.4 ± 1.8	122.6 ± 8.3 ^{Bi}	5,020 ± 454 $^{Bi, V}$	-5,207 ± 537 $^{Bi, v}$	86.0 ± 5.3	7.6 ± 1.0
Exercise	Baseline	5.5 ± 1.5	165.2 ± 1.6	6,560 ± 86	-6,372 ± 171	95.6 ± 1.0	7.8 ± 0.3
	Mid-dose	6.8 ± 1.4	82.2 ± 3.6 $^{Bi, R, V}$	2,818 ± 158 $^{Bi, R, V}$	-2,648 ± 185 $^{Bi, R, V}$	82.4 ± 1.1 $^{Bi, r}$	8.3 ± 0.2
	End-dose	6.5 ± 0.9	88.5 ± 5.6 $^{Bi, R, V}$	3,133 ± 248 $^{Bi, R, V}$	-2,929 ± 302 $^{Bi, R, V}$	82.1 ± 1.8 $^{Bi, r}$	8.2 ± 0.5
	End recovery	3.8 ± 1.6	133.2 ± 10.3 ^{Bi}	5,192 ± 419 ^{bi}	-5,104 ± 520 $^{bi, v}$	89.9 ± 1.1	7.5 ± 0.4
Carvedilol	Baseline	4.7 ± 0.8	147.9 ± 4.1	6,180 ± 385	-6,334 ± 637	89.0 ± 2.6	8.3 ± 0.8
	Mid-dose	5.0 ± 1.4	94.6 ± 11.0 $^{Bi, V}$	3,503 ± 396 $^{Bi, r, V}$	-3,578 ± 503 $^{Bi, r, V}$	85.0 ± 3.6 ^{ed}	8.6 ± 0.7
	End-dose	5.5 ± 1.6	101.9 ± 12.8 $^{Bi, V}$	3,665 ± 529 $^{Bi, V}$	-3,923 ± 719 $^{Bi, V}$	77.4 ± 2.3 $^{Bi, r}$	8.8 ± 0.5
	End recovery	5.4 ± 1.7	114.0 ± 8.7 $^{Bi, v}$	4,512 ± 479 $^{Bi, V}$	-4,706 ± 620 $^{Bi, v}$	85.8 ± 2.1	7.9 ± 0.7
Clenbuterol	Baseline	2.8 ± 0.5	171.5 ± 7.4	7,471 ± 622 ^{d}	-6,316 ± 287	96.0 ± 3.5	9.3 ± 0.8
	Mid-dose	3.1 ± 0.5	88.6 ± 8.5 $^{Bi, r, V}$	3,318 ± 380 $^{Bi, r, V}$	-3,380 ± 465 $^{Bi, V}$	84.3 ± 4.2 ^{Bi}	8.4 ± 0.4
	End-dose	3.8 ± 0.7	89.1 ± 8.1 $^{Bi, r, V}$	3,248 ± 289 $^{Bi, r, V}$	-3,201 ± 305 $^{Bi, r, V}$	84.8 ± 4.4 ^{Bi}	8.4 ± 0.4
	End recovery	6.2 ± 1.5	110.7 ± 4.9 $^{Bi, v}$	4,512 ± 412 $^{Bi, V}$	-4,389 ± 385 $^{Bi, v}$	89.1 ± 3.2	7.8 ± 0.6 ^{Bi}
Dobutamine	Baseline	5.5 ± 1.6	141.0 ± 5.7	5,286 ± 317	-5,237 ± 344	83.2 ± 2.4	7.8 ± 0.4
	Mid-dose	5.2 ± 1.3	71.4 ± 5.0 $^{Bi, R, V}$	2,355 ± 163 $^{Bi, R, V}$	-2,180 ± 212 $^{Bi, R, V}$	78.5 ± 1.8	8.9 ± 0.4 $^{bi, R}$
	End-dose	4.9 ± 1.1	81.0 ± 9.8 $^{Bi, R, V}$	2,718 ± 380 $^{Bi, R, V}$	-2,623 ± 476 $^{Bi, R, V}$	76.8 ± 2.3 ^{r}	8.8 ± 0.5 ^{R}
	End recovery	3.4 ± 1.2	117.6 ± 6.2 ^{bi}	4,418 ± 395 ^{V}	-4,479 ± 426 ^{v}	84.5 ± 2.4	7.3 ± 0.6

Continued

Table 23. Hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{ed}P < 0.05$ vs. its end-dose; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle; $^{d}P < 0.05$ vs. dobutamine.

Table 23. Continued

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Sedentary	Baseline	20.4 ± 1.2	18.9 ± 1.3	1.5 ± 0.3	605 ± 111	332.4 ± 27.0
	Mid-dose	20.6 ± 1.7	19.1 ± 1.7	1.5 ± 0.4	474 ± 132	160.6 ± 32.9 [Bi, R, v]
	End-dose	20.8 ± 1.7	19.1 ± 1.7	1.7 ± 0.5	570 ± 196	195.8 ± 42.3 [Bi, r, v]
	End recovery	20.3 ± 1.4	18.5 ± 1.5	1.8 ± 0.4	652 ± 181	256.8 ± 35.6 [bi]
Exercise	Baseline	19.9 ± 0.4	18.3 ± 0.6	1.6 ± 0.3	613 ± 118	330.8 ± 10.0
	Mid-dose	21.1 ± 0.9	19.4 ± 1.0	1.7 ± 0.3	498 ± 95	135.7 ± 11.2 [Bi, R, v]
	End-dose	21.5 ± 1.0	19.8 ± 1.1 [bi]	1.7 ± 0.3	500 ± 99	147.4 ± 13.2 [Bi, R, v]
	End recovery	20.6 ± 0.6	19.3 ± 0.9	1.4 ± 0.3	481 ± 113 [v]	251.5 ± 18.8 [Bi]
Carvedilol	Baseline	20.0 ± 1.0	17.9 ± 1.1	2.1 ± 0.5	805 ± 215	310.5 ± 17.9
	Mid-dose	20.4 ± 1.4	18.7 ± 1.5	1.8 ± 0.3	585 ± 111	174.5 ± 19.9 [Bi, v]
	End-dose	21.6 ± 1.4	19.2 ± 1.3	2.4 ± 0.8	692 ± 246	171.2 ± 21.9 [Bi, v]
	End recovery	21.0 ± 1.0	19.0 ± 1.1	2.0 ± 0.5	706 ± 168	214.1 ± 19.2 [Bi]
Clenbuterol	Baseline	22.1 ± 1.5	21.0 ± 1.4	1.0 ± 0.2 [v]	407 ± 91 [v]	353.5 ± 50.5
	Mid-dose	24.3 ± 1.9 [bi]	22.4 ± 1.6	1.9 ± 0.5 [bi]	571 ± 143	148.4 ± 31.7 [Bi, v]
	End-dose	24.7 ± 2.0 [Bi]	22.8 ± 1.6 [bi]	1.9 ± 0.5 [bi]	593 ± 168	138.9 ± 21.3 [Bi, r, v]
	End recovery	24.4 ± 1.4 [bi]	22.3 ± 1.1	2.1 ± 0.5 [Bi]	676 ± 146 [bi]	192.5 ± 29.4 [Bi, v]
Dobutamine	Baseline	19.8 ± 1.6	18.5 ± 1.4	1.3 ± 0.3 [v]	509 ± 122 [v]	278.3 ± 32.5
	Mid-dose	21.6 ± 1.9 [bi]	20.1 ± 1.7 [bi]	1.5 ± 0.4	471 ± 113	114.9 ± 15.1 [Bi, R, V]
	End-dose	21.5 ± 1.8 [bi]	20.0 ± 1.6	1.5 ± 0.4	456 ± 100	130.8 ± 18.5 [Bi, R, V]
	End recovery	20.3 ± 1.1	18.9 ± 0.8	1.4 ± 0.4	527 ± 118	222.2 ± 24.7 [bi]

Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle.

Expressed as % change from baseline-instrument (see table 24), imipramine infusion caused alterations in LV performance as described above in table 23. Moreover, there were several differences of significance produced by imipramine infusion among the imipramine challanged group. For instance, the exercise training produced a lesser % reduction of +dP/d*t* and (+dP/d*t*)/EDV at the end recovery period compared with the clenbuterol group (-21.0 ± 6.0 vs. -39.6 ± 2.8, $P < 0.05$; and -23.7 ± 5.8 vs. -45.4 ± 3.5, $P < 0.05$, repectively). The carvedilol group had a % reduction of LVESP at end-dose, as well as, % change of SV at mid-dose and end-dose periods compared with (i.e., lower than) the clenbuterol group ($P < 0.05$). Also, % reduction of LVESP in the clenbuterol group was significantly higher than for the dobutamine group at end recovery period ($P < 0.05$). Percent prolongation in tau of the clenbuterol group was lower than the dobutamine group at mid-dose and end-dose period ($P < 0.05$). Percent increase of LVEDV due to imipramine infusion in the clenbuterol group was higher than in the sedentary group at end recovery period ($P < 0.05$). Percent reduction of (+dP/d*t*)/EDV in the clenbuterol group was also higher than in the dobutamine and sedentary groups at end recovery period ($P < 0.05$).

Figure 25 to 30 depict impacts of imipramine on the values of LVESP, +dP/d*t*, and -dP/d*t* expressed as abslolute differences in raw data and % change from baseline-instrument of all interventions including vehicle group.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	20.0 ± 20.1	-45.9 ± 3.6 $^{Bi, R, V}$	-53.4 ± 5.0 $^{Bi, R, V}$	54.6 ± 5.4 $^{Bi, R, V}$	-6.1 ± 3.5	6.2 ± 5.7
	End-dose	14.9 ± 21.1	-35.7 ± 5.4 $^{Bi, r, V}$	-42.5 ± 8.1 $^{Bi, r, V}$	43.0 ± 7.8 $^{Bi, r, V}$	-7.1 ± 3.7 ^{v}	6.3 ± 5.5
	End recovery	-14.6 ± 19.8	-22.8 ± 3.5 $^{Bi, V}$	-24.7 ± 5.1 $^{Bi, V}$	24.4 ± 4.6 $^{Bi, V}$	-4.3 ± 2.5	-2.6 ± 4.0
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	45.5 ± 24.0	-50.2 ± 2.3 $^{Bi, R, V}$	-57.0 ± 2.6 $^{Bi, R, V}$	58.3 ± 3.1 $^{Bi, R, V}$	-13.7 ± 1.9 $^{Bi, V}$	5.9 ± 4.2
	End-dose	53.6 ± 30.4	-46.3 ± 3.7 $^{Bi, R, V}$	-52.2 ± 3.7 $^{Bi, R, V}$	54.2 ± 4.3 $^{Bi, R, V}$	-14.0 ± 2.5 $^{Bi, V}$	4.8 ± 5.6
	End recovery	-15.0 ± 32.6	-19.3 ± 6.4 $^{Bi, V}$	-21.0 ± 6.0 $^{Bi, V, cl}$	20.3 ± 6.9 $^{bi, V}$	-6.0 ± 1.0 ^{v}	-4.6 ± 2.7
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	0.3 ± 15.1	-36.1 ± 7.0 $^{Bi, r, V}$	-42.7 ± 6.6 $^{Bi, r, V}$	42.6 ± 7.6 $^{Bi, r, V}$	-3.5 ± 7.2 $^{ed, v}$	3.8 ± 5.1
	End-dose	10.5 ± 15.9	-31.3 ± 8.0 $^{Bi, V, cl}$	-41.0 ± 6.8 $^{Bi, r, V}$	38.7 ± 7.9 $^{Bi, V}$	-13.0 ± 2.1 $^{Bi, R, V}$	7.0 ± 5.7 ^{r}
	End recovery	9.2 ± 29.1	-23.1 ± 5.0 $^{Bi, V}$	-27.4 ± 5.2 $^{Bi, V}$	26.1 ± 5.0 $^{Bi, V}$	-3.4 ± 1.7	-4.9 ± 2.5
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	43.8 ± 52.6	-48.8 ± 3.1 $^{Bi, r, V}$	-55.6 ± 3.7 $^{Bi, r, V}$	46.5 ± 7.4 $^{Bi, r, V}$	-12.3 ± 1.5 $^{Bi, v}$	-7.5 ± 6.5 ^{d}
	End-dose	69.9 ± 54.8	-48.1 ± 3.7 $^{Bi, r, V}$	-55.7 ± 4.1 $^{Bi, r, V}$	49.2 ± 4.8 $^{Bi, r, V}$	-11.8 ± 2.3 $^{bi, V}$	-7.2 ± 6.7 ^{d}
	End recovery	150.6 ± 59.2	-35.4 ± 1.4 $^{Bi, V, d}$	-39.6 ± 2.8 $^{Bi, V, d}$	30.7 ± 4.9 $^{Bi, V}$	-7.0 ± 2.2 ^{v}	-14.9 ± 5.8 ^{bi}
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	32.7 ± 36.8	-48.8 ± 4.2 $^{Bi, R, V}$	-54.6 ± 3.9 $^{Bi, R, V}$	57.6 ± 4.2 $^{Bi, R, V}$	-5.5 ± 2.1	14.1 ± 3.8 $^{Bi, R}$
	End-dose	46.6 ± 49.4	-42.2 ± 6.9 $^{Bi, R, V}$	-47.9 ± 7.1 $^{Bi, R, V}$	49.4 ± 8.5 $^{Bi, R, V}$	-7.6 ± 2.2 $^{r, v}$	12.0 ± 5.4 $^{Bi, R}$
	End recovery	51.5 ± 83.3	-16.5 ± 3.2 $^{bi, v}$	-16.8 ± 4.0 $^{bi, V}$	15.0 ± 4.0 ^{V}	1.5 ± 0.8	-6.9 ± 3.2

Continued

Table 24. Hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{ed}P < 0.05$ vs. its end-dose; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle; $^{cl}P < 0.05$ vs. clenbuterol; $^{d}P < 0.05$ vs. dobutamine.

Table 24. Continued

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/dt)/EDV (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	0.3 ± 3.1	0.6 ± 3.8	0.6 ± 18.1	-18.2 ± 17.1	-53.3 ± 5.5 [Bi, R, V]
	End-dose	1.2 ± 3.3	0.2 ± 4.1	9.3 ± 18.9	-8.6 ± 18.7	-42.8 ± 8.4 [Bi, r, V]
	End recovery	-0.7 ± 2.8 [cl]	-2.2 ± 3.7	22.6 ± 20.6 [cl]	14.5 ± 25.4	-23.4 ± 6.6 [Bi, V, cl]
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	5.9 ± 3.2	5.9 ± 2.9	9.0 ± 14.8	-17.3 ± 11.3	-59.1 ± 3.0 [Bi, R, V]
	End-dose	8.2 ± 3.9	7.9 ± 3.4	16.1 ± 22.6	-14.8 ± 16.7	-55.6 ± 3.7 [Bi, R, V]
	End recovery	3.8 ± 1.7	5.0 ± 1.7	-9.5 ± 15.3 [cl]	-20.3 ± 13.9	-23.7 ± 5.8 [Bi, V, cl]
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	1.8 ± 3.3	3.6 ± 3.0	-6.2 ± 7.4 [cl]	-18.5 ± 7.4	-43.4 ± 6.3 [Bi, V]
	End-dose	7.4 ± 2.8	6.9 ± 3.0	10.1 ± 13.9	-17.1 ± 9.0	-44.5 ± 6.9 [Bi, V]
	End recovery	5.1 ± 1.4	6.0 ± 1.2	-0.2 ± 3.4 [cl]	-8.8 ± 3.0	-30.8 ± 5.1 [Bi, V]
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	10.0 ± 4.3 [bi]	6.6 ± 3.5	86.4 ± 30.7 [Bi]	41.3 ± 23.6	-58.9 ± 4.5 [Bi, V]
	End-dose	12.1 ± 4.9 [bi]	8.4 ± 3.7 [bi]	92.4 ± 35.7 [Bi, v]	41.1 ± 27.0	-59.5 ± 5.4 [Bi, r, V]
	End recovery	11.5 ± 3.2 [bi, v]	6.7 ± 2.3	115.9 ± 34.6 [Bi, v]	73.0 ± 27.3	-45.4 ± 3.5 [Bi, V, d]
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	8.6 ± 3.1 [bi]	8.1 ± 3.8	41.7 ± 28.6	12.9 ± 23.9	-58.4 ± 2.8 [Bi, R, V]
	End-dose	8.1 ± 2.3	7.7 ± 3.1	53.7 ± 41.2 [Bi]	17.4 ± 30.4	-52.0 ± 6.2 [Bi, R]
	End recovery	4.6 ± 5.3	3.7 ± 5.0	48.8 ± 43.2	37.2 ± 37.6	-19.2 ± 6.3 [bi, V]

Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [V]$P < 0.001$ vs. vehicle; [v]$P < 0.05$ vs. vehicle; [cl]$P < 0.05$ vs. clenbuterol.

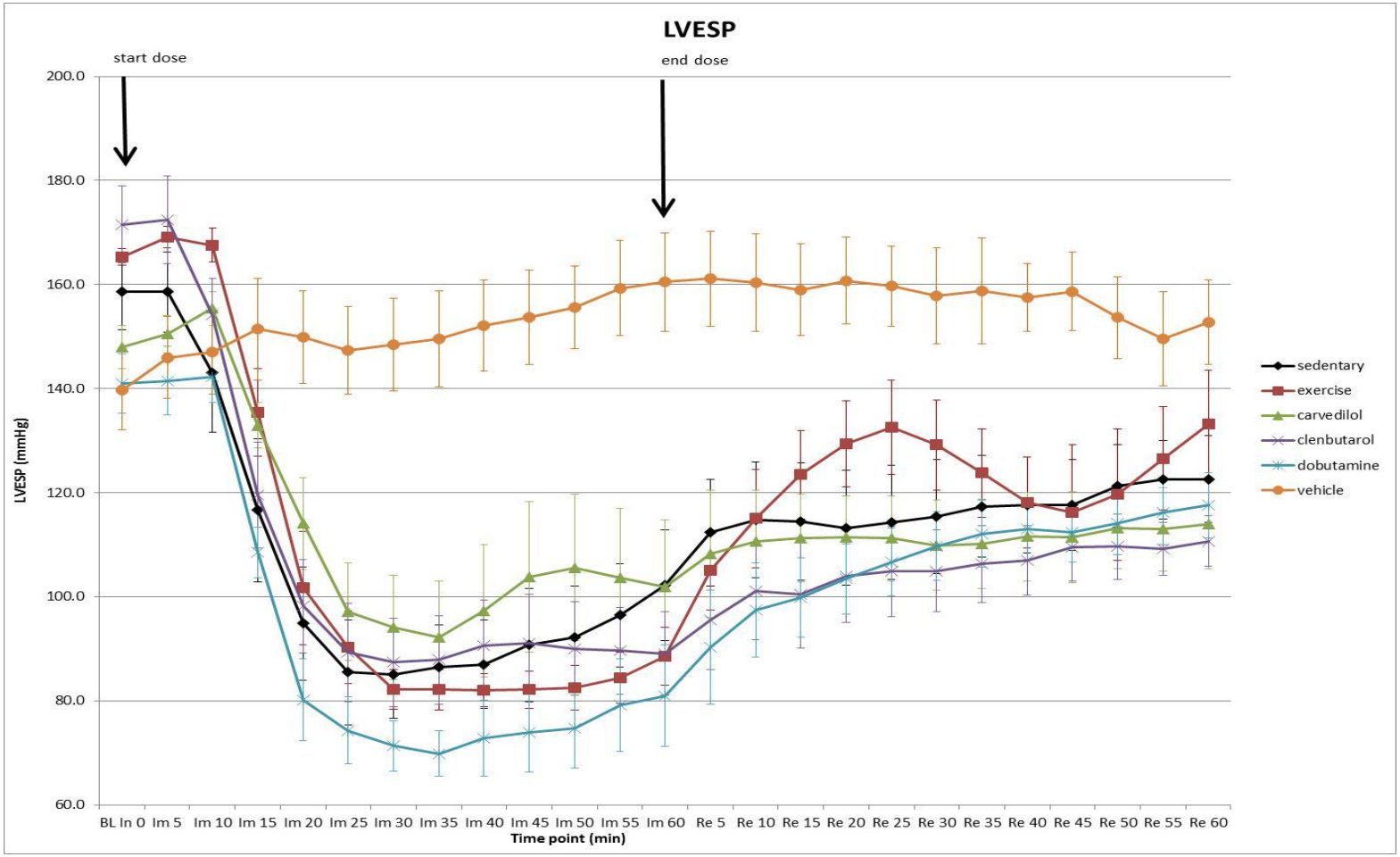

Figure 25. Effect of imipramine or vehicle infusion on LVESP in all interventions. Values are means ± SE. LVESP, left ventricular end systolic pressure.

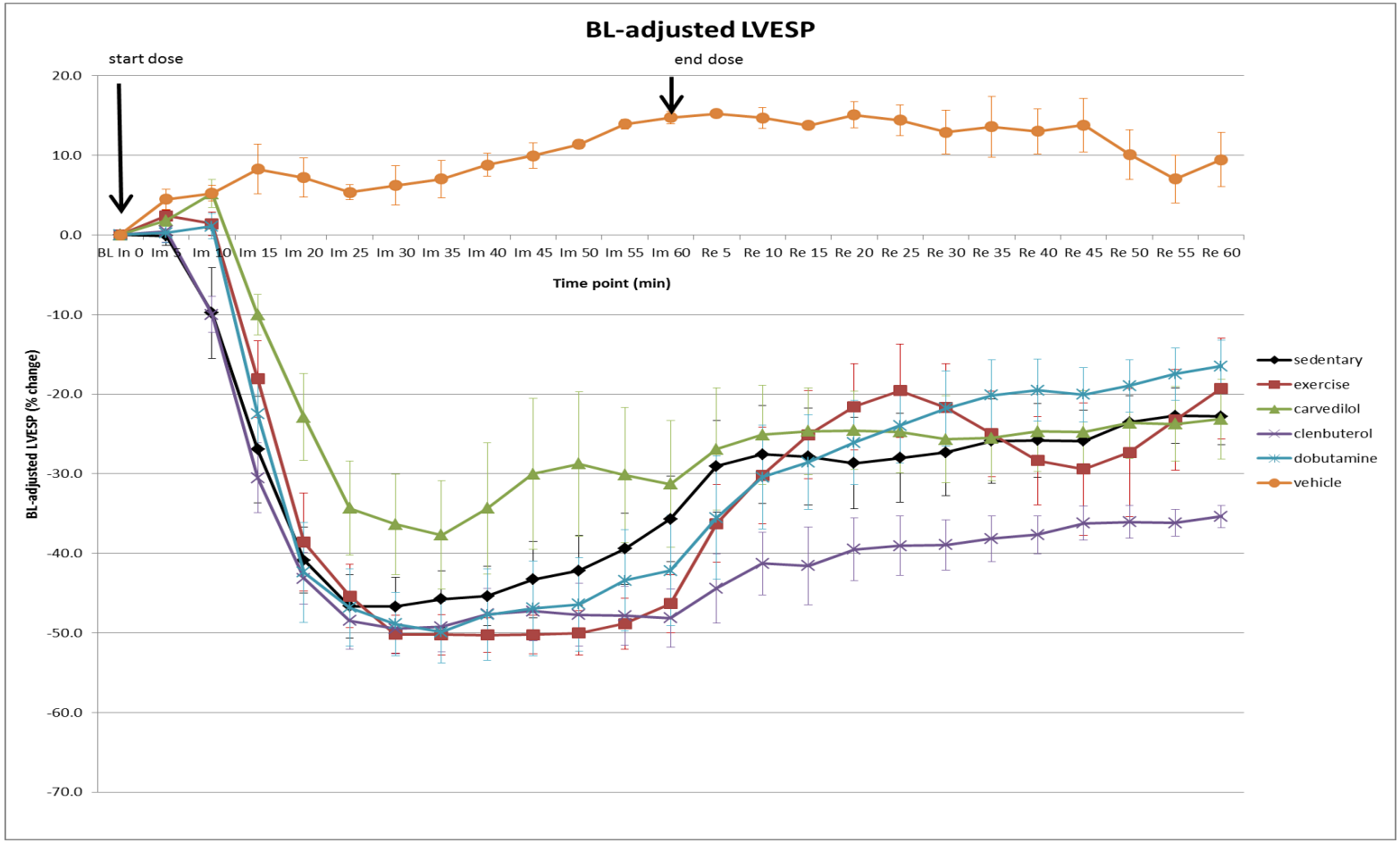

Figure 26. Effect of imipramine or vehicle infusion on BL-adjusted LVESP in all interventions. Values are means ± SE. BL-adjusted LVESP, % change from its baseline-instrumentation value of left ventricular end systolic pressure.

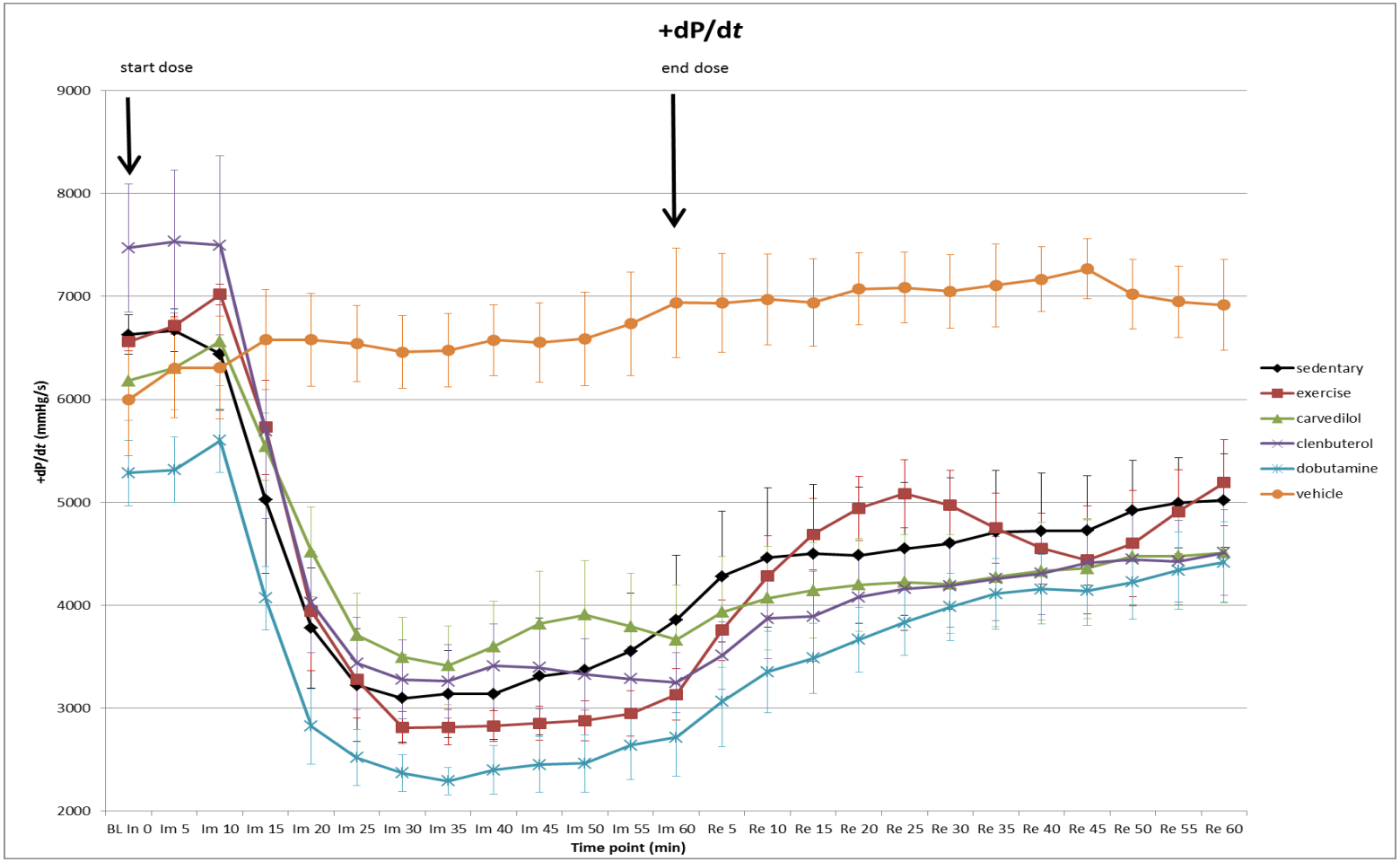

Figure 27. Effect of imipramine or vehicle infusion on +dP/d*t* in all interventions. Values are means ± SE. +dP/d*t*, maximum rate of increase in pressure during contraction.

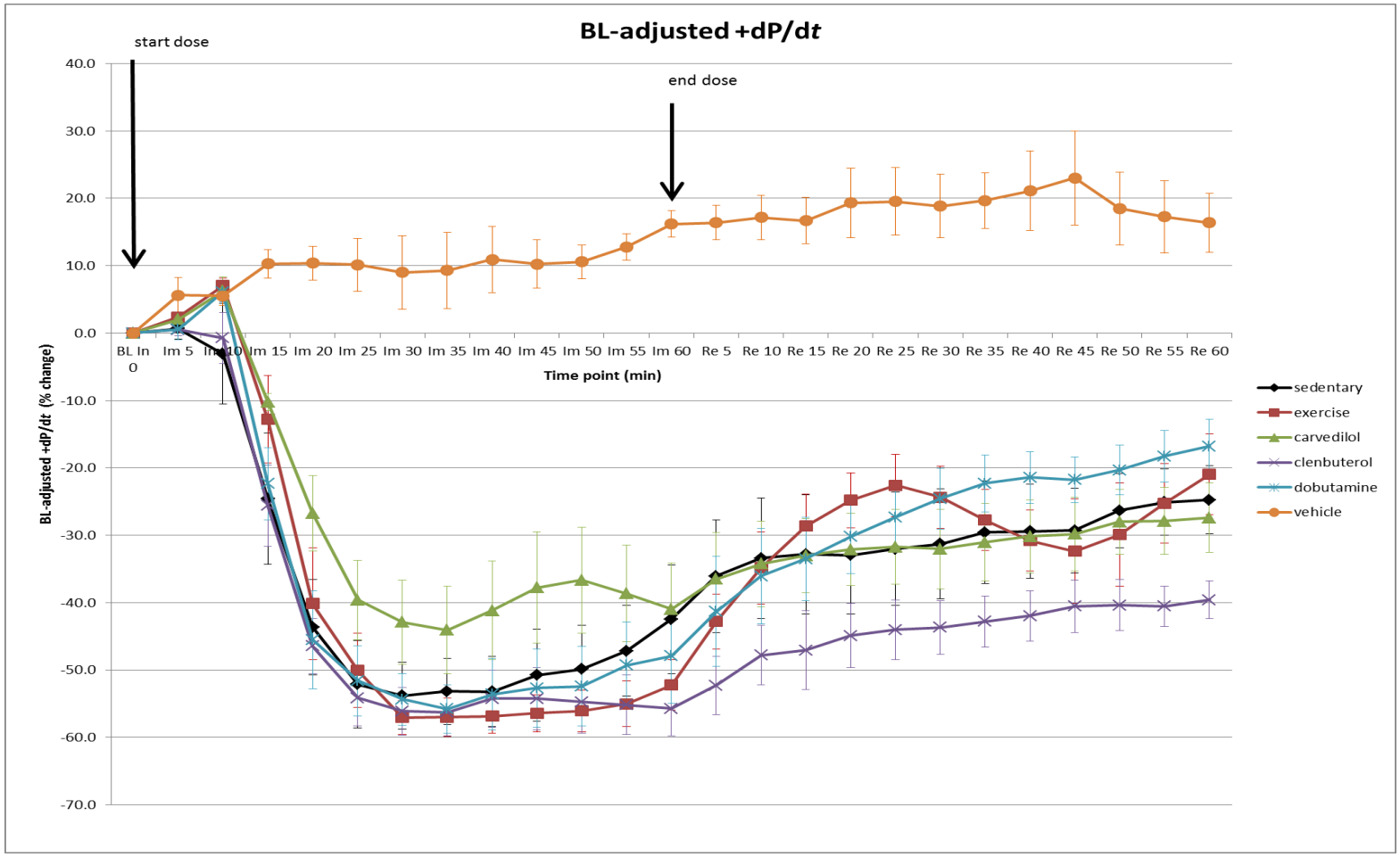

Figure 28. Effect of imipramine or vehicle infusion on BL-adjusted +dP/d*t* in all interventions. Values are means ± SE. BL-adjusted +dP/d*t*, % change from its baseline-instrumentation value of maximum rate of increase in pressure during contraction.

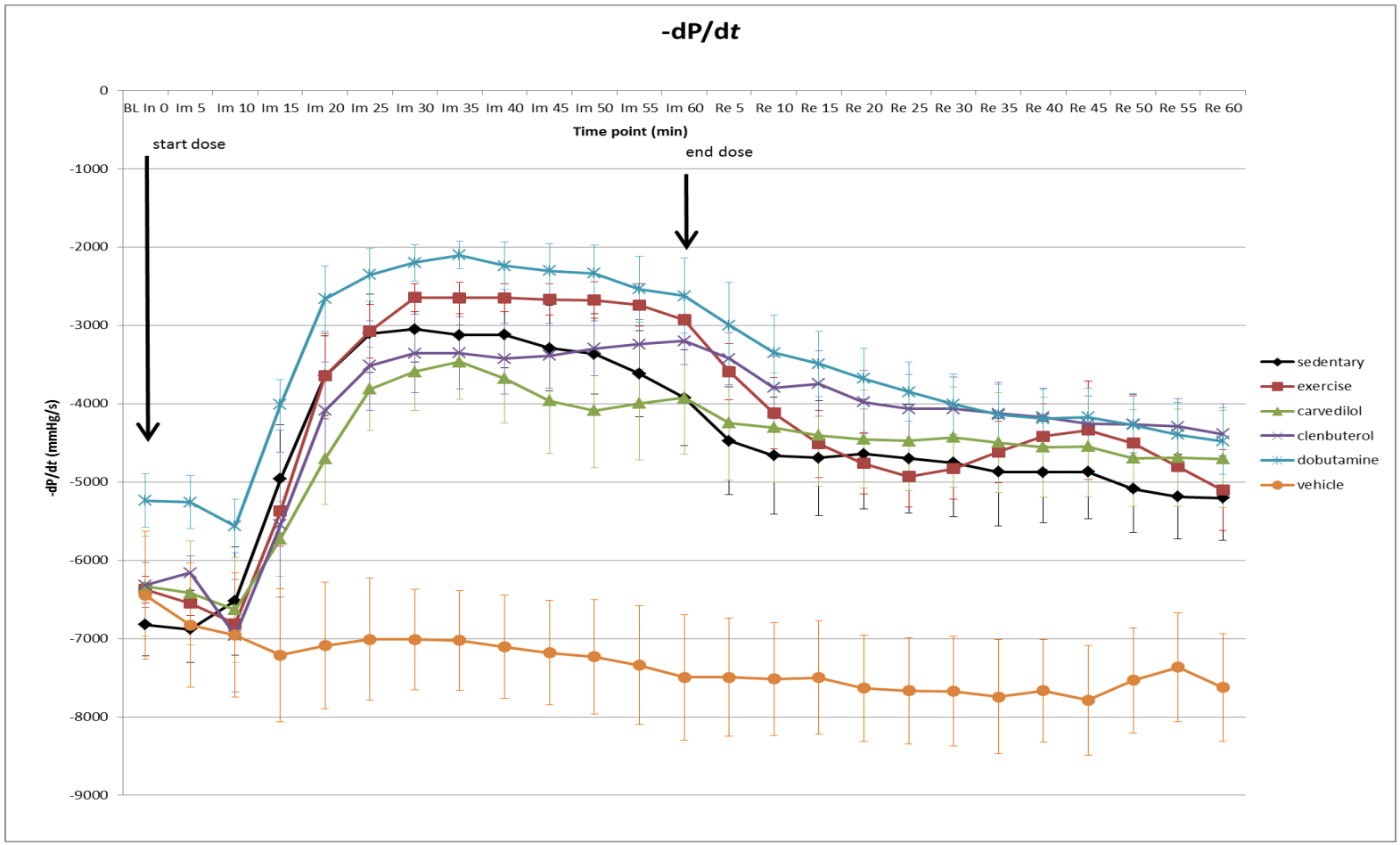

Figure 29. Effect of imipramine or vehicle infusion on -dP/d*t* in all interventions. Values are means ± SE. -dP/d*t*, maximum rate of decrease in pressure during relaxation.

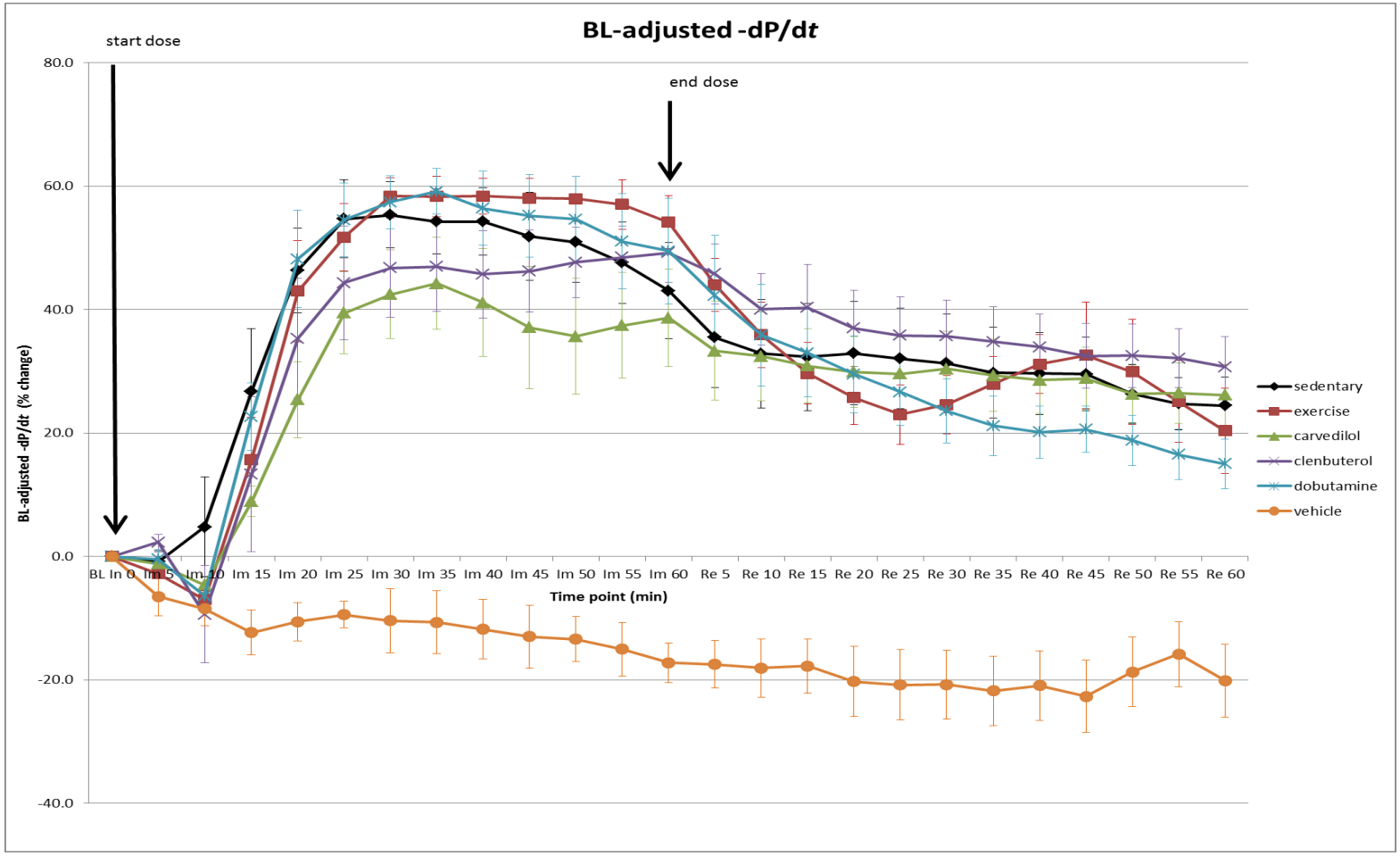

Figure 30. Effect of imipramine or vehicle infusion on BL-adjusted -dP/d*t* in all interventions. Values are means ± SE. BL-adjusted -dP/d*t*, % change from its baseline-instrumentation value of maximum rate of decrease in pressure during relaxation.

5.1.3 Maximum effects of imipramine on hemodynamics in all interventions

Table 25 shows alterations in aortic pressures produced by imipramine in rats receiving each intervention. The table contains (1) baseline-instrumentation values, (2) the values at the maximal effect of imipramine infusion or the greatest deviation of values from baseline (i.e. Max effect), (3) the values of the differences between the baseline-instrumentation values and the Max effect (i.e. Δ value), and (4) % change that Max effect was from the baseline-instrumentation values (i.e. Δ %). Although, the carvedilol group seemed to maintain blood pressure more steady than for other interventions, there was no obvious (statistical) difference among interventions in any parameter from the abdominal aorta hemodynamics.

Table 26 presents maximal effects of imipramine, on LV pressure and volume, on rats exposed to each intervention. The carvedilol group trended to have lesser effects of imipramine on LV pressure and volume; however, only the lesser LVESP (mmHg) reduction, compared with the clenbuterol group, achieved statistical significance (-58.4 ± 10.3 vs. -91.4 ± 4.7, $P < 0.05$). Also, the exercise group had significantly higher reduction in CI due to imipramine than that of dobutamine group (-15.4 ± 1.7 vs. -7.9 ± 1.8, $P < 0.05$). Interestingly, the clenbuterol intervention showed significantly different alterations of SV and CO in responses to imipramine (i.e. SV and CO were increased) compared with the carvedilol and the exercise groups ($P < 0.05$), both of which imipramine reduced SV and CO.

Times at imipramine induced maximal effects on each hemodynamic variable in all interventions are in table 27. Only maximal time of DBP reduction in the clenbuterol group was significantly lower than those of other interventions ($P < 0.05$).

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
Sedentary	Baseline	165.6 ± 8.5	123.8 ± 7.5	41.8 ± 4.7	140.4 ± 7.7	412.5 ± 21.2
	Max effect	77.8 ± 12.5	49.7 ± 10.1	25.4 ± 3.7	61.1 ± 11.5	313.5 ± 20.8
	Δ value	-87.7 ± 7.4	-74.0 ± 5.4	-16.4 ± 2.6	-79.3 ± 6.0	-99.0 ± 14.8
	Δ %	-53.8 ± 5.2	-61.1 ± 5.9	-39.6 ± 4.4	-57.6 ± 5.7	-24.0 ± 3.2
Exercise	Baseline	172.8 ± 2.5	121.4 ± 2.3	51.4 ± 2.9	143.4 ± 1.5	388.9 ± 12.9
	Max effect	76.7 ± 4.7	48.1 ± 4.3	26.4 ± 2.2	59.8 ± 4.3	281.0 ± 9.4
	Δ value	-96.1 ± 6.7	-73.3 ± 4.5	-25.0 ± 4.1	-83.6 ± 4.8	-107.9 ± 5.2
	Δ %	-55.4 ± 3.2	-60.3 ± 3.6	-47.6 ± 5.9	-58.2 ± 3.2	-27.7 ± 0.9
Carvedilol	Baseline	160.4 ± 4.3	119.7 ± 1.8	40.8 ± 4.4	135.9 ± 2.4	380.1 ± 11.0
	Max effect	95.2 ± 14.0	62.4 ± 8.5	30.8 ± 5.7	75.2 ± 10.2	295.1 ± 31.0
	Δ value	-65.2 ± 12.5	-57.2 ± 9.7	-9.9 ± 3.0[a]	-60.8 ± 10.5	-85.0 ± 27.7
	Δ %	-41.0 ± 7.8	-47.5 ± 7.6	-26.2 ± 7.5	-44.6 ± 7.5	-22.6 ± 7.8
Clenbuterol	Baseline	179.1 ± 8.3	129.4 ± 5.8	49.7 ± 4.9	149.8 ± 6.3	412.2 ± 9.9
	Max effect	79.2 ± 7.9	48.6 ± 5.2	26.7 ± 4.0	61.9 ± 5.8	288.3 ± 7.9
	Δ value	-99.9 ± 6.6	-80.8 ± 4.2	-23.0 ± 5.5	-87.9 ± 4.2	-123.9 ± 15.2
	Δ %	-56.0 ± 3.3	-62.8 ± 3.0	-44.3 ± 8.2	-59.0 ± 2.7	-29.8 ± 3.0
Dobutamine	Baseline	149.4 ± 6.2	116.8 ± 4.9	32.6 ± 2.6	129.3 ± 5.5	415.4 ± 14.4
	Max effect	64.3 ± 4.6	43.6 ± 4.8	19.0 ± 1.6	52.0 ± 4.7	309.5 ± 15.3
	Δ value	-85.0 ± 8.2	-73.2 ± 7.0	-13.6 ± 2.0	-77.3 ± 7.5	-105.9 ± 11.2
	Δ %	-56.5 ± 3.6	-62.3 ± 4.4	-41.0 ± 4.0	-59.4 ± 4.0	-25.5 ± 2.6

Table 25. Maximal hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE. n = 6. [a]*P* 0.053 vs. exercise.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
Sedentary	Baseline	7.0 ± 1.8	158.7 ± 7.3	6,627 ± 191	-6,821 ± 399	89.5 ± 3.4	7.7 ± 0.9
	Max effect	7.9 ± 1.6	82.6 ± 8.4	3,045 ± 426	-2,957 ± 413	78.9 ± 3.5	8.7 ± 1.0
	Δ value	0.9 ± 0.6	-76.1 ± 4.8	-3,582 ± 283	3,863 ± 451	-10.6 ± 1.3	1.0 ± 0.3
	Δ %	36.2 ± 27.7	-48.3 ± 3.3	-54.6 ± 5.0	56.7 ± 5.2	-11.9 ± 1.4	13.1 ± 3.5
Exercise	Baseline	5.5 ± 1.5	165.2 ± 1.6	6,560 ± 86	-6,372 ± 171	95.6 ± 1.0	7.8 ± 0.3
	Max effect	7.3 ± 1.4	79.2 ± 3.6	2,723 ± 159	-2,535 ± 195	80.4 ± 1.4	8.5 ± 0.3
	Δ value	1.7 ± 1.0	-86.0 ± 4.1	-3,836 ± 186	3,837 ± 233	-15.4 ± 1.7[d]	0.7 ± 0.4
	Δ %	63.8 ± 29.7	-50.1 ± 3.6	-58.4 ± 2.6	60.2 ± 3.1	-15.9 ± 1.9	9.0 ± 5.3
Carvedilol	Baseline	4.7 ± 0.8	147.9 ± 4.1	6,180 ± 385	-6,334 ± 637	89.0 ± 2.6	8.3 ± 0.8
	Max effect	6.0 ± 1.4	89.5 ± 11.1	3,316 ± 400	-3,326 ± 516	77.0 ± 2.5	8.9 ± 0.7
	Δ value	1.4 ± 0.7	-58.4 ± 10.3[cl]	-2,863 ± 489	3,008 ± 626	-12.1 ± 2.2	0.6 ± 0.4
	Δ %	25.8 ± 10.4	-39.8 ± 7.0	-45.8 ± 6.5	46.6 ± 7.7	-13.4 ± 2.2	8.2 ± 5.2
Clenbuterol	Baseline	2.8 ± 0.5	171.5 ± 7.4	7,471 ± 622 [d]	-6,316 ± 287	96.0 ± 3.5	9.3 ± 0.8
	Max effect	3.8 ± 0.7	80.1 ± 5.9	2, 989 ± 254	-2,911 ± 279	81.6 ± 4.0	9.0 ± 0.6
	Δ value	0.9 ± 0.9	-91.4 ± 4.7	-4,482 ± 529	3,405 ± 307	-14.4 ± 0.9	-0.3 ± 0.6
	Δ %	67.1 ± 52.3	-53.5 ± 2.2	-59.5 ± 3.0	53.9 ± 4.2	-16.4 ± 1.0[a]	-2.0 ± 6.3
Dobutamine	Baseline	5.5 ± 1.6	141.0 ± 5.7	5,286 ± 317	-5,237 ± 344	83.2 ± 2.4	7.8 ± 0.4
	Max effect	5.2 ± 1.2	67.6 ± 3.3	2,203 ± 99	-1,994 ± 134	75.3 ± 1.7	9.3 ± 0.4
	Δ value	-0.3 ± 1.5	-73.4 ± 7.6	-3,082 ± 354	3,244 ± 373	-7.9 ± 1.8	1.4 ± 0.3
	Δ %	52.2 ± 48.4	-51.5 ± 3.4	-57.5 ± 3.2	61.1 ± 3.2	-9.4 ± 2.0	18.9 ± 5.1

Continued

Table 26. Maximal hemodynamic effects of imipramine infusion in all interventions measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE. n = 6. [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine; [a] P 0.061 vs. dobutamine.

Table 26. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Sedentary	Baseline	20.4 ± 1.2	18.9 ± 1.3	1.5 ± 0.3	605 ± 111	332.4 ± 27.0
	Max effect	21.0 ± 1.7	19.5 ± 1.8	1.6 ± 0.6	433 ± 125	162.5 ± 31.4
	Δ value	0.6 ± 0.7	0.6 ± 0.8	0.5 ± 0.6	-172 ± 81 [cl]	-169.9 ± 15.1
	Δ %	2.5 ± 3.1	2.3 ± 4.0	10.8 ± 21.4	-26.9 ± 13.8	-53.9 ± 5.4
Exercise	Baseline	19.9 ± 0.4	18.3 ± 0.6	1.6 ± 0.3	613 ± 118	330.8 ± 10.0
	Max effect	21.7 ± 1.1	19.9 ± 1.1	1.3 ± 0.3	397 ± 81	129.7 ± 11.7
	Δ value	1.8 ± 0.8	1.6 ± 0.6	-0.3 ± 0.2 [cl]	-216 ± 57 [cl]	-201.0 ± 9.5
	Δ %	9.0 ± 4.0	8.5 ± 3.4	0.1 ± 18.2	-35.2 ± 7.2	-60.9 ± 3.1
Carvedilol	Baseline	20.0 ± 1.0	17.9 ± 1.1	2.1 ± 0.5	805 ± 215	310.5 ± 17.9
	Max effect	22.0 ± 1.3	19.5 ± 1.3	1.5 ± 0.3	509 ± 113	164.3 ± 19.9
	Δ value	2.0 ± 0.4	1.6 ± 0.5	-0.6 ± 0.3 [cl]	-296 ± 111 [cl]	-146.2 ± 21.6
	Δ %	9.5 ± 1.7	8.7 ± 2.6	-20.8 ± 6.6 [cl]	-29.4 ± 5.7	-46.7 ± 6.3
Clenbuterol	Baseline	22.1 ± 1.5	21.0 ± 1.4	1.0 ± 0.2 [v]	407 ± 91 [v]	353.5 ± 50.5
	Max effect	25.0 ± 1.9	23.1 ± 1.6	2.2 ± 0.6	640 ± 174	128.9 ± 19.6
	Δ value	3.0 ± 1.0	2.0 ± 0.7	1.2 ± 0.5	233 ± 127	-224.7 ± 37.7
	Δ %	13.4 ± 4.3	9.7 ± 3.2	118.1 ± 43.5	59.2 ± 33.7	-62.9 ± 3.8
Dobutamine	Baseline	19.8 ± 1.6	18.5 ± 1.4	1.3 ± 0.3 [v]	509 ± 122 [v]	278.3 ± 32.5
	Max effect	22.1 ± 2.0	20.7 ± 1.8	1.4 ± 0.3	394 ± 71	106.4 ± 14.0
	Δ value	2.3 ± 0.7	2.2 ± 0.7	0.1 ± 0.2	-115 ± 82	-171.8 ± 21.1
	Δ %	11.1 ± 3.2	11.5 ± 3.6	49.4 ± 42.9	9.6 ± 33.1	-61.5 ± 2.3

Values are means ± SE. n = 6. [cl]$P < 0.05$ vs. clenbuterol.

Group	Sedentary (min)	Exercise (min)	Carvedilol (min)	Clenbuterol (min)	Dobutamine (min)
SBP	25.0 ± 1.8	34.2 ± 3.5	37.5 ± 5.3	38.3 ± 6.3	32.5 ± 2.8
DBP	25.8 ± 2.4[cl]	28.3 ± 2.8[cl]	31.7 ± 3.1[cl]	47.5 ± 5.3	29.2 ± 2.4[cl]
PP	42.5 ± 5.0	47.5 ± 4.6	41.7 ± 6.4	30.8 ± 4.9	42.5 ± 3.1
MBP	25.8 ± 2.4	34.2 ± 3.5	37.5 ± 5.3	44.2 ± 6.5	34.2 ± 5.8
HR	45.8 ± 3.7	47.5 ± 4.4	49.2 ± 5.5	49.2 ± 6.9	49.2 ± 4.9
LVEDP	46.7 ± 4.8	37.5 ± 10.1	43.3 ± 9.8	39.2 ± 9.7	45.0 ± 6.3
LVESP	30.0 ± 3.7	39.2 ± 3.7	40.0 ± 4.7	37.5 ± 6.7	35.8 ± 3.0
+dP/d*t*	30.0 ± 3.2	38.3 ± 4.0	43.3 ± 5.7	39.2 ± 6.0	43.3 ± 5.3
-dP/d*t*	29.2 ± 3.5	40.8 ± 4.2	40.0 ± 4.7	38.3 ± 6.3	40.0 ± 4.8
CI	45.8 ± 6.2	33.3 ± 6.8	57.5 ± 2.5	45.0 ± 5.3	42.5 ± 7.3
tau	35.0 ± 9.0	28.3 ± 4.9	42.0 ± 6.4	18.3 ± 4.4	33.3 ± 4.0
LVEDV	51.7 ± 3.3	48.3 ± 5.6	52.5 ± 4.2	51.7 ± 4.9	52.5 ± 4.8
LVESV	50.0 ± 4.3	53.3 ± 3.1	49.2 ± 3.5	50.8 ± 4.9	47.5 ± 5.7
SV	45.0 ± 6.7	39.2 ± 7.4	35.8 ± 6.9	37.5 ± 7.4	39.2 ± 8.0
CO	42.5 ± 3.4	43.3 ± 7.5	38.3 ± 8.4	48.3 ± 6.4	49.2 ± 3.7
(+dP/d*t*)/LVEDV	35.8 ± 4.9	39.2 ± 3.7	50.8 ± 5.8	43.3 ± 4.9	45.8 ± 5.1

Table 27. Times at imipramine maximal effect on hemodynamics in all interventions. Values are means ± SE; n = 6. [cl]$P < 0.05$ vs. clenbuterol.

5.2 Effect of imipramine on ECG from lead I in all interventions

5.2.1 Effects of imipramine on ECG from lead I in all interventions

As shown in table 28, there was no significant difference among baseline-instrumentation values in any intervention. Imipramine infusion significantly reduced R_a and increase depth of S_a in lead I at both mid-dose and end-dose periods (see figure 31 and 33). There was no difference in change in depth of S_a of the clenbuterol group. None of the amplitude alterations due to imipramine infusion showed significant (not even a trend) spontaneous recovery. However, there was some recovery after cessation of imipramine infusion compared with end recovery period. This is not considered spontaneous since it did not occur during infusion. For instance, there were statistically significant increases in R_a in sedentary, carvedilol, and dobutamine groups ($P < 0.05$), and reduced depth of S_a in sedentary, exercise, and carvedilol groups ($P < 0.05$) compared with end-dose period. R_a reduction was partially reversed at end recovery period in the carvedilol and the dobutamine groups ($P < 0.05$), while the R_a recovery in the other interventions did not show significant difference when compared with their baseline-instrument values. Augmentations of the depth of S_a during imipramine infusion suddently and statistically recovered in all imipramine challanged groups.

T_a was significantly taller during imipramine infusion only in the exercise and the dobutamine groups at end-dose period compared with baseline-instrumentation values ($P < 0.05$), without spontaneous recovery (see figure 35). Nevertheless, this taller T_a instantly and markedly recovered without significant difference between the end recovery

period and the baseline-instrumentation period. P_a and Q_a did not alter significantly at any time points in any imipramine challanged groups.

Comparing magnitude of imipramine effects among interventions, there were statistical differences in augmentations of the depth of S_a waves among sedentary, exercise, and clenbuterol groups at mid-dose period. S_a of the clenbuterol group was significantly less negative compared with the sedentary and the exercise group ($P < 0.05$). Likewise, there were several significant differences between imipramine and vehicle infusion. For instance, R_a of the carvedilol at end-dose period was significantly smaller than in the vehicle group (0.008 ± 0.064 vs. 0.199 ± 0.046, $P < 0.05$). The vehicle group also had significantly less negative S_a compared with the sedentary (mid-dose value), and the exercise (mid- and end-dose values), $P < 0.05$.

Table 29 shows % changes in values of variables from their baseline-instrumentation values induced by imipramine infusion and their recovery. The same significant reductions in R_a occurred in all interventions. Increases in depth of S_a occurred in exercise, clenbuterol, and dobutamine interventions. Alterations in % changes of R_a and S_a are depicted in figure 32 and 34.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Sedentary	Baseline	0.254 ± 0.066	0.0063 ± 0.0036	0.0390 ± 0.0041	-0.0028 ± 0.0027	-0.128 ± 0.035
	Mid-dose	0.070 ± 0.018^{Bi}	0.0101 ± 0.0122	0.0374 ± 0.0058	0.0001 ± 0.0041	-0.343 ± 0.094$^{bi, r, v, cl}$
	End-dose	0.063 ± 0.014$^{Bi, r}$	0.0112 ± 0.0115	0.0352 ± 0.0073	-0.0030 ± 0.0065	-0.338 ± 0.093$^{bi, r}$
	End recovery	0.181 ± 0.054	0.0055 ± 0.0065	0.0370 ± 0.0071	-0.0092 ± 0.0080	-0.180 ± 0.057
Exercise	Baseline	0.179 ± 0.023	0.0135 ± 0.0074	0.0385 ± 0.0090	-0.0095 ± 0.0048	-0.146 ± 0.047
	Mid-dose	0.058 ± 0.040^{bi}	0.0305 ± 0.0114^{r}	0.0525 ± 0.0080	-0.0316 ± 0.0149	-0.377 ± 0.051$^{Bi, r, v, cl}$
	End-dose	0.051 ± 0.038^{bi}	0.0357 ± 0.0103$^{bi, R}$	0.0530 ± 0.0067	-0.0232 ± 0.0152	-0.397 ± 0.078$^{Bi, r, v}$
	End recovery	0.142 ± 0.044	0.0035 ± 0.0043	0.0378 ± 0.0082	-0.0140 ± 0.0135	-0.203 ± 0.059
Carvedilol	Baseline	0.250 ± 0.040	-0.0022 ± 0.0036	0.0282 ± 0.0071	-0.0240 ± 0.0146	-0.082 ± 0.008
	Mid-dose	0.053 ± 0.026^{Bi}	-0.0015 ± 0.0072	0.0301 ± 0.0068	-0.0556 ± 0.0311	-0.251 ± 0.085$^{bi, r}$
	End-dose	0.008 ± 0.064$^{Bi, r, v}$	0.0117 ± 0.0116	0.0325 ± 0.0095	-0.0710 ± 0.0477	-0.268 ± 0.079$^{bi, r}$
	End recovery	0.127 ± 0.032^{bi}	-0.0057 ± 0.0038	0.0225 ± 0.0139	-0.0458 ± 0.0249	-0.060 ± 0.015
Clenbuterol	Baseline	0.295 ± 0.043	0.0133 ± 0.0050	0.0513 ± 0.0034	-0.0090 ± 0.0049	-0.063 ± 0.022
	Mid-dose	0.152 ± 0.018^{bi}	0.0133 ± 0.0028	0.0514 ± 0.0094	-0.0017 ± 0.0033	-0.102 ± 0.027
	End-dose	0.112 ± 0.018^{Bi}	0.0153 ± 0.0062	0.0447 ± 0.0061	-0.0072 ± 0.0108	-0.186 ± 0.063
	End recovery	0.226 ± 0.021	0.0072 ± 0.0036	0.0395 ± 0.0076	-0.0087 ± 0.0053	-0.057 ± 0.013
Dobutamine	Baseline	0.302 ± 0.070	0.0027 ± 0.0047	0.0353 ± 0.0047	-0.0203 ± 0.0137	-0.073 ± 0.019
	Mid-dose	0.079 ± 0.011^{Bi}	0.0034 ± 0.0064^{ed}	0.0413 ± 0.0067	-0.0234 ± 0.0186	-0.253 ± 0.062$^{bi, r}$
	End-dose	0.052 ± 0.012$^{Bi, r}$	0.0240 ± 0.0164$^{bi, r}$	0.0395 ± 0.0068	-0.0057 ± 0.0034	-0.339 ± 0.084$^{Bi, R}$
	End recovery	0.169 ± 0.056^{bi}	-0.0037 ± 0.0053	0.0348 ± 0.0103	-0.0350 ± 0.0155	-0.101 ± 0.025

Table 28. Effects of imipramine infusion on ECG from lead I in all interventions. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{ed}P < 0.05$ vs. its end-dose; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle; $^{cl}P < 0.05$ vs. clenbuterol.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-52.1 ± 20.7[bi]	-111.5 ± 97.3	-4.5 ± 8.1	-27.7 ± 364.4	-208.8 ± 86.2
	End-dose	-48.0 ± 26.9[bi]	-70.9 ± 126.2	-7.3 ± 16.6	-209.2 ± 540.5	-197.6 ± 73.7
	End recovery	-15.1 ± 18.8	-106.6 ± 99.9	-5.9 ± 12.7	-924.9 ± 706.4	-32.0 ± 15.2
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-75.4 ± 26.3[Bi, v]	249.9 ± 158.6	64.8 ± 25.8	-213.0 ± 74.0	-346.9 ± 153.9 [bi, r]
	End-dose	-73.2 ± 21.6[Bi, v]	436.3 ± 323.9 [bi, r]	88.0 ± 47.8	-129.8 ± 88.3	-346.4 ± 166.3 [bi, r]
	End recovery	-33.2 ± 26.7	-59.7 ± 15.3	9.6 ± 16.2	-15.3 ± 61.1	-56.9 ± 30.6
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-71.9 ± 15.8[Bi, v]	0.1 ± 66.7	14.5 ± 14.5	-63.0 ± 42.7	-254.2 ± 141.4 [r]
	End-dose	-93.1 ± 30.5[Bi, v]	324.6 ± 347.8	26.9 ± 42.2	-196.3 ± 120.6	-262.5 ± 110.9 [r]
	End recovery	-45.9 ± 13.5[bi]	-88.3 ± 94.9	12.5 ± 81.3	-67.6 ± 27.4	21.9 ± 21.0
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-45.4 ± 5.7 [bi]	38.7 ± 33.5	1.0 ± 18.7	56.9 ± 21.7	-96.0 ± 65.2
	End-dose	-59.2 ± 7.4 [bi, v]	30.7 ± 122.3	-12.6 ± 11.0	62.2 ± 73.7	-281.8 ± 168.5 [bi]
	End recovery	-19.0 ± 7.1	-47.2 ± 44.7	-24.2 ± 11.5	-1.4 ± 12.1	-12.3 ± 24.9
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-66.3 ± 6.8 [bi, v]	58.9 ± 66.6	29.7 ± 24.1	-20.4 ± 88.2	-313.9 ± 100.5 [Bi]
	End-dose	-69.0 ± 12.9 [Bi, v]	430.1 ± 217.4 [r]	16.9 ± 24.4	5.3 ± 56.6	-520.5 ± 190.2 [Bi, R, v]
	End recovery	-46.7 ± 9.8 [bi]	-110.9 ± 60.5	1.8 ± 35.5	-285.6 ± 248.6	-46.0 ± 21.5

Table 29. Effects of imipramine infusion on ECG from lead I in all interventions as percentage change from their baseline-instrumentation values. Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle.

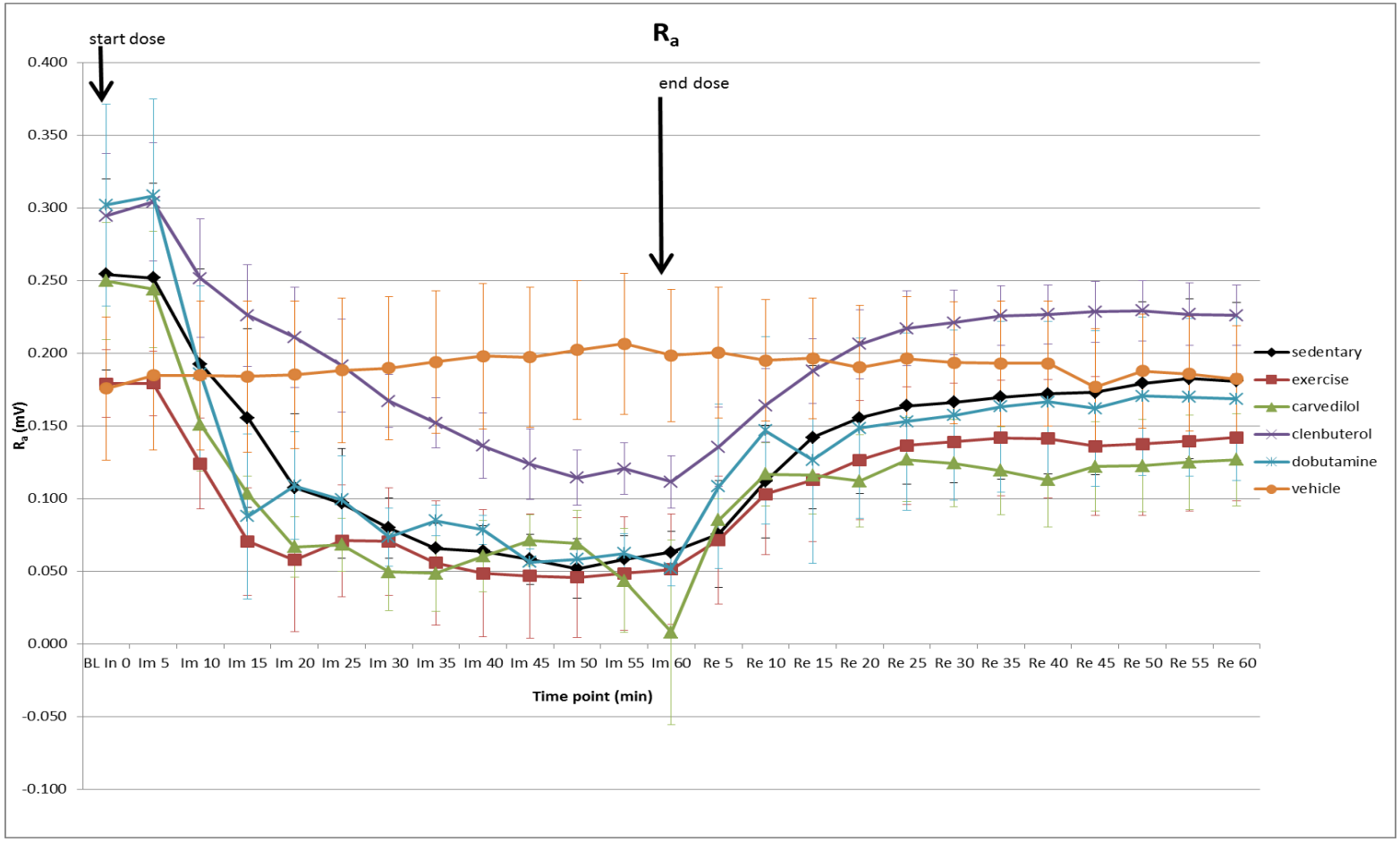

Figure 31. Effect of imipramine or vehicle infusion on R_a from lead I in all interventions. Values are means ± SE. R_a, R amplitude.

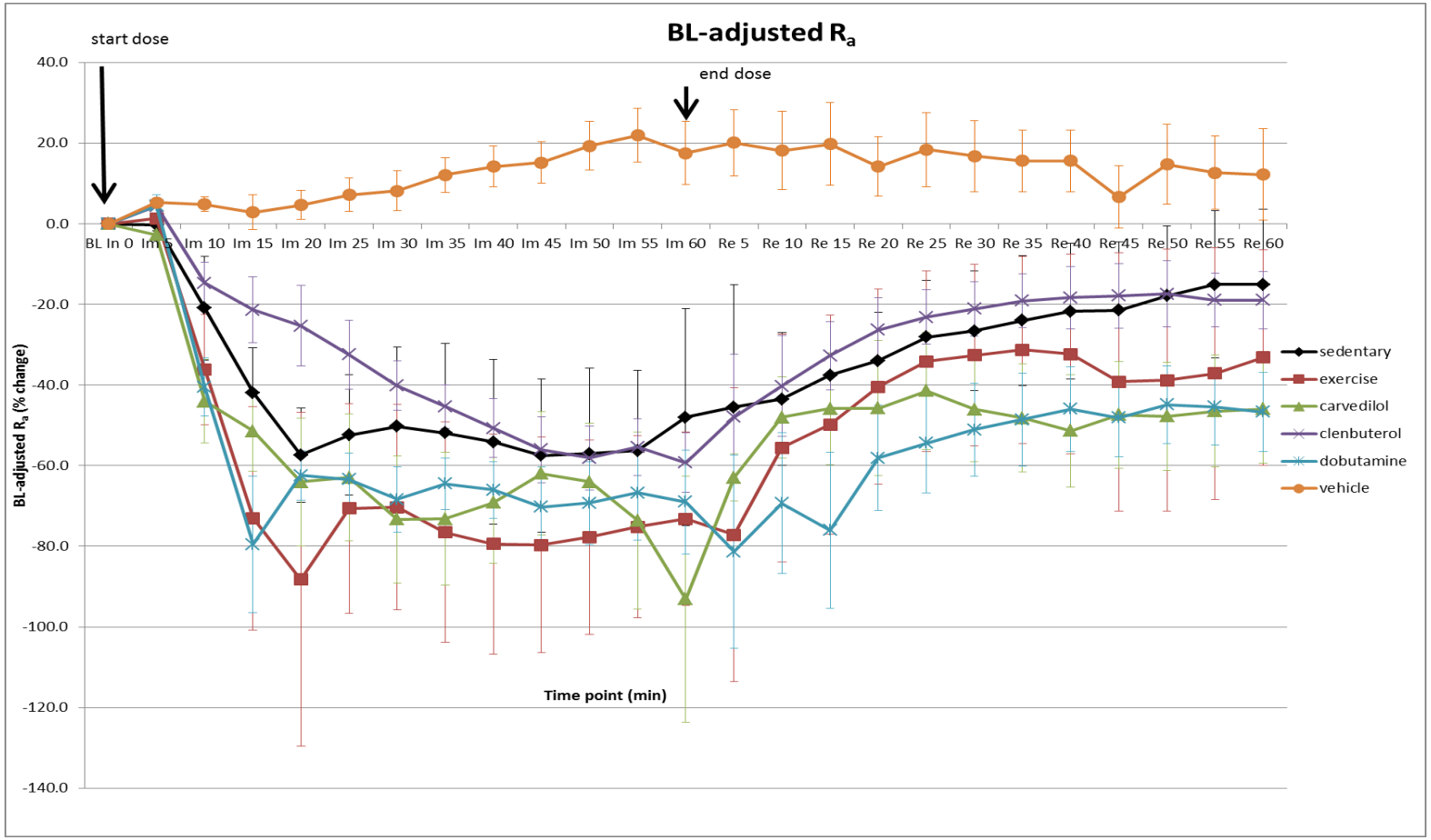

Figure 32. Effect of imipramine or vehicle infusion on BL-adjusted R_a from lead I in all interventions. Values are means ± SE. BL-adjusted R_a, % change from its baseline-instrumentation value of R amplitude.

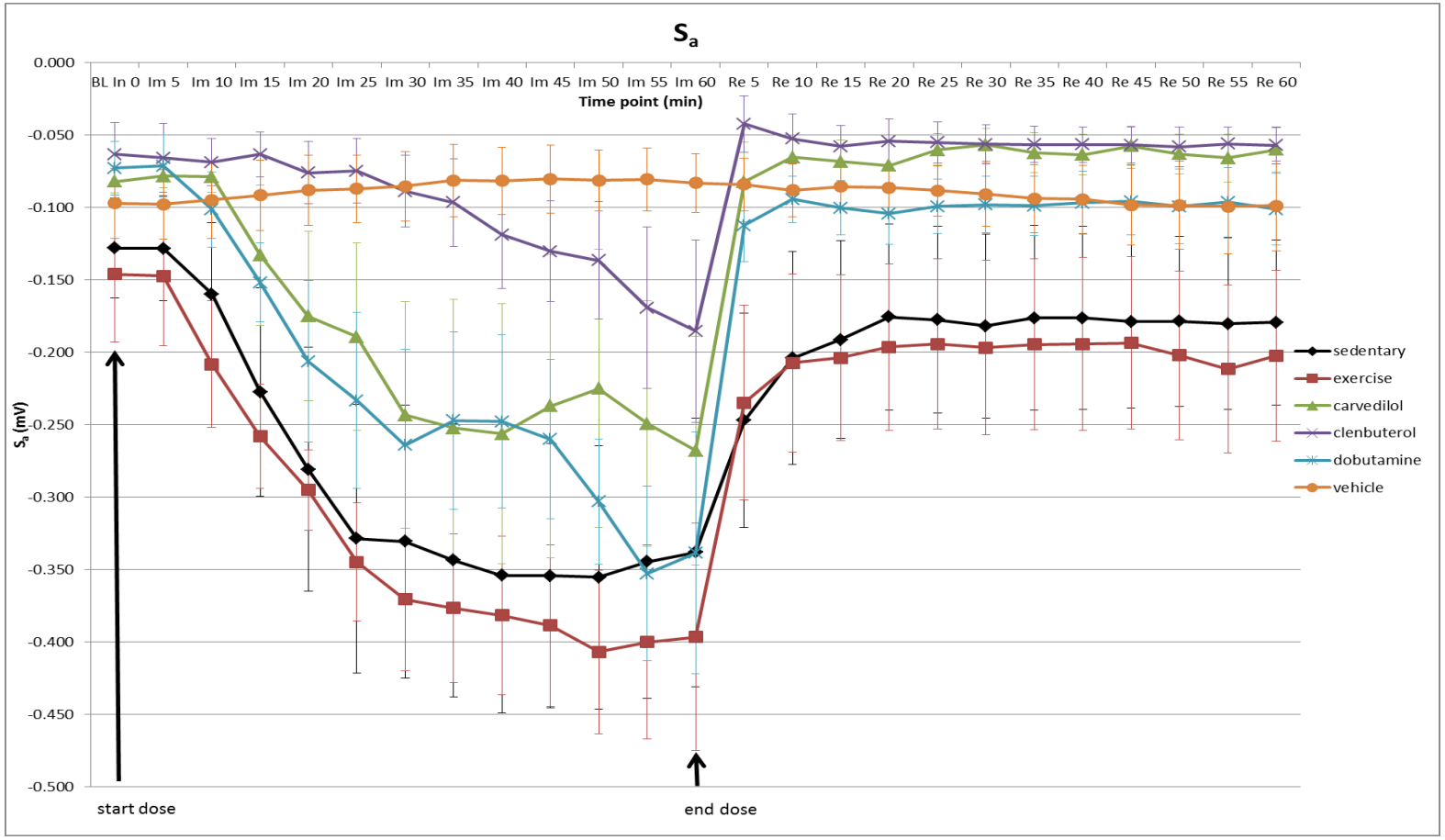

Figure 33. Effect of imipramine or vehicle infusion on S_a from lead I surface ECG in all interventions. Values are means ± SE. S_a, S amplitude.

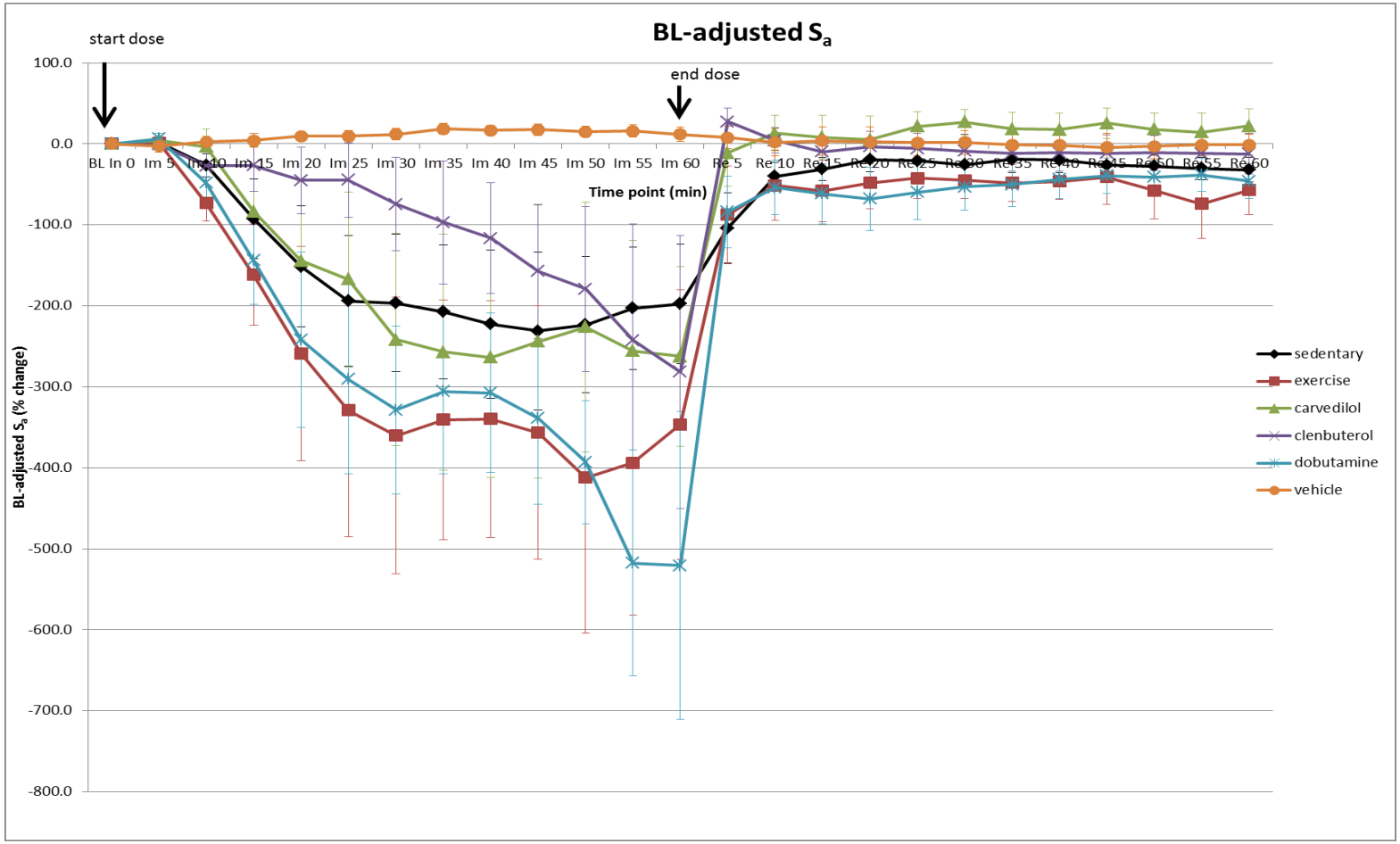

Figure 34. Effect of imipramine or vehicle infusion on BL-adjusted S_a from lead I in all interventions. Values are means ± SE. BL-adjusted S_a, % change from its baseline-instrumentation value of S amplitude.

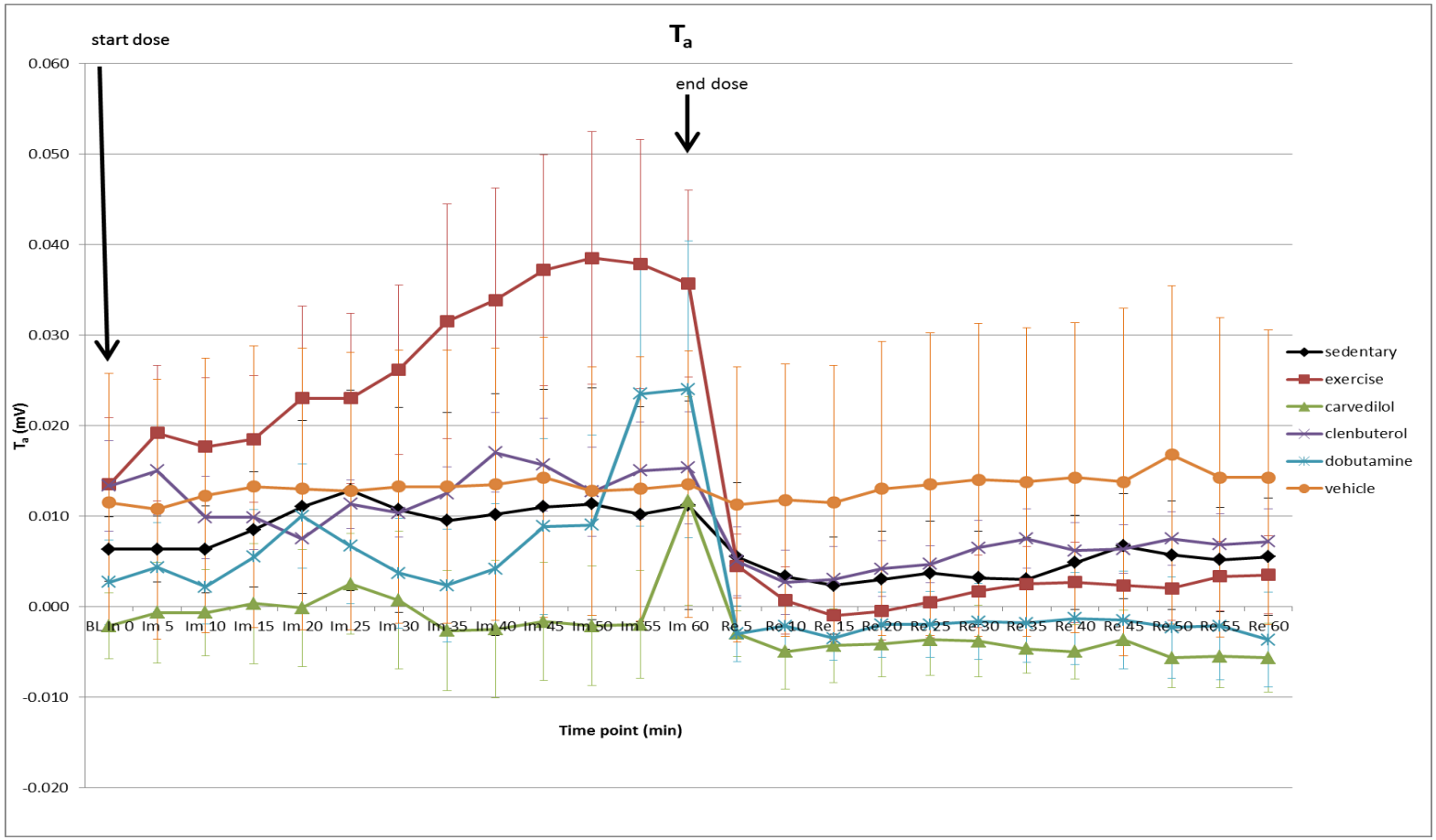

Figure 35. Effect of imipramine or vehicle infusion on T_a from lead I in all interventions. Values are means ± SE. T_a, T amplitude.

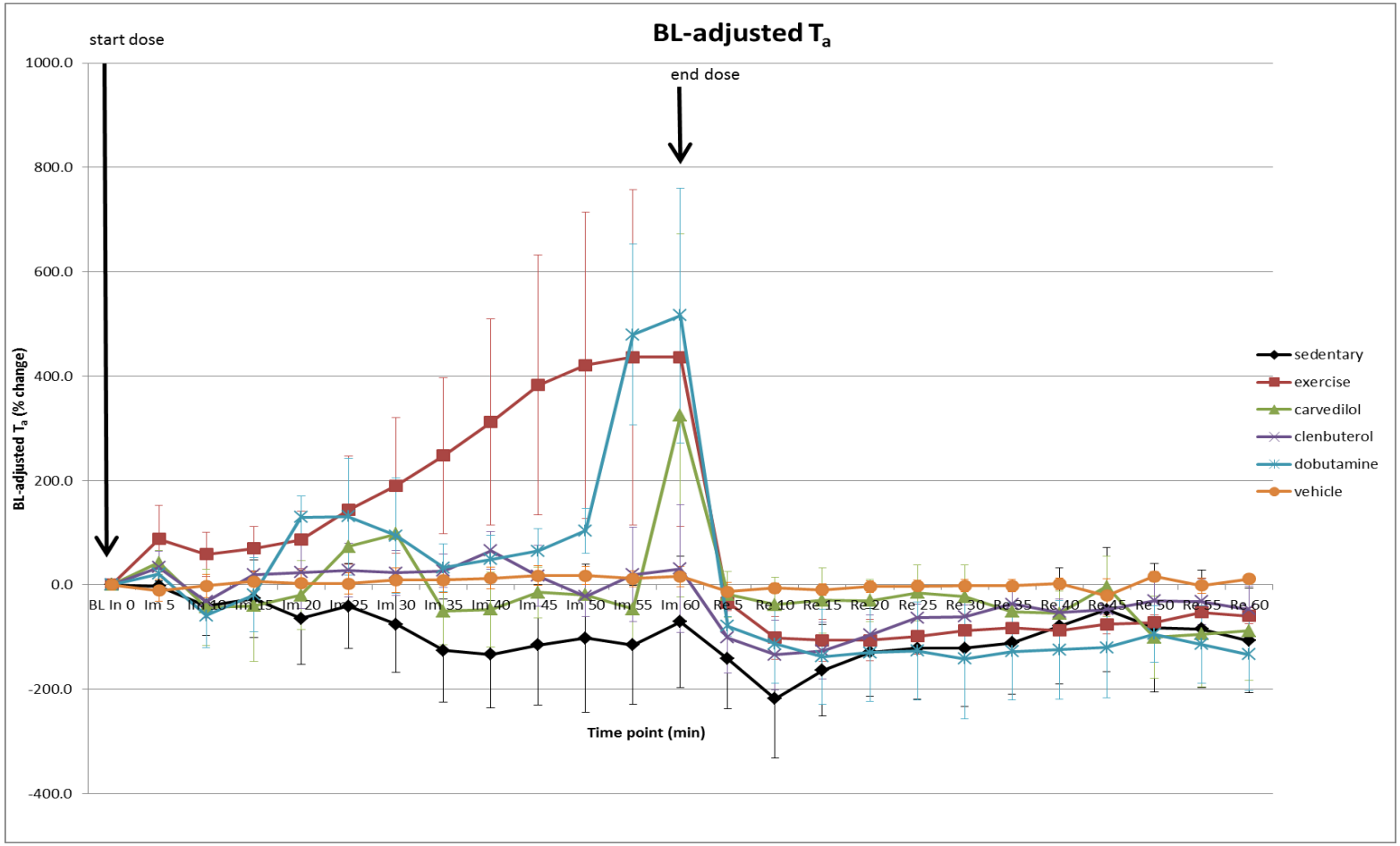

Figure 36. Effect of imipramine or vehicle infusion on BL-adjusted T_a from lead I in all interventions. Values are means ± SE. BL-adjusted T_a, % change from its baseline-instrumentation value of T amplitude.

5.2.2 Maximal effects of imipramine on ECG from lead I in all interventions

Table 30 represents raw data at maximal deviations, differences of values between maximal deviations and baseline-instrumentation values, as well as % changes form baseline-instrumentation values during imipramine infusion from lead I in all interventions. There was no statistically significant difference in any variables among interventions.

Times, of peak effects of imipramine, on variables from lead I are presented in table 31. From this table, the clenbuterol group trended to have more delay in the imipramine effects on R_a, Q_a, and S_a compared with other interventions. However, only significant difference that was found in time of peak augmentation of negative S_a between the clenbuterol and the sedentary group (58.3 ± 1.1 vs. 39.2 ± 3.0, $P < 0.05$).

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Sedentary	Baseline	0.254 ± 0.066	0.0063 ± 0.0036	0.0390 ± 0.0041	-0.0028 ± 0.0027	-0.128 ± 0.035
	Max effect	0.048 ± 0.018	0.0122 ± 0.0143	0.0330 ± 0.0092	-0.0052 ± 0.0084	-0.363 ± 0.097
	Δ value	-0.206 ± 0.072	0.0058 ± 0.0109	-0.0060 ± 0.0078	-0.0023 ± 0.0070	-0.235 ± 0.073
	Δ %	-53.5 ± 27.4	-169.9 ± 147.0	-17.2 ± 17.9	-148.2 ± 549.9	-234.6 ± 101.0
Exercise	Baseline	0.179 ± 0.023	0.0135 ± 0.0074	0.0385 ± 0.0090	-0.0095 ± 0.0048	-0.146 ± 0.047
	Max effect	0.018 ± 0.052	0.0418 ± 0.0133	0.0618 ± 0.0082	-0.0545 ± 0.0259	-0.429 ± 0.066
	Δ value	-0.161 ± 0.046	0.0283 ± 0.0148	0.0233 ± 0.0045	-0.0450 ± 0.0217	-0.282 ± 0.069
	Δ %	-106.3 ± 41.4	478.8 ± 320.2	107.3 ± 42.9	-382.6 ± 92.9	-433.8 ± 200.3
Carvedilol	Baseline	0.250 ± 0.040	-0.0022 ± 0.0036	0.0282 ± 0.0071	-0.0240 ± 0.0146	-0.082 ± 0.008
	Max effect	-0.012 ± 0.061	0.0117 ± 0.0122	0.0313 ± 0.0103	-0.0927 ± 0.0450	-0.347 ± 0.097
	Δ value	-0.261 ± 0.064	0.0138 ± 0.0103	0.0032 ± 0.0106	-0.0687 ± 0.0338	-0.264 ± 0.103
	Δ %	-108.1 ± 26.4	336.7 ± 344.7	39.9 ± 56.6	-330.1 ± 140.6	-303.4 ± 161.0
Clenbuterol	Baseline	0.295 ± 0.043	0.0133 ± 0.0050	0.0513 ± 0.0034	-0.0090 ± 0.0049	-0.063 ± 0.022
	Max effect	0.109 ± 0.019	0.0125 ± 0.0065	0.0425 ± 0.0127	-0.0070 ± 0.0109	-0.186 ± 0.063
	Δ value	-0.186 ± 0.042	-0.0008 ± 0.0095	-0.0088 ± 0.0126	0.0020 ± 0.0137	-0.123 ± 0.067
	Δ %	-60.5 ± 7.6	63.5 ± 120.8	-15.7 ± 26.0	81.3 ± 92.1	-283.5 ± 168.2
Dobutamine	Baseline	0.302 ± 0.070	0.0027 ± 0.0047	0.0353 ± 0.0047	-0.0203 ± 0.0137	-0.073 ± 0.019
	Max effect	0.016 ± 0.023	0.0278 ± 0.0151	0.0410 ± 0.0100	-0.0260 ± 0.0194	-0.396 ± 0.065
	Δ value	-0.286 ± 0.066	0.0252 ± 0.0119	0.0057 ± 0.0120	-0.0057 ± 0.0207	-0.323 ± 0.074
	Δ %	-94.8 ± 13.8	610.1 ± 221.9	23.7 ± 33.6	-52.6 ± 177.2	-600.4 ± 163.5

Table 30. Maximal effects of imipramine infusion on ECG from lead I in all interventions. Values are means ± SE. n = 6.

Group Variables	Sedentary (min)	Exercise (min)	Carvedilol (min)	Clenbuterol (min)	Dobutamine (min)
R_a	45.0 ± 8.1	38.3 ± 7.6	45.8 ± 8.2	51.7 ± 4.9	30.8 ± 8.1
T_a	31.7 ± 6.9	46.7 ± 5.4	35.0 ± 7.4	35.0 ± 8.0	47.5 ± 6.7
P_a	40.8 ± 8.4	29.2 ± 9.8	33.3 ± 8.3	28.3 ± 4.9	31.7 ± 5.1
Q_a	45.0 ± 8.2	30.0 ± 5.0	30.8 ± 8.2	55.8 ± 2.0	35.8 ± 8.0
S_a	39.2 ± 3.0^{cl}	49.2 ± 4.2	48.3 ± 4.8	58.3 ± 1.1	50.8 ± 4.9

Table 31. Times at imipramine maximal effect on ECG from lead I in all interventions. Values are means ± SE. n = 6. $^{cl}P < 0.05$ vs clenbuterol.

5.3 Effect of imipramine on ECG from lead AVF in all interventions

Table 32 presents lead AVF variables of P_a, Q_a, R_a, S_a, and T_a at baseline-instrumentation, mid-dose, end-dose, and end recovery periods. There was no significant difference on baseline-instrumentation values among groups. Likewise, there was no significant difference between vehicle and imipramine infusion. Also, Imipramine infusion showed no statistically significant alteration on Q_a and T_a.

Imipramine also caused statistically significant reductions of R_a in most of the interventions at mid-dose and end-dose periods, except for the sedentary group at the end-dose period, and the exercise group at both mid-dose and end-dose periods. These R_a reductions did not recovery spontaneously during imipramine infusion, but there was full recover toward their baseline-instrumentation values, without statistical difference at end recovery periods in any groups. P_a reductions during imipramine infusion showed statistical significance only in the carvedilol and the clenbuterol groups ($P < 0.05$), but they were fully recovery at end recovery period in both groups.

In lead AVF, increase in depth of S_a was smaller than in lead I, and significant changes were found only in the sedentary, the carvedilol, and the dobutamine groups at end-dose period ($P < 0.05$). They were also found in the dobutamine group at mid-dose period ($P < 0.001$). There was no significant difference in S_a between end recovery and baseline-instrumentation.

Comparing effects of imipramine infusion, and recovery from these effects, on lead AVF variables, only the sedentary group had significantly higher R_a than the clenbuterol group at end recovery period (0.352 ± 0.020 vs. 0.224 ± 0.039, $P < 0.05$).

Effects of imipramine on lead AVF in all interventions, as expressed as % change from their baseline-instrument values, are shown in table 33. Imipramine infusion did not significantly affect % changes of Q_a and T_a. Imipramine infusion produced statistically significant reductions of R_a as % change in the sedentary, the clenbuterol, and the dobutamine groups, but only the clenbuterol group remained different at end recovery period ($P < 0.05$). P_a was decreased by imipramine in the carvedilol and the clenbuterol groups at both mid-dose and end-dose periods ($P < 0.05$). Only the exercise group had significant increase in P_a at end recovery period compared with baseline-instrumentation values ($P < 0.05$), and % changes of its P_a was statistically higher than those of the clenbuterol group at the end recovery period (12.5 ± 3.4 vs. -18.4 ± 9.2, $P < 0.05$). Imipramine infusion on % change in S_a reached significance only in the carvedilol and the dobutamine groups.

There were greater differences among interventions exprerssede as % changes in ECG amplitudes than when using raw data from table 32. For example, % change of R_a at end recovery period of the clenbuterol group was significant lower than the sedentary and the exercise groups ($P < 0.05$). Also, % change of R_a of the vehicle group was significant higher at the same time point than those of the carvedilol, the clenbuterol, and the dobutamine groups ($P < 0.05$). Likewise, % changes of P_a showed significant difference between the exercise and the clenbuterol group at end recovery period ($P <$

0.05). Moreover, degree of increase in depth of S_a as % change was significantly higher in the dobutamine group compared with the sedentary, the exercise, and the clenbuterol groups ($P < 0.05$).

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Sedentary	Baseline	0.313 ± 0.025	0.099 ± 0.016	0.113 ± 0.007	-0.0053 ± 0.0058	-0.101 ± 0.043
	Mid-dose	0.247 ± 0.019$^{bi, R}$	0.099 ± 0.015	0.083 ± 0.018	-0.0041 ± 0.0018	-0.162 ± 0.050
	End-dose	0.282 ± 0.017^{r}	0.101 ± 0.015	0.093 ± 0.020	-0.0038 ± 0.0035	-0.193 ± 0.084$^{bi, r}$
	End recovery	0.352 ± 0.020^{cl}	0.100 ± 0.017	0.109 ± 0.022	-0.0052 ± 0.0053	-0.101 ± 0.032
Exercise	Baseline	0.282 ± 0.019	0.092 ± 0.011	0.062 ± 0.029	-0.0123 ± 0.0023	-0.150 ± 0.033
	Mid-dose	0.242 ± 0.030^{r}	0.101 ± 0.012	0.038 ± 0.016	-0.0028 ± 0.0021	-0.176 ± 0.041
	End-dose	0.263 ± 0.029^{r}	0.094 ± 0.017	0.027 ± 0.022	-0.0022 ± 0.0030	-0.198 ± 0.063
	End recovery	0.316 ± 0.020	0.090 ± 0.009	0.076 ± 0.021	-0.0037 ± 0.0027	-0.129 ± 0.026
Carvedilol	Baseline	0.337 ± 0.036	0.101 ± 0.010	0.094 ± 0.016	-0.0005 ± 0.0049	-0.128 ± 0.061
	Mid-dose	0.279 ± 0.034^{bi}	0.088 ± 0.013	0.020 ± 0.031$^{bi, r}$	-0.0041 ± 0.0042	-0.213 ± 0.070
	End-dose	0.284 ± 0.037^{bi}	0.094 ± 0.012	0.016 ± 0.034$^{bi, r}$	-0.0017 ± 0.0047	-0.222 ± 0.069^{bi}
	End recovery	0.310 ± 0.033	0.083 ± 0.013	0.080 ± 0.014	-0.0005 ± 0.0034	-0.161 ± 0.069
Clenbuterol	Baseline	0.286 ± 0.045	0.128 ± 0.012	0.109 ± 0.006	-0.0038 ± 0.0045	-0.249 ± 0.066
	Mid-dose	0.217 ± 0.027^{bi}	0.133 ± 0.014	0.070 ± 0.011^{bi}	-0.0034 ± 0.0074	-0.263 ± 0.041
	End-dose	0.214 ± 0.034^{bi}	0.102 ± 0.017	0.043 ± 0.019^{bi}	-0.0037 ± 0.0055	-0.230 ± 0.042
	End recovery	0.224 ± 0.039^{bi}	0.091 ± 0.017	0.053 ± 0.023	-0.0028 ± 0.0047	-0.198 ± 0.047
Dobutamine	Baseline	0.362 ± 0.033	0.089 ± 0.007	0.088 ± 0.014	-0.0012 ± 0.0031	-0.064 ± 0.028
	Mid-dose	0.268 ± 0.020$^{Bi, r}$	0.100 ± 0.014	0.048 ± 0.018	-0.0016 ± 0.0011	-0.205 ± 0.064$^{Bi, r}$
	End-dose	0.298 ± 0.031^{bi}	0.091 ± 0.015	0.060 ± 0.020	0.0003 ± 0.0017	-0.183 ± 0.062$^{bi, r}$
	End recovery	0.333 ± 0.036	0.089 ± 0.013	0.092 ± 0.007	-0.0023 ± 0.0041	-0.079 ± 0.028

Table 32. Effects of imipramine infusion on ECG from lead AVF in all interventions. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{cl}P < 0.05$ vs. clenbuterol.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-20.0 ± 5.4 [bi, R]	1.9 ± 7.6	-25.0 ± 16.9	-2.3 ± 44.4	-113.6 ± 61.0 [d]
	End-dose	-7.8 ± 7.4 [r]	3.0 ± 5.9	-17.0 ± 18.5	-2.3 ± 60.1	-104.2 ± 45.1
	End recovery	16.0 ± 11.5 [cl]	2.4 ± 7. 9	-4.0 ± 18.5	-24.2 ± 39.9	-19.4 ± 17.1
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-15.7 ± 5.9 [R]	21.4 ± 28.6	-0.9 ± 34.3 [r]	68.9 ± 24.1	-23.6 ± 14.0 [d]
	End-dose	-7.7 ± 7.1 [r]	14.1 ± 35.1	-35.1 ± 19.6 [r]	78.1 ± 31.1	-35.5 ± 20.5
	End recovery	12.5 ± 3.4 [cl]	2.0 ± 10.1	123.1 ± 108.5 [bi, cl]	50.6 ± 38.3	10.8 ± 8.8
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-17.2 ± 4.1	-12.9 ± 7.7	-149.3 ± 90.4 [bi, r]	-143.3 ± 69.1	-205.6 ± 155.1
	End-dose	-15.4 ± 6.4 [v]	-6.8 ± 5.3	-128.9 ± 63.7 [bi, r]	-99.0 ± 101.1	-272.4 ± 210.4 [bi]
	End recovery	-7.0 ± 4.8 [v]	-16.9 ± 8.7	1.1 ± 21.8	12.2 ± 62.5	-70.3 ± 32.0
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-16.4 ± 11.9	5.4 ± 10.8	-35.3 ± 9.8	31.5 ± 49.7	-20.0 ± 17.3 [d]
	End-dose	-18.2 ± 13.2 [bi, v]	-20.0 ± 12.5	-56.8 ± 17.1	42.5 ± 84.4	-8.3 ± 21.2
	End recovery	-18.4 ± 9.2 [bi, v]	-30.7 ± 9.1	-48.2 ± 19.6	-36.9 ± 66.5	15.5 ± 10.8
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	-24.8 ± 3.2 [bi, v]	15.7 ± 19.4	-14.9 ± 40.2	-12.2 ± 31.9	-339.4 ± 175.6 [Bi, r]
	End-dose	-17.4 ± 4.4 [v]	2.5 ± 16.0	-14.7 ± 33.0	4.6 ± 43.8	-248.5 ± 101.8 [bi]
	End recovery	-8.4 ± 3.3 [v]	-0.2 ± 11.7	26.8 ± 27.6	26.2 ± 84.3	-61.4 ± 49.4

Table 33. Effects of imipramine infusion on ECG from lead AVF in all interventions as percentage change from their baseline-instrumentation values. Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [v]$P < 0.05$ vs. vehicle; [cl]$P < 0.05$ vs. clenbuterol; [d]$P < 0.05$ vs. dobutamine.

5.4 Effects of imipramine on ECG from lead V3 in all interventions

5.4.1 Effects of imipramine on ECG from lead V3 in all interventions

Table 34 shows lead V3 variables at baseline-instrumentation, mid-dose, end-dose, and end recovery periods in all interventions that received imipramine. There was no significant difference in any baseline-instrument values in any group, including vehicle group.

Imipramine infusion resulted in statistically prolong RR intervals (reduction in HR) at mid-dose and end-dose periods compared with baseline-instrumentation values, except RR interval of carvedilol group at mid-dose period. There was no obvious spontaneous recovery from mid-dose to end-dose period of HR in any intervention. However, some of the interventions could fully recover by the end recovery period, such as the carvedilol and the dobutamine groups. The sedentary and the exercise groups still had significantly lower HRs at end recovery period ($P < 0.05$). Also, HR of the clenbuterol group was still significantly lower than in baseline-instrumentation values, $P < 0.001$.

P_d and PR interval were also statistically lengthened by imipramine infusion at end-dose and/or mid-dose in all interventions. Compared with the vehicle group, at end-dose period, the clenbuterol and the dobutamine groups had significantly longer PR interval (60.0 ± 8.5 and 56.8 ± 3.5 vs. 39.2 ± 3.1, $P < 0.001$). Likewise, there was no spontaneous recovery in these variables (i.e., P_d and PR interval) during imipramine infusion, but they showed fully recovery by the end recovery period in all groups (see

figure 37 for alteration of PR interval due to imipramine infusion). However, statistical prolongation of PR_{sect} was found only at the end-dose period in most of the interventions, except the sedentary group, and it returned dramatically toward baseline-instrumentation values.

Moreover, imipramine infusion caused significant increases in QRS duration at both mid-dose and end-dose period in all interventions, without spontaneous recovery. Only some of these prolongations of QRS were different from the vehicle group such as at the end-dose values of the exercise and the carvedilol group (26.6 ± 1.7 and 25.8 ± 1.0 vs. 21.5 ± 1.0, $P < 0.05$). These QRS prolongations due to imipramine infusion, at the end recovery period, fully returned toward normal, i.e., before start imipramine infusion, except in the dobutamine group.

Imipramine led to significant prolongation of QT interval in most interventions at both mid-dose and end-dose periods, except the carvedilol group, in which significant difference was not found at any period. QT was prolonged by imipramine in the dobutamine group more than in the exercise and the carvedilol groups, $P < 0.05$. The dobutamine group also showed significantly higher values of QT interval than the vehicle group in both mid-dose and end-dose values, $P < 0.05$. Beside QT interval, the dobutamine group exhibited significant lengthening of QTcB and QTcF in both mid-dose and end-dose values, before fully returning toward its baseline-instrumentation value. The dobutamine group, once again, had significantly longer QTcB than the exercise (at mid-dose, end-dose, and end recovery value) and the carvedilol groups (at mid-dose and end-dose values), $P < 0.05$. Similarly values of QTcF of the dobutamine group were

statistically higher than for the carvedilol group at both mid-dose and end-dose values, $P < 0.05$. There were no obvious alterations in QTcB and QTcF in other interventions at any of the time points. Interestingly, prolongation of QT_1 induced by imipramine was significant only at the end recovery period of the carvedilol and the dobutamine groups ($P < 0.05$).

QA interval was significantly prolonged without spontaneous recovery in most of the groups during imipramine infusion, except for the carvedilol group. QA return toward the baseline-instrumentation levels. Furthermore, only the exercise group had greater prolongation in QA than in the vehicle group at the end-dose values (62.5 ± 2.1 vs. 43.7 ± 1.6, $P < 0.05$).

Significant lengthening of T_d due to imipramine infusion was limited in the sedentary (at mid-dose period) and the dobutamine groups (both mid-dose and end-dose periods), and also return quickly toward baseline-instrumentation values (see figure 45). In fact, prolongated of T_d of the dobutamine group was significantly greater than for the exercise and the vehicle groups at both mid-dose and end-dose periods, $P < 0.05$.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Sedentary	Baseline	147 ± 8	413 ± 21	15.3 ± 0.7	40.4 ± 1.2	25.0 ± 1.4	19.7 ± 0.7
	Mid-dose	190 ± 14 [bi]	324 ± 21 [Bi, r]	17.3 ± 0.8	46.3 ± 1.6	29.0 ± 1.3	23.4 ± 0.9 [Bi]
	End-dose	186 ± 15 [bi]	333 ± 27 [Bi]	17.7 ± 0.7 [bi]	50.0 ± 1.3 [bi]	32.3 ± 0.9	24.1 ± 1.1 [Bi, r]
	End recovery	170 ± 18	371 ± 35 [bi]	16.5 ± 1.1	43.2 ± 1.3	26.8 ± 0.9	21.2 ± 0.7
Exercise	Baseline	155 ± 5	389 ± 13	15.0 ± 0.7	38.5 ± 2.4	23.5 ± 1.7	19.9 ± 0.3
	Mid-dose	205 ± 6 [bi]	294 ± 9 [Bi, r]	18.4 ± 0.9 [bi]	47.8 ± 1.6 [bi]	29.4 ± 1.0	24.3 ± 0.6 [Bi, r]
	End-dose	212 ± 7 [Bi, r]	285 ± 10 [Bi, r, v]	19.1 ± 1.2 [Bi, r]	50.7 ± 2.9 [bi, r]	31.6 ± 1.8 [bi, cl]	26.6 ± 1.7 [Bi, R, v]
	End recovery	177 ± 9	344 ± 18 [bi]	16.7 ± 1.1	42.0 ± 0.9	25.3 ± 1.0	21.7 ± 0.5
Carvedilol	Baseline	159 ± 4	380 ± 11	15.5 ± 0.9	38.8 ± 1.3	23.3 ± 0.9	20.8 ± 1.1
	Mid-dose	183 ± 5 [ed]	329 ± 9 [bi]	17.3 ± 0.9	44.7 ± 0.9	27.5 ± 0.9	23.9 ± 0.8 [bi, r]
	End-dose	221 ± 41 [Bi, r, v]	302 ± 33 [Bi, r]	17.9 ± 0.9 [bi]	50.3 ± 1.8 [bi]	32.3 ± 2.2 [bi]	25.8 ± 1.0 [Bi, R, v]
	End recovery	174 ± 6	348 ± 13	17.7 ± 1.1	42.6 ± 0.8	24.9 ± 1.3	21.3 ± 1.0
Clenbuterol	Baseline	146 ± 4	412 ± 10	16.2 ± 0.9	42.5 ± 1.3	26.3 ± 0.6	18.2 ± 0.3
	Mid-dose	192 ± 6 [bi]	314 ± 10 [Bi]	17.8 ± 0.7	49.6 ± 2.3 [ed]	31.8 ± 1.7 [ed]	21.4 ± 0.6 [bi]
	End-dose	198 ± 9 [Bi]	306 ± 14 [Bi]	19.0 ± 0.9 [bi]	60.0 ± 8.5 [Bi, r, V]	41.0 ± 7.8 [Bi, r, V]	23.2 ± 0.7 [Bi, r]
	End recovery	180 ± 7 [bi]	335 ± 13 [Bi]	17.6 ± 1.0	47.8 ± 2.9	30.2 ± 2.1	20.3 ± 0.7
Dobutamine	Baseline	145 ± 5	416 ± 14	14.7 ± 0.4	36.4 ± 0.7	21.7 ± 0.8	18.1 ± 0.6
	Mid-dose	184 ± 10 [bi]	330 ± 17 [Bi, R]	17.5 ± 1.0 [bi]	45.8 ± 2.0 [Bi, ed]	28.2 ± 1.0 [ed]	23.5 ± 1.1 [Bi, r]
	End-dose	189 ± 9 [bi]	322 ± 15 [Bi, R]	18.2 ± 1.1 [Bi, r]	56.8 ± 3.5 [Bi, R, V]	38.6 ± 3.8 [Bi, R, V]	25.1 ± 1.4 [Bi, R]
	End recovery	155 ± 9	394 ± 23	15.9 ± 0.5	40.5 ± 1.1	24.6 ± 1.3	20.8 ± 0.8 [bi]

Continued

Table 34. Effects of imipramine infusion on ECG from lead V3 in all interventions. Values are means ± SE. n = 6. [Bi]$P < 0.001$ vs. its baseline-instrumentation; [bi]$P < 0.05$ vs. its baseline-instrumentation; [ed]$P < 0.05$ vs. its end dose; [R]$P < 0.001$ vs. its recovery-60 min; [r]$P < 0.05$ vs. its recovery-60 min; [V]$P < 0.001$ vs. vehicle; [v]$P < 0.05$ vs. vehicle; [cl]$P < 0.05$ vs. clenbuterol.

Table 34. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Sedentary	Baseline	71.6 ± 2.5	187.1 ± 6.0	135.8 ± 4.2	9.06 ± 0.90	48.9 ± 1.7	42.5 ± 2.9
	Mid-dose	81.8 ± 4.2$^{Bi, r}$	189.0 ± 10.5	142.9 ± 7.5	8.27 ± 0.80	55.4 ± 3.7^{bi}	50.0 ± 4.0$^{bi, r}$
	End-dose	81.5 ± 4.6$^{Bi, r}$	190.3 ± 10.1	143.3 ± 7.4	9.52 ± 0.96	56.3 ± 4.5^{bi}	48.5 ± 4.8^{r}
	End recovery	73.7 ± 3.2	181.2 ± 8.6	134.1 ± 5.4	9.63 ± 1.30^{d}	50.4 ± 3.0	41.9 ± 4.2
Exercise	Baseline	67.5 ± 1.1	171.7 ± 4.5	125.8 ± 2.8	10.42 ± 0.59	49.8 ± 1.3	37.1 ± 1.6
	Mid-dose	75.7 ± 1.1$^{bi, d}$	167.8 ± 4.1^{d}	128.7 ± 2.6	9.52 ± 0.40^{r}	60.2 ± 3.0$^{Bi, r}$	42.1 ± 1.5^{d}
	End-dose	77.0 ± 1.7$^{bi, r, d}$	167.5 ± 3.2^{d}	129.3 ± 2.4	10.45 ± 0.50	62.5 ± 2.1$^{Bi, r, v}$	41.1 ± 2.1^{d}
	End recovery	69.9 ± 1.9	166.5 ± 2.9^{d}	124.6 ± 2.2	12.01 ± 0.41	53.7 ± 1.5	36.3 ± 1.9
Carvedilol	Baseline	69.4 ± 1.1	174.5 ± 2.3	128.3 ± 1.6	10.24 ± 1.00	51.8 ± 2.9	38.9 ± 1.3
	Mid-dose	73.0 ± 1.7^{d}	170.6 ± 4.2^{d}	128.6 ± 3.0^{d}	9.74 ± 0.74^{r}	56.0 ± 4.1	39.4 ± 1.5^{d}
	End-dose	74.6 ± 1.0^{d}	166.0 ± 11.4^{d}	126.8 ± 6.3^{d}	11.56 ± 0.57	57.1 ± 3.8	38.1 ± 1.9^{d}
	End recovery	72.5 ± 1.6	174.3 ± 4.1	130.1 ± 2.8	13.01 ± 1.14^{bi}	53.0 ± 3.2	38.5 ± 3.1
Clenbuterol	Baseline	74.0 ± 2.3	193.6 ± 4.9	140.5 ± 3.7	11.14 ± 0.42	42.5 ± 4.7	44.8 ± 2.5
	Mid-dose	83.8 ± 2.5^{Bi}	192.0 ± 8.2	145.6 ± 5.6	11.09 ± 0.64	57.9 ± 8.8$^{Bi, R}$	50.6 ± 3.2
	End-dose	84.3 ± 2.4^{Bi}	189.8 ± 5.5	144.8 ± 3.9	11.66 ± 0.98	56.5 ± 7.4$^{Bi, R}$	49.0 ± 2.6
	End recovery	80.0 ± 3.6	188.7 ± 7.0	141.7 ± 5.5	12.17 ± 0.69	47.5 ± 5.1	47.3 ± 4.0
Dobutamine	Baseline	71.2 ± 3.1	187.0 ± 6.7	135.5 ± 5.1	10.56 ± 0.80	51.6 ± 1.6	42.2 ± 2.4
	Mid-dose	88.0 ± 3.8$^{Bi, R, v}$	205.2 ± 6.8^{bi}	154.7 ± 5.4^{Bi}	9.64 ± 0.52^{R}	55.1 ± 2.6	54.9 ± 3.1$^{Bi, R, v}$
	End-dose	89.2 ± 4.2$^{Bi, R, v}$	205.1 ± 7.0^{bi}	155.3 ± 5.8^{Bi}	11.44 ± 0.60	58.6 ± 2.6$^{bi, r}$	53.1 ± 2.9$^{Bi, R, v}$
	End recovery	77.2 ± 3.1	196.5 ± 4.1	143.9 ± 3.6	13.37 ± 0.97^{bi}	51.9 ± 2.1	43.3 ± 2.3

Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrument; $^{bi}P < 0.05$ vs. its baseline-instrument; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{v}P < 0.05$ vs. vehicle; $^{d}P < 0.05$ vs. dobutamine.

Table 35 shows effects of imipramine infusion on lead V3 in all interventions as % changes from their baseline-instrument values. The ECG wave form durations and interval prolongations due to imipramine infusion were expressed as raw values. When using % change, greater differences were found between imipramine and vehicle. As can be seen in the values of RR, HR, P_d, PR, PR_{sect}, QRS, QT, and QA, there were more values with statistical significance. Statistical differences among groups were also more apparent using % change of PR for the dobutamine group at end-dose period (56.6 ± 10.5) than for the sedentary (24.1 ± 3.7) and the carvedilol groups (30.7 ± 7.4), $P < 0.05$. Likewise, % change of PR_{sect} for the dobutamine group at the end-dose period was significantly longer than those of the sedentary, the exercise, and the carvedilol groups $P < 0.05$.

Lengthening of QT as % change also showed significance among imipramine challanged groups, but it was found only between the carvedilol and the dobutamine groups (5.2 ± 2.5 vs. 24.5 ± 7.0 at mid-dose period, and 7.7 ± 2.8 vs. 25.6 ± 5.1 at end-dose period, $P < 0.001$). Furthermore, there were more numbers that had differences in QA within the imipramine challanged group. Percent prolongation of QA of the clenbuterol group was significant higher than that in the sedentary, the carvedilol, and the dobutamine groups at both mid-dose and end-dose values.

Figures 38, 40, 42, 44, 46, and 48 show lengthening of PR, QT, QTcB, QTcF, T_d, and QA when baseline-adjusted and presented as % change from baseline-

instrumentation values (i.e. BL-adjusted values) of all interventions, including vehicle group, in every 5 minutes time points.

Figure 49 to 56 show examples amplitudes and durations from rat ECGs from lead V3 in the exercise, the carvedilol, the clenbuterol, and the dobutamine groups, that recieved imipramine infusion.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	28.7 ± 5.6 bi, v	-21.6 ± 3.3 Bi, r, V	13.0 ± 3.2	14.8 ± 2.3	16.6 ± 4.5	19.5 ± 5.9 bi
	End-dose	26.3 ± 6.8 bi, v	-19.7 ± 4.3 Bi, V	15.4 ± 2.3	24.1 ± 3.7 bi, v, d	30.6 ± 6.1 d	23.5 ± 7.9 Bi, r, v
	End recovery	14.9 ± 8.6	-10.7 ± 6.2 bi	7.0 ± 4.1	7.1 ± 1.7	7.6 ± 2.8	8.4 ± 5.0
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	32.3 ± 3.0 Bi, v	-24.2 ± 1.8 Bi, r, V	23.8 ± 6.8 Bi, v	26.1 ± 6.5 bi, v	28.6 ± 10.2	22.0 ± 3.0 Bi, r, v
	End-dose	36.5 ± 1.3 Bi, r	-26.7 ± 0.7 Bi, R, V	28.6 ± 8.9 Bi, r, v	33.2 ± 8.1 Bi, r, v	37.0 ± 9.8 bi, d	33.3 ± 8.2 Bi, R, V
	End recovery	13.7 ± 4.0	-11.5 ± 2.9 bi, v	11.2 ± 2.9	11.0 ± 6.3	11.7 ± 11.6	8.8 ± 1.5
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	15.8 ± 2.9 ed	-13.4 ± 2.1 bi, v	12.5 ± 5.0	15.7 ± 3.9	19.0 ± 6.7	16.5 ± 6.6 bi, r
	End-dose	38.4 ± 23.4 Bi, r, v	-20.7 ± 8.6 Bi, r, V	18.0 ± 9.4 bi	30.7 ± 7.4 Bi, r, v, d	40.4 ± 12.2 bi, r, v, d	25.0 ± 6.3 Bi, R, v
	End recovery	9.4 ± 1.9	-8.5 ± 1.6	17.8 ± 12.8 bi	10.4 ± 4.1	7.3 ± 6.6	2.9 ± 3.3
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	31.8 ± 5.1 bi, v	-23.6 ± 2.7 Bi, V	10.8 ± 5.6	17.3 ± 7.2 ed	21.4 ± 8.5 ed	18.1 ± 2.8 bi
	End-dose	36.7 ± 8.4 Bi, v	-25.5 ± 4.4 Bi, V	17.7 ± 3.5 bi	40.3 ± 17.2 Bi, r, V	55.7 ± 28.9 Bi, r, v	28.0 ± 4.7 Bi, r, v
	End recovery	23.4 ± 3.4 bi	-18.6 ± 2.4 Bi, V, d	9.3 ± 6.4	13.2 ± 8.4	15.5 ± 9.9	12.1 ± 4.1
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	26.7 ± 4.1 bi	-20.6 ± 2.6 Bi, R, V	19.7 ± 6.0 Bi	26.2 ± 6.1 bi, ed, v	31.0 ± 6.9 ed, V	30.2 ± 4.0 Bi, r, v
	End-dose	30.1 ± 5.0 bi, r, v	-22.5 ± 3.2 Bi, R, V	24.3 ± 6.3 Bi, R	56.6 ± 10.5 Bi, R, V	78.6 ± 18.8 Bi, R	39.7 ± 8.9 Bi, R, V
	End recovery	6.6 ± 3.9	-5.5 ± 3.7	8.2 ± 3.0	11.4 ± 3.2	13.7 ± 5.8	15.5 ± 2.2 bi

Continued

Table 35. Effects of imipramine infusion on ECG from lead V3 in all interventions as percentage change from their baseline-instrumentation values. Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{ed}P < 0.05$ vs. its end dose; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle; $^{d}P < 0.05$ vs. dobutamine.

Table 35. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Sedentary	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	14.1 ± 4.0 $^{bi, r}$	0.8 ± 3.0	5.0 ± 3.1	-4.3 ± 12.2	12.8 ± 5.0 $^{bi, cl}$	17.6 ± 6.1 $^{bi, r}$
	End-dose	13.7 ± 4.5 $^{bi, r}$	1.4 ± 2.8	5.3 ± 3.1	8.6 ± 11.0	14.4 ± 7.0 $^{bi, r, cl}$	13.2 ± 7.6 ^{r}
	End recovery	2.9 ± 2.0	-3.3 ± 2.4	-1.4 ± 1.6	6.8 ± 8.8	2.6 ± 3.7	-2.6 ± 4.5
Exercise	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	12.4 ± 2.9 ^{bi}	-2.0 ± 3.2	2.6 ± 3.1	-6.2 ± 9.5	20.5 ± 3.3 $^{Bi, r, v}$	15.0 ± 8.5 ^{r}
	End-dose	14.3 ± 3.2 $^{bi, r}$	-2.1 ± 2.9	3.1 ± 3.0	2.5 ± 9.4	25.3 ± 2.2 $^{Bi, R, V}$	11.9 ± 8.2
	End recovery	3.6 ± 2.8	-2.8 ± 2.5	-0.7 ± 2.5	16.2 ± 4.0	7.8 ± 1.7	-1.5 ± 5.7
Carvedilol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	5.2 ± 2.5 ^{D}	-2.1 ± 3.2	0.3 ± 2.9 ^{d}	-0.2 ± 12.2 ^{r}	7.5 ± 3.1 ^{Cl}	1.5 ± 3.7 ^{d}
	End-dose	7.7 ± 2.8 ^{D}	-4.6 ± 7.1	-0.9 ± 5.7 ^{d}	19.7 ± 14.7	10.1 ± 3.8 ^{cl}	-1.8 ± 5.0 ^{d}
	End recovery	4.5 ± 2.5	0.0 ± 2.7	1.5 ± 2.6	29.7 ± 9.7 ^{bi}	2.2 ± 2.6	-1.4 ± 5.4
Clenbuterol	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	13.5 ± 2.9 ^{bi}	-0.9 ± 3.3	3.7 ± 3.1	-0.8 ± 2.5	33.9 ± 8.8 $^{Bi, R, V, D}$	13.3 ± 5.4
	End-dose	14.2 ± 3.2 ^{bi}	-1.6 ± 3.8	3.3 ± 3.3	3.9 ± 5.9	33.2 ± 8.0 $^{Bi, R, V, d}$	10.1 ± 5.1
	End recovery	8.1 ± 2.4	-2.6 ± 2.4	0.9 ± 2.3	9.3 ± 5.5	13.5 ± 6.3 ^{bi}	5.4 ± 5.5
Dobutamine	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
	Mid-dose	24.5 ± 7.0 $^{Bi, R, V}$	10.8 ± 6.8	15.2 ± 6.8 ^{Bi}	-7.3 ± 5.6 ^{R}	6.6 ± 2.8	31.5 ± 8.8 $^{Bi, R, v}$
	End-dose	25.6 ± 5.1 $^{Bi, R, V}$	10.0 ± 3.5	14.9 ± 3.9 ^{Bi}	11.7 ± 10.6	13.6 ± 3.0 $^{bi, r}$	26.1 ± 4.4 $^{Bi, r, v}$
	End recovery	8.7 ± 2.2	5.5 ± 2.3	6.5 ± 2.1	29.0 ± 10.4 ^{bi}	0.6 ± 1.4	3.2 ± 4.6

Values are means ± SE. n = 6. $^{Bi}P < 0.001$ vs. its baseline-instrumentation; $^{bi}P < 0.05$ vs. its baseline-instrumentation; $^{R}P < 0.001$ vs. its recovery-60 min; $^{r}P < 0.05$ vs. its recovery-60 min; $^{V}P < 0.001$ vs. vehicle; $^{v}P < 0.05$ vs. vehicle; $^{Cl}P < 0.001$ vs. clenbuterol ; $^{cl}P < 0.05$ vs. clenbuterol ; $^{d}P < 0.05$ vs. dobutamine.

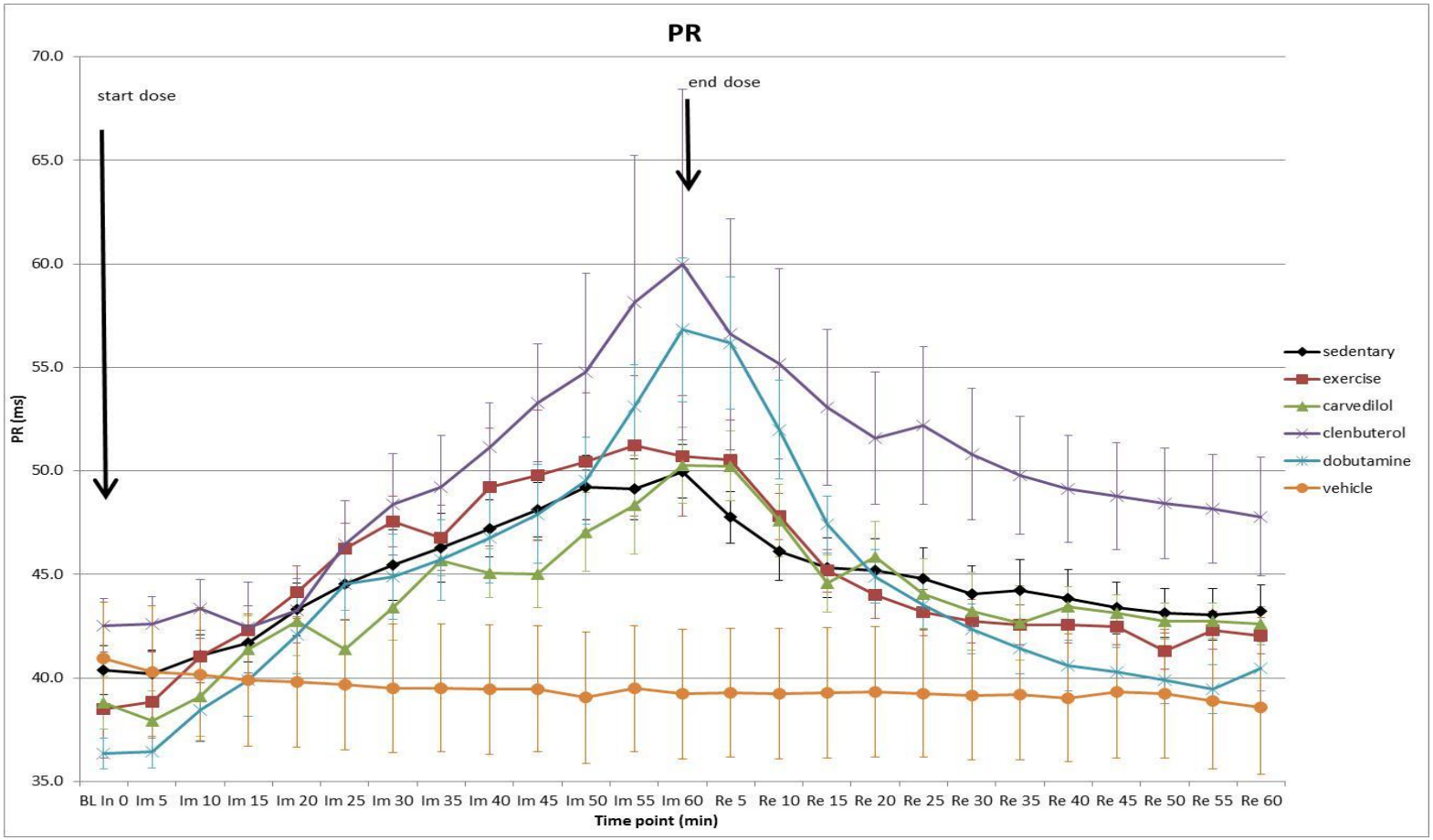

Figure 37. Effect of imipramine or vehicle infusion on PR from lead V3 in all interventions. Values are means ± SE. PR, duration from beginning of P wave to beginning of Q wave.

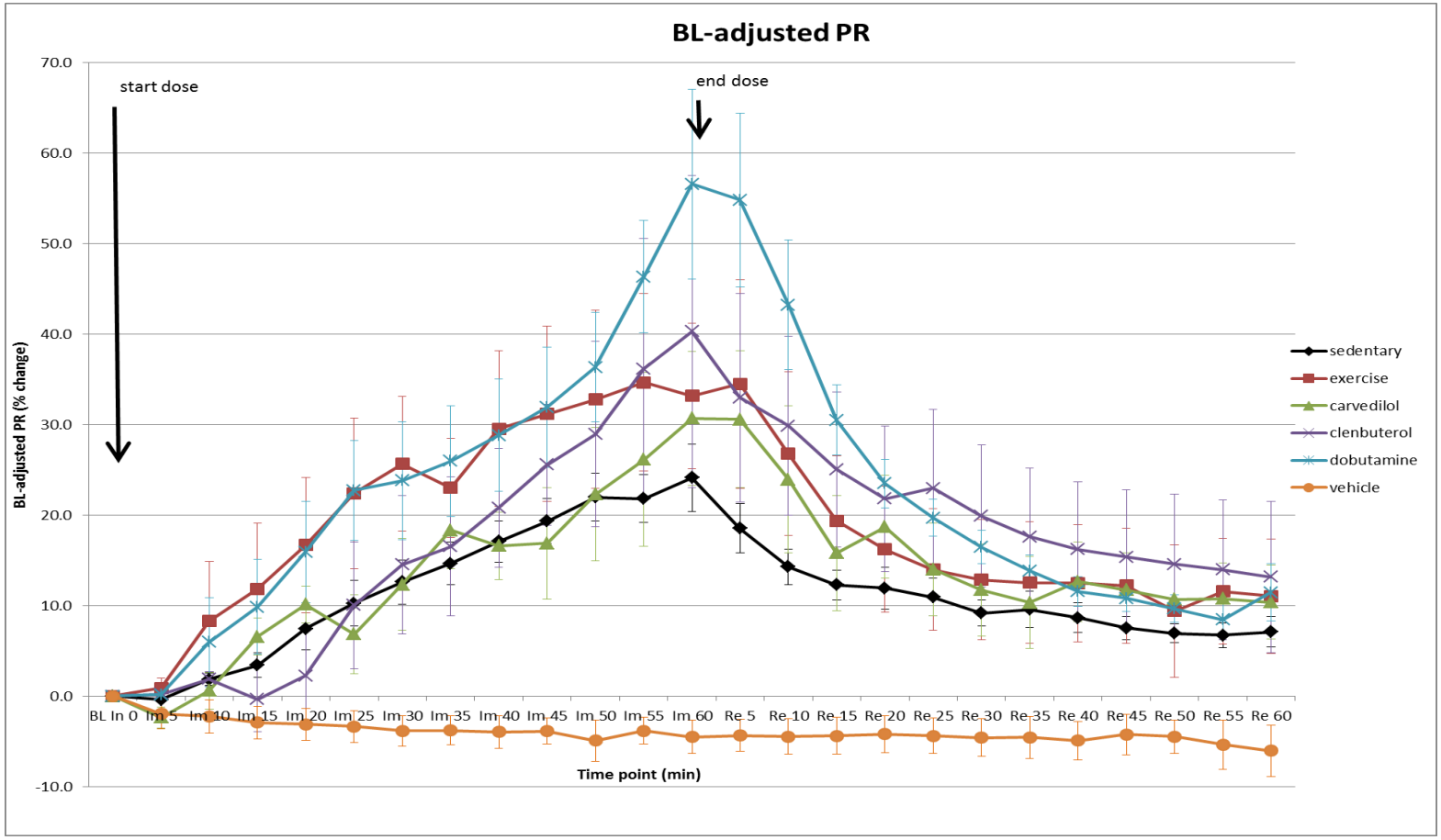

Figure 38. Effect of imipramine or vehicle infusion on BL-adjusted PR from lead V3 in all interventions. Values are means ± SE. BL-adjusted PR, % change from its baseline-instrumentation value of duration from beginning of P wave to beginning of Q wave.

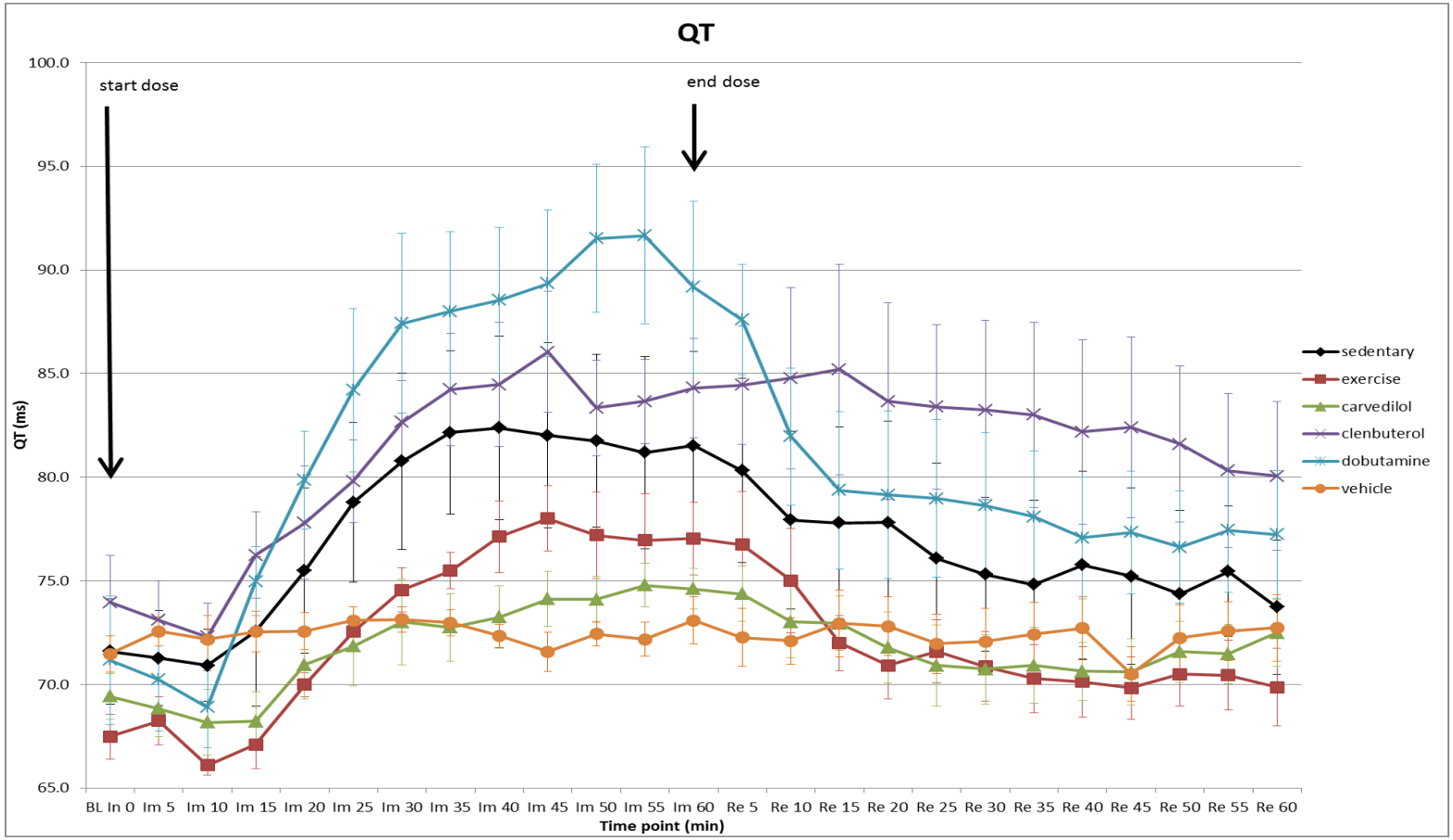

Figure 39. Effect of imipramine or vehicle infusion on QT from lead V3 in all interventions. Values are means ± SE. QT, duration from beginning of Q wave to end of T wave.

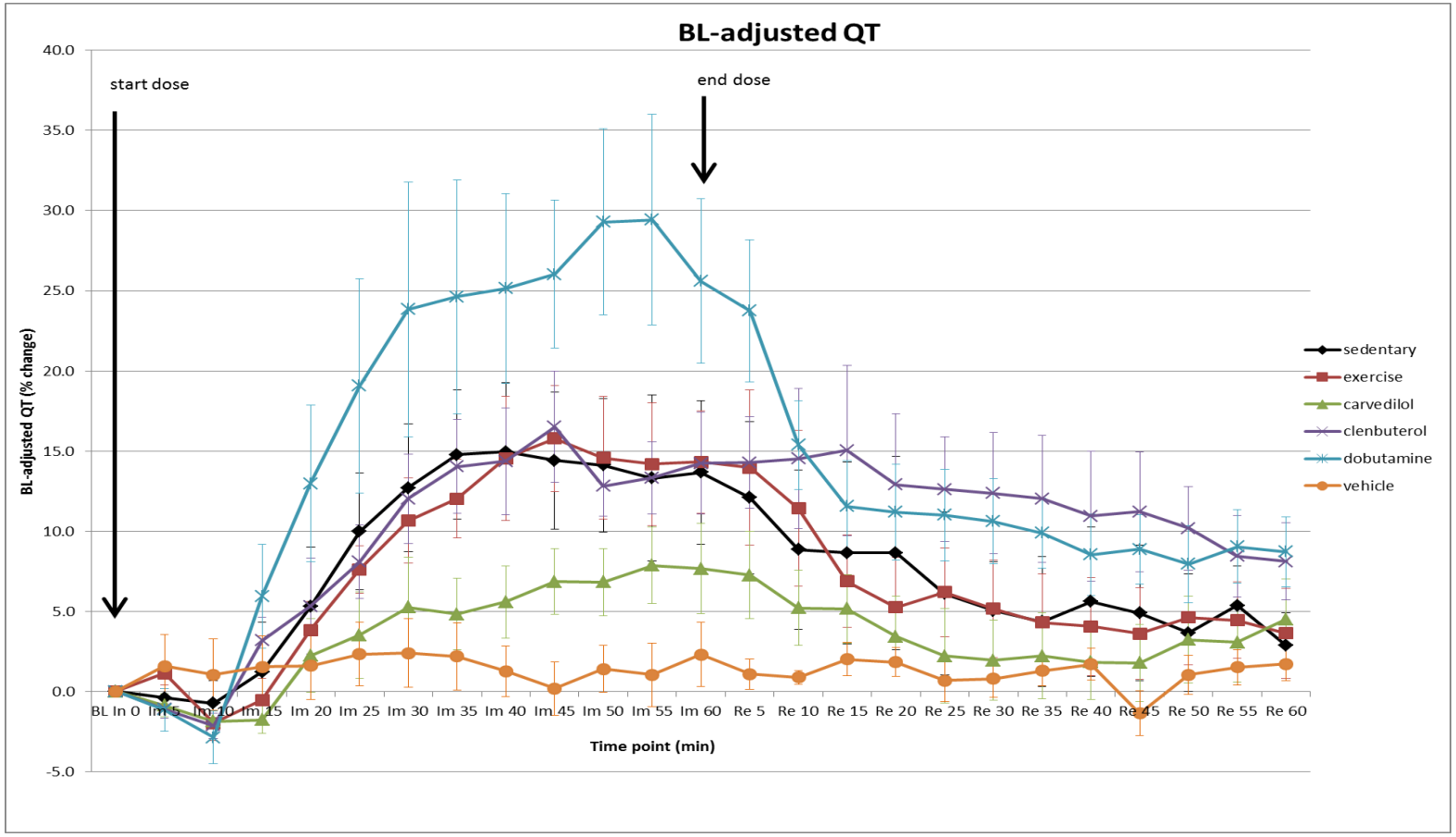

Figure 40. Effect of imipramine or vehicle infusion on BL-adjusted QT from lead V3 in all interventions. Values are means ± SE. BL-adjusted QT, % change from its baseline-instrumentation value of duration from beginning of Q wave to end of T wave.

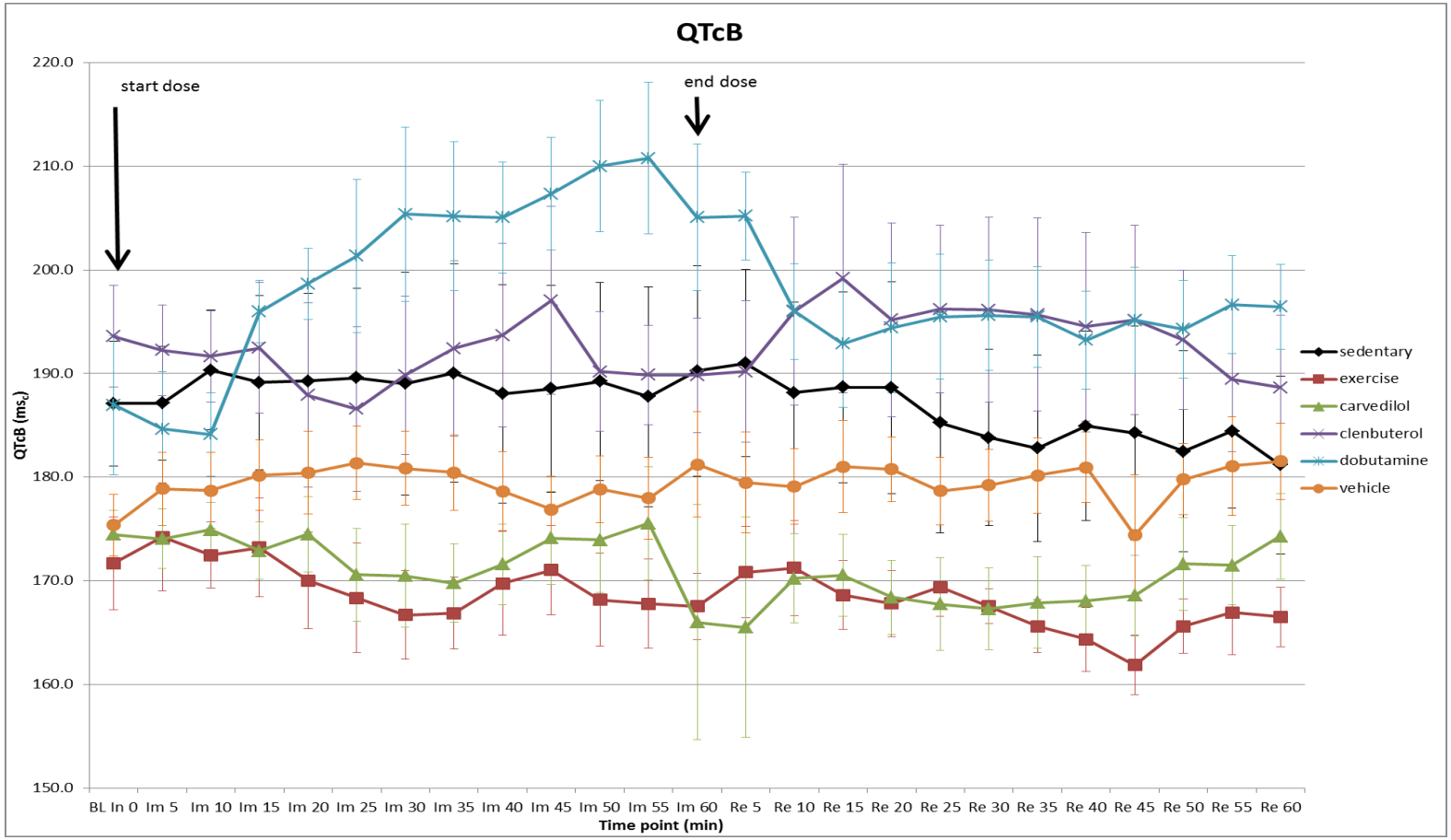

Figure 41. Effect of imipramine or vehicle infusion on QTcB from lead V3 in all interventions. Values are means ± SE. QTcB, corrected QT by Bazett‘s formula.

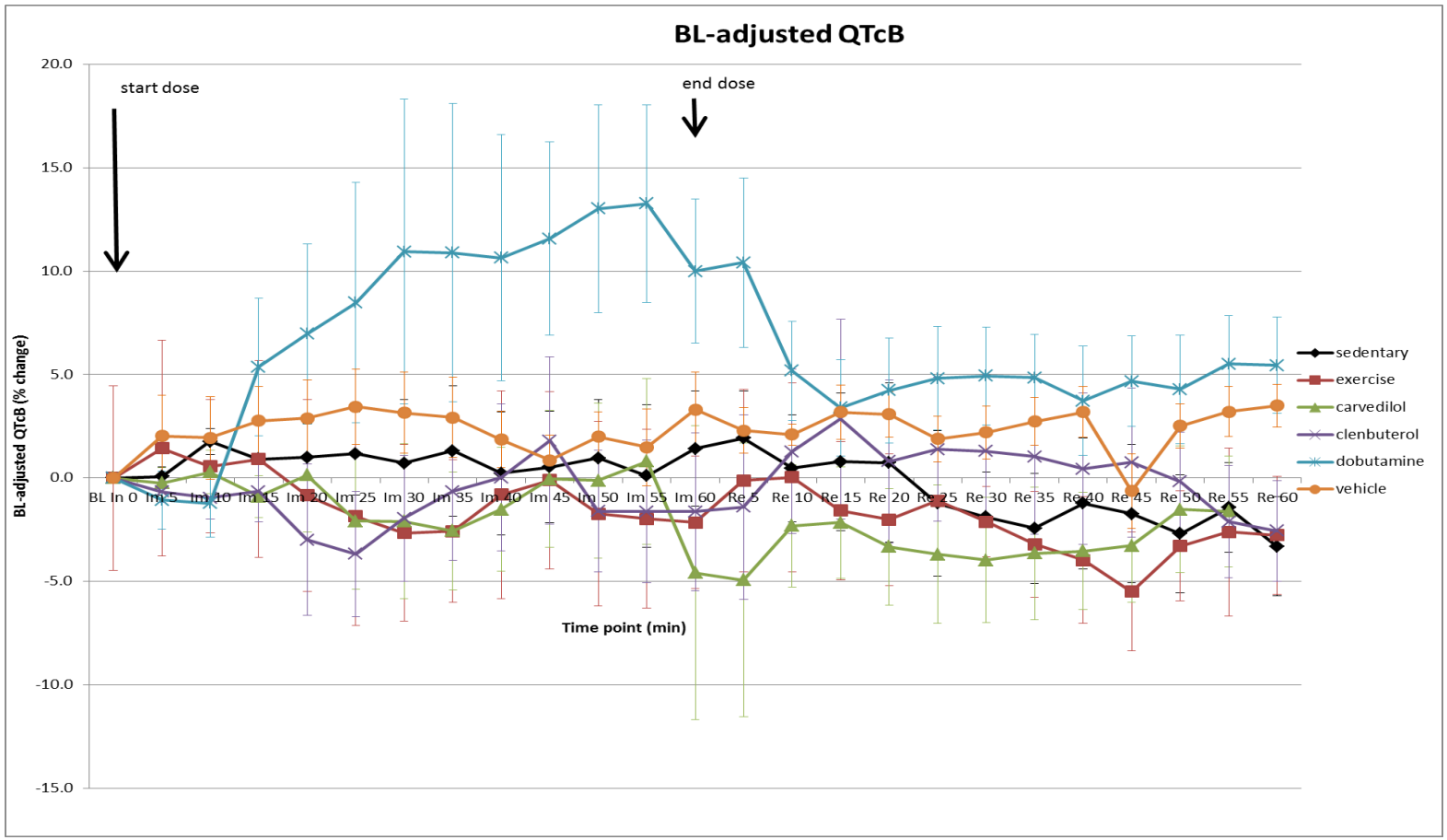

Figure 42. Effect of imipramine or vehicle infusion on BL-adjusted QTcB from lead V3 in all interventions. Values are means ± SE. BL-adjusted QTcB, % change from its baseline-instrumentation value of corrected QT by Bazett ‘s formula.

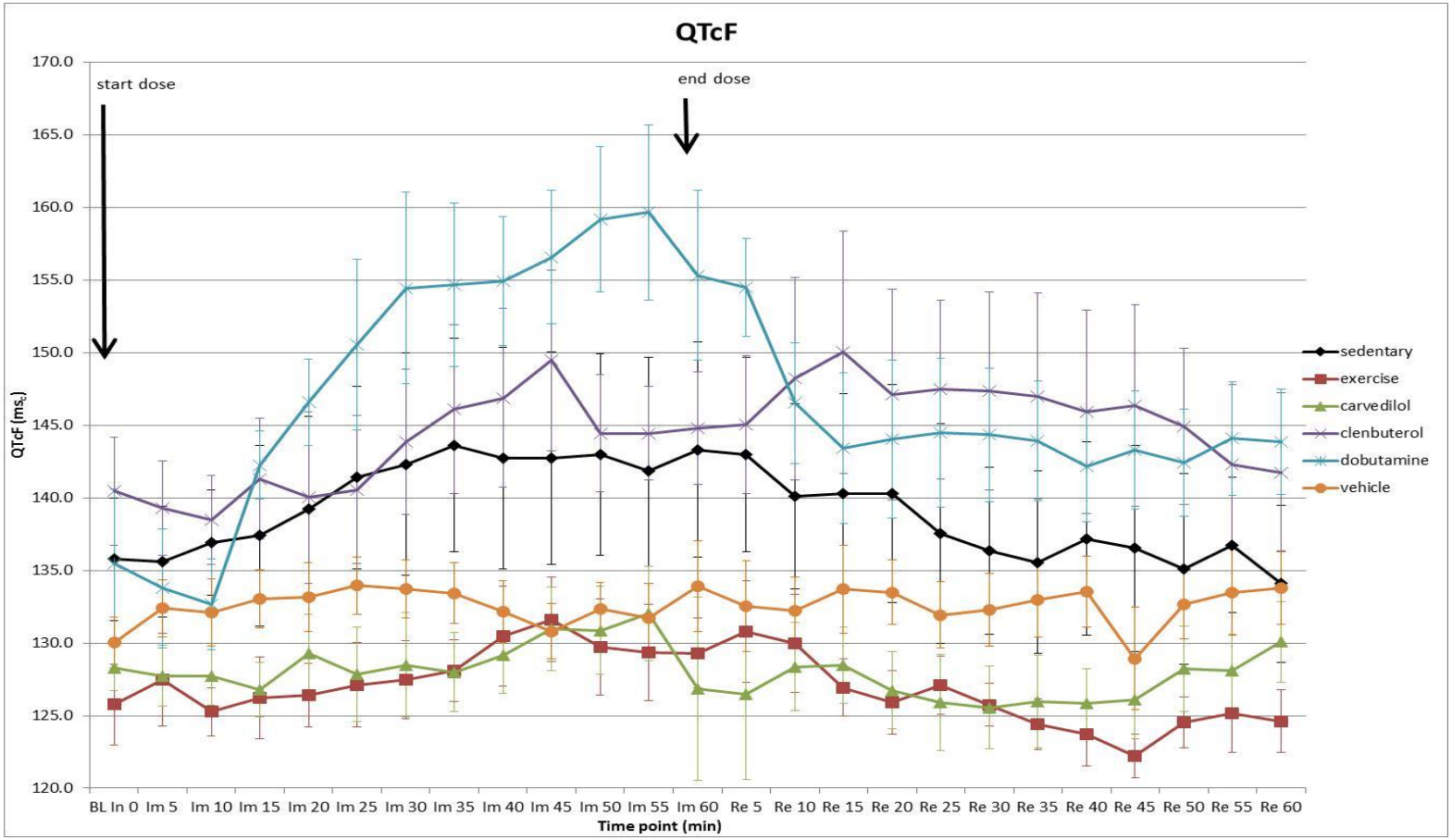

Figure 43. Effect of imipramine or vehicle infusion on QTcF from lead V3 in all interventions. Values are means ± SE. QTcF, corrected QT by Fridericia 's formula.

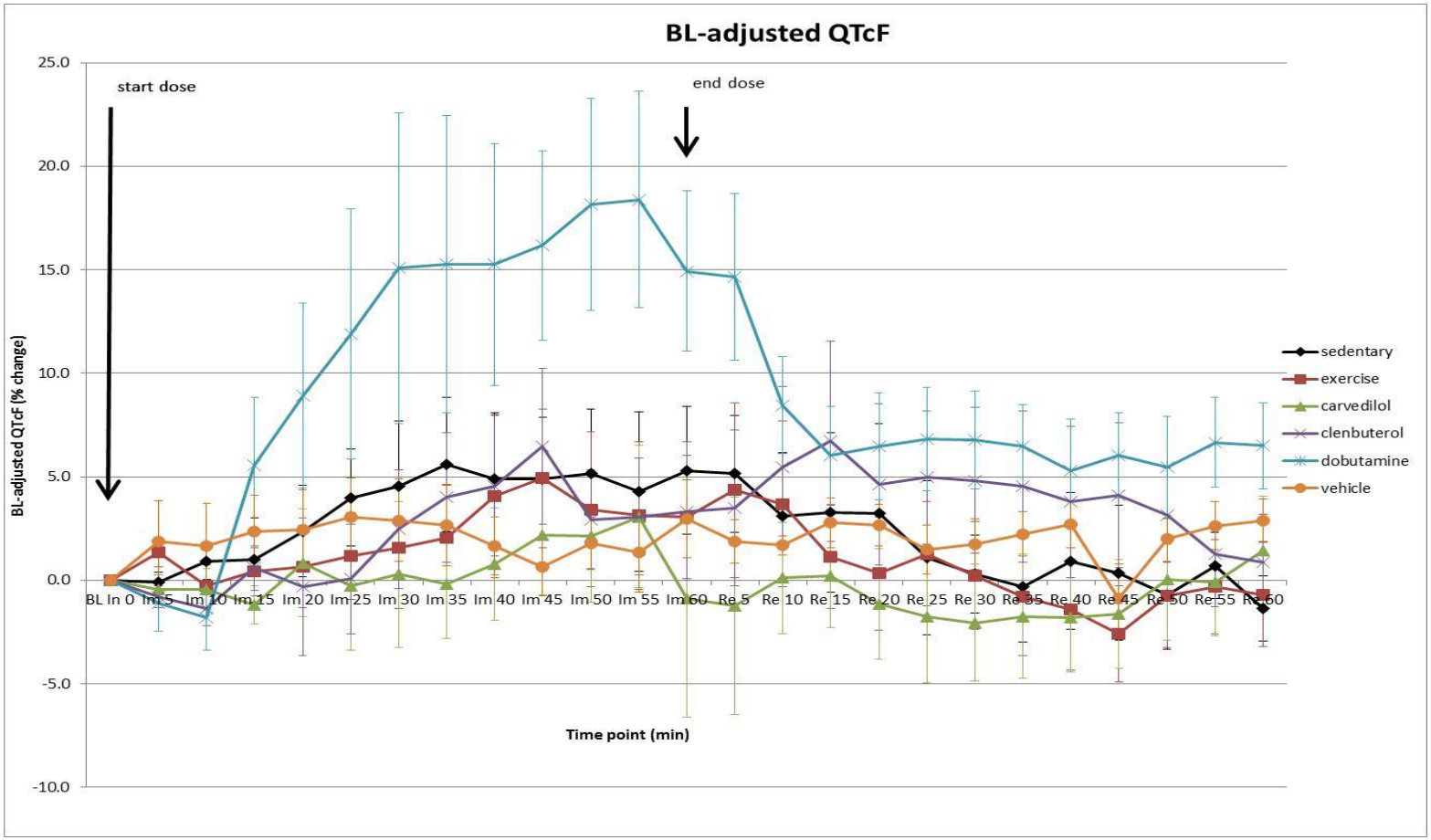

Figure 44. Effect of imipramine or vehicle infusion on BL-adjusted QTcF from lead V3 in all interventions. Values are means ± SE. BL-adjusted QTcF, % change from its baseline-instrumentation value of corrected QT by Fridericia ‘s formula.

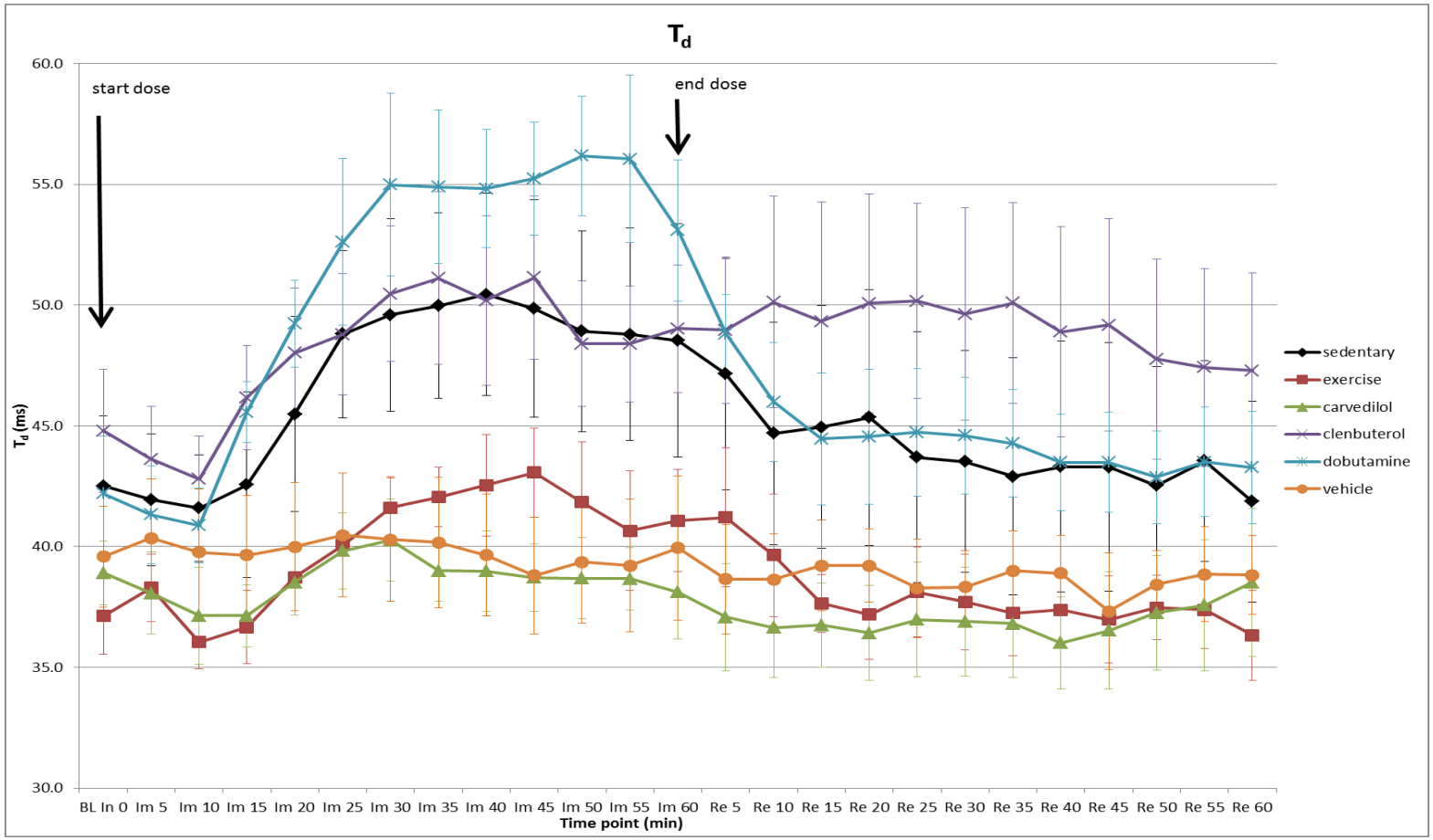

Figure 45. Effect of imipramine or vehicle infusion on T_d from lead V3 in all interventions. Values are means ± SE. T_d, duration of T wave.

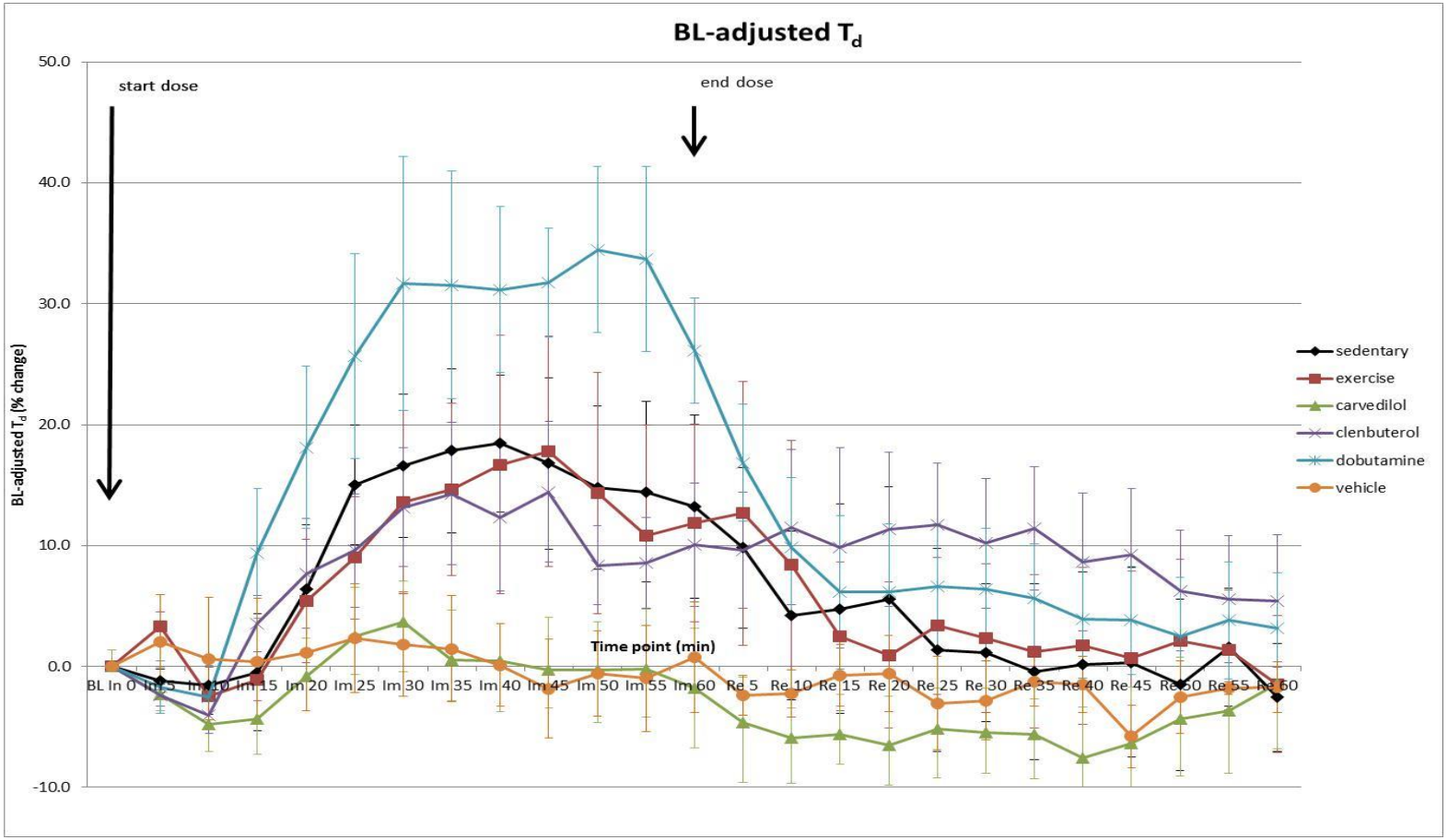

Figure 46. Effect of imipramine or vehicle infusion on BL-adjusted T_d from lead V3 in all interventions. Values are means ± SE. BL-adjusted T_d, % change from its baseline-instrumentation value of T wave duration.

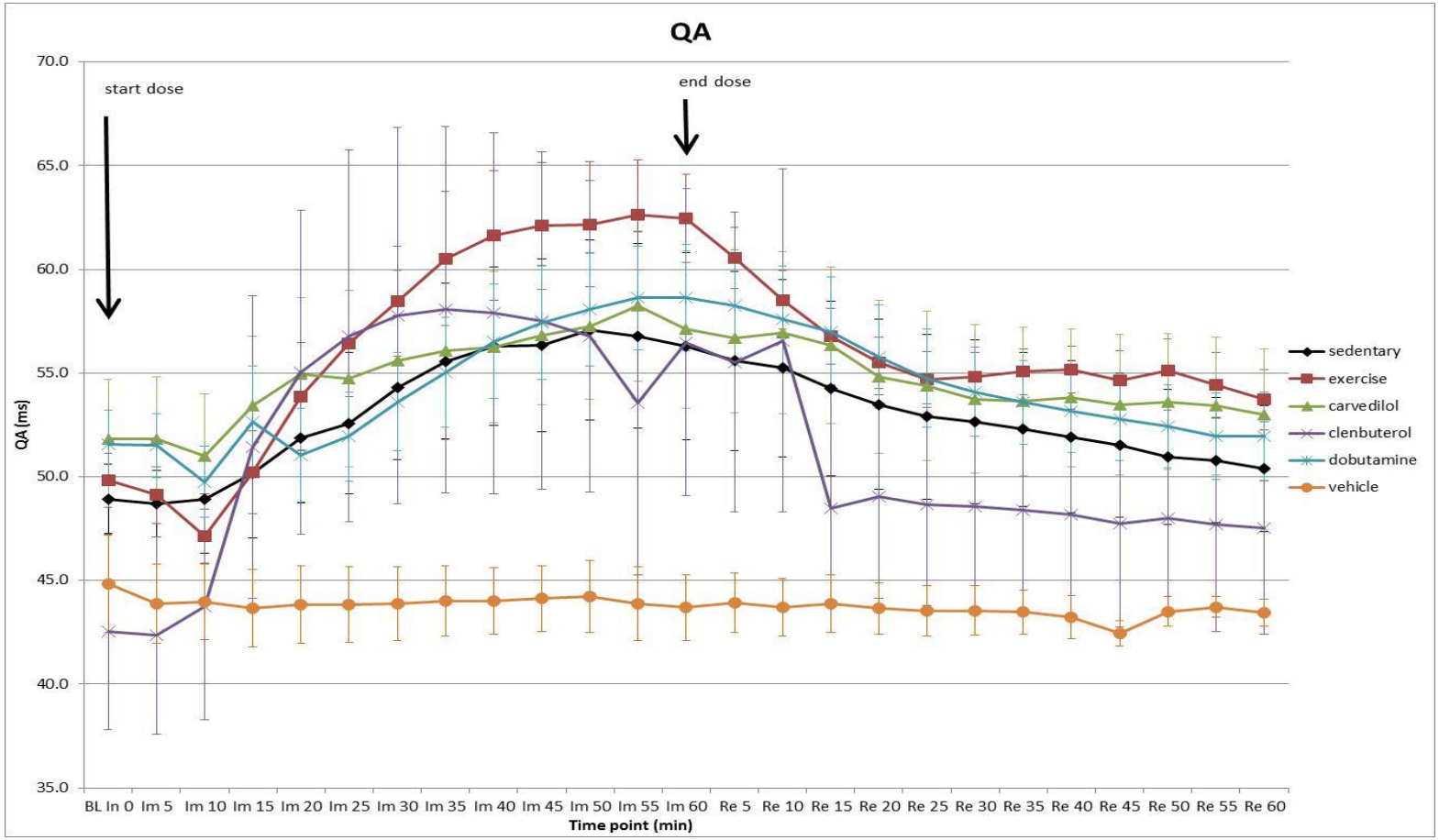

Figure 47. Effect of imipramine or vehicle infusion on QA from lead V3 in all interventions. Values are means ± SE. QA, duration from beginning of Q to point of aortic pressure upstroke.

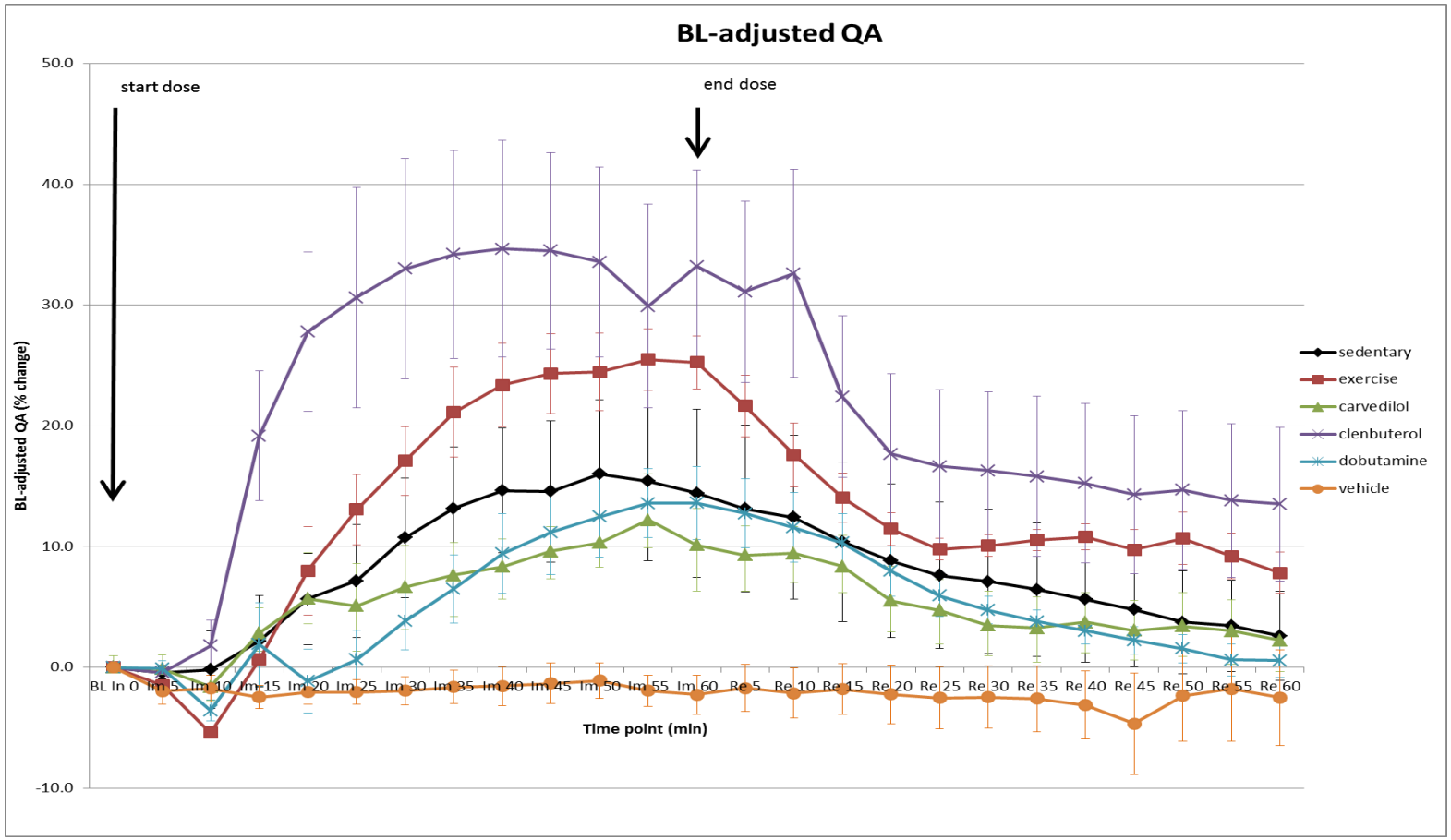

Figure 48. Effect of imipramine or vehicle infusion on BL-adjusted QA from lead V3 in all interventions. Values are means ± SE. BL-adjusted QA, % change from its baseline-instrumentation value of duration from beginning of Q to point of aortic pressure upstroke.

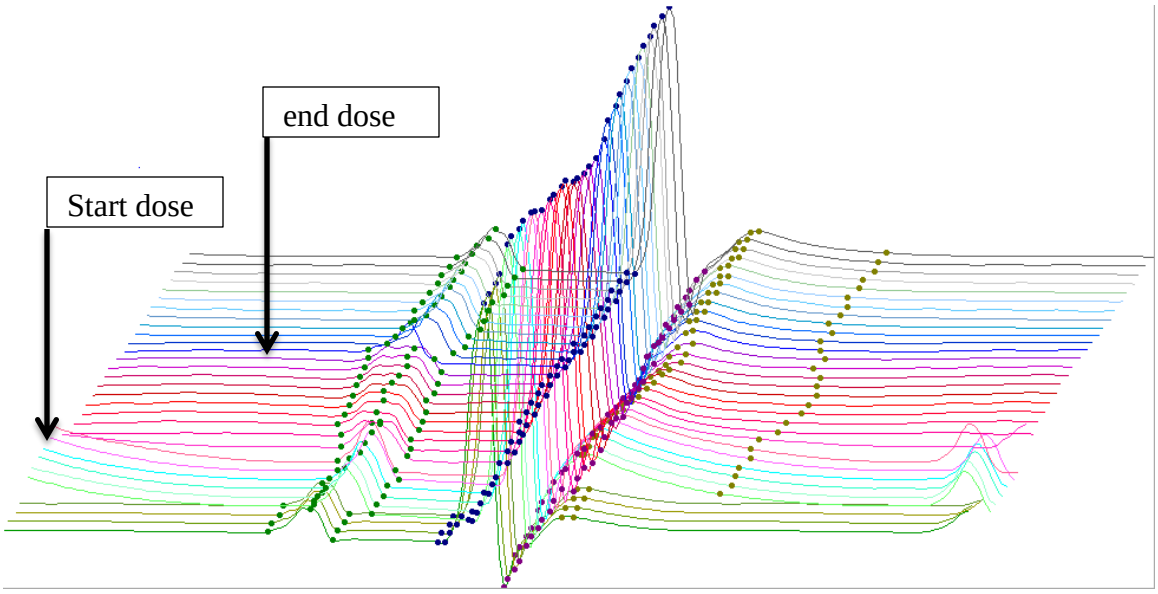

Figure 49. Effects of imipramine infusion on ECG from lead V3 in exercise rat.

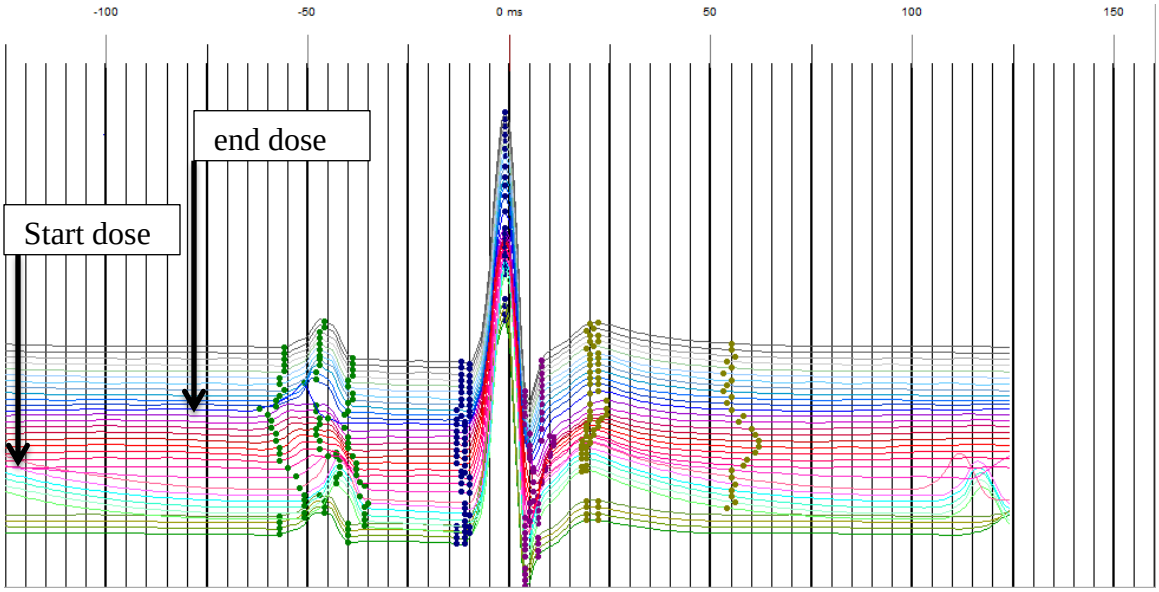

Figure 50. Effects of imipramine infusion ECG durations from lead V3 in exercise rat.

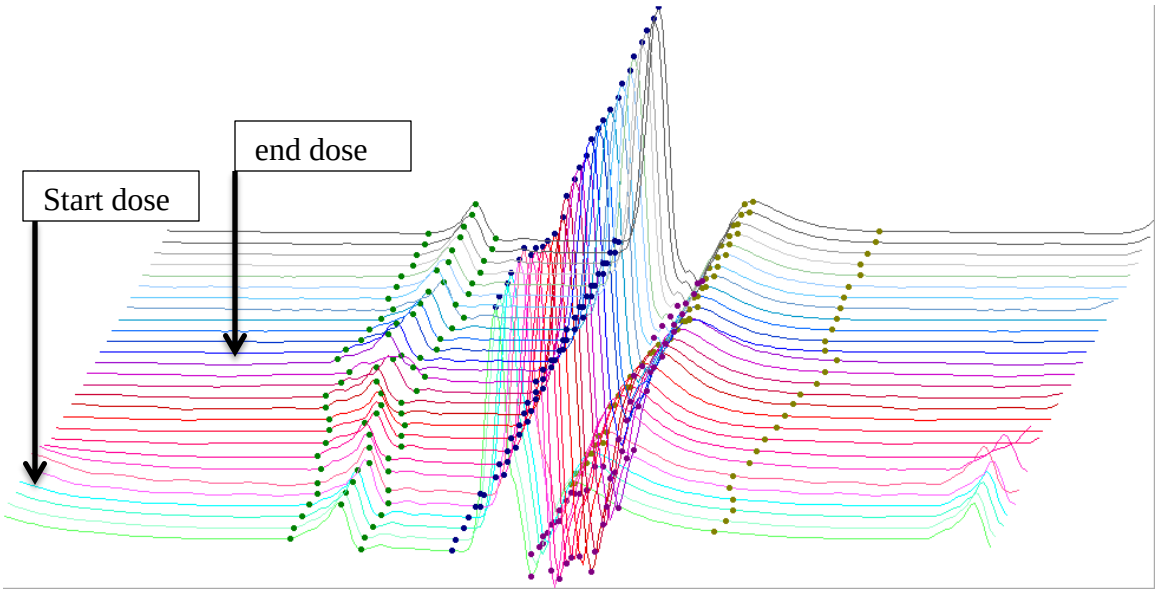

Figure 51. Effects of imipramine infusion on ECG from lead V3 in carvedilol rat.

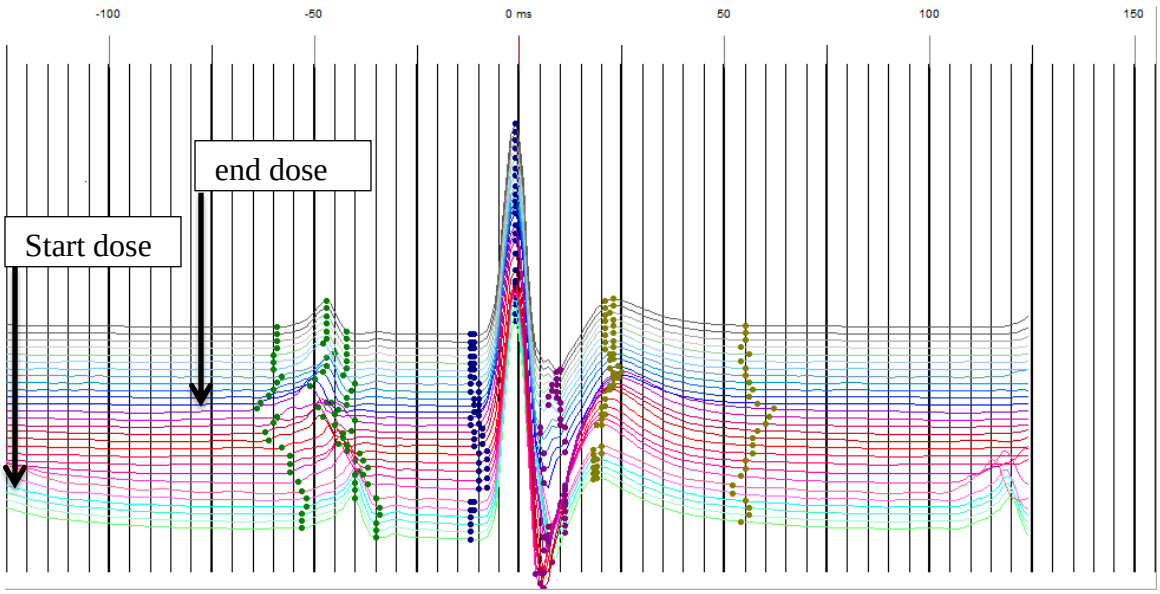

Figure 52. Effects of imipramine infusion on ECG durations from lead V3 in carvedilol rat.

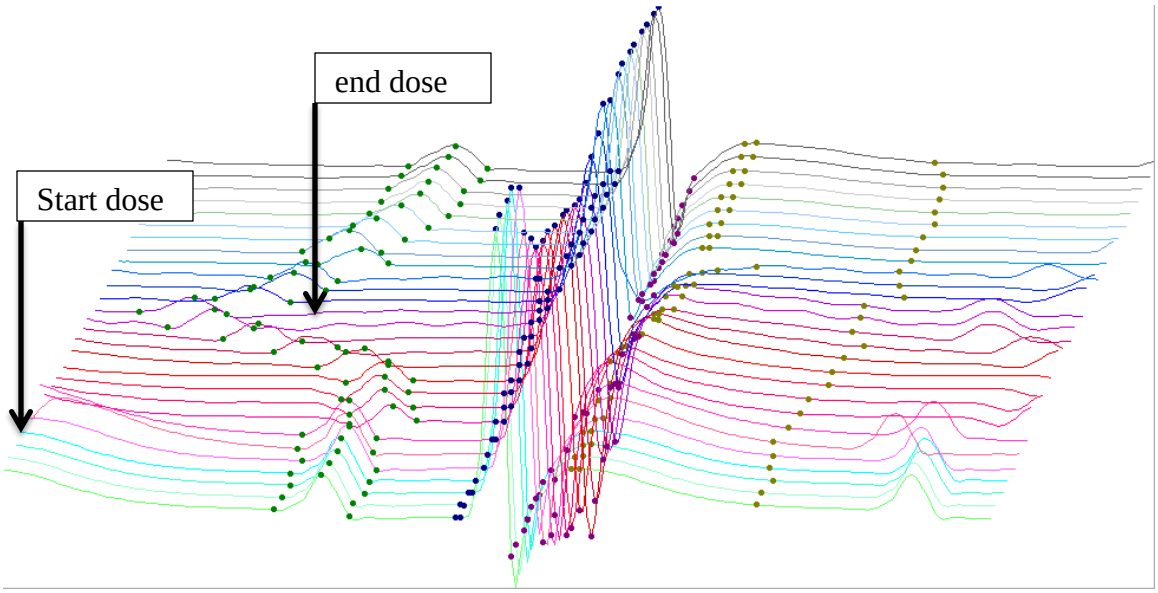

Figure 53. Effects of imipramine infusion on ECG from lead V3 in clenbuterol rat.

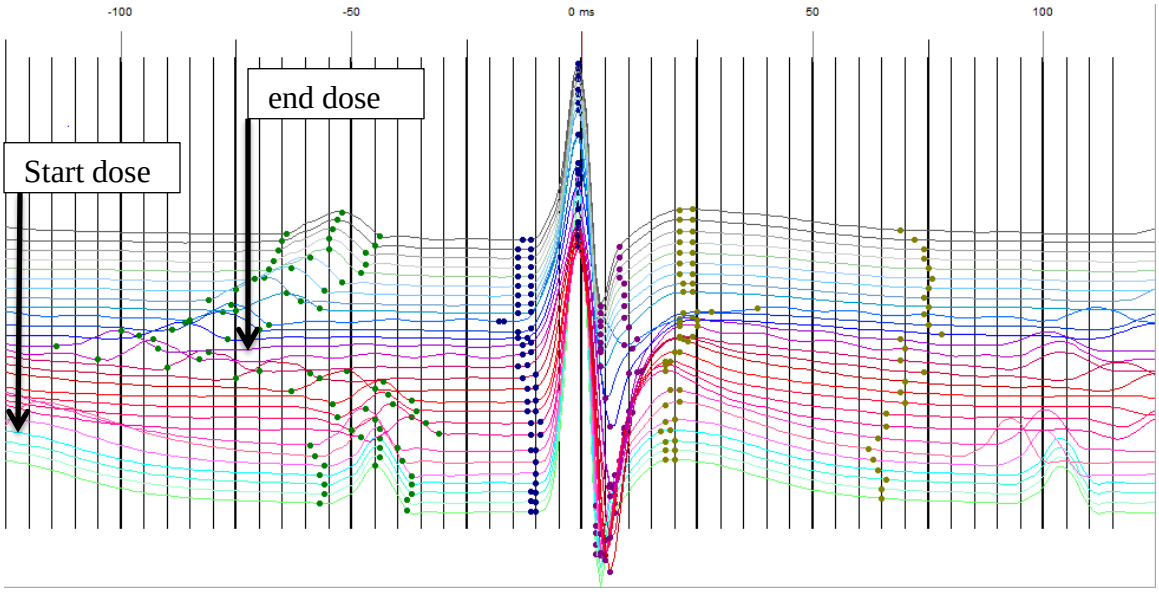

Figure 54. Effects of imipramine infusion on ECG durations from lead V3 in clenbuterol rat.

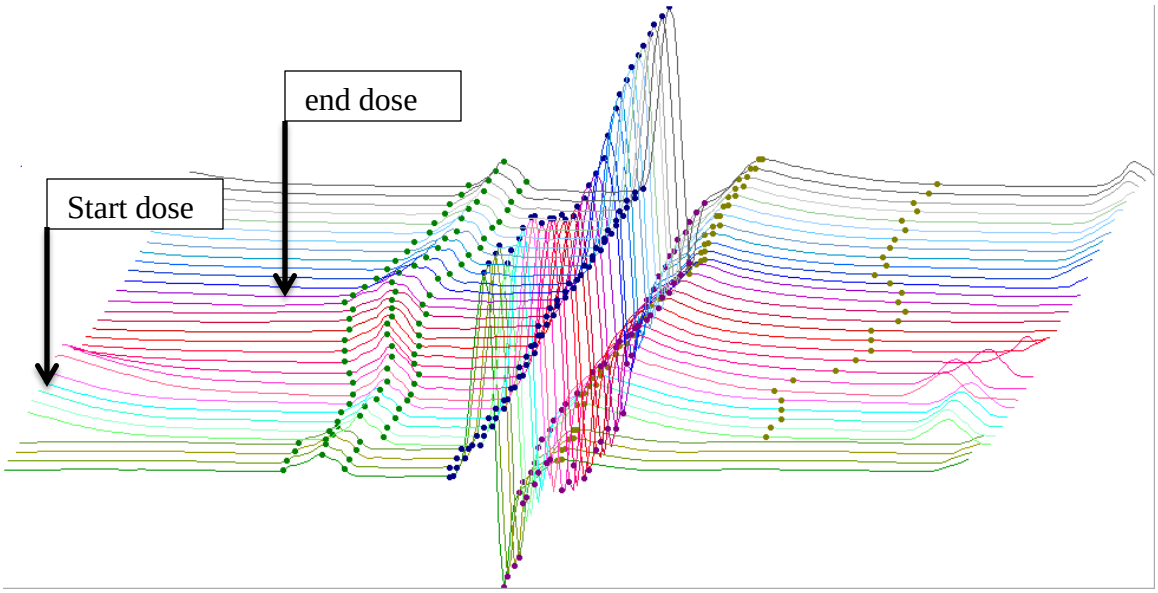

Figure 55. Effects of imipramine infusion on ECG from lead V3 in dobutamine rat.

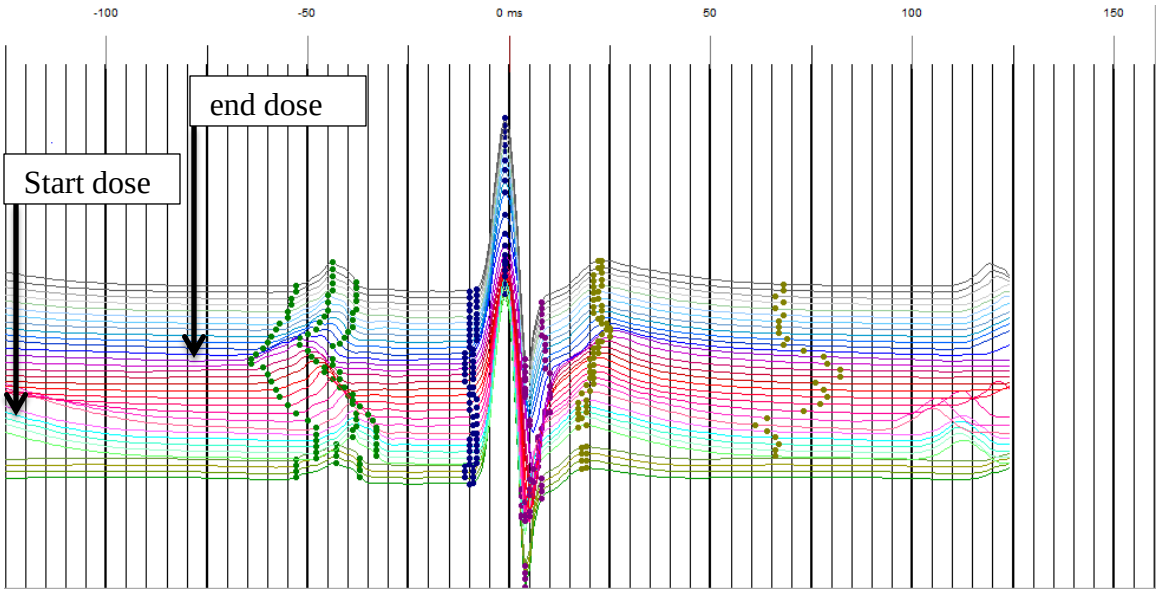

Figure 56. Effects of imipramine infusion on ECG durations from lead V3 in dobutamine rat.

5.4.2 Maximal effects of imipramine on ECG from lead V3 in all interventions

Maximal effects of imipramine on lead V3 in all interventions expressed as the Max effect, Δ value, and Δ % were presented in table 36. There were no statistically significances among imipramine challanged groups in the alterations of RR, HR, P_d, PR, PR_{sect}, and QRS.

However, QT interval was significantly difference in the dobutamine group when compared with other groups. QT intervals (expressed as Max effect, Δ value, and/or Δ %) of the dobutamine group was significantly higher than in other interventions. There were also some differences in impact of imipramine on QTcB and QTcF among interventions. Max effect of QTcB and QTcF of the dobutamine group were significantly higher than in the exercise and the carvedilol groups. Max effect value of QTcB of the clebuterol group was significantly higher than in the carvedilol group ($P < 0.05$). Moreover, Max effect of QT_1 in the sedentary group was significantly lower than those of the carvedilol and the clenbuterol groups. QA expressed as Δ % of the clenbuterol group was significantly higher than most interventions ($P < 0.05$), except the exercise group. Comparing imipramine impact on T_d prolongation, the values of Max effect, Δ value, and Δ % of the dobutamine group were significantly higher than those of the carvedilol group. The value of Max effect of the dobutamine group was also significantly higher than the exercise group ($P < 0.05$).

However, times at the maximal effect on lead V3 were not significant different among imipramine challanged groups (see table 37).

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Sedentary	Baseline	147 ± 8	413 ± 21	15.3 ± 0.7	40.4 ± 1.2	25.0 ± 1.4	19.7 ± 0.7
	Max effect	196 ± 14	313 ± 21	18.1 ± 0.8	50.3 ± 1.1	32.7 ± 0.8	24.6 ± 1.1
	Δ value	49 ± 8	-100 ± 15	2.7 ± 0.5	9.9 ± 1.3	7.7 ± 1.3	4.9 ± 1.3
	Δ %	33.0 ± 5.6	-24.2 ± 3.1	18.1 ± 3.5	25.0 ± 3.6	32.4 ± 6.1	25.5 ± 7.4
Exercise	Baseline	155 ± 5	389 ± 13	15.0 ± 0.7	38.5 ± 2.4	23.5 ± 1.7	19.9 ± 0.3
	Max effect	215 ± 6	281 ± 9	19.6 ± 1.1	52.5 ± 2.9	33.4 ± 1.9	26.8 ± 1.6
	Δ value	60 ± 3	-108 ± 5	4.6 ± 1.2	14.0 ± 3.4	9.9 ± 2.5	6.8 ± 1.6
	Δ %	38.6 ± 1.7	-27.8 ± 0.9	32.0 ± 8.7	38.8 ± 10.5	46.3 ± 14.1	34.2 ± 8.1
Carvedilol	Baseline	159 ± 4	380 ± 11	15.5 ± 0.9	38.8 ± 1.3	23.3 ± 0.9	20.8 ± 1.1
	Max effect	225 ± 40	294 ± 31	18.9 ± 1.1	51.9 ± 1.4	34.3 ± 1.5	26.7 ± 1.1
	Δ value	67 ± 38	-86 ± 28	3.4 ± 1.1	13.1 ± 2.5	10.9 ± 2.2	5.9 ± 1.2
	Δ %	41.1 ± 22.7	-22.9 ± 7.8	23.8 ± 8.3	34.9 ± 7.3	48.9 ± 10.9	29.7 ± 6.3
Clenbuterol	Baseline	146 ± 4	412 ± 10	16.2 ± 0.9	42.5 ± 1.3	26.3 ± 0.6	18.2 ± 0.3
	Max effect	209 ± 6	288 ± 8	19.1 ± 0.9	60.5 ± 8.3	41.9 ± 7.5	23.5 ± 0.7
	Δ value	63 ± 8	-124 ± 15	3.0 ± 0.4	18.0 ± 7.7	15.6 ± 7.4	5.4 ± 0.8
	Δ %	43.8 ± 6.3	-29.8 ± 3.0	18.8 ± 3.2	41.5 ± 16.7	59.1 ± 27.7	29.8 ± 4.4
Dobutamine	Baseline	145 ± 5	416 ± 14	14.7 ± 0.4	36.4 ± 0.7	21.7 ± 0.8	18.1 ± 0.6
	Max effect	163 ± 29	310 ± 15	19.4 ± 0.9	56.9 ± 3.4	38.8 ± 3.7	25.7 ± 1.3
	Δ value	18 ± 31	-106 ± 11	4.7 ± 0.8	20.6 ± 3.5	17.1 ± 3.8	7.7 ± 1.3
	Δ %	35.0 ± 4.3	-25.5 ± 2.6	32.4 ± 5.3	56.9 ± 10.4	79.6 ± 18.7	42.4 ± 8.4

Continued

Table 36. Maximal effects of imipramine on ECG from lead V3 in all interventions. Values are means ± SE. n = 6.

Table 36. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Sedentary	Baseline	71.6 ± 2.5	187.1 ± 6.0	135.8 ± 4.2	9.06 ± 0.90	48.9 ± 1.7	42.5 ± 2.9
	Max effect	84.3 ± 4.5	199.6 ± 9.8	147.9 ± 7.7	9.19 ± 1.10 [ca, cl]	58.4 ± 3.9	51.8 ± 4.1
	Δ value	12.7 ± 3.1 [d]	12.5 ± 4.6	12.1 ± 4.7	0.1 ± 1.1	9.5 ± 2.8	9.3 ± 2.3
	Δ %	17.7 ± 4.4	6.4 ± 2.3	8.7 ± 3.3	5.7 ± 13.6	19.0 ± 5.3 [cl]	21.8 ± 5.9
Exercise	Baseline	67.5 ± 1.1	171.7 ± 4.5	125.8 ± 2.8	10.42 ± 0.59	49.8 ± 1.3	37.1 ± 1.6
	Max effect	79.3 ± 1.7[d]	180.2 ± 3.5 [d]	134.4 ± 2.7 [d]	11.80 ± 0.42	63.5 ± 2.8	44.9 ± 1.9 [d]
	Δ value	11.8 ± 2.1 [d]	8.5 ± 3.2	8.7 ± 3.5	1.4 ± 0.5	13.7 ± 1.8	7.8 ± 2.8
	Δ %	17.7 ± 3.3	5.1 ± 2.1	7.1 ± 3.0	14.7 ± 6.6	27.2 ± 3.0	22.6 ± 9.4
Carvedilol	Baseline	69.4 ± 1.1	174.5 ± 2.3	128.3 ± 1.6	10.24 ± 1.00	51.8 ± 2.9	38.9 ± 1.3
	Max effect	75.7 ± 1.0[D]	170.0 ± 12.3 [d, cl]	128.7 ± 6.7 [D, cl]	12.74 ± 0.70	58.8 ± 3.8	41.5 ± 1.6 [d]
	Δ value	6.3 ± 1.5 [D]	-4.4 ± 13.1	0.4 ± 7.6	2.5 ± 0.7	7.0 ± 1.5	2.6 ± 1.3 [d]
	Δ %	9.2 ± 2.3 [d]	-2.3 ± 7.5	0.5 ± 5.9 [d]	28.7 ± 10.6	13.3 ± 2.6 [cl]	6.9 ± 3.5 [d]
Clenbuterol	Baseline	74.0 ± 2.3	193.6 ± 4.9	140.5 ± 3.7	11.14 ± 0.42	42.5 ± 4.7	44.8 ± 2.5
	Max effect	86.8 ± 3.0	206.0 ± 5.9	153.2 ± 5.0	12.41 ± 0.68	59.7 ± 8.3	53.0 ± 3.3
	Δ value	12.8 ± 2.4 [d]	12.4 ± 4.8	12.8 ± 4.3	1.3 ± 0.3	17.2 ± 4.5	8.2 ± 2.4
	Δ %	17.5 ± 3.3	6.5 ± 2.5	9.2 ± 3.1	11.1 ± 2.4	39.9 ± 8.3	18.8 ± 5.6
Dobutamine	Baseline	71.2 ± 3.1	187.0 ± 6.7	135.5 ± 5.1	10.56 ± 0.80	51.6 ± 1.6	42.2 ± 2.4
	Max effect	95.1 ± 2.7	218.5 ± 4.8	165.3 ± 3.6	11.92 ± 0.50	59.0 ± 2.5	59.5 ± 2.3
	Δ value	23.9 ± 3.6	31.5 ± 9.4	29.9 ± 6.8	1.4 ± 0.7	7.5 ± 1.5	17.3 ± 2.6
	Δ %	34.6 ± 6.3	17.4 ± 5.6	22.7 ± 5.8	15.3 ± 8.2	14.4 ± 2.8 [cl]	42.8 ± 8.0

Values are means ± SE. n = 6. [ca]$P < 0.05$ vs. carvedilol; [cl]$P < 0.05$ vs. clenbuterol; [D]$P < 0.001$ vs. dobutamine; [d]$P < 0.05$ vs. dobutamine.

Group	Sedentary (min)	Exercise (min)	Carvedilol (min)	Clenbuterol (min)	Dobutamine (min)
RR	45.8 ± 3.7	46.7 ± 4.0	50.8 ± 5.8	49.2 ± 6.9	49.2 ± 4.9
HR	45.8 ± 3.7	46.7 ± 4.0	50.8 ± 5.8	49.2 ± 6.9	49.2 ± 4.9
PR	51.7 ± 4.0	43.3 ± 6.4	48.3 ± 4.9	52.5 ± 4.6	47.5 ± 5.9
P_d	55.8 ± 2.7	48.3 ± 6.7	52.5 ± 6.6	55.8 ± 3.3	57.5 ± 1.7
QRS	55.8 ± 2.7	48.3 ± 6.7	52.5 ± 6.6	55.0 ± 3.4	57.5 ± 2.5
QT	46.7 ± 6.1	56.7 ± 1.7	50.8 ± 4.7	55.0 ± 2.2	53.3 ± 4.0
QTcB	45.8 ± 4.4	45.8 ± 3.3	50.8 ± 4.4	46.7 ± 4.6	48.3 ± 3.3
QTcF	28.3 ± 6.5	23.3 ± 7.1	33.3 ± 10.5	37.5 ± 8.4	45.0 ± 5.2
PR_{sect}	31.7 ± 6.0	34.2 ± 6.2	40.8 ± 10.6	40.8 ± 7.2	48.3 ± 3.3
QT_1	48.3 ± 5.3	26.7 ± 9.5	34.2 ± 11.6	32.5 ± 8.6	48.3 ± 6.9
QA	51.7 ± 4.8	52.5 ± 4.0	50.0 ± 4.5	45.0 ± 4.8	55.0 ± 1.8
T_d	38.3 ± 6.7	39.2 ± 6.2	30.8 ± 6.8	38.3 ± 3.6	49.2 ± 4.4

Table 37. Times at imipramine maximal effect on ECG from lead V3 in all interventions. Values are means ± SE; n = 6.

5.5 Effect of imipramine or vehicle infusion on arrhythmia

There was no obvious arrhythmia in any of the sedentary group during imipramine infusion and recovery periods. However, there were some incidences of arrhythmias and impairments of cardiac conduction that may be associated with instrumentation procedure and/or imipramine or matched-volume vehicle infusion. For instant, there were two out of six rats in the exercise group that exhibited left side ventricular premature depolarization (VPD) that were last only few beats during imipramine infusion or recovery period (see figure 57 and 58).

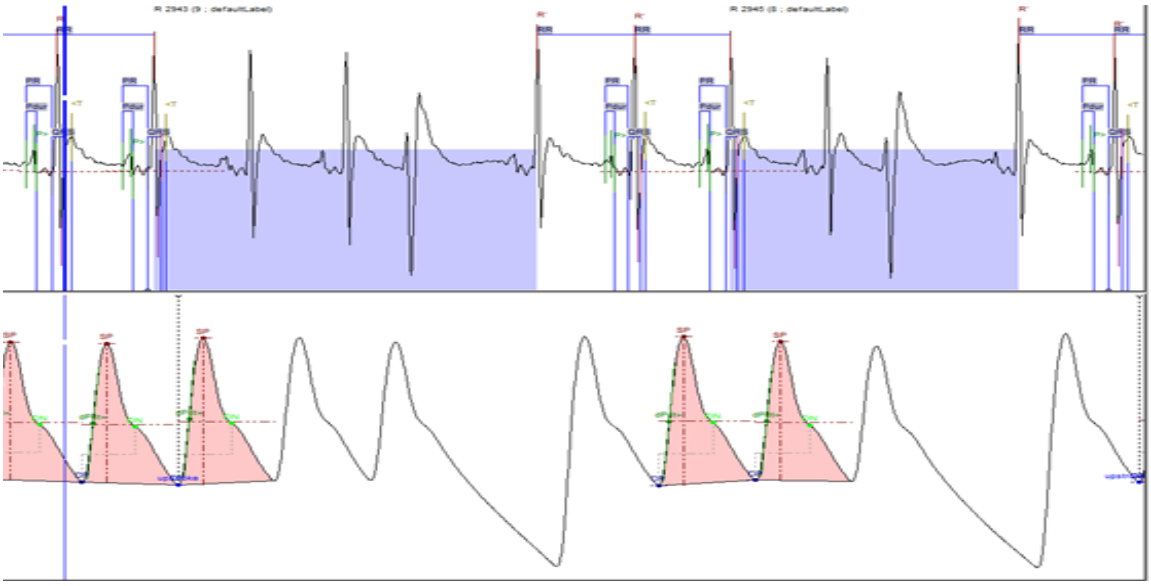

Figure 57. Rat ID 693 in exercise group had couple left side VPD at 15 min after start imipramine infusion.

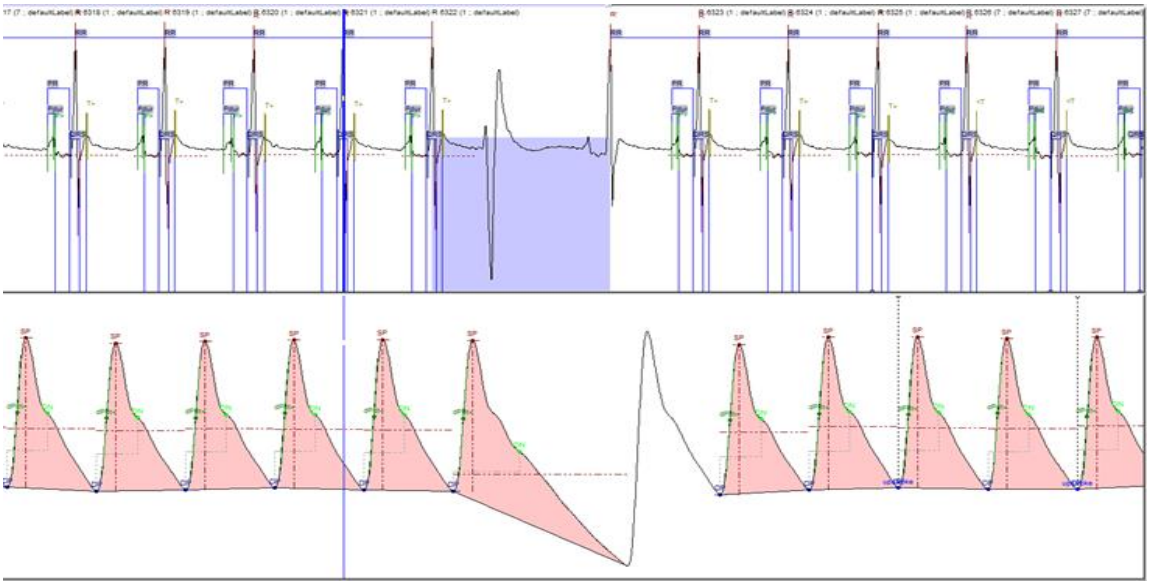

Figure 58. Rat ID 696 in exercise group had couple left side VPD at 15 min after cessation of imipramine.

In the carvedilol group, there were three out of six rats that had alterations in ECG rhythm, two of those had left side VPD, and one rat had 2nd degree atrioventricular (AV) block, see figures 59 to 61. Only one out of six rats in the clenbuterol group had couple left side VPD at 10 min after imipramine infusion (see figure 62). In the dobutamine group, two out of six rats experienced couple VPD episodes and one out of six rats had couple left side VPD, see figures 63 to 65.

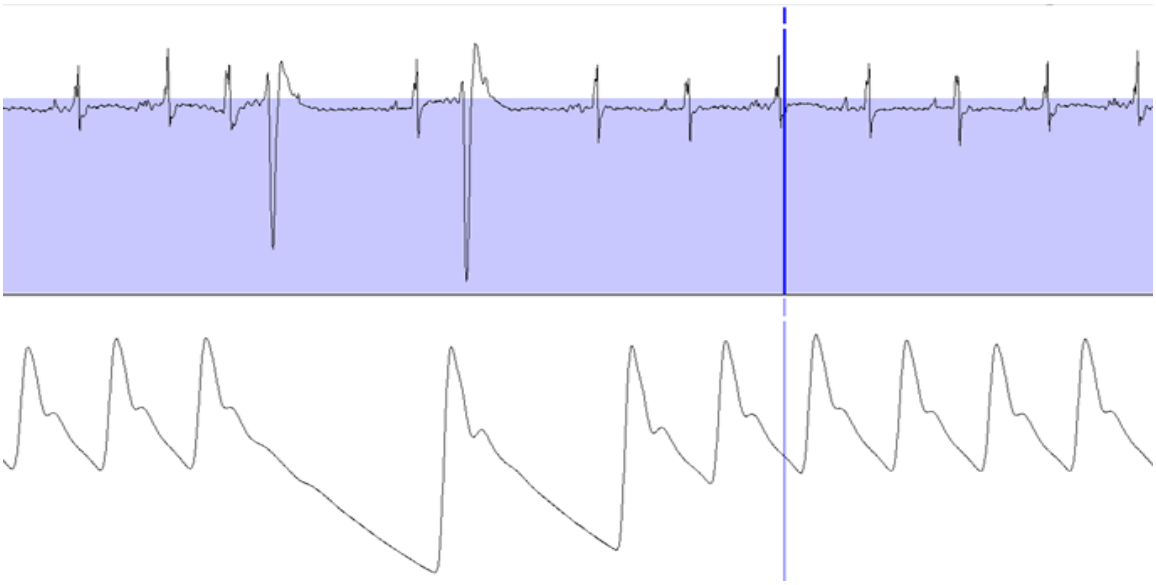

Figure 59. Rat ID 601 in carvedilol group had couple left side VPD at 10 min after cessation of imipramine.

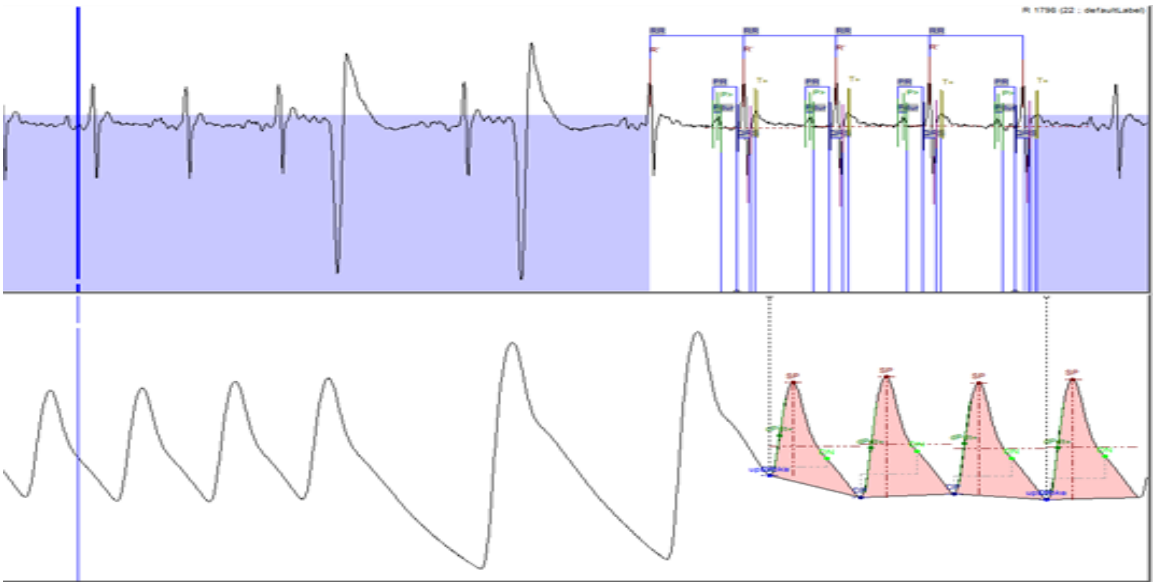

Figure 60. Rat ID 612 in carvedilol group had couple left side VPD at 20 min after start imipramine infusion.

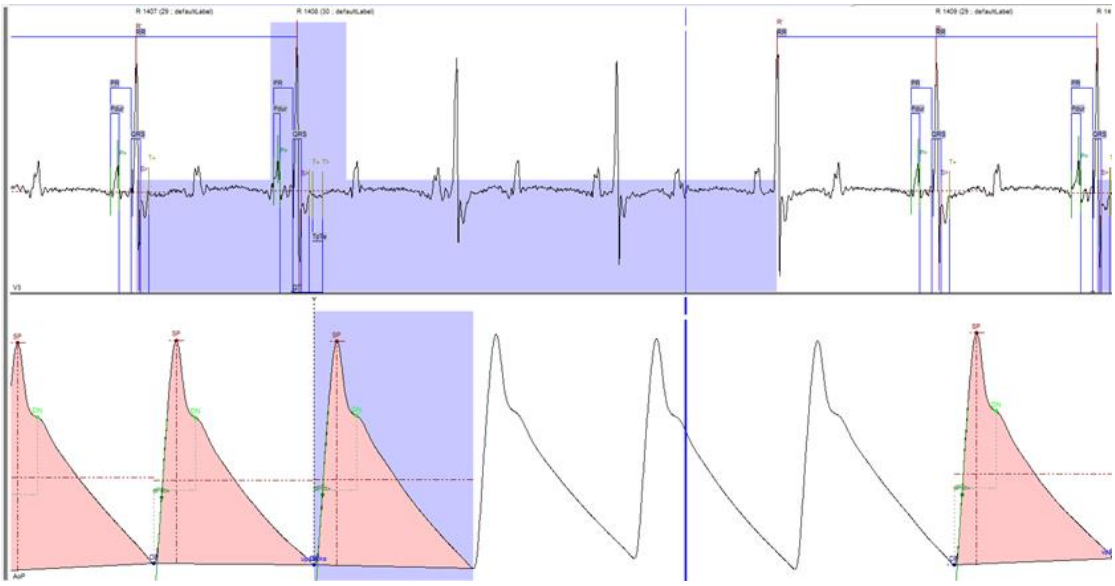

Figure 61. Rat ID 12 in carvedilol group had 2nd degree atrioventricular (AV) block at 59 min after start imipramine infusion to 5 min after cessation of imipramine.

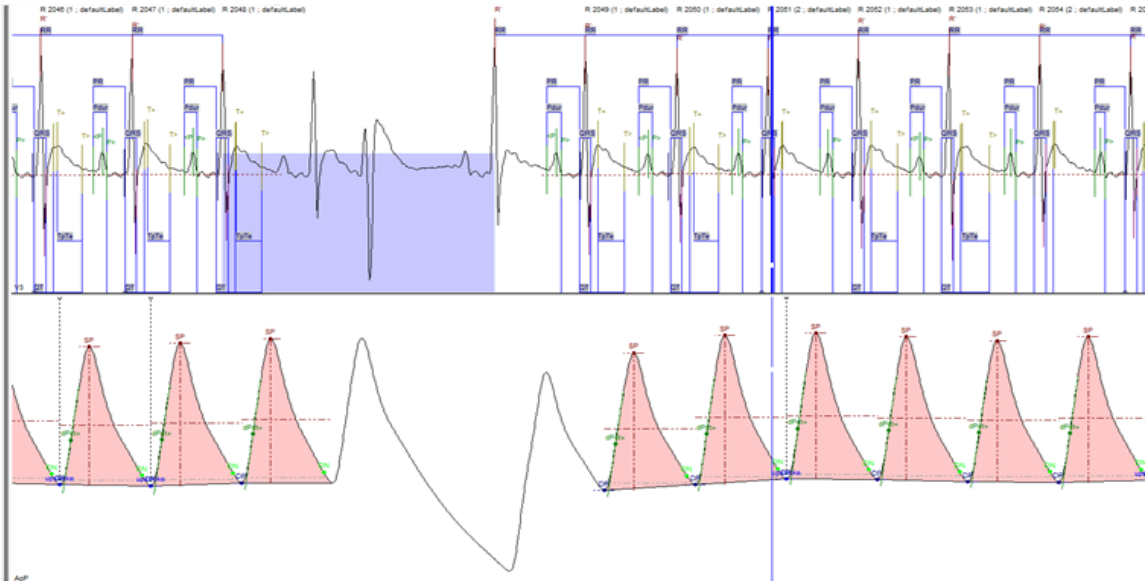

Figure 62. Rat ID 14 in clenbuterol group had couple left side VPD at 10 min after start imipramine infusion.

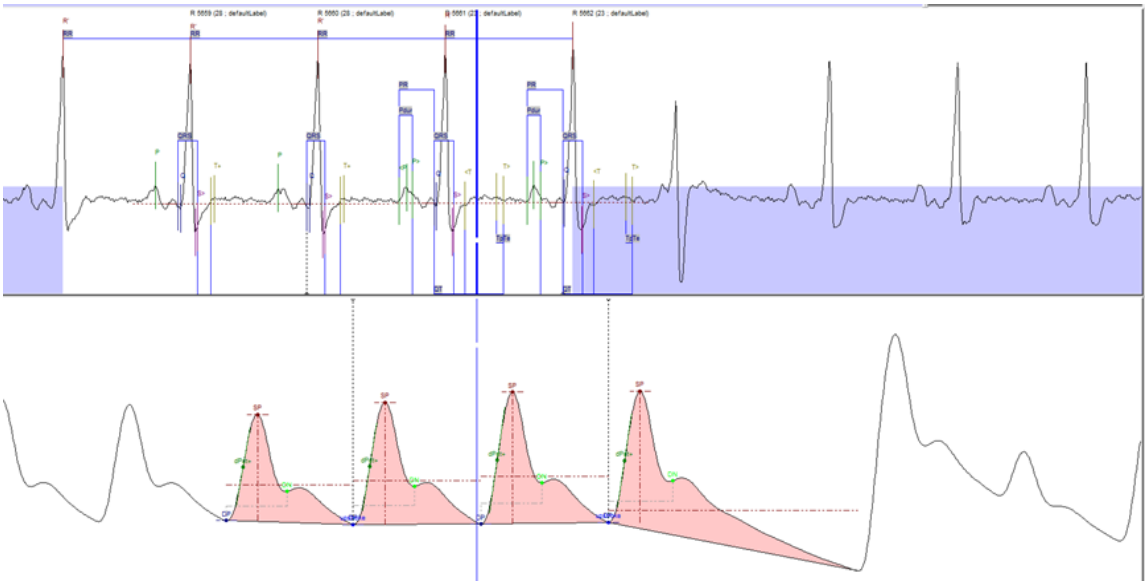

Figure 63. Rat ID 615 in dobutamine group had single VPD at 30 min after cessation of imipramine.

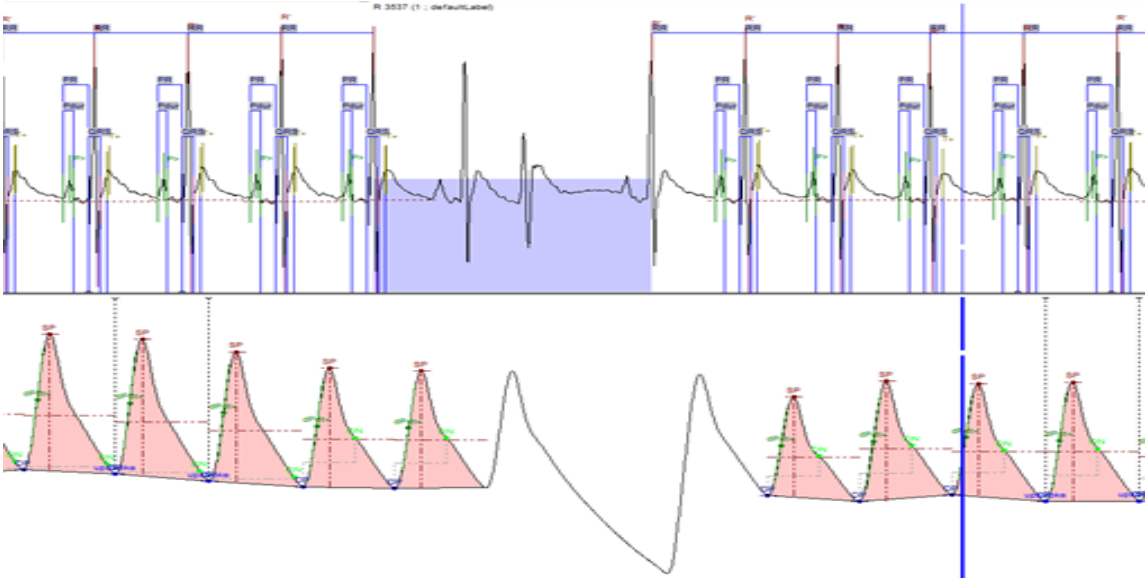

Figure 64. Rat ID 8 in dobutamine group had VPD at multiple time points (5, 10, and 20 min after start imipramine infusion).

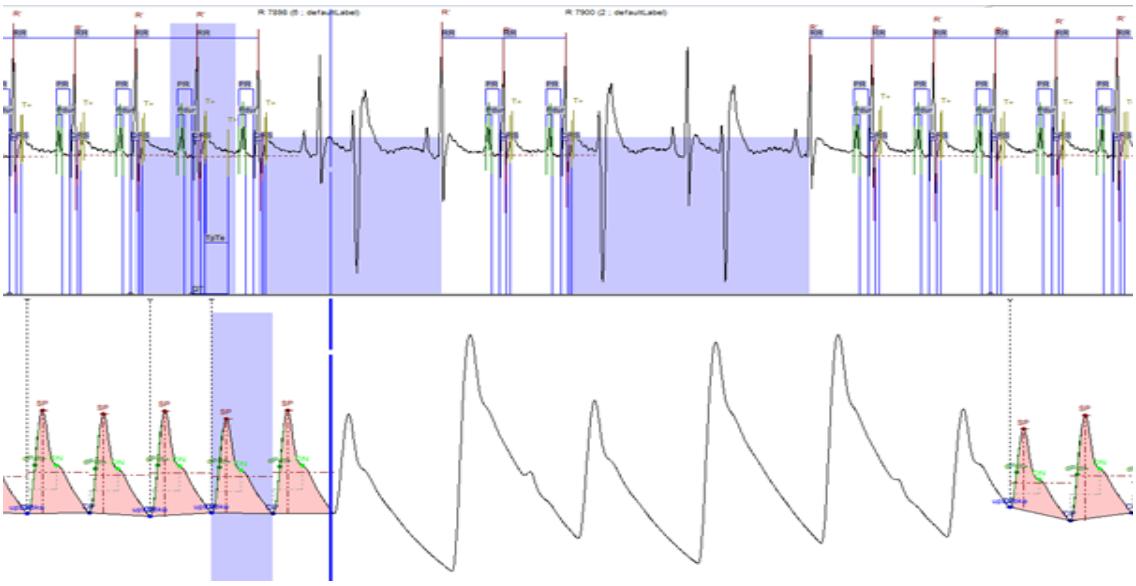

Figure 65. Rat ID 9 in dobutamine group had couple left side VPD at multiple time points (5 and 35 min after imipramine infusion, as well as, 40, and 60 min after cessation of imipramine).

However, left side VPD episodes were also found in two out of four rats receiving matched-volume vehicle infusion, one of those rats (ID 6) showed multiple episodes of couple left side VPD per minute from the baseline-instrumentation period until the end recovery period, without obvious alteration in mean of hemodynamic parameters (data not show). However, at 50 min after cessation of imipramine infusion this rat developed higher grade of this arrhythmia (bigeminy) for 10 seconds. The other rat (ID 1) had one episode of couple left side VPD during imipramine infusion, and trended to have lower in hemodynamic values than other vehicle rats throughout the time points (data not show). Figure 66 and 67 show examples of arrhythmia episodes in the vehicle group.

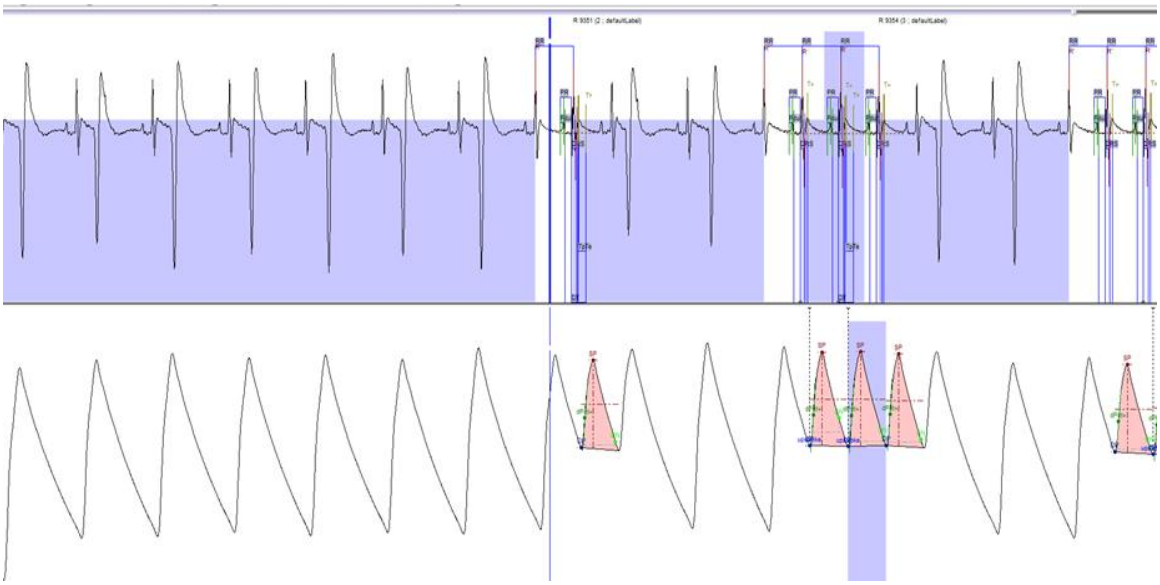

Figure 66. Rat ID 6 of vehicle group had 10 second of left side VPD (bigeminy) at 50 min after cessation of imipramine.

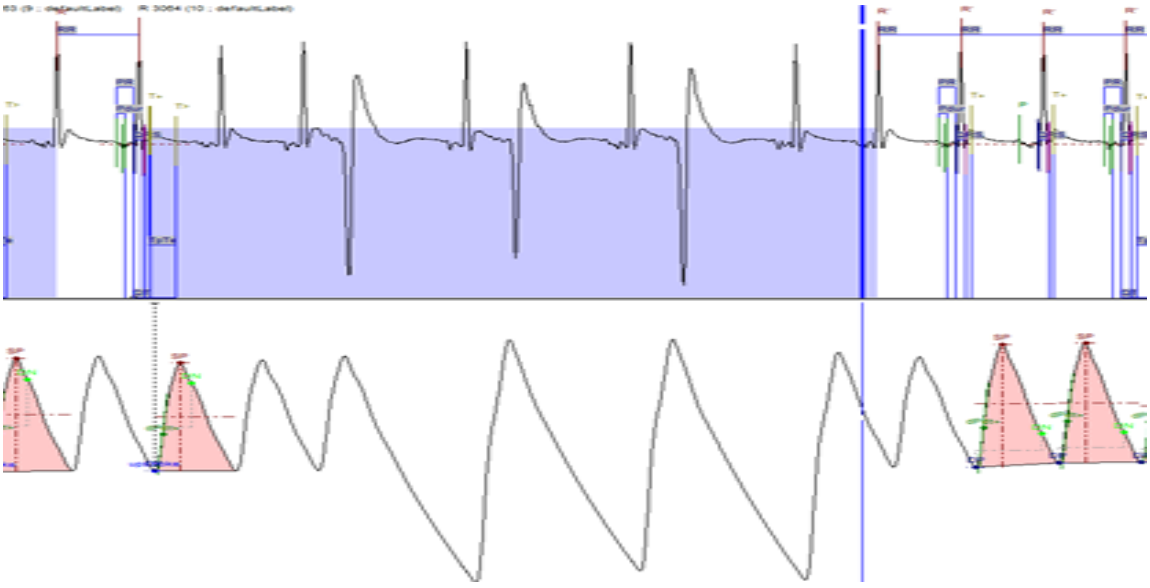

Figure 67. Rat ID 1 of vehicle group had couple left side VPD at 40 min after start imipramine infusion.

Chapter 6: Discussion, study limitations, future studies, and conclusion

6.1 Discussion: Effects of interventions on physiological parameters

6.1.1 Effects of interventions on body weight, heart weight, brain weight, and their ratios

Although, aerobic training can result in significant reduction in body weight in humans [175] and animals [173], exercise training can also increase muscle mass [101, 175] that may contribute to weight gain. Also, a non-significant alteration in body weight found in this study agreed with results in exercise-trained rats studied by De Souza and colleagues (2014) [176]. They found no significant alteration in body weight among control, aerobic trained, resistance trained, and concurrent training (combined aerobic and resistance training). Nevertheless, there were significant alterations in LV morphologies associated with the types of exercise training.

However in this study both body weight and hW/BW of the exercise group were significantly higher than in the dobutamine group. Body weight seemed to be lowest in the dobutamine group, i.e., no statistical difference in body weight compared with sedentary. This difference is not likely due to an age difference since the age all rats at termination was more than 11 weeks old, an age above which growth rate is very slow. Rats receiving pharmacological preconditioning other than dobutamine were

(approximately) of the same ages when observartions were made. Dobutamine causes significant increase in lipolysis (~5 fold) mediated via β_3-adrenergic receptor in human isolated fat cells [177]. Stimulating of β_3–induced lypolyisis may increase by increasing β_1 activity, as chronic stimulation with a β_1-adrenergic agonist can significantly increase β_3-adrenergic receptor expression [178]. Moreover, dobutamine may also mimic other catecholamine-induced catabolism, such as glycolysis and gluconeogenesis, all of which could result in significantly lower body weight compared with that in the exercise group.

The clenbuterol intervention also produced significant increase in hW/bW ratio more than existed in the sedentary group. This significance could result from the slightly higher heart weights of rats in the clenbuterol group, although there was a lesser difference in brain weight between these groups. The increase in hW/bW may be explainede by clenbuterol-inducing cardiac hypertrophy found in both normal and failing rat hearts [134, 141].

In term of stress assesed by adrenal gland weight/body weight ratio, there were no statistical differences among sedentary, pharmacologically trained, and exercise trained rats. This indicates that interventions were not great enough to induce stresses sufficieint to result in pathophysiological alteration(s).

6.1.2 Effects of interventions on hemodynamics

As shows in table 7, compared to clenbuterol, dobutamine produced statistically lower SBP, PP, LVESP, CI, and +dP/d*t*. This could result from chronic administration of the predominantly β_1-adrenergic agonist, dobutamine, at the dose that could mimic exercise-induced cardiac stress and lead to down-regulation of β_1-adrenergic receptor in

the heart. Chronic administration of clenbuterol, the β_2-adrenergic agonist, could down-regulate only β_2-adrenergic receptor expression. As showed by Ufer and Germack (2009), chronic stimulation of rat myocardial cells with a β_1-adrenergic agonist caused significant down-regulation of β_1-adrenergic receptor expression; chronic stimulation with a β_2-adrenergic agonist did not [178]. Chronic or high doses of clenbuterol in humans showed augmentation in β_1-adrenergic function of the heart [131]. Chronic clenbuterol administration in post-MI rats improved cardiac performances (increase EF and HR) concomitant with cardiac hypertrophy [141]. This increase in cardiac contraction and SBP is consistant with the slight cardiac hypertrophy found in the clenbuterol group.

The half-life of dobutamine is very brief (2-3 min) and there are no active metabolites that might persist [179], thus less than 1 day after termination of chronic exposure to dobutamine, any effects observed could not have been due to the direct and/or residual effect of dobutamine. Clenbuterol metabolites have long residual effect in body tissue of rats (up to 8 days after single oral administration), with relatively high amount at first 48 hours [180], therefore, effects of clenbuterol on the hemodynamics approximately 24 hours after last dose could still play important role in inotropy, as well as higher values of LVESP. Likewise, when comparing LVESP of the clenbuterol group with the group receiving chronic administration of β-blocker (β_1-, β_2-, and α_1-adrenergic antagonist: carvedilol), the clenbuterol group showed statistically higher value of LVESP at the baseline-instrumentation period. The half-life of carvedilol, in dog, is up to 1,021 minute after a single IV administration [181]. Carvedilol also showed inhibitory effects on activities of the stellate ganglion, the vagus, and on the superior left ganglionated

plexus as long as 3 days after withdraw from chronic clenbuterol treatment in dog [182]. Thus, effects of both clenbuterol and carvedilol are expected to persist following therapy.

Like clenbuterol and more than for dobutamine, the group with exercise training had significantly improved cardiac contraction (indicated by CI and LVESP). These findings are well-known and may be attributable to increase phospholylation of PLB and SERCA-2a activity, and to increased amplitude of Ca^{2+} transients [92]. This, no doubt, is responsible for the increase in contractility [95]. The difference in contraction is more obvious when compared with the group with elevated potentially β_1-adrenergic function group or the group that was exercised.

6.1.3 Effects of interventions on ECGs

Significant differences existed in ECG parameters among rats subjected to different interventions, and will be discussed for leads I, AVF, and V3.

In lead I (not compared to sedentary existence but compared to dobutamine, or exercise group), rats receiving chronic treatment of clenbuteral had less negative T waves due, no doubt, to altered pathways of repolarization (i.e., "primarily") and not ("secondarily") due to altered ventricular activation. Marked T wave inversion has been commonly reported in endurance athlete [183] and isoproterenol (non-selective β-adrenergic agonist) HF rat model [56], thus this inversed T wave may result from either exercise or chronic dobutamine administration. This study demonstrated similarly deep T waves in both exercise and dobutamine. Sedentary rats trended to have more negative than clenbuterol.

Also, chronic clenbuterol injection in these rats significantly increased amplitude of P waves (compared with carvedilol and dobutamine groups). In general, taller P wave is due, most often, to right atrial enlargement caused, possibly, by increased hindrance to ejection from the right. However, clenbuterol has a direct and potent bronchodilator effects, and should redudce right arial size leading to diminution of the right atrium. Thus if the right atrium was truly enlarged (resulting in larger P waves) by clenbuteral, it is more likely to have resulted from an anabolic effect and/or alteration in gene expression-induced by clenbuterol [134], rather than from pulmonary hypertension.

That clenbuterol-induced diminution of the S wave compared with the exercise group may reflect alterations in right ventricular activation as might occur with left anterior aborization (hemi fascicular) block, or possibly to a Brody effect [184] generated by changes in differences in resistivity between blood and myocardium. However, this significant difference may simply result from augmentation of S waves induced as in endurance athletes [183]. Nevertheless, neither the clenbuterol nor exercise groups showed statistically different S wave amplitudes compared with sedentary rats. Finally, depth of S waves of the exercise group seemed to be the greatest while those of the clenbuterol seemed to be the lowest. Combination of these opposite deviations may have made the difference achieve statistical significance.

Clenbuterol also led to decreased in amplitude of the R wave in lead AVF compared with the dobutamine group. This may indicate deviation of electrical axis, or decreased heart size as has been demonstrated in humans when R wave amplitude varies

during changes in heart size during ventilation [185]. However, there was no significant alteration in heart weight of rats receiving clenbuterol or dobutamine, and rats receiving dobutamine seemed to have highest R amplitude. Also, rats receiving clenbuterol trended to have highest LV volume. Thus, this alteration in R amplitude was less likely to result from differences in heart size. Highest R amplitude occurred with dobutamine; lowest R amplitude occurred with clenbuterol; statistical significance was detected between the clenbueteral and the dobutamine group.

The Brody effect must be considered in impacting on the amplituides in various leads. Changes in voltages depend upon the relationship between the lead and the boundary of activation (sheet of dipoles). Effects on height of deflections depend upon if the dominant activation process is radial or tangential through the myocardium, therefore, alteration in R wave might not be detected in any given lead and may occur in any other lead. Why these changes should occur with response to clenbuterol is equivocal. In order to determine which--if any--are operative would require a detailed ECG study in which each is evaluated separately and definitively.

In all ECGs obtained in the Faraday cage, rats receiving clenbuterol had statistically higher HR than the exercise group, with no difference compared with the sedentary group. This suggests that the slightly increased HR may have been due to chronic stimulation by clenbuterol. This has been found in 2 other studies in which increased HR resulted from clenbuterol [141, 134]. On the other hand, bradycardia can be

induced by exercise training resulted in altered ANS [80, 183] and/or change in intrinsic activity of SA node.

Alterations of ECG wave form durations derived from chronic interventions could also be detected in lead V3 as show in table 10. Exercise training showed statistically significant shortening of QTcB, QTcF, and T duration compared with the sedentary group, indicating more homogeneous of repolarization. The shortening of QTc and/or T durations are preferable adaptations, since some pharmacological heart failure animal models {isoproterenol- [186], imipramine- [69]} showed significant prolongation of QT. The shortening of QTc and T duration also could reduce the risk of arrhythmia (ventricular tachycardia, ventricular fibrillation, and torsade de pointes), due to delay repolarization. As shown by Dor-Haim and colleagues (2013) in rats [187], 4 to 8 weeks of treadmill exercise training could significantly reduce probability and duration of pacing-induced ventricular fibrillation, and this exercise-induced cardioprotective effect showed an association with an intrinsic cardiac remodeling related to a broader spectral range and faster frequency components in the ECG. Moreover, endurance exercise training in a canine ventricular fibrillation model can shorten repolarization (measured as shortening of QTc and duration from peak of T wave to end of T wave) and prevent ventricular fibrillation during aversive stimuli compared with sedentary controls. In this canine study, protection against arrhythmia was a result of normalizations in cellular electrophysiology and/or calcium handling [188].

Likewise, chronic treatment of carvedilol resulted in shorten QTcB, QTcF, and T duration compared with sedentary group. This shorten of QTc after chronic carvedilol treatment was also consistent with the findings in Oflaz and colleagues (2013)'s study [189], in which cavedilol treatment for 6 months resulted in reduction in QTc, QT-interval dispersion or QTd (marker for protection against torsades de pointes and possibly other reentrant arrhythmias that may lead to fibrillation and sudden death). It also augmented heart rate variability (HRV), ventricular function, and clinical score in children with dilated cardiomyopathy. The carvedilol-induced reduction in QTd and heart rate variability that was found in that study could be as function of adrenergic antagonism or any of the other effects of this pleotrophic drug. Moreover, effects of carvedilol on antiapoptotic and inhibition of cardiac remodeling may lead to increase in homogenization of ventricular repolarization as well as reduce in risk of arrhythmia that were found in chronic heart failure patients [190]. This improvement of heterogeneity of ventricular repolarization was also found in animal models given low dose carvedilol (0.25 mg/kg twice daily) for 8 weeks and resulting in decrease transmural heterogeneity of ventricular repolarization in rabbit with chronic heart failure [191].

On the other hand, chronic administration of dobutamine in this study led to significant prolongations of QT, QTc, and T duration compared with other interventions, except sedentary group. This significant lengthening of QTc after dobutamine treatment was also reported in stress cardiomyopathy patients who were received IV injections of epinephrine or dobutamine [192], consistent with findings in the isoproterenol-induced heart failure rat model [186]. However, there was no prolongation to QT or QTc in the

clenbuterol group compared with other interventions. In fact, clenbuterol had significantly shorter QT, QTc, and T durations than the dobutamine group, as well as, shorter T duration than the sedentary group, all of which may indicate that alterations in QT components and/or T duration are complex and may rely more on chronic stimulation of β_1-adrenergic pathway rather than β_2-adrenergic pathway.

6.2 Discussion: Effects of imipramine on hemodynamics and ECGs in sedentary rats

6.2.1 Effects of imipramine on systemic blood pressure and cardiac function in sedentary rats

In this study, continuous IV infusion of imipramine (20 mg/kg/hr) caused an initial and slight increase in HR, followed by significant persistent reduction in HR. Sinus tachycardia is the first and general cardiac effect induced by tricyclic antidepressants, including imipramine. This effect is complex but anticholinergic effect as well as norepinephrine reuptake inhibition could be the main factors that lead to tachycardia [63]. However, subsequent bradycardia could result from different mechanisms, such as reduction in β1-adrenergic receptor function, as well as, alterations in cardiac ion currents and conduction systems. In terms of β_1-adrenergic receptor function, acute imipramine treatment in a rat study showed reduction in β_1-adrenergic receptor-induced positive chronotropic effect (i.e. dobutamine IV admisitration), and chronic imipramine treatment caused depression in preganglionic cardiac sympathetic nerve-induced tachycardia, pointing to a negative impact of imipramine on β_1-adrenergic receptor mediated cardiovascular function [193]. Alterations in HR due to imipramine or other tricyclic

antidepressants may be due to effects on cardiac ion currents and the conduction system (His-Purkinje system) impulse formation and conduction via inhibition of fast Na^+ channel has been shown to result in slower phase 0 depolarization [63]. This, of course, should prolong QRS duration and favor reentrant arrhythmia.

Infusion of imipramine also resulted in significant persistent hypotension (i.e. SBP, DBP, and MBP) until the mid-dose period, with concomitant reduction in LV performances (e.g., LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV. Interestingly, there were trends of spontaneous recovery during imipramine infusion from mid-dose to end-dose, however, this trend did not achieve statistical significance. On the other hand, matched-volume vehicle infusion trended to increase LV function. Thus, attenuations of hemodynamic parameters that were found in this study were less likely to result from operative interventions or from the anesthesia regimen. Moreover, these negative hemodynamic findings were in agreement with the results of Fiedler and colleagues (1985)'s study [69], in which imipramine infusion in anesthetized rats caused initial tachycardia before bradycardia and progressive hypotension, and then cardiovascular failure at approximately 20 minute after imipramine (1 mg/kg/min IV) infusion. Imipramine also depressed +dP/d*t* in anesthetized dogs. Likewise, Lucas and colleagues (1992) demonstrated that imipramine created a reduction in +dP/d*t* and LV pressure in anesthetized dogs [68]. Also, a related molecule, amitriptyline (0.18 mg/kg/min IV) infusion caused significant reduction in cardiac output, peak LV dP/d*t*, and MBP [194].

Reduction in myocardial contractile function as LVESP, +dP/d*t* and (+dP/d*t*)/ EDV in this study pointed to the negative inotropic property of imipramine, as proven in

Watts and colleagues's (1998) rat study, in which exposure of imipramine caused inhibition of intracellular Ca^{2+} transient in electrically paced cardiomyocytes, and Ca^{2+} signals in KCl depolarized cardiomyocytes [73]. The Ca^{2+} antagonism by imipramine in that study could be prevented by increased alkalinization in the medium but not by increased extracellular Na^{+} or by altered caffeine, indicating that the effect is independent to SR Ca^{2+}, and less dependent on Ca^{2+} from Na^{+}/H^{+} and Na^{+}/Ca^{+} exchangers. Also, Zahradník and colleagues (2008) revealed that imipramine blocked Ca^{2+} current ($I_{Ca,\,L}$) in rat hearts through specific interaction on the receptor site. As well, it shifted the steady-state inactivation curve of I_{Ca} toward more negative voltage [72]. Furthermore, in severe tricyclic antidepressants toxicity, inhibition of norephinephrine reuptake could also result in norepinephrine depletion at nerve ending, leading to more cardiac depression [63]. In this study, imipramine infusion also showed negative lusitropy (i.e., significant reduction in -dP/d*t*) that may associate with reduction in β_1-adrenergic function due to NE depletion, and/or inhibitions of cardiac ion currents, especially I_{to}.

Besides cardiotoxicity, tricyclic antidepressants also cause systemic effects such as vasodilation mediated by adenosine A_{2a} receptor activation [195], blocking α-adrenergic receptor and suppress noradrenaline-induced intracellular Ca^{2+} increase [60]. Furthermore, continuous reduction of blood pressure, parallel with bradycardia, may indicate the imipramine effects on blunting baroreflex function. In fact, therapeutic doses of imipramine also showed significant reduction of baroreflex sensitivity (supine rest) in major depressive-disorder patients [196]. Thus, combination of significantly depressed myocardial contraction and reduction in HR (approximately 20%) that was found in this

study, as well as, potentially vasodilation effect of imipramine (as no obvious increase in LVEDV or LVESV at lower HR) , played critical roles in marked hypotension in this sedentary group.

Interestingly, several statistical differences among mid-dose and end-dose periods of SBP, DBP, and MBP that were found in this study indicated spontaneous recovery from imipramine (see table 11), even during continuous imipramine infusion. Other parameters, such as HR, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV also showed trends of improvement but did not achieve statistical significance. This spontaneous recovery in blood pressure was not reported in other imipramine infusion studies in animal models, however, it could result from differences in dosage and infusion time: 20 mg/kg/hr for 1 hour in this study vs. 60 mg/kg/hr for approximately 25 min in the study of Fiedler and colleagues's (1985) anesthetized rat study [69], and 7.5 mg/kg/hr. for 30 min in Lucas and colleagues's (1992) anesthetized dog study [68]. This spontaneous recovery may be associated with augmentation of imipramine metabolism in the liver by cytochrome P450 2C19 [197] via barbiturate (hepatic enzyme inducer) that was used throughout the anesthetized period in this study. Nevertheless, partial recovery in depressed hemodynamic values were found in both systemic and cardiac parameters (SBP, DBP, MBP, HR, LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV) at 60 minutes after cessation of imipramine infusion. In fact pulse pressure was fully recovery (i.e., no significant difference compared with baseline-instrumentation value). This result was also exhibited by Lucas and colleagues's (1992) in their anesthetized dog study [68], indicating that imipramine-induced heart failure was reversible.

6.2.2 Effects of imipramine on ECGs in sedentary rats

Besides alterations in hemodynamic variables, imipramine infusion also led to significant and gradual reductions in R amplitude, as well as augment negativity of S waves of lead I throughout the infusion period in the sedentary group, while in lead AVF significant reduction in R amplitude occurred only at the mid-dose. Unlike hemodynamic parameters, there was no obvious spontaneous recovery in negative alteration of R and S wave amplitudes during imipramine infusion. Moreover, there was no significant alteration in amplitudes of any wave forms in the matched-volume, vehicle infusion group. Actually, R wave in lead I trended to be higher during infusion. Thus, reduction of R waves and deeper S waves constituted clear effects of imipramine on the heart.

From these results, attenuation of R amplitude was less likely to have resulted from decrease blood conductance [Brody effect (dilution effect)] since vehicle infusion trended to elevate R amplitude. The possible explanations of smaller R amplitude may be associated with (a) smaller LV size [185], induced by vasodilation (Reduction in HR did not create obviously increase in LVEDV, as expected in response to other general negative inotropic situations.), (b) loss of viable myocardium, and (c) alterations in cardiac cell membrane electrical properties. However, there was no significant change in LVEDV and LVESV; therefore, a smaller LV may not play a major role in reduction of R wave amplitude. Moreover, a case report of imipramine intoxication presented a junctional escape rhythm with low QRS voltage and right bundle branch-like pattern [198]. Likewise, deeper S waves may be associated with hindrance in cardiac conduction

such as right bundle branch block, as reported in TCAs-poisoned case reports [67] or right bundle branch-like pattern [198], or relatively increased RV size.

HR and RR interval were also impacted by imipramine as described above in hemodynamic section. As expected, imipramine resulted in alterations of wave form duration such as lengthening of P, PR, PR_{sect}, QRS, QT, and T duration throughout infusion period, with spontaneous recovery limited only to PR and PR_{sect}. On the other hand, vehicle infusion did not significantly alter any of the ECG duration. Noted, the vehicle group had significantly shorter PR, PR_{sect}, QRS, and QA during dosing compared with the imipramine group.

These findings are also consistent with imipramine–induced prolongation in cardiac impulse conduction as reported in humans [198, 199], as well as rats [69]. Imipramine infusion gradually decreased R amplitude, together with, lengthening of PR, QRS, and QT, until the rats had cardiovascular collapse; however, carbocomene co-administration showed protective effects on these rats on both hemodynamic and electrocardiographic outcomes. Carbocomene (1) shifts the energy utility from free fatty acid to glucose, (2) improves hypoxia tolerance during IR, (3) stabilizes membrane, (4) and attenuates effect of imipramine on Na^+ current [63]. A temporary cardiac pacemaker has been reported to terminate the junctional escape rhythm, regulate atrial activity, regulate bundle branch-like pattern, and reduce prolongation QT resulting from imipramine intoxication in human [198]. Therefore, imipramine-induced alterations in

the ECG could predominantly rely on the direct effect of imipramine on action potential generation and the conduction system.

In fact, effects of imipramine on the generation of the membrane potential were already demonstrated by Rawling and Fozzard (1979) in sheep cardiac Purkinje fibers, in which imipramine led to a dose-dependent reduction in overshoot amplitude and maximal upstroke velocity at Phase 0 (fast depolarization phase), abbreviation of Phase 2 (plateau phase), and slow Phase 3 (fast repolarization), resulting in marked reduction in action potential duration. They also found that conduction velocity was reduced (dose-dependent) to approximately one-third of baseline value before cell became inexcitabile, similar to its attenuation of Na^+ conductance. Imipramine had little to no effect on the resting membrane conductance, measured by cable analysis [200]. In another study on dog Purkinje fibers, imipramine also produced comparable negative effects on action potential amplitude and duration, maximal upstroke velocity, membrane responsiveness, decrease in spontaneous rate of automaticity when provoked by epinephrine, as well as effective refractory period duration [201].

However, in smaller animal models such as rabbits and rats, the uniqueness in ion channels could lead to differences in electrocardiographic behavior induced by imipramine. As shown in the rabbit atrial fiber, imipramine caused negative effects such as decreased action potential amplitude, but prolonged action potential duration with slower depolarization and repolarization, reduced diastolic depolarization of S-A nodal fiber together with progressively decreased atrial rate until the activity was dissipated.

These alterations partially recovered after reduction in imipramine, and improved further by added catecholamine [202]. In another study, imipramine also affected transient outward potassium current (I_{to}) in isolated atrial myocytes of rabbit by concentration-dependent inhibition of the I_{to} peak amplitude, but not at inactivated or resting state of I_{to}, indicating that inhibition of the I_{to} may also played important role in prolongation of the action potential-induced by imipramine [203]. Such an effect on I_{to} may, in fact, obfuscate the ability to detect the end of depolarization by using an ECG, since I_{to} contributes monumentally to the J wave that represent early repolarization and prevents identifying the true end of depolarization.

Likewise, imipramine attenuates responsiveness, to isoprenaline, of K^+-depolarized rat atrial fibers. The fibers manifest reduced contractility, slowed phase 0 of the action potential, reduced resting membrane potential, shift of membrane responsiveness and recovery time curves down and to the right, prolonged action potential duration and effective refractory period [204]. Therefore, imipramine electrocardiotoxicity is multifactorial and produces negative alterations in many ion currents, leading to attenuations in impulse generation and conduction.

Besides prolongations of QT, imipramine also significantly lengthens QA interval in both mid-dose and end-dose peroids; QA in vehicle group was not change. QA interval is considered as an indirect-index of cardiac contractility and has an inverse relationship with +dP/d*t* [35], however QA is also determined by electropressor latency, elasticity modulus of the aorta, and aortic diastolic pressure. A vasodilator that decreases arterial

stiffness will slow pulse wave conduction. In dogs, QA prolongation also occurred with AH-108, a Ca^{2+} channel blocker with negative chronotropic, inotropic, and dromotropic effects [36]. QA prolonged and +dP/d*t* decreased, however, this drug caused an increase in HR. Likewise, atenolol (β_1-blocker) decreased +dP/d*t*, lengthened QA, but had less effect on HR [36]. Therefore, in this study, prolongation of QA due to imipramine was more likely associated with reduction in cardiac contractility and vasodilatation rather than simple alteration of HR.

However, the negative effects of imipramine on electrophysiology were markedly reversible at the end recovery. Both R and S amplitude in lead I partially returned toward baseline-instrumentation values with absence of statistical significance. Also, P, PR_{sect}, QRS, QT, QA, and T durations partially recovered (i.e. no sigfnicant difference) toward values obtained before imipramine. RR, HR, and PR intervals were also partially recovery, but they still manifested differences between baseline-instrument and end recovery period. These partial recoveries of electrical cardiac attenuations induced by imipramine were consistent with the rabbit atria study of Matsuo (1967) [202]. Rate of recovery occurred with 2 tempoeral relations: abrupt recovery of R, S, and T amplitude of lead I (see figure 31, 33, and 35), and gradual recovery of PR, QT, QTcF, T, and QA duration of lead V3 (see figure 37, 39, 43, 45, and 47). These differences in recovery indicate that prolonged cardiac conduction required a longer time to recover than attenuation of wave form amplitude. This could result, of course, from differences in rates of binding and release from specific receptor sites.

6.3 Discussion: Effects of imipramine on hemodynamics and ECGs in all interventions

6.3.1 Effects of imipramine on systemic blood pressure and cardiac function in all interventions

There were trends and significant differences in hemodynamics (e.g., HR, +dP/d*t*, SV, CO) among intervention groups (e.g., exercise, carvedilol, and dobutamine) at the baseline-instrumentation (i.e., after exercise and drug interventions but immediately before imipamine challenge). For example, exercise and carvedilol seemed to have lower HR, clenbuterol had higher +dP/d*t* than dobutamine, clenbuterol and dobutamine group had lower SV and CO than vehicle group. The possible explanations were mentioned in previous section (6.1.2).

At the mid-dose period, compared with their baseline-instrumentation values or vehicle group, imipramine infusion significantly reduced SBP, DBP, MBP, and HR in most of the treatment groups possibly via both cardiac depression and vasodilation. Also, in all groups, imipramine significantly depresse LV performance measured as LVESP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV (compared with their baseline-instrumentation values or vehicle group), but not LVEDP. The less alteration in LVEDP while HR was marked reduced in all groups of rats, may point to equal vasodilation in all types of interventions.

Adverse hemodynamic [e.g., PP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV] effects of imipramine appeared to be modulated differently among the 5 different interventions/groups (Tables 22 through 29).

In response to imipramine, reductions in PP were slightly attenuated by carvedilol, while the other interventions did not show attenuation. This effect could be attributable to an effect, or effects, on parameters determining systolic and diastolic pressures. These include (principally) elasticity (Em), systemic vascular resistance, HR, SV. That is, carvedilol might have blunted changes induced by imipramine to aortic elasticity, systemic vascular resistance, HR, SV. Chronic carvedilol treatment might result in a smaller difference in impact in cardiac depression and vasodilations, compared with other treatment groups. That the difference in % reduction of HR tended to be smaller (~13%) with carvedilol than other interverntions (~20 to 24%), could account for the potential benefit of carvedilol compared with the others. This less negative chronotropic effect is consistent with the known ability of carvedilol to block β_1-adrenergic receptors leading to fewer receptors available for the impact of imipramine. Also with carvedilol, the brief initial increase in HR, and the sustained decresase in HR, trended to be smaller than sedentary (see figure 23 and 24). Also, chronic carvedilol treatment blocks pre-junctional β_2-adrenergic receptors leading to reduction in norepinephrine release measured as total body and cardiac norepinephrine spillover [205]. This could attenuate imipramine-induced norepinephrine depletion at nerve terminals, resulting in the smaller negative chronotropic impact of imipramine.

The lesser reduction in PP in the carvedilol group may result, also, from lesser reduction in inotropy and vasodilation due to imipramine, rather than from a direct effect of carvedilol in increasing PP that was found in chronic carvedilol treatment in patients with chronic heart failure [205]. There was no significant difference in PP compared

with the sedentary group at the baseline-instrumentation period. This reduced effect on PP reduction is also consistent with the trends of reduced negative impact of imipramine on % changes of SBP, DBP, and MBP, compared with other interventions. Thus, residual adrenergic blockade from carvedilol, and imipramine effects on sympathetic function, may have competitive actions on nerve endings and/or adrenergic receptors. However, future studies on interaction between carvedilol and imipramine on adrenergic receptor and norepinephrine release, especially during concomitant administration, are required to confirm this hypothesis.

Variation in the adverse effects of imipramine was also exhibited on other parameters. For example, the dobutamine group/intervention had no significant reduction in CI (same as sedentary group), but +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV were reduced significantly. This indicates that dobutamine also had, as much as other interventions, a significant impact on imipramine-induced negative inotropy. Because at the baseline, the dobutamine group had statistically lower in SBP, PP, LVESP, CI, and +dP/d*t* compared with the clenbuterol group, and maximal effect on CI trended to be the lowest in dobutamine group compared with other groups. Thus the slightly reduced CI at the baseline-instrumentation value (due to down-regulation of β_1-adrenergic receptor) may mask the effect of reduction in CI in this group. Interestingly, there was no obvious synergist effect of imipramine and down-regulation of β_1-adrenergic receptor in attenuation of cardiac contraction, since Δ value and Δ % change at maximal effect-induced by imipramine of CI in dobutamine group appeared to be lower than those of

exercise, and clenbuterol group, respectively, but not different when compared with sedentary group.

Nevertheless, the dobutamine group was the only group that had significant prolongation in tau due to imipramine infusion. This could be attributed to the down-regulation of β_1-adrenergic receptor rendered attenuation in myocardium relaxation (negative lusitropy). This prolongation of tau is also associated with greater lengthening of QT, QTcB, QTcF, and duration of T than with other groups, and is consistant with slower rate of resequestration of Ca^{2+} through SERCA into the SR and retarded repolarization. Further explanation on this topic will be discussed more in next section.

Besides directly affecting systemic and cardiac contraction, alterations, shown among groups, of LV volume-induced by imipramine could also alter mechanics via Cyon-Frank-Starling heterometric autoregulation. As can be seen in LV volume, both clenbuterol and dobutamine groups exhibited significant increase in LVEDV, and only dobutamine had significant increase in LVESV at the mid-dose. There was no significant change in other treatments at the mid-dose period. LV volume expansion could be the result of a higher degree of reduction in contractility and/or lesser degree of vasodilation, rather than to primary increase in afterload since all of the groups still exhibited severe hypotension with reduction in LVESP. However, there was no statistically significant difference in degree of depressed of contraction among any intervention, but dobutamine trended to lowest +dP/d*t*, -dP/d*t*, +dP/d*t*/EDV, and CI at all periods. Thus chronic clenbuterol treatment might attenuate the vasodilation produced by imipramine, while dobutamine treatment might have a combination of effects to increase attenuation (i.e.,

imipramine has a greater adverse effect) in cardiac contraction but less vasodilation leading to significant expansion of LVEDV at the mid-dose period in both group, and to increase LVESV only in dobutamine group.

Although, acute clenbuterol administration lead to marked reduction in MBP and hepatic blood flow due to vasodilatory effects [206], chronic clenbuterol treatment may show different results. This can be seen in SBP and DBP of the clenbuterol group in this study in which values were slightly higher than those of other groups. Also, in the study by Encabo and colleagues (1996), chronic treatment of clenbuterol in rats for two weeks led to desensitization of presynaptic β_2-adrenergic receptor resulting in reduction in noradrenaline release, as well as reduction effects of phentolamine on tritium overflow (indicating alteration in α-adrenergic receptor activity) [207]. Clenbuterol showed, consistently in this study, that the fall in DBP in respose to imipramine was more gradual when compared with other interventions. Therefore, both presynaptic β_2-adrenergic receptor desensitization and modulated relationship between α- and β-adrenergic receptor may augment baseline vasoconstriction and/or attenuate (or slow down) imipramine-induced vasodilation as compared with other treatments.

In the case of the dobutamine group, significant LVEDV and LVESV expansion (i.e., the hearts were larger with imipramine) at mid-dose period could result from a combination of effects of (predominantly) slightly more attenuation in contractility and (possibly) less vasodilation. Dobutamine appeard to have vastly different impacts on the vascular resistance depend on treatment regimen and species. For instance, acute infusion of dobutamine did not change carotid arterial compliance or brachial artery diameter,

while carotid peak blood flow was increased in chronic heart failure patients; dobutamine may have less effect on vascular tone than direct influence on the heart [208]. Also, in horses dobutamine at low or high doses has no or non-significant alterations in systemic vascular resistance, but in humans who receive high doses it can develope reduction in systemic vascular resistance [209]. Nevertheless, short-term intermittent IV, low-dose dobutamine therapy for 4 months caused improvement in endothelial function measured by endothelial-dependent brachial flow-mediated dilation and systemic vascular resistance in severe chronic heart failure patients [210]. This mechanism is likely associated with repeated increases in blood flow or shear stress-induced (same as during exercise training) endothelium-derived relaxing substance release, most likely NO. Thus, increase in both LVEDV and LVESV, concomitantly, indicate a greater degree of cardiac contractile dysfunction. However, increased LVEDV may positively affect CI due to Cyon-Frank-Starling law of the heart, leading to non-significant reduction of the CI and a significant increase in SV. Nevertheless, this impacts positively on contraction but was not able to maintain LVESV.

Interestingly, hemodynamic attenuation-induced by imipramine appeared to be maximal at the mid-dose period, since at the end-dose period most of the hemodynamic values were improved albeit with variations among groups and among variables. For instance, at the end-dose period, SBP, DBP, PP, and MBP in most of the groups showed non-statistical improvement compared with their mid-dose values, but they still were significantly lower than at baseline-instrumentation.

Except sedentary group, responses in HR did not show an obvious trend of spontaneous recovery. Also, only the exercise group had HR significantly lower than the vehicle group, and they trended to have the lowest HR compared with other groups. This sugests that the exercise group had slightly more negative chronotropic effect of imipramine compared with other groups. This result could attributable to a combination effects of exercise training induced augmentation in cardiac vagal activity (especially in high-intensity interval training [211]), and imipramine-induced attenuation in cardiac impulse generation and electrical conduction. Moreover, even with higher sympathetic drive that occurs at the onset of exercise, exercise training can increase vagal influence over the sinus node, leading to slower HR compared with sedentary control men [212]. Thus, in pathophysiological states in which sympathetic system are augmented such as hypotensive or shock, as well as with imipramine-induced hypotensive and heart failure, exercise training may be able to similarly influence HR.

Furthermore, PP of sedentary and dobutamine groups showed significant spontaneous recovery as there was no longer significant difference with baseline-instrumentation values. Whereas, other systemic blood pressure parameters were still significantly lower than baseline-instrumentation values and vehicle group. This variation in spontaneous recovery of systemic hemodynamic parameters could result from matched-improvement of cardiac depression and vasodilation in the sedentary group, in which there was less alteration in ANS function, and the slightly lower baseline-instrumentation value of PP in the dobutamine group.

The trends to spontaneous recovery of LV functions were exhibited in most of the groups, except clenbuterol group, in which LV contraction and LVEDV seemed to be stable. In the clenbuterol group, LVESV slowly increased during onest of imipramine infusion, and reached a significant difference at the end-dose. These variations in attenuation of LV volume are consistent with the observation that the maximal adverse effects (in DBP, MBP, HR, CI, and cardiac contractile dysfunction) of imipramine occur later in rats given clenbuterol than rats given other interventions. Also the times of maximal effects on volumes of the clenbuterol group also appeared after the mid-dose period (see table 27). At the mid-dose, LVEDV had increased slightly and contractility had decreased rather remarkably, but LVESV did not increase significantly due to the summation of decrease in contractility in the presence of increase in preload. However, at the end-dose period, the clenbuterol group achieved the maximal reduction in contractility (due to imipramine infusion) indicating that the increase in LVEDV could not overcome the impaired contractility.

Rates of spontaneous recovery in most hemodynamic parameters, i.e., occurring during infusion of imipramine, appeared to vary both within an intervention and among interventions. Nevertheless, differences in these rates did not acieve statistical significance.

With respect to the maximal effects of imipramine infusion on hemodynamic values, regardless of time point, intervetion with carvedilol showed a lesser maximal reduction in PP than by the exercise group ($P = 0.053$); it showed a significantly lower maximal reduction of LVESP than that of the clenbuterol group ($P < 0.05$); and it also

had slightly lower (but not significant) values of maximal changes in SBP, DBP, MBP, HR, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV.

At the end of the recovery period, most parameters returned partially toward baseline, however some (e.g., SBP, DBP. MBP, HR, LVEDSP, +dP/d*t*, -dP/d*t*, and (+dP/d*t*)/EDV) differed significantly from baseline, whereas PP (in all intervetions), SBP in the dobutamine groupd, HR in both carvedilol, and dobutamine, CI in exercise and caervedilol, +dP/d*t* and -dP/d*t* in dobutamine returned to a level not different from baseline. These partial recoveries were in agreement with other anesthetized animal models as discussed in effect of imipramine in sedentary rat section.

Although it appears that degrees of recovery among groups vary (i.e., some more complete than others), none of the absolute values of any parameter was different among groups. However comparing the absolute differences of parameters, between baseline and the final recovery measurement, some parameters (e.g., SBP, HR, and +dP/d*t*) in some groups (e.g., dobutamine and clenbuterol) did not differ significantly. For example, the recovery values for SBP, HR, +dP/d*t*, -dP/d*t*, CI, tau, LVEDV, and LVESV in the dobutamine group did not differ from baseline; the recovery was robust. These "desirable" findings may be due to intervention-induced effects on down-regulation of β_1-adrenergic receptor leading to lower sympathetic tone preceding imipramine infusion, since the effects of imipramine on cardiovascular function are highly-dependent on sympathetic autonomic activity. However, dobutamine also trended to have lower baseline hemodynamics, thus statistical improvement may be easier to achieve. Whereas, the clenbuterol group, in which basal sympathetic tone seemed to be higher than other

groups (except the exercise training group), trended to have lower ability to recover to the value during baseline-instrumentation. However, for example, in the dobutamine group, because of down-regulation of β_1 receptors, baseline value of HR was lower than on other groups, so even though the value of the HR returned to baseline for dobutamine, it still differed from the value at recovery for rats in another intervention groups.

Rats with the carvedilol intervention showed great ability to recovery from the negative effects of imipramine, especially HR and CI. This favorable difference could be explained by possible pharmacological competition with imipramine on sympathetic nerves, by effects on specifc ion channels, or by its antioxidative capacity that may make cardiac cells more resistant to the negative impacts of imipramine. This postulate can be supported from another rat study, in which imipramine altered mitochondrial function measure by the mitochrondial respiratory chain complex, and creatinine kinase activity in rat brains [62]. This is also supported by the fact that carbocromene (that also produces reestablishes positive energatic balance and stabilizes membranes) can significantly alleviate imipramine-induced cardiovascular collapse and prolong survival times in both rats and dogs [69].

Likewise, the exercise group showed the potential of better recovery in LVESP, +dP/d*t*, -dP/d*t*, LVEDV, and (+dP/d*t*)/EDV than the clenbuterol group when examining the absolute values of parameters at the end recovery period. If this subtle difference is correct, it could well result in a positive adaptation of cardiovascular the systems, i.e., improvement in contractile functions, antioxidative status, and cardiac autonomic balance.

However, there was no obvious trend to response of hemodynamic alteration-induced by imipramine in sedentary rats when compared with rats in other intervention treatment groups.

6.3.2 Effects of imipramine on ECGs in all interventions

There were some differences in HR, P_a, R_a, T_a, as well as in PR, QT, QTc, and T_d from rats in all intervention groups under general anesthesia and in a Faraday cage, but these differences were not present at the baseline instrumentation period. However exposure to imipramine infusion gradually and significantly reduced R amplitude in most of the groups in lead I and AVF. On the other hand, vehicle infusion seemed to increase R amplitude. As discussed above that reduction in R amplitude-induced by imipramine could have resulted from decreased LVEDV due to venodilatation (venous pooling) and/or decreased lusitropy. In the other hand, a failing heart may dilate and produce increased voltages. The net effect depends upon which factor dominates. Whether the changes are more pronounced in one lead or the other—or occur similarly in both leads—depends upon the orientation of the heart within the torso and the orientation of the electrodes and limbs to the heart within the torso. In this study, limbs were kept constant in relation to the torso, and all rats were of the same strain so that topography should have been similar. Thus the changes in amplitudes of component deflections should have been due to the imipramine. Decreased amplitude of R waves may result from decrease magnitude of the sheet of dipoles traversing a smaller LV free-wall, or from a Brody effect in which the image dipole becomes smaller due to reduction in differences in resistivity between myocardium and blood, or from increased resistance between primary

and image dipoles. Alternatively, the mangitude of component dipoles may be reduced by alterations of ionic mileau between intra- and extra-cellular compartments. This latter determinant may be dominant since the QRS was prolonged consistent with electrophysiological effects.

In response to imipramine, R_a in lead I, decreased significantly, but only tended to decrease in AVF in the exercise group. There were differences in the reduction in R_a between leads I and AVF (lead I affected more than lead AVF in all groups but more so in the exercise group). There was no significant reduction of LVEDV in any group during imipramine infusion; therefore the altered QRS orientation must be attributable to altered pathways of ventricular activation, e.g., left anterior hemiblock affecting LV free-wall. Nevertheless, exercise treatment seemed to mimimize the reduction in R amplitude predominantly in the long axis of the heart. Chronic aerobic exercise training is well-known to produce physiological adaptations of cardiovascular structures, cardiac ANS regulation, as well as antioxidative status. Therefore, exercise training may improve cardiac cell functions and may increase threshold to aversive stimuli. Moreover, one cardiac adaptation that may be important in the cardiac depolarization process is chronic exercise-induced upregulation of myocardial channel subunit expressions, including Na^+, Ca^{2+}, and K^+ channel, regardless of cellular hypertropy, as shown in a mouse study [213]. This up-regulation or more preserved Na^+ channel may lead to less attenuation on ventricular depolarization or R wave amplitude when challenge with imipramine that can directly depress all of those ion currents.

Imipramine also augmented depth of S wave of lead I throughout infusion time in most of the groups. However, changes in S amplitude in the clenbuterol group did not acieve statistical significance. Concordant with alterations of R wave amplitude, depth of S wave in lead I was increased less than in AVF. Changes in the S waves from lead AVF were found only in sedentary, carvedilol, and dobutamine group. These findings support the fact that alterations of S wave amplitude were due more likely to more changes in the LV free wall, reflected better in lead AVF. As mentioned before, increased magnitude of negative S wave could result from relatively increased RV size or abnormal cardiac conduction system such as a right intraventricular conduction defect. However, in this study, there was no direct measurement for RV size or volume.

In lead AVF, clenbuterol trended to have the deepest S waves that might mask the actual impact of imipramine on their augmentation. Nevertheless, clenbuterol intervention may generate greater protection since the S wave was significantly less affected by imipramine than in sedentary or exercised groups at mid-dose period. In addition, there were significantly slower changes in response to imipramine in the clenbuterol group, compared to the sedentary group, in time to the maximal effect. The exact mechanism is not well understand and requires further study.

Likewise, T amplitude in lead I was also significantly and gradually increased during imipramine infusion in the exercise and the dobutamine groups, whereas there were only trends for increase in T amplitude in other groups. This trend of taller T wave was not found in lead AVF in any groups, indicating predominant effects probably arose from the LV free wall. T wave amplitude can be augmented by many factor such as

alterations in ion concentration (mainly hyperkalemia and hyponatremia), cardiac temperature, and time-course of ventricular repolarization. Since in both lead I and AVF of the vehicle group, T wave amplitude were very stable, especially lead AVF, therefore, alteration of temperature was less likely to be a major factor. Imipramine showed ability to alter ion current of myocardium and His-Purkinje system leading to abnormal impulse generation and prolonged repolarization period, and could play an important role in augmentation of T waves. However, why this effect was found to be limited in the exercise and dobutamine groups is not well understood. Although, both of theses group had marked T wave inversion at baseline pre-surgery, they seemed to have differences in cardiac adaptation involving the repolarization process, as baseline pre-surgery QT and/or QTc, as well as T duration were significantly shorter in the exercise group than those of the dobutamine group. Nevertheless, they might share other mechanisms that can account for the taller T wave.

As expected, imipramine infusion led to a reduction in HR, prolonged P duration, PR, and QRS intervals in all groups of rats. As discussed in hemodynamic effects of imipramine in sedentary rats, imipramine is most likely to generate negative chronotropy and dromotropy via depressed β_1-adrenergic function, by inhibition of Na^+ current at phase 0 of depolarization, as well as causing alterations in ion currents associated with repolarization, especially I_{to}. However, there was no significant difference among groups in maximal effect or time at maximal effects of HR, indicating that the imipramine-induced negative chronotropic effect is potent and could not be effectively prevented by any of the preconditioning treatment in this study.

Lengthening of P duration as well as PR interval during imipramine infusion are also consistent with other studies and case reports, in which imipramine can hinder the atrioventricular (AV) conduction system and in more severe cases can cause AV block [11, 63, 69]. In rabbits and rat, imipramine can alter the atrial action potential generation and atrial propagation [202, 204]. Also, imipramine has a large negative impact on His-Purkinje system function. Moreover, lengthening of P duration may indicate slowed intratatrial conduction and/or left atrial enlargement. There was no obvious indication of left atrial enlargement in this study, together with only limited increase in LVEDV only in the clenbuterol and the dobutamine groups. Thus, prolongation of P wave predominantly relies on conduction of atrial tissue, while lengthening of PR interval is the integrative effect on atrial, AV nodal, and His-Purkinje conduction. Likewise, degree of PR prolongation was not obviously different among groups, despite the fact that before surgery, the exercise group had a significantly longer PR interval than dobutamine.

Widening of QRS is one manifestation of TACs cardiotoxicity, and has been reported in humans [63, 67] and animals [69]. Maximal QRS duration also proved to be the predictive parameters (as well as the time from administration to the onset of the symptoms) in univariable logistic regression model; but also, the terminal 40-ms frontal plane QRS vector (T40) can be used to predict serious TCAs toxication events in the multivarible logistic regression model [214]. This lengthening of QRS could directly result from imipramine impacts on ion currents, impulse generation and conduction as mention before. Also, with equally altered duratioins of QRS values at both mid-dose and end-dose periods, as well as, the maximal effects and time at maximal effects in each

group, it can be assumed that none of the treatments could protect the heart for imipramine-induced negative dromotropy at this dose of imipramine.

However, some treatments showed ability to alleviate, or aggravate imipramine effects on electrical conductivity. First of all, the sedentary group appeared to have less effect of imipramine on PR_{sect}, since there was only a trend of prolongation during infusion while other groups had significant lengthening, especially the clenbuterol and the dobutamine treatments, but also in the carvedilol and the exercise groups the degree of this prolongation seemed to be lower than those of the clenbuterol and the dobutamine groups. Moreover, at the end-dose period, the exercise group had significant lower PR_{sect} than that of the clenbuterol group. However, the higher degree of variation within the group (measured as SE) of the clenbuterol and dobutamine treatments may make these differences of PR_{sect} prolongation among groups less significance. Nevertheless, these findings may indicate that chronic stimulation of the sympathetic nerves system may aggravate conduction of the heart, especially at the level of AV node and His-Purkinje system. These augmentations of negative dromotropy could also be associated with thickening of the interventricular septal wall induced by chronic clenbuterol treatment as described in Sleeper and colleagues's (2002) study [144] (the hearts from clenbuterol group in this study were also slightly heavier than other groups), or down-regulation of basal β_1-adrenergic receptor induced by chronic stimulation of dobutamine, both of which could lead to slow conduction velocity.

Secondly, imipramine's prolongation of QT interval showed a greater change in the dobutamine group than in the exercise or the carvedilol groups, as at both mid-dose and end-dose period, QT interval of the dobutamine group was significant higher than those of the exercise and the carvedilol group. Moreover, QT interval of the carvedilol group was not statistically affected by imipramine at either time point, while this QT effect in the sedentary group seemed to render in the middle of all groups. This augmentation of QT prolongation-induced by imipramine in the dobutamine group was supported by the significant prolongation of QTcB and QTcF, as the dobutamine group was the only group that showed significant prolongation of QTcB and QTcF. Furthermore, the dobutamine group had significantly longer QTcB than that of the exercise and the carvedilol group, together with significantly longer QTcF than that of the carvedilol group. In term of maximal effect of imipramine on QT, the dobutamine group had significant greater QT maximal effect than that of the exercise and the carvedilol groups, significantly higher QT Δ value than those of the other groups, together with significant higher QT Δ % than that of the carvedilol group. For QTcB and QTcF, the dobutamine group also had statistically higher maximal effect value of QTc than those of exercise group and carvedilol groups.

Likewise, chronic stimulation of clenbuterol in this study also augmented maximal negative dromotropic effects of imipramine in term of QTc and QT_1 as it significantly prolong QTcB and QTcF more than in the carvedilol group, and significantly prolonged QT_1 more than in the sedentary group. All of these findings indicate that chronic dobutamine or clenbuterol treatment could exacerbate negative

dromotropy, predominantly in the repolarization period, at the level of ventricular myocardium and/or Purkinje fiber. This could occur due to alteration of sympathetic function such as down-regulation of β_1-adrenergic receptor (in case of dobutamine treatment), since β_1-adrenergic sympathetic level is an important modulator of cardiac conduction, or via alteration of cardiac structures and/or β_2-adrenergic sympathetic functions (in case of clenbuterol treatment), since in a Langendorff mouse heart study, anti- β_2-adrenergic receptor antibody could generate conduction block between atrium and ventricle and clenbuterol loading could significantly improve this conduction block [215]. Also, in the neonatal rat cardiomyocyte culture of Stagg and colleagues (2007), clenbuterol increased conduction velocity without alteration of the local field potential duration or increased automaticity, but local field potential duration was shortened by blocked of the β_1-adrenergic receptor, indicating that β-adrenergic receptor subtypes and/or signaling pathways were responsible for different outcome in electrical activities of cardiomyocytes [216]. Furthermore, the negative dromotropy induced by fibrosis was less likely to occur in the dobutamine treatment in this study since longer chronic dobutamine treatment in rats (i.e. 2 mg/kg SC 5 day/week for 8 weeks) did not create an increase in fibrosis, but did augment SERCA-2a levels as well as protect against cardiac dysfunction induced by acute LV pressure overload [217]. Therefore, the main factor that controls the prolongation of QTc in the clenbuterol group was likely to be Purkinje fiber function. Moreover, ANS regulation and intrinsic properties of cardiac conductive system, especially at ventricular repolarization, that were altered by interventions seem to be the major mechanisms in this alteration of QT duration.

On the other hand, chronic treatment of carvedilol showed cardioprotection in this imipramine challenge, possibly due to competitive effects on adrenergic receptors and ion channels, and/or direct membrane-stabilization [218]. Inaddition, its antioxidative effect could lead to better cardiac performance in pathological states. Nevertheless, maximal effect of QT_1 in the carvedilol group were statistically greater than that in the sedentary group, indicating that carvedilol intervention may have a positive effect on the the relative refractory period. In terms of exercise training, several studies have showen positive adaptation of the cardiovascular structure leading to more arrhythmia tolerance during exposure to the adverse events as can be seen in patients with catecholaminergic polymorphic ventricular tachycardia type 1 [219], in dogs with atrial fibrillation [182], and in rats during IR [98]. Moreover, exercise training is also well known for its antioxidative effects and positive cardiac ANS adaptation. Thus, in this study, it was not surprising to see some degree of cardioprotective effects from exercise training in cardiac electrical activity. However, future studies on antioxidative status in all groups, as well as an effect of direct co-administration of imipramine and carvedilol, clenbuterol, or dobutamine could provide direct mechanisms in this topic.

Thirdly, lengthening of T duration from imipramine infusion was observed in the sedentary and the dobutamine groups, while the rest of the groups had no significant prolongation. The non-significant prolongation of T wave was more obvious in the carvedilol group, in which T wave prolongation was not noticeable and significantly lower than that of dobutamine group, as well as maximal effect values, Δ value, and Δ % compared with those of the dobutamine group. Also, the exercise group, T duration and

maximal effects of T duration were statistically shorter than those of the dobutamine group. End of T waves and duration from peak of T to end of T can translate to homogeneity of ventricular repolarization and time of ventricular repolarization including absolute and relative refractory period, therefore, chronic treatment with carvedilol and exercise training could improve homogeneity of ventricular repolarization more than sedentary existence, and chronic β-adrenergic stimulation (i.e. clenbuterol, or dobutamine). These findings were also consistent with Akdeniz and colleagues's (2006) of carvedilol treatment in chronic heart failure patients [190], and Bonilla and colleagues's (2012) study of effect of exercise training in ventricular fibrillation canine model [188].

Finally, QA interval (indirect-index of cardiac contractility) was not significantly prolonged in the carvedilol group during imipramine infusion, while the other groups all had significant prolongation of QA. There are three main factors that can contribute to QA prolongation: (1) reduction in myocardial contractility, (2) increased aortic compliance, and (3) prolongation of QRS and/or electromechanical coupling. Since several studies also showed inverse association of QA interval and a direct cardiac contractility variable (+dP/d*t*) [35, 36], TCAs-induced vasodilation effects on rat aorta [195], and imipramine-induced attenuations in cardiac ion currents [72, 73], as well as, in this study, QRS were significantly lengthened during imipramine infusion in all groups of rats. Thus all of the main pathological mechanisms above could combine and lead to lengthened QA. Nevertheless, degree of QRS prolongation in the carvedilol group was

equal to those of other interventions, thus it was possible that less QA alteration in the carvedilol group could result predominantly from preserve cardiac contractility.

However, the load-dependent commonly-used direct measures of cardiac contraction such as +dP/d*t*, or CI (another cardiac index) were significantly reduced from baseline-instrumentation values in the carvedilol group. Moreover, in the sedentary group, +dP/d*t* was significantly reduced, with significant prolongation of QA interval, while CI (cardiac index) was slightly decreased without statistical significant. Therefore, significant reduction in direct measurements of cardiac contraction may not generate significant prolongation of QA interval in all cases. These observations may point to the fact that +dP/d*t* may not be the ideal contractility index due to its load-dependence on both pre-load and after-load, thus interpretation of +dP/d*t* as the only cardiac contractility can be misleading.

Types of interventions in this study could show significance in degree of imipramine-induced prolongation of QA, as the clenbuterol group had a significantly higher impact on QA prolongation as Δ % at the maximal effect point compared with those of the sedentary, carvedilol, and dobutamine group, indicating that chronic clenbuterol treatment could excert imipramine-induced depression of cardiac contractility. On the other hand, chronic treatment of carvedilol could alleviate negative inotropic effect induced by imipramine when compared with its own baseline-instrumentation values, but not with the sedentary group. The possible mechanisms were discussed before in previous section.

In term of recovery ability, there was no trend of spontaneous recovery in the changes of R, S, and T amplitude during imipramine infusion in any groups of rats. Focusing on ECG recovery after cessation of infusion, at the end recovery period, these attenuations in S and T amplitude were partially reversed in all groups. Their partial recovery in all groups occurred without significant differences with their baseline-instrumentation values, or with other groups, in both lead I and AVF.

However, at the end recovery period, some groups still had statistically significant lower R amplitude compared with their baseline-instrumentation values such as in lead I of carvedilol and dobutamine groups, and in lead AVF of clenbuterol group. These results may point to the interesting aspects that chronic treatments with carvedilol or dobutamine produce slight blunting to recovery of ventricular depolarization (measured as R amplitude) from LV free wall, while chronic treatment of clenbuterol may reduce this recovery ability predominantly manifested by ECGs monitoring the long axis of the hearts. These findings might lead to the assumption that background sympathetic function that could be recruited after imipramine-induced attenuation of the electrocardiogram, especially β-adrenergic pathways associated with ventricular depolarization, is the major modulator of this acute recovery capacity. However, a longer period to follow recovery may yield the absolute recovery capacity of each treatment. Also, further analyzis of the recovery curve is needed for quantitative estimation of recovery.

There was a significant difference of these recovered amplitude values among groups at this time point, as the sedentary group had significantly higher R amplitude in lead AVF than that of the clenbuterol group at the end recovery period. Also the

clenbuterol group seemed to have lower ability in return R amplitude toward its pre-imipramine dosing value. This finding together with significantly elevated LVEDV at the end of the recovery period of the clenbuterol group may imply that reduction of R amplitude was more associated with attenuation of LV free wall electrical properties rather than heart size, and that chronic treatment of clenbuterol did not/would not improve, but might worsen, the recovery process from imipramine's negative effects on R amplitude. The possible explanation may be the adaptation of LV structures such as thickening of interventricular septum after chronic treatment of clenbuterol [144].

Consistent with the alterations in wave form amplitudes, there was no trend of spontaneous recovery from mid-dose to end-dose period of wave form durations (i.e. RR, HR, P duration, PR, QRS, QT, QTc, and T duration) in any groups of rats. However, these prolongations of wave form durations or intervals partially return toward their baseline values, without statistical significance between time points (i.e. baseline-instrument and end recovery period) in most of the groups.

Moreover, when using magnitude of improvement compared with its own baseline-instrumentation values, type of intervenention seemed to show different recovery capacities in some parameters. For example, carvedilol and dobutamine groups could partially increase HR, toward their values before starting imipramine infusion, to the point that significance could not be established between those two time points, while the rest of the interventions still had significantly lower HR at the end of recovery point. This observation may imply that pre-reduction of basal β_1-adrenergic activation may facilitate improvement of negative chronotropy after cessation of imipramine infusion.

Moreover, with chronic administration of carvedilol in dogs, persistence of the drug effect occurs (a 30% reduction of vagal nerve activity and a 16-19 % reduction in sympathetic activity) at least up to the third day of withdrawal [182]. This depression in parasympathetic activity may facilitate HR restoration after cessation of imipramine infusion. Interstingly, the effect of chronic dobutamine treatment could lead to down-regulation in β_1-adrenergic receptors, resulting in significantly negative inotropy measured by +dP/d*t*, but lesser effect on HR at baseline-instrumentation. Also, the surgical procedure could increase HR (from baseline-before surgical procedure to baseline-instrumentation period) that was observed in all treatments including the dobutamine group. Moreover, maximal effect of imipramine on HR was not significantly different from other groups. Thus down-regulation in β_1-adrenergic receptor at basal level was less likely to aggravate negative chronotropic, but may favor HR restoration. However, there was no significant difference among groups in HR at the end recovery period, thus it can not be generalized that chronic treatment with carvedilol or dobutamine is more beneficial than other treatments in term of chronotropic restoration.

Nevertheless, QRS lengthening in the dobutamine group was not improved enough to achieve difference in QRS duration between values at the end recovery period and baseline-instrumentation value, unlike the rest of the treatments. However, there were no obvious differences in QRS durations among groups either at the end of the recovery time point or the maximal effect of imipramine; also, there was no trend that QRS interval of the dobutamine group was the longest one. Therefor, this slight variation in QRS recovery may depend more on statistical factors such as the basal value of QRS

duration and its variation within group, rather than actual recovery that might impact clinical significance.

In terms of QT interval, all of the treatment groups could partially return QT and QTc interval back toward their basal level with no remaining statistical significance, however the values of QT, QTcB, and QTcF in the clenbuterol and the dobutamine groups seemed to be higher when compared to the rest of the groups, while the exercise and carvedilol groups seemed to be lower, but there were no significance differences among groups. Therefore, increased homogeneity of ventricular repolarization leading to shortening of QT that was found in exercise training [188], and chronic administration of carvedilol [191] may have a slight effect on the restoration of QT interval, but without group differences.

Unlike QT and QTc, QT_1 intervals were still prolonged and, for the first time, they were significant longer than their baseline-instrumentation values at the end recovery period for the carvedilol and dobutamine groups. Also, QT_1 interval of the dobutamine group was significantly longer than that of the sedentary group at this time point. The longer QT_1 interval may indicate prolongation of the absolute refractory period, in which I_{to} is the main determination in this process. This finding may point to the possibility that imipramine may alter I_{to} physiology up to at least 1 hr after cessation on infusion, and the effect on the relative refractory period may be the major factor in the restoration process of QT lengthening. Furthermore, carvedilol may inhibit several repolarizing K^+ currents such as I_{Kr}, I_{Ks}, and I_{to} in rabbit the ventricular myocyte [220]. However, the explanation of the QT_1 prolongation in the dobutamine group may be

related to the same mechanism that led to slight prolongation of QT interval at the baseline. Nevertheless, it was possible that chronic treatment of carvedilol or dobutamine may impair I_{to} recovery after challenge with imipramine compared with other interventions.

6.4 Discussion: Effects of imipramine or vehicle infusion on arrhythmia

Imipramine is well-known to create arrhythmia such as heart block, ventricular reentry arrhythmias [199], right bundle branch block, Brugada-type pattern [221], ventricular fibrillation, torsades des pointes, and asystole [67]. In this study, the studied arrhythmias were limited to VPDs, and AV block. However, as reported in chapter 5, most of the treatment groups (i.e. exercise, carvedilol, clenbuterol, and dobutamine group) and vehicle group had approximately the same incidence and/or severity of VPDs, thus this type of ventricular arrhythmia may only be a normal variation that could be induced in rats in general or in rats under anesthesia. Nevertheless, one of six rats in the carvedilol group developed 2nd degree AV block, while none of the rats in other groups or the vehicle group showed 2nd degree AV block. Thus, it may be assumed that 20 mg/kg/hr of imipramine IV infusion in rats could effectively delay AV conduction. However, it is difficult to compare degree of attenuation in AV conduction among groups since only one rat in 30 rats that had imipramine dosing presented with this brady-arrthymia. It is likely that its occurance in this study was by chance.

6.5 Study limitations

There were several limitations of this study. First of all, there were differences in the age of rats at the data collection day. As general knowledge, age of rats could be a major factor determining body weight, organ weight, and their ratios. In order to minimize the effect from age difference, the terminal study days of the rats were plan to create differences of age among rats of approximately within 4 weeks, and balance the age of the rats among groups. Moreover, when looking at the growth rate chart, these rats were already past their rapid growth phase. Thus effect of age differences should be minimal and not significant to influence tissue weights, hemodynamic values, or ECG parameters.

Secondly, in exercise training group, it was possible that rats received effects of exercise training from both aerobic training and resistance training, due to their behavior and the size of the rats that allowed them to be able to lift themselve on the individual-bar separator from time to time. This resistance exercise might augment skeletal muscle hypertrophy and body weights. However, the main effect should arise from aerobic training since those unwanted behaviors were discouraged by gentle pushing animals back down to the running lane or by placing clear plastic plate on the top to simulate a roof.

Thirdly, in order to get the corrected volume from the LV chamber, both parts of the conductance rings on conductant/micromnaomiter catheter tip need to be positioned within the LV chamber vertically. In some cases, the posterior conductance ring may be misplaced at above the aortic value and give inaccurate number. However, the values for

LV volumes appear reasonable and the pressure-volume loop characteristics seem to be in the normal range. Also, in this study, the conductance/micromanometer catheter needed to be pulled a little bit out when the catheter was touching the LV chamber and inducing VPDs in some rats, but in all of those cases the conductant/micromnaometer catheter was still inside the LV as confirmed by values of LVP and LVV, together with pressure-volume loop characteristics. Nevertheless, there was a possibility that the posterior conductance ring could be above aortic valve leading to less precise values of volume.

Finally, there were some difficulties in analyzed ECG values due to the micromovement of muscle and/or electrical noise from infusion pumps during infusion periods leading to unclear wave forms or unstable isoelectric lines. Furthermore, the uniqueness of rat ECG (i.e. lack of isoelectric line among wave forms and definited end point of S wave and onset of T wave) is particularly perplexing. Separation of end of QRS from onset of ST-T is virtually impossible. However, several approaches were done to improve quality of analysis without excessive use of filtering, such as grounding the surgical table and/or infusion pumps. A veterinary cardiologist was consulted to determine wave form markers before analysis, and manually checking and readjusting wave form markers after finishing analysis by the ECG Auto program. Moreover, ECG variables in this study were equally treated and the same criteria were applied to determine wave form markers in all groups. Thus, comparisons of ECG variables among the groups in this study should still be acceptable to reveal effects of intervetions and/or

imipramine on ECG values. The results of this study are applicable to this strain of rats, only, and may not be applicable to other mammals.

6.6 Future studies

This study describes, extensively and continuously, hemodynamic and ECG adaptations in response imipamine and to interventions (i.e., sedentary existence, AIT, and pharmacological preconditioning), and how those interventions might have altered the response to imipramine. The study did not permit the ability to hypothesize putative mechanisms (i.e., oxidative stress, NOS function, and cardiac ANS regulation) by which the intervention might have modulated responses to imipramine, therefore a future study should investigate potential interactionas of each intervention with imipramine.

The first mechanism that needs to be evaluated is oxidative stress, since this form of biological stress is so important to pathogeneisis of diseases and untoward drug effects. For example, it is well-known that oxidative stress depends heavily on both ROS production and scavenging by antioxidative enzymes. ROS is produced from both intrinsic and extrinsic cardiovascular sources, is known to induce cardiovascular depression due to lipid peroxidation of cell membranes and major organels, and to disruption of DNA. This oxidative stress (i.e., imbalance between ROS production and degradation) has proved to play a major role in pathophysiologies of several cardiotoxicities, such as ischemia-reperfusion injury [97], and intoxications by doxorubicin [50, 51, 54, 55], isoproterenol [59], and carbon monoxide [96]. Many/most of the interventions in this study are known to improve antioxidative status: ET [89, 95-

97, 99, 100], carvedilol [106, 108-112], clenbuterol [143], and dobutamine [162]. Interestingly, although imipramine depressed cardiocytes viability, it reduces ROS production significantly [222]. In another study, however, imipramine miminmized the increase of hydrogen peroxide and redeuced other expressions of oxidative stress in the rat ventricular cardiocytes. This beneficial effect may be mediated by inhibition of serotonin-induce activation of the serotonin-degrading enzyme monoamine oxidase A (MAO A), a major hydrogen peroxide producer in rat heart [223]. The future study should measure cardiac ROS production/level after rats recieve the interventions, and should seek associations between ROS level and hemodynamic or ECG outcomes during imipramine challenge.

A second study should investigate the relation between NOS expression/activity, and/or NO production/level. NOS, as briefly mention in chapter 1, is an important enzyme that synthesizes NO is known to modulate myocardial contractility and Ca^{2+} handling [93-95], as well as to facilitate improvement in cardiovascular functions in patients with HF [121, 122]. Vasodilation is another clinically relevant/important well-known function of NO. Alterations in NOS and/or NO level were/was also reported in other studies associated with the interventions (i.e., ET [95, 224], carvedilol [120-122], clenbuterol [225], and dobutamine [226]) in this study. Imipramine has been shown to modify tissue (e.g., brain, and smooth muscle) levels of NO in several studies [227- 229], and NO production is associated with hypotension produced by TCAs [230]. Therefore, a quantitative evaluation of NOS and/or NO levels from hearts of rats given the

interventions may provide information on NO-dependent cardiac adaptations, and/or cardioprotective effects during imipramine challenge in these rats.

However, in this study, after baseline pre-surgery ECG, hearts from four out of ten rats in each intervention, that had not received imipramine, were removed, weighed and were stored at -70° C for future analyses of ROS and NOS/NO.

Another mechanism by which interventions may moderate hemodynamic and ECG responses to imipramine may involve alterations in basal adrenergic sympathetic functions. As shown and discussed previously, these variations are more obvious among rats preconditioned with carvedilol, clenbuterol, and dobutamine than with ET or sedentary existence. All drugs used in this study can either stimulate or suppress sympathetic receptors, but their impacts (e.g., stimulation, suppression, or down-regulation) also depend on duration of administration. Thus, a future study should measure sympathetic receptor expression and function (1) after completing each intervention, (2) during co-administration of drug and imipramine, and (3) 1 hour after imipramine cessation. This future study may give an indication of sympathetic-dependent pathways by which interventions, and interactions of interventions and imipramine, can explain hemodynamic and ECG outcomes.

Quantitative assessment of the impact of imipramine was presented in time-dependent (i.e., % changes from their baseline values), and time-independent (i.e., Max effect, Δ value, and Δ %) manner. Effects of imipramine on parameters measured, and how those effects were identified (e.g., in which ECG lead), varied. For example, ECG amplitudes changed more in lead I than in lead AVF for all of the interventions. Thus a

future study should focus on detection of imipramine electrocardiotoxicity in leads that "interrogate" the LV free-wall (e.g., I in rats and V3 in humans). This future study may require analysis of additional components (e.g., QT variability [i.e., SD of QT = squre root of {[(mean of QT) ● (Δduration of QT)^2] – [(mean of QT)^2 ● (Δduration of QT)]}, QT instability (i.e., differences between upper quartile and the lower quartile of QT) [231], ventricular restitution (i.e., QT/TQ), and electromechanical window [(S1-S2)-QT]) of each lead to provide additional infomation useful to the clinician. Examples of clinical uses of these parameters are: (1) absolute (i.e., sinus and non-sinus beat) beat-to-beat QT variability and instability can quantify repolarization homogeneity and can be a high sensitivity and specificity predictors of ventricular fibrillation outcomes in rat hearts [231], (2) QT interval variability index (QTVI) shows association with head concussion-induced acute negative impacts on vagal cardiac autonomic function [232], (3) "ventricular restitution" measured as Regional Restitution Instability Index (R2I2) can indicate cardiac electrical instability associated with heterogeneity in electrical restitution and can identify ischemic cardiopathy patients with high risk of ventricular arrhythmia and sudden cardiac death [233], (4) electromechanical window (EMW), i.e. time difference between end of electrical systole and end of ventricular relaxation (duration from end of T wave to end of LVP curve) [234], is mainly QT duration-dependent, but it also allows prediction of torsades de pointes in animal models [235]. From all of the above examples, these arrthymogenic indicators may provide further insight into mechanisms of interventions or of imipramine.

Finally, rates of recovery of physiological variables altered by interventions and imipramine in this study should be quantified for 2 conditions. Condition 1 is recovery even during imipramine infusion; conditioin 2 is recovery following cessation of imipramine infusion. Rates of recovery should be expressed for (1) sponataneous recovery during infusion [i.e., (values at Max effect minus values at the end-dose)/time from Max effect to the end-dose time point], and (2) recovery following cessation of infusion [i.e., (values at the end of recovery period minus values at the end-dose)/ 60 min]. Tangents constructed to various points on the reovery curves quantify and allow for compariosons of rates of recovery. Also rates of recovery may be expressed as time-constants, i.e., the time required for a curve to return from a point to 63% of the baseline value.

6.7 Conclusion

In term of the effects of interventions on physiological parameters, there were several alterations induced by each intervention at the end of intervention period in this study. Exercise and clenbuterol trended to increase growth more than dobutamine. AIT protocol trended to increase BW and hW/BW ratio. Clenbuterol increase hW/bW ratio. On the other hand, the dobutamine rats were smaller in BW and hW/BW ratio. However, none of the interventions (i.e. sedentary existence, exercise training, and pharmacological preconditionings) produced significant differences in stress level among groups.

Types of treatments also had several significant effects on hemodynamic variables with variations depended on types of treatment. The treatments that could augment

hemodynamic functions of systemic and/or LV variables were the AIT and the clenbuterol, while the chronic treatment of carvedilol and dobutamine resulted in reduction of hemodynamic functions associated with sympathetic control such as SBP, LVSP, and +dP/d*t*. These variations were statistically significant only when comparing groups with the highest and lowest values. None of the differences achieved statistical significance when compared with sedentary existence. However, these statistical variations may point to the fact that exercise training, and chronic stimulation or inhibition of sympathetic functions could lead to alteration in cardiovascular functions even in normal healthy animals, thus using these interventions in sick patients (greater variability) may require more precautions and effective monitoring systems.

Likewise, treatments also affected several ECG variables at the end of the intervention (before start instrumentation surgery) and created variations among treatments that had highest-value with the lowest-value group. The main findings in this part were (1) AIT could produce cardiac adaptation in ECG (athletic heart): big inverted T wave in lead I, slight physiological bradycardia in all leads, and improvement in homogeneity of ventricular repolarization (shorter QTc and T duration) in lead V3, (2) chronic treatment with carvedilol could also augment homogeneity of ventricular repolarization: shorter QTc and T duration in lead V3, (3) chronic treatment of clenbuterol could lead to possible cardiac hypertrophy: tall T and P waves with shallow S wave in lead I, but smaller R amplitude in lead AVF, and shorten T duration in lead V3, (4) chronic dobutamine treatment could lead to mixed effect of pseudo athletic heart and

attenuation in homogeneity of ventricular repolarization: big inverted T wave in lead I, tall R wave in lead AVF, but prolong QTc and T duration in lead V3.

When examining the effects of IV imipramine infusion at 20 mg/kg/hr in pentobarbital anesthetized sedentary rats compared with matched-volume vehicle (sterile water) infusion group, imipramine attenuated both systemic and LV hemodynamic values. At mid-dose period, imipramine caused gradual hypotension (as reduction in SBP, DBP, PP, and MAP) concomitant with depressed LV performances (as decreased HR, LVESP, +dP/d*t*, -dP/d*t*, and +dP/d*t*/LVEDV). Interestingly, these cardiovascular attenuations (i.e. negative chronotropy, inotropy, and lusitropy) showed spontaneous recovery even during imipramine infusion (from mid-dose to end-dose period), and finally they partially returned toward their baseline-instrumentation values, with statistically significant differences between the baseline and the end recovery period. PP markedly recovered to the point that it did not differ from baseline. Concomitantly with hemodynamics, electrocardiographic alterations due to imipramine also pointed out that imipramine had negative impacts on impulse generation and conduction (dromotropy) in the hearts manifested by reductions R_a (both lead I and AVF), deeper S_a (lead I), and prolongation of several wave form durations in lead V3 (i.e. P, PR, PR_{sect}, QRS, QT, QA, and T duration). However, these ECG alterations did not show obvious spontaneous recovery, but at the end the recovery period these parameters did show partial recover but without statistically significant differences between the baseline and the end recovery period. PR interval remained prolonged compared to baseline.

These imipramine induced alterations in cardiovascular function were related to its major ability in inhibit sympathetic regulation of the heart, elicit vasodilation, and affect cardiac ion currents (I_{Na}, $I_{Ca,\ L}$, and I_{to}), leading to negative chronotropy, inotropy, lusitropy, and dromotropy. All of those negative effects resulted in hypotensive, bradycardia, reduction in force of cardiac contraction, and changes in ECG. Therefore, patients or animals with depressed cardiovascular function or using other cardiovascular medications should be more informed and receiving vigorous monitoring when receiving TCAs.

With combination of interventions (i.e. sedentary existence, AIT, or pharmacological preconditioning) and imipramine infusion challenge, most of the alterations in cardiovascular function showed the same trends (hypotensive; negative chronotropic, inotropic, lusitropic, and dromotropic; ECG alterations) among the groups and were consistent with sedentary animals. The lack of significant protection of hemodynamic effects constituting a failing heart in this study may be result from: (1) inabilility to measure differences (i.e. the measurement methods were less sensitive or the direct mechanisms were not observed), (2) the interventions are truly ineffective in this model (i.e. no cardioprotective effects was induced by interventions that could attenuate imipramine cardiotoxicity), and (3) results from a failing heart produced by imipramine may not be applicable to a failing heart occurring naturally.

Nevertheless, there were some variations in response to imipramine infusion or recovery ability due to the effects of types of treatments. The conclusions according to effects of treatment groups are as follows:

Eeven though AIT did not generate obvious cardioprotective in term of hemodynamic values compared with the sedentary group and may even have more imipramine effect on CI, it could minimize negative cardiac electrical generation and conduction impacts of imipramine, i.e. reductions of R and S amplitudes in lead AVF, prolongation PR_{sect}, QT, QTc, and T duration in lead V3 (especially when compared with the dobutamine group that had heavier imipramine effects on QT and T duration). These minimized heterogeneity of ventricular repolarization (measured as QT and T duration) are likely to produce by physiological adaptation of the ANS and cardiac structural and functional properties, which may be important in the reduction of arrhythmia risk.

Likewise, chronic treatment of carvedilol that presented slight β-blocking effects at the baseline, not only showed positive effects on alterations of the ECG induced by imipramine similar to AIT, but also had superior changes in QA, in homogeneity of ventricular repolarization, and in chronotropy, measured as lengthening of QA, prolongations of QT, QTc, and T duration, and HR recovery. Moreover, this treatment also had better outcomes of Δ value at maximal effect of LVESP (especially when compared with that of the clenbuterol group) and PP (especially when compared with that of the exercise group), together with overall PP alterations and HR recovery. Nevertheless, it showed greater increases of LVESV, and diminished P amplitude in lead AVF, and R amplitude recovery in lead I. Some of these variations may result from competitive effects of carvedilol and imipramine on the same receptor or pathways of actions such as sympathetic activation and cardiac ion currents.

On the other hand, chronic administration of clenbuterol, that seemed to have augmented sympathetic drive to the cardiovascular system at basal level, could aggravate the impacts of imipramine on ECG alterations (such as prolong PR and PR_{sect} durations), ventricular repolarization (measured as maximal effect of QT_1), and indirect cardiac contractility (Δ % of QA at maximal effect). Moreover, it created relatively greater alterations in expansion of LVEDV and LVESV, shortening of Tau, and diminished P amplitude in lead AVF. However, it had uniqueness in responses to imipramine's cardiotoxic effects as its increased SV and CO, prolongation of time to maximal effect of DBP, and less augmentation of negative S wave in both amplitude and time to maximal effect compared with other groups.

Finally, chronic dobutamine treatment could induce slight depressions in sympathetic control of cardiovascular functions at the baseline (down-regulation of β_1) and more attenuations in hemodynamics during imipramine challenge (i.e. SBP, DBP, PP, MBP, +dP/d*t*, -dP/d*t*, and +dP/d*t*/LVEDV, LVEDV, LVESV, and Tau), but did not significantly alter HR regulation. Moreover, it could generate relatively greater impact of imipramine on ECG deviation such as blunted amplitudes of R, T wave in lead I, as well as lengthened durations of PR, PR_{sect}, QT, QTc, QT_1, and T duration, although, it seemed to relatively preserve Δ value of CI at maximal effect. This increment of AV conduction and heterogeneity of ventricular repolarization could point to the possibility that patients or animals who received chronic dobutamine treatment concomitant with imipramine therapy may have more risk of AV block and ventricular arrhythmia.

However, the failure to statistically identify protection against adverse imipramine-produced hemodynamic effects does not imply that none of the interventions have cardioprotective effects. The statistical analysis method may also have influence in the outcomes, since this study used 2-way ANOVA with repeated measure design to compare all interventions; whereas paired *t*-test comparisons of each intervention against sedentary (i.e. nothing) could have more robust comparison. However, comparing each intervention against only nothing was not the goal of this study.

References

1. Rush, J. “Chronic Valvular Heart Disease in Dogs.” OSU Symposium. Waltham USA, 2002.
2. Fleming, J. M., K. E. Creevy, and D. E. L. Promislow. “Mortality In North American Dogs From 1984 To 2004: An Investigation Into Age-, Size-, And Breed-Related Causes Of Death.” *Journal Of Veterinary Internal Medicine.* 25.2 (2011): 187-198.
3. Gomes, A. C., I. Falcão-Pires, A. L. Pires, C. Brás-Silva, and A. F. Leite-Moreira. “Rodent models of heart failure: an updated review.” *Heart Failure Reviews.* 18.2 (2013): 219-249.
4. Monnet, E., and J. C. Chachques. “Animal models of heart failure: what is new?” *The Annals of thoracic surgery.* 79.4 (2005): 1445–1453.
5. Wisløff, U., J. P. Loennechen, S. Currie, G. L. Smith, and Ø. Ellingsen. “Aerobic exercise reduces cardiomyocyte hypertrophy and increases contractility, Ca^{2+} sensitivity and SERCA-2 in rat after myocardial infarction.” *Cardiovascular Research*. 54.1 (2002): 162-174.
6. Anderson, P. G., S. P. Bishop, and J. T. Peterson. “Chapter 26 - Cardiovascular Research” In: The Laboratory Rat (Second Edition), a volume in American College of Laboratory Animal Medicine., edited by SuckowSteven, M. A., H. WeisbrothCraig, L. Franklin (eds). Academic Press, Burlington. (2006): 773-802.
7. Anderson, P. G., S. B. Digerness, J. L. Sklar, and P. J. Boor. “Use of the isolated perfused heart for evaluation of cardiac toxicity.” *Toxicologic pathology*. 18.4 (1990): 497-510.
8. Neely, H. L., E. J. Battersby, and H. E. Morgan. “Effect of pressure development on oxygen consumption by isolated rat heart.” *American Journal of Physiology*. 212.4 (1967): 804-814.
9. Pacher, P., J. G. Mabley, L. Liaudet, O. V. Evgenov, A. Marton, G. Hasko, M. Kollai, and C. Szabo. “Left Ventricular Pressure-Volume Relationship in a Rat Model of Advanced Aging-Associated Heart Failure.” *American Journal of Physiology: Heart & Circulatory Physiology*. 56.5 (2004): H2132-H2137.
10. Lujan, H. L., H. Janbaih, H. Z. Feng, J. P. Jin, and S. E. Dicarlo. "Ventricular function during exercise in mice and rats." *AJP: Regulatory, Integrative and Comparative Physiology.* 302.1 (2011): R68-R74.

11. Pacher, P., T. Nagayama, P. Mukhopadhyay, S. Bátkai, and D. A. Kass. "Measurement of Cardiac Function Using Pressure-Volume Conductance Catheter Technique in Mice and Rats." *Nature Protocols*. 3.9 (2008): 1422-34.
12. Hamlin, R. L., and C. Del Rio. "Dp/dtmax — a Measure of baroinometry." *Journal of Pharmacological and Toxicological Methods*. 66.2 (2012): 63-65.
13. Castagno, D., H. Skali, M. Takeuchi, K. Swedberg, S. Yusuf, C. B. Granger, E. L. Michelson, M. A. Pfeffer, J. J. McMurray, and S. D. Solomon. "Association of Heart Rate and Outcomes in a Broad Spectrum of Patients with Chronic Heart Failure: Results from the Charm (candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Program." *Journal of the American College of Cardiology*. 59.20 (2012): 1785-1795.
14. Xu, M., H. Ji,, D. Z. Dai, X. Y. Tang, Y. Dai. "Protective effect of the endothelin antagonist CPU0213 against isoprenaline-induced heart failure by suppressing abnormal expression of leptin, calcineurin and SERCA2a in rats." *Journal of pharmacy and pharmacology*. 60.6 (2008): 739-745.
15. Bonnie, K., F. Benjamin, K. A. May, T. Plappert, A. Wang, B. J. A. Chirinos, J. Fang, N. K. Sweitzer, B. A. Borlaug, D. A. Kass, and T. P. Cappola. "Ventricular-arterial coupling, remodeling, and prognosis in chronic heart failure." *Journal of the American College of Cardiology*. 62.13 (2013): 1165-1172.
16. Solomon, S. D., N. Anavekar, H. Skali, J. J. McMurray, K. Swedberg, S. Yusuf, C. B. Granger, E. L. Michelson, D. Wang, S. Pocock, and M. A. Pfeffer. "Influence of Ejection Fraction on Cardiovascular Outcomes in a Broad Spectrum of Heart Failure Patients." *Circulation*. 112.24 (2005): 3738-3744.
17. Chowdhury, S. M, R. J. Butts, J. Buckley, A. M. Hlavacek, T. Y. Hsia, S. Khambadkone, and G. H. Baker. "Comparison of Pressure–volume Loop and Echocardiographic Measures of Diastolic Function in Patients with a Single-Ventricle Physiology." *Pediatric Cardiology*. 35.6 (2014): 998-1006.
18. Matyas, C., A. Olah, B. Nemeth, L. Hidi, E. Birtalan, M. Ruppert, G. Kokeny, G. Szabo, B. Merkely, and T. Radovits. "P758 Cinaciguat Prevents Diabetes Mellitus Related Cardiac Alterations in Rats." *Cardiovascular Research*. 103 (2014): 139.
19. Adler, D., S. D. Nikolic, E. H. Sonnenblick, and E. L. Yellin. "Time to dP/dtmax, a preload-independent index of contractility: open-chest dog study." *Basic research in cardiology*. 91.1 (1996): 94-100.
20. Letac, B., R. Cannon, Jr. W. B. Hood, B. Lown. "Measurement of the second derivative of left ventricular pressure using a fiberoptic catheter." *Proceeding of the Society for Experimental Biology & Medicine*. 127 (1968): 63-66.
21. Little, W. C. "The left ventricular dP/dt(max)-end-diastolic volume relation in closed-chest dogs." *Circulation Research*. 56 (1985): 808-815.
22. Cheng, C. P., Z. Shihabi, and W. C. "Little. Acute effects of mildly intoxicating levels of alcohol on left ventricular function in conscious dogs." *Journal of Clinical Investigation*. 85 (1990): 1858-1865.

23. Mason, D. T., E. Braunwald, J. W. Covell, E. H. Sonnenblick, EJr. J. Ross. "Assessment of cardiac contractility. The relation between the rate of pressure rise and ventricular pressure during isovolumic systole." *Cardiovascular Research*. 5 (1971): 15-23.
24. Kijtawornrat, A., Y. Ueyama, C. del Rio, S. Sawangkoon, C. Buranakarl, N. Chaiyabutr, and R. L. Hamlin. "Test of the Usefulness of a Paradigm to Identify Potential Cardiovascular Liabilities of Four Test Articles with Varying Pharmacological Properties in Anesthetized Guinea Pigs." *Toxicological Sciences*. 137.2 (2014): 458-468.
25. Waller A. D. "A Demonstration on Man of Electromotive Changes accompanying the Heart's Beat." *The Journal of physiology*. 8.5 (1887): 229-34.
26. Zareba, W. "New Era for Digital ECG: FDA Requires Digital ECG Submission for Tested Drugs." *Annals of Noninvasive Electrocardiology*. 7.1 (2001): 1-3.
27. Chen, X., S. Hongli, Z. Jinlong, H. Yuan, B. Yunlong, S. Iihua, P. Zhenwei, Z. Yong, Y. Baofeng, and D. Zhimin. "L-type Calcium Current ($I_{Ca\ ,\ L}$) and Inward Rectifier Potassium Current (I_{k1}) Are Involved in QT Prolongation Induced by Arsenic Trioxide in Rat." *Cellular Physiology and Biochemistry*. 26.6 (2010): 967-974.
28. Farraj, A. K., M. S. Hazari, and W. E. Cascio. "The utility of the small rodent electrocardiogram in toxicology." *Toxicological sciences*. 121.1 (2011): 11-30.
29. Driscoll P. "The normal rat electrocardiogram." In: The Rat Electrocardigram in Pharmacology and Toxicology. Budden R., D. K. Detweiler, G. Zbinden (eds). Pergamon Press Ltd, England. (1981): 1-14.
30. Antzelevitch C., and J. Fish. "Electrical heterogeneity within the ventricular wall." Basic Research Cardiology. 96 (2001): 517-527.
31. Ravens, U., and E. Cerbai. "Role of Potassium Currents in Cardiac Arrhythmias." *Europace*. 10.10 (2008): 1133-37.
32. Sorodoc, V., L. Sorodoc, D. Ungureanu, A. Sava, and I. M. Jaba. "Cardiac Troponin T and NT-proBNP as Biomarkers of Early Myocardial Damage in Amitriptyline-Induced Cardiovascular Toxicity in Rats." *International Journal of Toxicology*. 32.5 (2013): 351-357.
33. Kharin, S., V. Krandycheva, A. Tsvetkova, M. Strelkova, and D. Shmakov. "Remodeling of ventricular repolarization in a chronic doxorubicin cardiotoxicity rat model." *Fundamental & Clinical Pharmacology*. 27.4 (2013): 364-372.
34. Farraj A. K., M. S. Hazari, D. W. Winsett, A. Kulukulualani, A. P. Carll, N. Haykal-Coates, C. M. Lamb, E. Lappi, D. Terrell, W. E. Cascio, D. L. Costa. "Overt and Latent Cardiac Effects of Ozone Inhalation in Rats: Evidence for Autonomic Modulation and Increased Myocardial Vulnerability." *Environmental health perspectives*. 120.3 (2012): 348-354.
35. Adeyemi, O., S. Roberts, J. Harris, H. West, S. Shome, and M. Dewhurst. "QA Interval as an Indirect Measure of Cardiac Contractility in the Conscious Telemeterised Rat: Model Optimisation and Evaluation." *Journal of Pharmacological and Toxicological Methods*. 60.2 (2009): 159-166.

36. Takahara, A., H. Dohmoto, R. Yoshimoto, A. Sugiyama, and K. Hashimoto. "Cardiovascular Action of a Cardioselective Ca $^{2+}$channel Blocker Ah-1058 in Conscious Dogs Assessed by Telemetry." *European Journal of Pharmacology*. 413.1 (2001): 101-108.
37. Weiss, C. S., M. Hagenmuller, M. Pichler, S. Munz, M. Ochs, S. J. Buss, R. Bekeredjian, H. A. Katus, HS. E. Hardt. "Activation of PPARgamma by pioglitazone does not attenuate left ventricular hypertrophy following aortic banding in rats." *Naunyn-Schmiedeberg's archives of pharmacology*. 381.4 (2010): 285-295.
38. Ku, H. C., M. J. Su, and K. Urbanek. "Dpp4 Deficiency Preserved Cardiac Function in Abdominal Aortic Banding Rats." *Plos One*. 9.1 (2014): e85634.
39. Wei, S., A. Guo, B. Chen, W. Kutschke, Y. P. Xie, K. Zimmerman, R. M. Weiss, M. E. Anderson, H. Cheng, and L. S. Song. "T-tubule Remodeling During Transition from Hypertrophy to Heart Failure." *Circulation Research*. 107.4 (2010): 520-531.
40. Vistnes, M., J. M. Aronsen, I. G. Lunde, I. Sjaastad, C. R. Carlson, G. Christensen, and N. Frangogiannis. "Pentosan Polysulfate Decreases Myocardial Expression of the Extracellular Matrix Enzyme Adamts4 and Improves Cardiac Function in Vivo in Rats Subjected to Pressure Overload by Aortic Banding." *Plos One*. 9.3 (2014): e89621.
41. Feldman, A. M., E. O. Weinberg, P. E. Ray, and B. H. Lorell. "Selective changes in cardiac gene expression during compensated hypertrophy and the transition to cardiac decompensation in rats with chronic aortic banding." *Circulation Research*. 73.1 (1993): 184-192.
42. Norton, G. R., A. J. Woodiwiss, W. H. Gaasch, T. Mela, E. S. Chung, G. P Aurigemma, and T. E. Meyer. "Heart failure in pressure overload hypertrophy." *Journal of the American College of Cardiology*. 39.4 (2002): 664-671.
43. Harris G. S., R. M. Lust, J. De Antonio, L. C. Katwa, " Chronic Volume Overload, a Model of Congestive Heart Failure, Increase PPAR-Gamma Expression." *The FASEB journal*. 20.5 (2006): A1435.
44. Gerdes, A. M., S. E. Campbell, and D. R. Hilbelink. "Structural Remodeling of Cardiac Myocytes in Rats with Arteriovenous Fistulas." *Laboratory Investigation*. 59.6 (1988): 857-861.
45. Roscani, M. G., B. F. Polegato, S. E. Minamoto, A. P. Lousada, M. Minicucci, P. Azevedo, L. S. Matsubara, and B. B. Matsubara. "Left Ventricular Sphericity Index Predicts Systolic Dysfunction in Rats with Experimental Aortic Regurgitation." *Journal of Applied Physiology*. 116.10 (2014): 1259-62.
46. Mazzo, F. R. R., C. D. Frimm, A. I. S. Moretti, M. C. Guido, and M. K. Koike. "Acute aortocaval fistula: role of low perfusion pressure and subendocardial remodeling on left ventricular function." *International Journal of Experimental Pathology*. 94 (2013): 178-187.

47. Naito, Y., T. Tsujino, M. Matsumoto, T. Sakoda, M. Ohyanagi, and T. Masuyama. “Adaptive Response of the Heart to Long-Term Anemia Induced by Iron Deficiency.” *American Journal of Physiology: Heart & Circulatory Physiology*. 65.3 (2009): H585-93.
48. Kemi, O. J., I. Arbo,M. A. Høydal, J. P. Loennechen, U. Wisloff, G. L. Smith, Ø. Ellingsen. “Reduced pH and contractility in failing rat cardiomyocytes.” *Acta physiologica*. 188.3-4 (2006): 185-193.
49. Loennechen J. P., U. Wisløff, G. FALCK and Ø. Ellingsen. “Cardiomyocyte contractility and calcium handling partially recover after early deterioration during post-infarction failure in rat.”*Acta physiologica Scandinavica*. 176.1 (2002): 17-26.
50. Delgado-Roche, L., Y. Hernandez-Matos, E. A. Medina, D. A. Morejon, M. R. Gonzalez, and G. Martenez-Sanchez. “Ozone-oxidative Preconditioning Prevents Doxorubicin-Induced Cardiotoxicity in Sprague-Dawley Rats.” *Sultan Qaboos University Medical Journal*. 14.3 (2014): e342-48.
51. Segredo, M. P. D., F. C. F. Moretto, C. R. Correa, R. S. Reis, L. S. Matsubara, B. B. Matsubara, A. Ferreira, D. F. Salvadori, E. A. Camargo, D. D. Almeida, C. M. Freire, M. G. Braz, N. S. Rocha, G. Tang, and K. J. Yeum. “Oxidative Stress on Cardiotoxicity After Treatment with Single and Multiple Doses of Doxorubicin.” *Human and Experimental Toxicology*. 33.7 (2014): 748-760.
52. Aryal, B., J. Jeong, and V. A. Rao. “Doxorubicin-induced carbonylation and degradation of cardiac myosin binding protein C promote cardiotoxicity.” *Proceedings of the National Academy of Sciences*. 111.5 (2014): 2011-16.
53. Salouege, I., R. Ali, D. Saïd, N. Elkadri, N. Kourda, M. Lakhal, and A. Klouz. “Means of Evaluation and Protection from Doxorubicin-Induced Cardiotoxicity and Hepatotoxicity in Rats. (original Article)(report).” *Journal of Cancer Research and Therapeutics*. 10.2 (2014): 274-278.
54. Mendes, R. h., C. Mostarda, G. O. Candido, I. C. Moraes-Silva, V. D'almeida, A. Bello-Klein, M.c. Irigoyen, and K. Rigatto. “Moderate hyperhomocysteinemia provokes dysfunction of cardiovascular autonomic system and liver oxidative stress in rats.” *Autonomic Neuroscience*. 180 (2013): 43-47.
55. Norsidah, K. Z, A. Y. Asmadi, A. Azizi, O. Faizah, and Y. Kamisah. “Palm Tocotrienol-Rich Fraction Improves Vascular Proatherosclerotic Changes in Hyperhomocysteinemic Rats.” *Evidence-based Complementary and Alternative Medicine*. 2013 (2013): 976967.
56. Shrestha, A., P. T. Krishnamurthy, P. Thomas, B. D. Hammock, and S. H. Hwang. “Soluble Epoxide Hydrolase Inhibitor, T-Tucb, Protects against Myocardial Ischaemic Injury in Rats.” *Journal of Pharmacy and Pharmacology*. 66.9 (2014): 1251-58.

57. Ríha, M., M. Vopršalová, V. Pilařová, V. Semecký, M. Holečková, J. Vávrová, V. Palicka, T. Filipský, R. Hrdina, L. Nováková, and P. Mladěnka. "Oral Administration of Quercetin Is Unable to Protect against Isoproterenol Cardiotoxicity." *Naunyn-schmiedeberg's Archives of Pharmacology.* 387.9 (2014): 823-835.
58. Soraya, H., A.S. Clanachan, M. Rameshrad, N. Maleki-Dizaji, M. Ghazi-Khansari, and A. Garjani. "Chronic Treatment with Metformin Suppresses Toll-Like Receptor 4 Signaling and Attenuates Left Ventricular Dysfunction Following Myocardial Infarction." *European Journal of Pharmacology.* 737 (2014): 77-84.
59. Sahu, B. D., H. Anubolu, M. Koneru, J. M. Kumar, M. Kuncha, S. S. Rachamalla, and R. Sistla. "Cardioprotective Effect of Embelin on Isoproterenol-Induced Myocardial Injury in Rats: Possible Involvement of Mitochondrial Dysfunction and Apoptosis." *Life Sciences.* 107 (2014): 59-67.
60. Nojimoto, F. D., A. Mueller, F. Hebeler-Barbosa, J. Akinaga, V. Lima, L. R. Kiguti, and A. S. Pupo. "The Tricyclic Antidepressants Amitriptyline, Nortriptyline and Imipramine Are Weak Antagonists of Human and Rat Alpha1b-Adrenoceptors." *Neuropharmacology*. 59 (2010): 49-57.
61. Ilkaya, F., S. S. Bilge, A. Bozkurt, D. B. Baş, A. Erdal, E. Çiftçioğlu, and Y. Kesim. "The antinociceptive effect of intravenous imipramine in colorectal distension-induced visceral pain in rats: The role of serotonergic and noradrenergic receptors." *Pharmacology Biochemistry and Behavior*. 122 (2014): 1-6.
62. Réus, G. Z., R. B. Stringari, K. F. Ribeiro, Karine F., T. Luft, H. M. Abelaira, G. R. Fries, B. W. Aguiar, F. Kapczinski, J. E. Hallak,A. W. Zuardi, J. A. Crippa, J. Quevedo. "Administration of cannabidiol and imipramine induces antidepressant-like effects in the forced swimming test and increases brain-derived neurotrophic factor levels in the rat amygdala." *Acta Neuropsychiatrica*. 23.5 (2011): 241-248.
63. Pimentel, L., and L. Trommer. "Cyclic Antidepressant Overdoses. a Review." *Emergency Medicine Clinics of North America*. 12.2 (1994): 533-547.
64. Smaga, I., B. Bystrowska, D. Gawlinski, B. Pomierny, P. Stankowicz, and M. Filip. "Antidepressants and Changes in Concentration of Endocannabinoids and N-Acylethanolamines in Rat Brain Structures." *Neurotoxicity Research*. 26.2 (2014): 190-206.
65. Kathol, R. G., andF. A. Henn. "Tricyclics--the most common agent used in potentially lethal overdoses." *The journal of nervous and mental disease.* 171.4 (1983): 250-252.
66. Glassman, A. H. "Cardiovascular Effects of Antidepressant Drugs: Updated." *The Journal of Clinical Psychiatry*. 59 (1998): 13-18.
67. Sanaei-Zadeh, H., F. Shahmohammadi, N. Zamani, and B. Mostafazadeh. "Can Death Unrelated to Secondary Causes Be Predicted in Intubated Comatose Tricyclic Antidepressant-Poisoned Patients?" *Clinical Toxicology*. 49.5 (2011): 379-384.

68. Lucas, C. M., E. C. Cheriex, F. H. Vandeveen, J. Habets, T. Vandernagle, O. C. Penn, and H. J. Wellens. “Imipramine Induced Heart Failure in the Dog: a Model to Study the Effect of Cardiac Assist Devices.” *Cardiovascular Research*. 26.8 (1992): 804-809.
69. Fiedler, V. B., B. Kettenbach, H. GöBel, and R. E. Nitz. “Treatment of haemodynamic and electrocardiographic side-effects resulting from imipramine toxicity in rats and dogs.” *Naunyn-Schmiedeberg's Archives of Pharmacology.* 330.2 (1985): 155-161.
70. Lee, M. Y., S. J. Kim, J. S. Kim, and H. S. Kang. “Imipramine-Induced Cardiac Depression Is Responsible for the Increase in Intracellular Magnesium and the Activation of ERK 1/2 in Rats.” *Journal of cardiovascular pharmacology and therapeutics.* 15.3 (2010): 303-310.
71. Sasyniuk, B. I., and V. Jhamandas. “Mechanism of reversal of toxic effects of amitriptyline on cardiac Purkinje fibers by sodium bicarbonate.” *The Journal of pharmacology and experimental therapeutics*. 231.2 (1984): 387-394.
72. Zahradník, I., I. Minarovic, and A. Zahradnikova. “Inhibition of the Cardiac L-Type Calcium Channel Current by Antidepressant Drugs.” *Journal of Pharmacology and Experimental Therapeutics.* 324.3 (2007): 977-984.
73. Watts, J. A., K. M. Yates, S. K. Badar, M. B. Marcengill, and J. A. Kline. “Mechanisms of Ca^{2+} antagonism in imipramine-induced toxicity of isolated adult rat cardiomyocytes.” *Toxicology and applied pharmacology.* 153.1 (1998):95-101.
74. Schoors, D. F., H. Reynaert, L. Huyghens, L. Vanhaelst, and A. G. Dupont. “Protective effects of felodipine and verapamil against imipramine-induced lethal cardiac conduction disturbances in the anaesthetized rat.” *Cardiovascular Drugs and Therapy*. 5.2 (1991): 489-494.
75. Sebai, M., S. Lu, L. Xiang, and R. L. Hester. “Improved functional vasodilation in obese Zucker rats following exercise training.” *AJP: Heart and Circulatory Physiology.* 301.3 (2011): H1090-96.
76. Mischler, I., Y. Boirie, P. Gachon, V. Pialoux, R. Mounier, P. Rousset, J. Coudert, and N. Fellmann. “Human albumin synthesis is increased by an ultra-endurance trial.” *Medicine and science in sports and exercise*. 35.1 (2003): 75-81.
77. Nagashima, K., G. W. Mack, A. Haskell, T. Nishiyasu, and E. R. Nadel. “Mechanism for the posture-specific plasma volume increase after a single intense exercise protocol.” *Journal of Applied Physiology*. 86 (1999): 867-873.
78. Goodman, J. M., P. P. Liu, and H. J. Green. “Left ventricular adaptations following short-term endurance training.” *Journal of Applied Physiology.* 98 (2005): 454-460.
79. Ulrich, G., P. Bärtsch, and B. Friedmann-Bette. “Total haemoglobin mass and red blood cell profile in endurance-trained adolescent athletes.” *European Journal of Applied Physiology*. 111 (2011): 2855-64.

80. Masson, G. S., T. S. Costa, L. Yshii, D. C. Fernandes, P. P. Soares, F. R. Laurindo, C. Scavone, and L. C. Michelini. "Time-dependent Effects of Training on Cardiovascular Control in Spontaneously Hypertensive Rats: Role for Brain Oxidative Stress and Inflammation and Baroreflex Sensitivity." *Plos One*. 9.5 (2014): e94927.
81. De Rossi, G., J. R. Matos-Souza, A. De A. C. E. Silva., L. F. Campos, L. G. Santos, E. R. Azevedo, K. C. Alonso, L. R. Paim, R. Schreiber, J. I. Gorla, C. Jr. Alberto, and W. Nadruz. "Physical Activity and Improved Diastolic Function in Spinal Cord-Injured Subjects." *Medicine & Science in Sports & Exercise*. 10 (2014): 887-892.
82. Perhonen, M. A., F. Franco, L. D. Lane, J. C. Buckey, C. G. Blomqvist, J. E. Zerwekh, R. M. Peshock, P. T. Weatherall, and B. D. Levine. "Cardiac Atrophy After Bed Rest and Spaceflight." *Journal of Applied Physiology*. 91.2 (2001): 645-653.
83. Utomi, V., D. Oxborough, E. Ashley, R. Lord, S. Fletcher, M. Stembridge, R. Shave, M. D. Hoffman, G. Whyte, and J. Somauroo. "Predominance of Normal Left Ventricular Geometry in the Male "athlete's Heart"." *Heart London Bmj Publishing Group*. 100.16 (2014): 1264-71.
84. Kisvistö, S., M. Perhonen, M. Holmström, and K. Lauerma. "Assessment of the effect of endurance training on left ventricular relaxation with magnetic resonance imaging." *Scandinavian Journal of Medicine & Science and Sports*. 16.32 (2006): 321-328.
85. Carneiro-Junior, M. A., A. J. Natali, J. G. Mill, J. S. Cruz, E. M. Oliveira, L. B. Felix, F. R. Drummond, V. N. Lavorato, L. R. Drummond, J. F. Quintao-Junior, and T. N. Primola-Gomes. "Regional effects of low-intensity endurance training on structural and mechanical properties of rat ventricular myocytes." *Journal of applied Physiology*. 115.1 (2013): 107-115.
86. Fujimoto, N., A. Prasad, J. L. Hastings, A. Arbab-Zadeh, P. S. Bhella, S. Shibata, D. Palmer, and B. D. Leivine. "Cardiovascular effects of 1 year of progressive and vigorous exercise training in previously sedentary individuals older than 65 years of age." *Circulation*. 122 (2010): 1797-1805.
87. Carlsson, L., B. Lind, M. S. Laaksonen, B. Berglund, L. A. Brodin, and H. C. Holmberg. "Enhanced systolic myocardial function in elite endurance athletes during combined arm-and-leg exercise." *European Journal of Applied Physiology*. 111 (2011): 905-913.
88. Kemi, O. J., P. M. Haram, U. Wisløff, and Ø. Ellingsen. "Aerobic fitness is associated with cardiomyocyte contractile capacity and endothelial function in exercise training and detraining." *Circulation*. 109 (2004): 2897-904.
89. Fenning, A., G. Harrison, D. Dwyer, R. R. Meyer, and L. Brown. "Cardiac adaptation to endurance exercise in rats." *Molecular and Cellular Biochemistry*. 251.1-2 (2003): 51-59.

90. Hastings, J. L., S. B. Paul, S. Shigeki, N. Fujimoto, G. Carrick-Ranson, N. Minniefield, J. McLoughlin, K. Boyd, M. D. Palmer, and B. D. Levine. “Lifelong Exercise Training Demonstrates a Dose Dependent Effect on Left Ventricular Compliance and Distensibility.” *Medicine & Science in Sports & Exercise*. 42 (2010): 6.
91. Sheehan, K. A., K. Yunbo, and R. J. Solaro. “P21-activated Kinase-1 and Its Role in Integrated Regulation of Cardiac Contractility.” *American Journal of Physiology: Regulatory, Integrative & Comparative Physiology*. 62.3 (2007): R963-73.
92. Kemi, O. J., Ø. Ellingsen , M. Ceci, S. Grimaldi, G. L. Smith, G. Condoreli, and U. Wisløff . “Aerobic interval training enhances cardiomyocyte contractility and Ca^{2+} cycling by phosphorylation of CaMK II and Thr-17 of phospholamban.” *Journal of Molecular and Cellular Cardiology*. 43.3 (2007): 354-361.
93. Wang, H., S. Viatchenko-Karpinski, J. Sun, I. Györke, N. A. Benkusky, M. J. Kohr, H. H. Valdivia, E. Murphy, S. Györke, and M. T. Ziolo. "Regulation of Myocyte Contraction via Neuronal Nitric Oxide Synthase: Role of Ryanodine Receptor S-Nitrosylation." *The Journal of Physiology*. 588.15 (2010): 2905-2917.
94. Khan, S. A., M. W. Skaf, R. W. Harrison, K. Lee, K. M. Minhas, A. Kumar, M. Fradley, A. A. Shoukas, D. E. Berkowitz, and J. M. Hare. “Nitric Oxide Regulation of Myocardial Contractility and Calcium Cycling: Independent Impact of Neuronal and Endothelial Nitric Oxide Synthases.” *Circulation Research*. 92.12 (2003): 1322-29.
95. Høydal, M. A., U. Wisløff, O. J. Kemi, S. L. Britton, L. G. Koch, G. L. Smith, and Ø. Ellingsen. “Nitric oxide synthase type-1 modulates cardiomyocyte contractility and calcium handling: association with low intrinsic aerobic capacity.” *European Journal of Cardiovascular Prevention & Rehabilitation*. 14.2 (2007): 319-325.
96. Farah, C., P. Obert, C. Reboul, S. Tanguy, F. Boucher, S. Richard, O. Cazorla, S. Gayrard, J. Boissiere, L. Andre, and G. Meyer. “Moderate exercise prevents impaired Ca^{2+} handling in heart of CO-exposed rat: implication for sensitivity to ischemia-reperfusion.” *AJP: Heart and Circulatory Physiology*. 299.6 (2010): H2076-81.
97. French, J. P., K. L. Hamilton, J. C. Quindry, Y. Lee, P. A. Upchurch, and S. K. Powers. “Exercise-induced protection against myocardial apoptosis and necrosis: MnSOD, calcium-handling proteins, and calpain.” *The FASEB Journal*. 22.8 (2008): 2862-71.
98. Quindry, J. C., L. E. Schreiber, G. R. McGinnis, J. M. Irwin, M. Landram, Z. Urbiztondo, L. Allums. “Exercise and endogenous antioxidant enzyme activity in perfused and ischemic cardiac tissue.” *The FASEB Journal*. 24 (2010): 619.16.

99. Rinaldi, B., G. Corbi, S. Boccuti, W. Filippelli, G. Rengo, D. Leosco, F. Rossi, A. Filippelli, and N. Ferrara. "Exercise training affects age-induced changes in SOD and heat shock protein expression in rat heart." *Experimental gerontology*. 41.8 (2006): 764-770.
100. Palma, R. K., C. Paixao, G. Shimojo, N. Bernardes, C. Barboza, A. Lopes, K. De Angelis, and C. Malfitano. "P599 Previous Exercise Training Reduces Arterial Pressure, Adipose Tissue and Improves Oxidative Stress in a Model of Menopause." *Cardiovascular Research*. 103 (2014): S108.
101. Gielen, S., G. Schuler, and V. Adams. "Cardiovascular Effects Of Exercise Training: Molecular Mechanisms." *Circulation*. 122.12 (2010): 1221-38.
102. Parry, T. L., D. S. Hydock, B. T. Jensen, C.Y. Lien, C. M. Schneider, and R. Hayward. "Endurance Exercise Attenuates Cardiotoxicity Induced by Androgen Deprivation and Doxorubicin." *Canadian Journal of Physiology and Pharmacology*. 92.5 (2014): 356-362.
103. Riess, M. L., D. F. Stowe, and D. C. Warltier. "Cardiac pharmacological preconditioning with volatile anesthetics: from bench to bedside?." *AJP: Heart and Circulatory Physiology*. 286.5 (2004): H1603-07.
104. Starkopf, J., S. Hegna, O. E. Johansen, J. Munch-Ellingsen, O. D. Mjøs, and K. Ytrehus. "In Vivo Chronic Carvedilol Treatment in Rats Attenuates EX Vivo Regional Infarction of the Heart." *Scandinavian Cardiovascular Journal*. 40.4 (2006): 240-247.
105. Minou, A. F., A. M. Dzyadzko, A. E. Shcherba, and O. O. Rummo. "The Influence of Pharmacological Preconditioning with Sevoflurane on Incidence of Early Allograft Dysfunction in Liver Transplant Recipients." *Anesthesiology Research and Practice*. 2012 (2012): 1-5.
106. Sgobbo, P., C. Pacelli, I. Grattagliano, G. Villani, and T. Cocco. "Carvedilol Inhibits Mitochondrial Complex I and Induces Resistance to H2o2-Mediated Oxidative Insult in H9c2 Myocardial Cells." *Bba - Bioenergetics*. 1767.3 (2007): 222-232.
107. Amin, J., L. Xiao, D. R. Pimental, P. J. Pagano, K. Singh, D. B. Sawyer, and W. S. Colucci. "Reactive Oxygen Species Mediate Alpha-Adrenergic Receptor-Stimulated Hypertrophy in Adult Rat Ventricular Myocytes." *Journal of Molecular and Cellular Cardiology*. 33.1 (2001): 131-139.
108. Monteiro, P., A. I. Duarte, A. Moreno, L. M. Gonçalves, and L. A. Providência. "Carvedilol Improves Energy Production During Acute Global Myocardial Ischaemia." *European Journal of Pharmacology*. 482 (2003): 1-3.
109. Asanuma, H., T. Minamino, S. Sanada, S. Takashima, H. Ogita, A. Ogai, M. Asakura, Y. Liao, Y. Asano, Y. Shintani, J. Kim, Y. Shinozaki, H. Mori, K. Node, S. Kitamura, H. Tomoike, M. Hori, and M. Kitakaze. "Beta-adrenoceptor blocker carvedilol provides cardioprotection via an adenosine-dependent mechanism in ischemic canine hearts." *Circulation*. 109 (2004): 2773-79.
110. Minamino, T., and M. Kitakaze. "Cellular Mechanisms for the Treatment of Chronic Heart Failure: the Nitric Oxide and Adenosine-Dependent Pathways." *Expert Opinion on Emerging Drugs*. 7.1 (2002): 99-110.

111. Asanuma, H., M. Kitakaze, S. Sanada, S. Takashima, Y. Sakata, M. Asakura, T. Kuzuya, M. Hori. "Carvedilol limits infarct size via adenosine-dependent mechanisms in dogs." *Journal of the American College of Cardiology*. 35.2 (2000): 350A.
112. Yue-Chun, L., G. Li-Sha, R. Jiang-Hua, Y. Peng-Lin, L. Jia-Feng, T. Ji-Fei, C. Peng, and Y. Zhan-Qiu. "Protective Effects of Carvedilol in Murine Model With the Coxsackievirus B3-Induced Viral Myocarditis." *Journal of Cardiovascular Pharmacology*. 51.1 (2008): 92-98.
113. Shioi, T., A. Matsumori, R. Nishio, K. Ono, T. Kakio, and S. Sasayama. "Protective role of interleukin-12 in viral myocarditis." *Journal of molecular and cellular cardiology*. 29.9 (1997): 2327-34.
114. Henke, A., R. Zell, U. Martin, and A. Stelzner. "Direct interferon-gamma-mediated protection caused by a recombinant coxsackievirus B3." *Virology*. 315.2 (2003): 335-344.
115. Arozal, W., V. Soetikno, K. Watanabe, F. R. Sari, K. Suzuki, S. Mito, Y. Kobayashi, A. P. Lakshmanan, V. Sukumaran, R. A. Thandavarayan, M. Ma, P. T. Veeraveedu, and S. Arumugam. "Carvedilol-Afforded Protection against Daunorubicin-Induced Cardiomyopathic Rats In Vivo: Effects on Cardiac Fibrosis and Hypertrophy." *ISRN Pharmacology*. 2011 (2011): 1-8.
116. Zendaoui, A., D. Lachance, E. Roussel, J. Couet, and M. Arsenault. "Usefulness of Carvedilol in the Treatment of Chronic Aortic Valve Regurgitation." *Circulation: Heart Failure*. 4.2 (2011): 207-213.
117. Barone, F. C., R. N. Willette, A. H. Nelson, E. H. Ohlstein, D. P. Brooks, and R. W. Coatney. "Carvedilol Prevents and Reverses Hypertrophy-Induced Cardiac Dysfunction." *Pharmacology*. 80.2-3 (2007): 166-176.
118. Yeh, C. H, T. P. Chen, Y. C. Wang, Y. M. Lin, and S. W. Fang. "Carvedilol Treatment After Myocardial Infarct Decreases Cardiomyocytic Apoptosis in the Peri-Infarct Zone During Cardioplegia-Induced Cardiac Arrest." *Shock*. 39.4 (2013): 343-352.
119. Sun, Y. L., S. J. Hu, L. H. Wang, Y. Hu, and J. Y. Zhou. "Effect of beta-Blockers on Cardiac Function and Calcium Handling Protein in postinfarction heart failure rats." *Chest*. 128.3 (2005): 1812-21.
120. Chen, J., C. Huang, B. Zhang, Q. Huang, J. Chen, and L. Xu. "The Effects of Carvedilol on Cardiac Structural Remodeling: the Role of Endogenous Nitric Oxide in the Activity of Carvedilol." *Molecular Medicine Reports*. 7.4 (2013): 1155-58.
121. Fan, Y., J. H. Lin, G. Dong, J. Zhu, F. Yin, and S. S. Yang. "The effect of carvedilol on coronary flow reserve in patients with dilated cardiomyopathy." *Zhonghua nei ke za zhi*. 49.3 (2010): 217-219.
122. Shashurin, D. A., A. A. Timoshin, O. S. Medvedev, and A. F. Vanin. "Effects of Carvedilol and Proxodolol on Nitric Oxide (NO) Metabolism in Various Organs in a Congestive Heart Failure Model." *Eksperimental'naia I Klinicheskaia Farmakologiia*. 74.1 (2011): 19-23.

123. Ripley, T. L., and J. J. Saseen. “B-blockers: a Review of Their Pharmacological and Physiological Diversity in Hypertension.” *The Annals of Pharmacotherapy.* 48.6 (2014): 723-733.
124. Smith, J. N., J. A. Campbell, A. L. Busby-Hjerpe, S. Lee, T. S. Poet, D. B. Barr, and C. Timchalk. “Comparative Chlorpyrifos Pharmacokinetics Via Multiple Routes of Exposure and Vehicles of Administration in the Adult Rat. (report).” *Toxicology*. 261 (2009): 1-2.
125. Bølling, R., N. M. Scheller, L. Køber, H. E. Poulsen, G. H. Gislason, and C. Torp-Pedersen. “Comparison of the Clinical Outcome of Different Beta-Blockers in Heart Failure Patients: a Retrospective Nationwide Cohort Study.” *European Journal of Heart Failure*. 16.6 (2014): 678-684.
126. Remme, W. J., C. Moullet, C. Torp-Pedersen, M. A. Lukas, A. Scherhag, P. Spark, A. Di Lenarda, K. Swedberg, M. Komajda, M. Metra, P. A. Poole-Wilson, and J. G. f. Cleland. “Carvedilol Protects Better Against Vascular Events Than Metoprolol in Heart Failure.” *Journal of the American College of Cardiology*. 49.9 (2007): 963-971.
127. Jonsson, G., M. Abdelnoor, C. Müller, S. E. Kjeldsen, I. Os, and A. Westheim. “A Comparison of the Two B-Blockers Carvedilol and Atenolol on Left Ventricular Ejection Fraction and Clinical Endpoints After Myocardial Infarction.” *Cardiology*. 103.3 (2005): 148-155.
128. Kim, Y. H., S. M. Park, M. Kim, S. H. Kim, S. Y. Lim, J. C. Ahn, W. H. Song, and W. J. Shim. “Cardioprotective Effects of Rosuvastatin and Carvedilol on Delayed Cardiotoxicity of Doxorubicin in Rats.” *Toxicology Mechanisms and Methods*. 22.6 (2012): 488-498.
129. Hori, M., R. Nagai, T. Izumi, and M. Matsuzaki. "Erratum To: Efficacy and Safety of Bisoprolol Fumarate Compared with Carvedilol in Japanese Patients with Chronic Heart Failure: Results of the Randomized, Controlled, Double-Blind, Multistep Administration of Bisoprolol in Chronic Heart Failure Ii (main-Chf Ii) Study.” *Heart and Vessels*. 29.2 (2014): 248.
130. Watanabe, K., Y. Ohta, M. Nakazawa, H. Higuchi, G. Hasegawa, M. Naito, K. Fuse, M. Ito, S. Hirono, N. Tanabe, H. Hanawa, K. Kato, M. Kodama, and Y. Aizawa. “Low Dose Carvedilol Inhibits Progression of Heart Failure in Rats with Dilated Cardiomyopathy.” *British Journal of Pharmacology*. 130.7 (2000): 1489-1495.
131. Daubert, G. P., V. H. Mabasa, V. W. Y. Leung, and C. Aaron. “Acute Clenbuterol Overdose Resulting in Supraventricular Tachycardia and Atrial Fibrillation.” *Journal of Medical Toxicology*. 3.2 (2007): 56-60.
132. Spiller, H. A, K. J. James, S. Scholzen, and D. J. Borys. “A Descriptive Study of Adverse Events from Clenbuterol Misuse and Abuse for Weight Loss and Bodybuilding.” *Substance Abuse*. 34.3 (2013): 306-312.
133. Pokorny, M., I. Netuka, J. Pirk, M. Konarik, J. Maly, L. Cervenka, M. Pokorny, L. Cervenka, and I. Netuka. “Ventricular Assist Devices in Heart Failure: How to Support the Heart but Prevent Atrophy?” *Physiological Research*. 63.2 (2014): 147-156.

134. Lara-Pezzi, E., C. M. N. Terracciano, G. K. R. Soppa, R. T. Smolenski, L. E. Felkin, M. H. Yacoub, and P. J. R. Barton. "A Gene Expression Profile of the Myocardial Response to Clenbuterol." *Journal of Cardiovascular Translational Research*. 2.2 (2009): 191-197.
135. Moore, D., M. Anderson, and D. Larson. "Effect of clenbuterol administration on the healthy murine heart." *Perfusion*. 23.5 (2008): 297-302.
136. Talan, M. I., I. Ahmet, R. P. Xiao, and E. G. Lakatta. "beta (2) AR Agonists in Treatment of Chronic Heart Failure: Long Path to Translation." *Journal of Molecular and Cellular Cardiology*.51.4 (2011): 529-533.
137. Bhavsar, P. K., N. J. Brand, L. E. Felkin, P. K. Luther, M. E. Cullen, M. H. Yacoub, and P. J. R. Barton. "Clenbuterol Induces Cardiac Myocyte Hypertrophy via Paracrine Signalling and Fibroblast-derived IGF-1." *Journal of Cardiovascular Translational Research*. 3.6 (2010): 688-695.
138. Siedlecka U., N. Manoraj, G. Ajay, S. Adarsh, E. H. Sian, H. Y. Magdi, and M. T. Cesare M. "Clenbuterol Affects Cardiomyocyte Contractility Via A beta 2-Adrenoceptor Independent Pathway." *Circulation.* 124.21 (2011): A10240.
139. Navaratnarajah, M., U. Siedlecka, M. Ibrahim, D. C. van, G. Soppa, A. Gandhi, A. Shah, P. Kukadia, M. H. Yacoub, and C. M. Terracciano. "Impact of Combined Clenbuterol and Metoprolol Therapy on Reverse Remodelling During Mechanical Unloading." *Plos One*. 9.9 (2014): e92909.
140. Heidrun, G., and N. Susanne. "Tissue Doppler Imaging and Two-Dimensional Speckle Tracking of Left Ventricular Function in Horses Affected with Recurrent Airway Obstruction Before and After Clenbuterol Treatment." *Journal of Equine Veterinary Science*. 34.4 (2014): 471-478.
141. Navaratnarajah, M., C. D. Van, U. Siedlecka, M. Ibrahim, A. Shah, A. Gandhi, P. Dias, M. H. Yacoub, C. Terracciano. "Clenbuterol and its (d)-isomer Induce Physiological Cardiac Hypertrophy in Both Normal and Failing Rat Hearts, but Do Not Prevent Myocardial Atrophy Associated with Prolonged Mechanical Unloading." *Circulation*. 124.21 (2011): A11931.
142. Zhang, Q., J. Xiang, X. Wang, H. Liu, B. Hu, M. Feng, and Q. Fu. "B2-adrenoceptor Agonist Clenbuterol Reduces Infarct Size and Myocardial Apoptosis After Myocardial Ischaemia/reperfusion in Anaesthetized Rats." *British Journal of Pharmacology*. 160.6 (2010): 1561-1572.
143. Liu, P., J. Z. Xing, L. Zhao, L. Yang, B. R. Hu, and Q. Fu. "Effect of B_2-Adrenergic Agonist Clenbuterol on Ischemia/reperfusion Injury in Isolated Rat Hearts and Cardiomyocyte Apoptosis Induced by Hydrogen Peroxide." *Acta Pharmacologica Sinica*. 29.6 (2008): 661-669.
144. Sleeper, M. M., C. F. Kearns, and K. H. Mckeever. "Chronic clenbuterol administration negatively alters cardiac function." *Medicine & Science in Sports & Exercise*. 34.4 (2002): 643-650.
145. Burniston, J. G., L. B. Tan, and D. F. Goldspink. "Relative cardiotoxic and haemodynamic effects of the beta-agonists fenoterol and clenbuterol measured in conscious unrestrained rats." *Journal of Molecular and Cellular Cardiology*. 40.6 (2006): 1010-1011.

146. Burniston, J. G, L. B. Tan, and D. F. Goldspink. "β_2-adrenergic Receptor Stimulation in Vivo Induces Apoptosis in the Rat Heart and Soleus Muscle." *Journal of Applied Physiology*. 98.4 (2005): 1379-1386.
147. Zaugg, M., W. Xu, E. Lucchinetti, S. A. Shafiq, N. Z. Jamali, and M. A. Q. Siddiqui. "Basic Science Reports - β-Adrenergic Receptor Subtypes Differentially Affect Apoptosis in Adult Rat Ventricular Myocytes." *Circulation*. 102.3 (2000): 344-350.
148. Beregovich, J., C. Bianchi, R. D'angelo, R. Diaz, and S. Rubler. "Haemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure." *Heart*. 37.6 (1975): 629-634.
149. Leier, C. V., and D. V. Unverferth. "Drugs five years later. Dobutamine." *Annals of internal medicine*. 99.4 (1983): 490-496.
150. Sonnenblick, E. H., W. H. Frishman, and T. H. LeJemtel. "Dobutamine: a New Synthetic Cardioactive Sympathetic Amine." *The New England Journal of Medicine*. 300.1 (1979): 17-22.
151. O'connor, C. M., M. Gheorghiade, R. M. Califf, K. Swedberg, F. Zannad, W. J. Mckenna, S. H. Grossman, S. E. Mcnulty, K. F. Adams, B. F. Uretsky, and W. A. Gattis. "Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: Insights from the Flolan International Randomized Survival Trial (FIRST)." *American Heart Journal*. 138.1 (1999): 78-86.
152. Elkayam, U., T. Demarco, C. V. Leier, J. G. Rogers, B. K. Rayburn, J. B. Young, J. W. Warnica, M. Gheorghiade, L. W. Stevenson, C. Binanay, and G. Tasissa. "Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure." *American Heart Journal*. 153.1 (2007): 98-104.
153. Cardoso, J. N, A. Grossi, C. C. H. Del, R. C. M. dos, M. Curiati, M. E. Ochiai, M. V. Lima, A. R. Scipioni, A. C. Pereira-Barretto, and R. K. Filho. "Mortality Rates Are Going Down in Clinical Use of Inotropics. Temporal Trends for Prognosis in Acute Decompensated Heart Failure (1992/1999 – 2005/ 2006)." International Journal of Cardiology. 175.3 (2014): 584-586.
154. Unverferth, D. V., R. D. Magorien, R. Altschuld, A. J. Kolibash, R. P. Lewis, and C. V. Leier. "The Hemodynamic and Metabolic Advantages Gained by a Three-Day Infusion of Dobutamine in Patients with Congestive Cardiomyopathy." *American Heart Journal*. 106.1 (1983): 29-34.
155. Leier, C. V., P. Huss, R. P. Lewis, and D. V. Unverferth. "Drug-induced Conditioning in Congestive Heart Failure." *Circulation*. 65.7 (1982): 1382-87.
156. Mielgo, V., S. A. Valls, and C. Rey-Santano. "Dobutamine in Paediatric Population: a Systematic Review in Juvenile Animal Models." *Plos One*. 9.4 (2014): e95644.
157. Amour, J., X. Loyer, P. Michelet, A. Birenbaum, B. Riou, and C. Heymes. "Preservation of the Positive Lusitropic Effect of Beta-Adrenoceptors Stimulation in Diabetic Cardiomyopathy." *Anesthesia and Analgesia*. 107.4 (2008): 1130-8.

158. Fink, T., P. Heymann, S. Taha-Melitz, A. Taha, B. Wolf, H. Rensing, T. Volk, and A. M. Mathes. "Dobutamine Pretreatment Improves Survival, Liver Function, and Hepatic Microcirculation After Polymicrobial Sepsis in Rat." *Shock*. 40.2 (2013): 129-135.
159. Zausig, Y. A., D. Geilfus, G. Missler, B. Sinner, B. M. Graf, and W. Zink. "Direct Cardiac Effects of Dobutamine, Dopamine, Epinephrine, and Levosimendan in Isolated Septic Rat Hearts." *Shock*. 34.3 (2010): 269-74.
160. Kandemir, U., F. Maltepe, B. Ugurlu, N. Gokmen, and A. Celik. "The effects of levosimendan and dobutamine in experimental bupivacaine-induced cardiotoxicity." *BMC Anesthesiology*. 13.1 (2013): 28
161. Chou, M. T., S. H. Lo, K. C. Cheng, Y. X. Li, L. J. Chen, and J. T. Cheng. "Activation of β-Adrenoceptors by Dobutamine May Induce a Higher Expression of Peroxisome Proliferator-Activated Receptors δ (PPARδ) in Neonatal Rat Cardiomyocytes." Thescientificworldjournal. 278.3 (2012): 248320.
162. Wang, J., H. Yang, X. Hu, W. Fu, J. Xie, X. Zhou, W. Xu, and H. Jiang. "Dobutamine-mediated Heme Oxygenase-1 Induction Via Pi3k and P38 Mapk Inhibits High Mobility Group Box 1 Protein Release and Attenuates Rat Myocardial Ischemia/reperfusion Injury in Vivo." *Journal of Surgical Research*. 183.2 (2013): 509-516.
163. Roesslein, M., C. Froehlich, F. Jans, T. Piegeler, U. Goebel, and T. Loop. "Dobutamine mediates cytoprotection by induction of heat shock protein 70 in vitro." *Life Sciences*. 98 (2014): 88-95.
164. Akagi, S., A. Ogawa, K. Miyaji, H. Matsubaral, S. Akagi, K. Kusano, and H. Ito. "Catecholamine Support at the Initiation of Epoprostenol Therapy in Pulmonary Arterial Hypertension." *Annals of the American Thoracic Society*. 11.5 (2014): 719-727.
165. O'Driscoll, J. M., A. Marciniak, K. K. Ray, K. Schmid, R. Smith, and R. Sharma. "The Safety and Clinical Usefulness of Dobutamine Stress Echocardiography Among Octogenarians." *Heart*. 100.13 (2014): 1001-07.
166. Shah, B., J. S. Pabla, K. Zacharias, G. Balaji, I. Ramzy, A. Alhajiri, A. Ahmed, S. Gurunathan, A. Elghamaz, R. Khattar, and R. Senior. "145 Stress Echocardiography Demonstrates Excellent Feasibility, Safety and Diagnostic Accuracy in Patients with Significant Obesity: First Results from the Stress Ultrasonography in Morbid Obesity (sumo) Study." *Heart*. 100 (2014): A85.
167. Neto-Neves, E. M., R. F. Gerlach, J. E. Tanus-Santos, R. Schulz, B. C. Maciel, L. G. Gali, M. M. D. Romano, C. S. Ceron, E. Rizzi, K. C. Ferraz, and O. Sousa-Santos. "Matrix metalloproteinase inhibition attenuates right ventricular dysfunction and improves responses to dobutamine during acute pulmonary thromboembolism." *Journal of Cellular and Molecular Medicine*.17.12 (2013): 1588-97.

168. Tontodonati, M., N. Fasdelli, P. Repeto, and R. Dorigatti. “Characterisation of Rodent Dobutamine Echocardiography for Preclinical Safety Pharmacology Assessment.” *Journal of Pharmacological and Toxicological Methods*. 64.2 (2011): 129-133.
169. Grimes, K. M, A. K Reddy, M. L. Lindsey, and R. Buffenstein. “And the Beat Goes On: Maintained Cardiovascular Function During Aging in the Longest-Lived Rodent, the Naked Mole-Rat.” *American Journal of Physiology*. 307.2 (2014): H284-91.
170. Williams, S., M. Pourrier, D. McAfee, S. Lin, and D. Fedida. “Ranolazine Improves Diastolic Function in Spontaneously Hypertensive Rats.” *American Journal of Physiology*. 306.3 (2014): H867-81.
171. Chen, X., M. C. Hsiung, and Y. Mu. “The Impact of Segmental Volumetric Changes on Functional Mitral Regurgitation: A Study Using Three-Dimensional Regional Time-Volume Analysis Combined with Low-Dose Dobutamine.” *Echocardiography*. 31.2 (2014): 172-178.
172. Sullivan, M. J., P. F. Binkley, D. V. Unverferth, J. H. Ren, H. Boudoulas, T. M. Bashore, A. J. Merola, and C. V. Leier. “Prevention of Bedrest-Induced Physical Deconditioning by Daily Dobutamine Infusions. Implications for Drug-Induced Physical Conditioning.” *The Journal of Clinical Investigation*. 76.4 (1985): 1632-42.
173. Roof, S. R., L. Tang, J. E. Ostler, M. Periasamy, S. Gyorke, G. E. Billman, and M. T. Ziolo. “Neuronal Nitric Oxide Synthase Is Indispensable for the Cardiac Adaptive Effects of Exercise.” *Basic Research in Cardiology*. 108.2 (2013): 332.
174. Koga, C., H. Emoto, H. Yokoo, H. Ishii, M. Yoshida, T. Kameyama, and M. Tanaka. “Effect of an Irritable Stress Model (intermaxillary Fixation) on the Rat Immunological System and Brain Noradrenaline Turnover.” *Journal of Brain Science.* 25 (1999): 27-34.
175. Ko, I. G., and P. B. Choi. “Regular Exercise Modulates Obesity Factors and Body Composition in Sturdy Men.” *Journal of Exercise Rehabilitation*. 9.2 (2013): 256-262.
176. De Souza, M. R, L. Pimenta, T. C. Pithon-Curi, M. Bucci, R. G. Fontinele, and R. R. De Souza. “Effects of Aerobic Training, Resistance Training, or Combined Resistance-Aerobic Training on the Left Ventricular Myocardium in a Rat Model.” *Microscopy Research and Technique*. 77.9 (2014): 727-734.
177. Hoffstedt, J., M. Shimizu, S. Sjöstedt, and F. Lönnqvist. “Determination of B_3-Adrenoceptor Mediated Lipolysis in Human Fat Cells.” *Obesity Research*. 3.5 (1995): 447-457.
178. Ufer, C., and R. Germack. “Cross-regulation between β_1- and β_3-Adrenoceptors Following Chronic β-Adrenergic Stimulation in Neonatal Rat Cardiomyocytes.” *British Journal of Pharmacology*. 158.1 (2009): 300-313.
179. Lehtonen, L. A., S. Antila, and P. J. Pentikäinen. “Pharmacokinetics and Pharmacodynamics of Intravenous Inotropic Agents.” *Clinical Pharmacokinetics*. 43.3 (2004): 187-203.

180. Zalko, D., L. Debrauwer, G. Bories, and J. Tulliez. “Metabolism of Clenbuterol in Rats.” *Drug Metabolism and Disposition: the Biological Fate of Chemicals*. 26.9 (1998): 891-899.
181. Arsenault, W. G., D. M. Boothe, S. G. Gordon, M. W. Miller, J. R. Chalkley, and I. Petrikovics. “Pharmacokinetics of Carvedilol After Intravenous and Oral Administration in Conscious Healthy Dogs.” *American Journal of Veterinary Research*. 66.12 (2005): 2172-76.
182. Choi, E. K., M. J. Shen, S. F. Lin, P. S. Chen, and S. Oh. “Effects of Carvedilol on Cardiac Autonomic Nerve Activities During Sinus Rhythm and Atrial Fibrillation in Ambulatory Dogs.” *Europace*. (2014): 1083-91.
183. Pelliccia, A., F. M. Di Paolo, B. J. Maron. “The athlete's heart: remodeling, electrocardiogram and preparticipation screening.” *Cardiology in review*. 10.2 (2002): 85-90.
184. Brody, D. A. “A Theoretical Analysis of Intracavitary Blood Mass Influence on the Heart-Lead Relationship.” *Circulation Research*. 4.6 (1956): 731-738.
185. Cannesson, M., G. Keller, O. Desebbe, and J. J. Lehot. “Relations between Respiratory Changes in R-Wave Amplitude and Arterial Pulse Pressure in Mechanically Ventilated Patients.” *Journal of Clinical Monitoring and Computing*. 24.3 (2010): 203-207.
186. Krandycheva, V., S. Kharin, M. Strelkova, K. Shumikhin, A. Sobolev, and D. Shmakov. “Ventricular Repolarization in a Rat Model of Global Heart Failure.” *Clinical and Experimental Pharmacology and Physiology*. 40.7 (2013): 431-437.
187. Dor-Haim, H., O. Berenfeld, M. Horowitz, C. Lotan, M. Swissa, and M. Rota. “Reduced Ventricular Arrhythmogeneity and Increased Electrical Complexity in Normal Exercised Rats.” Plos One. 8.6 (2013): e66658.
188. Bonilla, I. M., A. E. Belevych, A. Sridhar, Y. Nishijima, H. T. Ho, Q. He, M. Kukielka, D. Terentyev, R. Terentyeva, B. Liu, V. P. Long, S. Györke, C. A. Carnes, and G. E. Billman. “Endurance Exercise Training Normalizes Repolarization and Calcium-Handling Abnormalities, Preventing Ventricular Fibrillation in a Model of Sudden Cardiac Death.” *Journal of Applied Physiology*. 113.11 (2012): 1772-83.
189. Oflaz, M. B., S. Balli, A. E. Kibar, I. Ece, C. Akdeniz, and V. Tuzcu. “Effects of Carvedilol Therapy on Cardiac Autonomic Control, QT Dispersion, and Ventricular Arrhythmias in Children with Dilated Cardiomyopathy.” *Medical Science Monitor*. 19.1 (2013): 366-372.
190. Akdeniz, B., S. Guneri, I. Z. Savas, O. Aslan, N. Baris, O. Badak, O. Kirimli, and O. Goldeli. “Clinical Studies - Effects of Carvedilol Therapy on Arrhythmia Markers in Patients with Congestive Heart Failure.” *International Heart Journal*. 47.4 (2006): 565-573.
191. Zhong, J. H., X. P. CHEN, M. L. YUN, W. J. LI, Y. F. CHEN, and Z. YAO. “Low-dose Carvedilol Reduces Transmural Heterogeneity of Ventricular Repolarization in Congestive Heart Failure.” *Acta Pharmacological Sinica*. 28.8 (2007): 1161-65.

192. Abraham, J. O. Mudd, N. Kapur, K. Klein, H. C. Champion, and I. S. Wittstein. "Stress Cardiomyopathy After Intravenous Administration of Catecholamines and Beta-Receptor Agonists." *Journal of the American College of Cardiology*. 53.15 (2009): 1320-1325.
193. Sohn, U. D., and I. H. Huh. "Differential inhibition induced by imipramine and electroconvulsive shock of beta1 and beta2 adrenoceptor-mediated peripheral cardiovascular responses in rats." *Asia Pacific Journal of Pharmacology.* 12.3 (1997): 81-88.
194. Vernon, D. D., W. J. Banner, J. S. Garrett, and J. M. Dean. "Efficacy of Dopamine and Norepinephrine for Treatment of Hemodynamic Compromise in Amitriptyline Intoxication." *Critical Care Medicine*. 19.4 (1991): 544-549.
195. Kalkan, S., N. Hocaoglu, A. Akgun, S. Gidener, and Y. Tuncok. "Effects of Adenosine Receptor Antagonists on Amitriptyline-Induced Vasodilation in Rat Isolated Aorta." *Clinical Toxicology*. 45.5 (2007): 600-604.
196. Volkers, A. C., J. H. M. Tulen, B. W. W. Den Van, J. A. Bruyn, J. Passchier, and L. Pepplinkhuizen. "Effects of Imipramine, Fluvoxamine and Depressive Mood on Autonomic Cardiac Functioning in Major Depressive Disorder." *Pharmacopsychiatry*. 37 (2004): 18-25.
197. Attia, T. Z., T. Yamashita, M. A. Hammad, A. Hayasaki, T. Sato, M. Miyamoto, Y. Yasuhara, T. Nakamura, Y. Kagawa, H. Tsujino, M. A. Omar, O. H. Abdelmageed, S. M. Derayea, and T. Uno. "Effect of cytochrome P450 2C19 and 2C9 amino acid residues 72 and 241 on metabolism of tricyclic antidepressant drugs." *Chemical & pharmaceutical bulletin.* 62.2 (2014): 176-181.
198. Sert, A., E. Aypar, D. Odabas, and M. U. Aygul. "Temporary Cardiac Pacemaker in the Treatment of Junctional Rhythm and Hypotension Due to Imipramine Intoxication." *Pediatric Cardiology*. 32.4 (2011): 521-524.
199. Pacher, P., Z. Ungvari, P. P. Nanasi, S. Furst, and V. Kecskemeti. "Speculations on difference between tricyclic and selective serotonin reuptake inhibitor antidepressants on their cardiac effects. Is there any?" *Current medicinal chemistry*. 6.6 (1999): 469-480.
200. Rawling, D. A., and H. A. Fozzard. "Effects of imipramine on cellular electrophysiological properties of cardiac Purkinje fibers." *The Journal of pharmacology and experimental therapeutics*. 209.3 (1979): 371-375.
201. Muir, W. W., S. M. Strauch, and S. F. Schaal. "Effects of Tricyclic Antidepressant Drugs on the Electrophysiological Properties of Drug Purkinje Fibers." *Journal of Cardiovascular Pharmacology*. 4.1 (1982): 82-90.
202. Matsuo, S. "Comparative effects of imipramine and propranolol on the transmembrane potentials of the isolated rabbit atria." *Japanese journal of pharmacology*. 17.2 (1967): 279-286.

203. Delpón, E., J. Tamargo, and J. Sánchez-Chapula. "Effects of Imipramine on the Transient Outward Current in Rabbit Atrial Single Cells." *British Journal of Pharmacology*. 106.2 (1992): 464-469.
204. Manzanares, J., and J. Tamargo. "Electrophysiological Effects of Imipramine in Nontreated and in Imipramine-Pretreated Rat Atrial Fibers." *British Journal of Pharmacology*. 79.1 (1983): 167-75.
205. Azevedo, E. R, T. Kubo, S. Mak, A. Al-Hesayen, A. Schofield, R. Allan, S. Kelly, G. E. Newton, J. S. Floras, and J. D. Parker. "Clinical Investigation and Reports - Nonselective Versus Selective B-Adrenergic Receptor Blockade in Congestive Heart Failure: Differential Effects on Sympathetic Activity." *Circulation*. 104.18 (2001): 2194-2199.
206. Masnatta, L D., and M. C. Rubio. "Hemodynamic effects on hepatic blood flow of a selective beta 2-adrenoceptor agonist, clenbuterol, in rat." *European journal of drug metabolism and pharmacokinetics*. 17.4 (1992): 247-250.
207. Encabo, A., M. Ferrer, M. Salaices, R. Manso, J. Marin, and G. Balfagon. "Effect of clenbuterol on the modulation of noradrenaline release in the rat tail artery." *Journal of autonomic pharmacology*. 16.5 (1996): 243-250.
208. Lagudis, S., A. T. Yamada, M. L. Vieira, C. C. Medeiros, A. J. Mansur, and S. G. Lage. "The Effect of Dobutamine Without and with L-Arginine on Arterial Compliance in Heart Failure Patients." *Echocardiography*. 26.8 (2009): 934-942.
209. Schauvliege, S., and F. Gasthuys. "Drugs for cardiovascular support in anesthetized horses." *The Veterinary clinics of North America. Equine practice.* 29.1 (2013): 19-49.
210. Freimark, D., M. S. Feinberg, S. Matezky, N. Hochberg, and M. Shechter. "Impact of Short-Term Intermittent Intravenous Dobutamine Therapy on Endothelial Function in Patients with Severe Chronic Heart Failure." *American Heart Journal*. 148.5 (2004): 878-882.
211. Kiviniemi, A. M., M. P. Tulppo, J. J. Eskleinen, A. M. Savolainen, J. Kapanen, I. H. A. Heinonen, H. V. Huikuri, J. C. Hannukainen, and K. K. Kalliokoski. "Cardiac Autonomic Function and High-Intensity Interval Training in Middle-Age Men." *Medicine and Science in Sports and Exercise*. 46.10 (2014): 1960-67.
212. Zaniqueli, D., E. A. Morra, E. M. Dantas, M. P. Baldo, L. Carletti, A. J. Perez, S. L. Rodrigues, and J. G. Mill. "Heart Rate at 4 S After the Onset of Exercise in Endurance-Trained Men." *Canadian Journal of Physiology and Pharmacology*. (2014): 1-5.
213. Yang, K. C., Y. T. Tseng, and J. M. Nerbonne. "Exercise training and PI3Kα-induced electrical remodeling is independent of cellular hypertrophy and Akt signaling." *Journal of molecular and cellular cardiology.* 53.4 (2012): 532-541.
214. Eyer, F., J. Stenzel, T. Schuster, N. Felgenhauer, R. Pfab, C. von Bary, and T. Zilker. "Risk assessment of severe tricyclic antidepressant overdose." *Human & experimental toxicology*. 28.8 (2009): 511-519.

215. Escobar, A. L., R. Fernandez-Gomez, J. C. Peter, R. Mobini, J. Hoebeke, and A. Mijares. "IgGs and Mabs against the beta2-adrenoreceptor block A-V conduction in mouse hearts: A possible role in the pathogenesis of ventricular arrhythmias." *Journal of molecular and cellular cardiology*. 40.6 (2006): 829-837.
216. Stagg, M. A., N. G. Patel, U. Siedlecka, G. K. R. Soppa, J. Lee, M. H. Yacoub, and C. M. N. Terracciano. "The effects of β_2-adrenoceptor agonists on conduction velocity, field potentials and automaticity in cardiomyocytes." *Journal of molecular and cellular cardiology*. 42 (2007): S25.
217. Gonçalves, D., T. Henriques-Coelho, H. Fonseca1, R. Ferreira, A. I.Padrão, C. Santa, S. Vieira1, F. Amado, A. Leite-Moreira, and J. A. Duarte. "Intermittent dobutamine administration mimicked exercise-induced cardiac phenotype and protected against left ventricular acute pressure overload." *The FASEB journal*. 26 (2012): 1139.11.
218. Naccarelli, G. V., and M. A. Lukas. "Carvedilol's Antiarrhythmic Properties: Therapeutic Implications in Patients with Left Ventricular Dysfunction." *Clinical Cardiology*. 28.4 (2005): 165-173.
219. Manotheepan, R., J. Saberniak, T. K. Danielsen, T. Edvardsen, I. Sjaastad, K. H. Haugaa, and M. K. Stokke. "Effects of Individualized Exercise Training in Patients with Catecholaminergic Polymorphic Ventricular Tachycardia Type 1." *The American Journal of Cardiology*. 113.11 (2014): 1829-33.
220. Cheng, J. H., R. Niwa, K. Kamiya, J. Toyama, and I. Kodama. "Carvedilol blocks the repolarizing K+ currents and the L-type Ca2+ current in rabbit ventricular myocytes." *European journal of pharmacology*. 376.1-2 (1999): 189-201.
221. Tashiro, N., N. Sato, A. K. Talib, A. K. Talib, E. Saito, M. Okura, M. Yamaki, N. Nakagawa, N. Sakamoto, H. Ota, Y. Tanabe, T. Takeuchi, K. Akasaka, J. Kawabe, Y. Kawamura, and N. Hasebe. "Brugada syndrome case: difficult differentiation between a concealed form and tricyclic antidepressant-induced Brugada sign." *Internal medicine*. 48.17 (2009): 1535-39.
222. Lee, Mun-Young. "Effect of Imipramine on Cardiocyte Viability." *Journal of the Korea entertainment industry association*.7.2 (2013): 125-130.
223. Bianchi, P., D. R. Pimentel, M. P. Murphy, W. S. Colucci, and A. Parini. "A new hypertrophic mechanism of serotonin in cardiac myocytes: receptor-independent ROS generation." *The FASEB journal*. 19.6 (2005): 641-655.
224. Higashi, Y., and M. Yoshizumi. "Exercise and endothelial function: role of endothelium-derived nitric oxide and oxidative stress in healthy subjects and hypertensive patients." *Pharmacology & therapeutics*.102.1 (2004): 87-96.
225. Ferrer, M., M. Salaices, M. Sanchez, and G. Balfagon. "Different effects of acute clenbuterol on vasomotor response in mesenteric arteries from young and old spontaneously hypertensive rats." *European journal of pharmacology*. 466.3 (2003): 289-299.

226. Lobo, S. M., F. G. Soriano, D. F. Barbeiro, D. De Backer, Q. H. Sun, Z. Z. Tu, G. Dimopoulos, J. C. Prelser, B. Vray, V. Vercruysse, and J. L. Vincent. "Effects of dobutamine on gut mucosal nitric oxide production during endotoxic shock in rabbits." *Medical science monitor*. 15.2 (2009): BR37-BR42.
227. Salam, O. M. E. A., N. A. Mohammed, A. A. Sleem, and A. R. Farrag. "The effect of antidepressant drugs on thioacetamide-induced oxidative stress." *European review for medical and pharmacological sciences*. 17.6 (2013): 735-744.
228. Krass, M., G. Wegener, E. Vasar, and V. Volke. "The antidepressant action of imipramine and venlafaxine involves suppression of nitric oxide synthesis." *Behavioural brain research*. 218.1 (2011): 57-63.
229. Gocmez, S. S., T. Utkan, and N. Gacar. "Chronic administration of imipramine but not agomelatine and moclobemide affects the nitrergic relaxation of rabbit corpus cavernosum smooth muscle." *European journal of pharmacology*. 714(2013): 442-447.
230. Pentel, P. R., W. Wananukul, W. Scarlett, and D. E. Keyler. "Nitric oxide contributes to desipramine-induced hypotension in rats." *Human & experimental toxicology*. 15.4 (1996): 320-328.
231. Sarusi, A., F. Rárosi, M. Szu˝cs, N. Csík, A. S. Farkas, J. Gy Papp, A. Varró, T. Forster, M. J. Curtis, and A. Farkas. "Absolute beat-to-beat variability and instability parameters of ECG intervals: biomarkers for predicting ischaemia-induced ventricular fibrillation." *British journal of pharmacology*. 171 (2014): 1772-82.
232. La Fountaine, M. F., J. D. Gossett, R. E. De Meersman, and W. A. Bauman. "Increased QT interval variability in 3 recently concussed athletes: an exploratory observation." *Journal of athletic training*. 46.3 (2011): 230-233.
233. Nicolson, W. B., G. P. McCann, M. I. Smith, A. J. Sandilands, P. J. Stafford, F. S. Schlindwein, N. J. Samani, and G. A. Ng. "Prospective evaluation of two novel ECG-based restitution biomarkers for prediction of sudden cardiac death risk in ischaemic cardiomyopathy." *Heart (British Cardiac Society).* 100.23 (2014): 1878-85.
234. Vargas, H. M. "A new preclinical biomarker for risk of Torsades de Pointes: drug-induced reduction of the cardiac electromechanical window." *British journal of pharmacology*. 161.7 (2010): 1441-43.
235. Stams, T. R. G., V. J. A. Bourgonje, H. D. M.Beekman, M. Schoenmakers, R. van der Nagel, P. Oosterhoff, J. M. Opstal, and M. A. Vos, MA. "The electromechanical window is no better than QT prolongation to assess risk of Torsade de Pointes in the complete atrioventricular block model in dogs." *British journal of pharmaco*. 171.3 (2014): 714-722.

Appendix A: Intrapersonnal variation in ECG analysis

Date	P	PR_{sect}	PR	QRS	QT	QT_1	T
11/1/2014	8.71	11.48	20.00	8.86	30.00	2.77	17.68
11/2/2014	8.64	11.30	20.20	8.89	30.21	2.89	17.95
11/3/2014	7.90	11.23	19.17	8.75	29.76	3.00	17.94
11/4/2014	8.41	11.02	19.57	8.87	29.77	3.14	17.73
11/5/2014	8.16	11.37	19.73	8.94	29.63	2.98	17.78
11/6/2014	8.72	10.83	19.72	9.27	31.17	3.31	18.27
11/7/2014	8.54	11.00	19.51	9.32	30.04	2.95	17.64
11/8/2014	8.56	11.13	19.80	9.17	30.73	3.22	17.96
11/9/2014	8.58	11.57	20.34	9.09	30.22	3.31	18.24
11/10/2014	8.71	11.18	19.70	9.05	30.59	3.22	18.09
Mean	8.5	11.2	19.8	9.0	30.2	3.1	17.9
SE	0.1	0.1	0.1	0.1	0.2	0.1	0.1
C_V	1.0	0.6	0.5	0.7	0.5	1.9	0.4

Table 38. Intrapersonnal variation in ECG analysis. C_V, coefficient of variation.

Appendix B: Hemodynamic raw data during imipramine or vehicle infusion

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	145.5 ± 9.7	110.6 ± 5.9	34.9 ± 6.6	126.9 ± 7.1	360.2 ± 11.1
Vehicle	5 min	150.7 ± 11.5	113.8 ± 6.1	36.9 ± 7.5	130.7 ± 8.0	365.3 ± 13.2
	10 min	148.8 ± 9.7	111.8 ± 6.3	37.0 ± 7.5	128.6 ± 7.1	368.2 ± 12.7
	15 min	151.3 ± 9.0	113.6 ± 6.0	37.8 ± 7.2	130.9 ± 6.7	370.5 ± 13.3
	20 min	152.2 ± 8.7	114.4 ± 5.6	37.8 ± 7.2	131.8 ± 6.2	371.7 ± 13.2
	25 min	149.8 ± 7.7	112.0 ± 2.7	37.8 ± 7.3	129.4 ± 3.9	369.8 ± 12.8
	30 min	150.2 ± 8.2	112.1 ± 2.6	38.1 ± 7.2	129.7 ± 4.1	367.1 ± 12.2
	35 min	151.0 ± 7.9	112.7 ± 3.1	38.3 ± 7.2	130.3 ± 4.1	366.9 ± 11.4
	40 min	155.2 ± 7.4	115.9 ± 2.8	39.3 ± 7.0	133.7 ± 3.8	365.6 ± 12.4
	45 min	155.3 ± 7.2	116.2 ± 3.2	39.1 ± 6.9	134.0 ± 3.9	366.5 ± 12.4
	50 min	158.5 ± 6.5	118.2 ± 3.1	40.3 ± 6.8	136.5 ± 3.4	365.7 ± 10.9
	55 min	160.5 ± 7.2	119.3 ± 4.0	41.3 ± 6.6	138.0 ± 4.5	365.0 ± 11.1
	60 min	164.0 ± 7.8	122.0 ± 4.2	42.0 ± 6.6	140.8 ± 5.0	369.0 ± 12.1
Recovery	5 min	164.0 ± 7.1	122.2 ± 4.0	41.8 ± 6.3	140.9 ± 4.5	370.7 ± 12.5
	10 min	162.5 ± 8.1	121.0 ± 3.8	41.6 ± 7.3	139.8 ± 4.7	370.4 ± 11.7
	15 min	160.4 ± 6.7	119.4 ± 4.3	41.0 ± 6.8	138.0 ± 4.4	369.7 ± 11.0
	20 min	161.2 ± 6.9	119.7 ± 3.8	41.5 ± 6.8	138.6 ± 4.0	370.3 ± 10.5
	25 min	161.1 ± 7.2	119.8 ± 3.3	41.3 ± 7.0	138.7 ± 4.0	369.6 ± 11.1
	30 min	158.7 ± 8.0	118.1 ± 4.4	40.6 ± 7.1	136.8 ± 5.1	371.1 ± 10.7
	35 min	157.2 ± 8.0	116.3 ± 4.9	40.9 ± 7.0	135.0 ± 5.4	368.3 ± 9.4
	40 min	160.2 ± 6.4	118.5 ± 3.5	41.7 ± 6.8	137.5 ± 3.6	369.3 ± 10.1
	45 min	160.3 ± 7.3	119.2 ± 4.0	41.1 ± 7.2	138.0 ± 4.3	371.6 ± 10.4
	50 min	155.8 ± 7.4	115.1 ± 5.4	40.7 ± 6.9	133.7 ± 5.2	358.6 ± 14.3
	55 min	152.5 ± 9.0	113.3 ± 6.7	39.3 ± 7.5	131.4 ± 6.7	360.8 ± 13.8
	60 min	153.4 ± 7.5	114.1 ± 5.4	39.3 ± 7.7	132.4 ± 5.1	369.3 ± 11.6

Table 39. Hemodynamic effects of matched-volume vehicle (sterile water) in sedentary rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 4.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	3.4 ± 1.5	2.9 ± 1.5	5.1 ± 1.6	2.9 ± 1.5	1.4 ± 1.2
	10 min	2.3 ± 0.9	1.0 ± 1.3	5.6 ± 1.4	1.4 ± 0.9	2.2 ± 1.4
	15 min	4.2 ± 1.9	2.8 ± 2.3	8.3 ± 1.2	3.3 ± 1.9	2.8 ± 1.2
	20 min	4.9 ± 1.6	3.6 ± 1.9	8.5 ± 1.2	4.0 ± 1.6	3.2 ± 1.4
	25 min	3.4 ± 2.7	1.8 ± 3.0	8.3 ± 2.2	2.5 ± 2.9	2.7 ± 1.4
	30 min	3.6 ± 3.3	1.9 ± 3.5	9.7 ± 3.5	2.7 ± 3.5	1.9 ± 1.6
	35 min	4.2 ± 2.8	2.4 ± 2.8	10.4 ± 3.9	3.2 ± 2.9	1.9 ± 1.6
	40 min	7.2 ± 3.0	5.3 ± 3.0	14.0 ± 4.5	5.9 ± 3.1	1.5 ± 1.6
	45 min	7.3 ± 2.8	5.5 ± 3.0	13.4 ± 3.1	6.1 ± 3.0	1.8 ± 1.6
	50 min	9.6 ± 3.5	7.4 ± 3.6	17.5 ± 4.4	8.2 ± 3.7	1.6 ± 1.0
	55 min	10.9 ± 3.2	8.3 ± 3.5	20.4 ± 3.5	9.2 ± 3.3	1.4 ± 0.8
	60 min	13.2 ± 3.3	10.8 ± 3.8	22.6 ± 4.0	11.4 ± 3.5	2.5 ± 1.1
Recovery	5 min	13.4 ± 3.5	11.0 ± 3.6	22.7 ± 5.2	11.6 ± 3.6	2.9 ± 1.2
	10 min	12.2 ± 2.4	9.8 ± 2.7	20.6 ± 4.6	10.6 ± 2.7	2.8 ± 1.2
	15 min	10.9 ± 3.2	8.4 ± 3.6	19.6 ± 4.5	9.3 ± 3.3	2.7 ± 1.3
	20 min	11.4 ± 3.3	8.7 ± 3.5	21.2 ± 5.3	9.8 ± 3.4	2.9 ± 1.3
	25 min	11.4 ± 3.7	8.9 ± 3.6	20.5 ± 5.9	9.9 ± 3.8	2.7 ± 1.3
	30 min	9.6 ± 3.5	7.2 ± 3.6	18.1 ± 5.3	8.3 ± 3.5	3.1 ± 1.2
	35 min	8.5 ± 3.7	5.5 ± 3.7	19.2 ± 5.8	6.9 ± 3.5	2.3 ± 1.3
	40 min	10.9 ± 4.4	7.7 ± 4.3	22.3 ± 7.3	9.0 ± 4.3	2.6 ± 1.4
	45 min	10.9 ± 4.2	8.4 ± 4.6	19.8 ± 7.1	9.4 ± 4.3	3.2 ± 1.0
	50 min	7.8 ± 5.2	4.6 ± 5.5	19.0 ± 7.6	6.0 ± 5.0	-0.3 ± 3.4
	55 min	5.3 ± 4.8	2.8 ± 5.7	13.9 ± 7.2	4.0 ± 4.9	0.3 ± 3.3
	60 min	6.1 ± 4.5	3.7 ± 5.4	14.3 ± 9.9	4.9 ± 4.6	2.6 ± 1.5

Table 40. Hemodynamic effects of matched-volume vehicle (sterile water) in sedentary rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	165.6 ± 8.5	123.8 ± 7.5	41.8 ± 4.7	140.4 ± 7.7	412.5 ± 21.2
Imipramine	5 min	165.3 ± 8.4	123.1 ± 8.2	42.3 ± 4.3	139.8 ± 8.1	416.1 ± 21.8
	10 min	148.7 ± 13.9	106.4 ± 12.3	42.3 ± 5.2	123.1 ± 13.2	433.8 ± 19.9
	15 min	117.8 ± 17.4	80.8 ± 15.3	37.0 ± 5.1	95.7 ± 16.3	411.9 ± 20.9
	20 min	92.0 ± 14.7	60.6 ± 12.9	31.3 ± 4.1	73.4 ± 13.7	382.5 ± 23.7
	25 min	80.7 ± 14.3	52.9 ± 12.7	27.8 ± 3.3	64.1 ± 13.4	352.4 ± 24.8
	30 min	80.7 ± 12.1	53.1 ± 11.0	27.5 ± 3.4	64.3 ± 11.6	331.1 ± 21.4
	35 min	83.1 ± 12.0	54.8 ± 9.7	28.3 ± 4.5	66.0 ± 10.8	324.5 ± 21.6
	40 min	84.2 ± 12.2	56.0 ± 9.7	28.2 ± 4.8	67.2 ± 10.9	316.0 ± 21.2
	45 min	88.9 ± 14.8	60.1 ± 11.4	28.9 ± 5.5	71.2 ± 12.9	322.6 ± 24.7
	50 min	91.2 ± 13.9	61.8 ± 10.3	29.5 ± 6.0	73.2 ± 11.8	326.2 ± 23.3
	55 min	97.2 ± 14.2	65.8 ± 9.7	31.4 ± 6.9	78.1 ± 11.5	325.6 ± 25.1
	60 min	104.8 ± 14.9	70.9 ± 8.3	33.9 ± 8.0	84.2 ± 10.9	332.6 ± 26.6
Recovery	5 min	116.4 ± 15.0	81.1 ± 8.4	35.3 ± 8.2	94.9 ± 11.0	346.6 ± 28.6
	10 min	119.7 ± 16.2	82.9 ± 9.1	36.8 ± 8.6	97.3 ± 11.9	358.2 ± 31.3
	15 min	120.0 ± 16.1	82.1 ± 9.2	37.9 ± 8.5	96.8 ± 12.0	363.3 ± 32.3
	20 min	119.0 ± 16.0	80.2 ± 9.2	38.8 ± 8.4	95.4 ± 12.0	363.9 ± 33.6
	25 min	120.3 ± 15.7	80.3 ± 9.1	39.9 ± 8.4	96.0 ± 11.8	365.4 ± 34.4
	30 min	121.5 ± 15.5	80.4 ± 9.3	41.1 ± 8.3	96.7 ± 11.8	366.9 ± 35.0
	35 min	123.8 ± 14.1	82.4 ± 9.0	41.5 ± 7.8	98.8 ± 11.1	368.1 ± 34.8
	40 min	123.9 ± 13.2	82.1 ± 8.5	41.8 ± 7.6	98.6 ± 10.5	369.5 ± 34.6
	45 min	124.2 ± 12.2	81.5 ± 7.7	42.7 ± 7.3	98.4 ± 9.6	369.8 ± 35.4
	50 min	128.3 ± 10.6	84.9 ± 7.1	43.3 ± 6.7	102.2 ± 8.4	371.5 ± 35.6
	55 min	129.5 ± 9.5	84.9 ± 6.6	44.6 ± 6.6	102.7 ± 7.6	367.8 ± 34.2
	60 min	129.3 ± 10.3	84.0 ± 6.8	45.3 ± 6.7	102.0 ± 8.1	371.1 ± 35.2

Table 41. Hemodynamic effects of imipramine in sedentary rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 6.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.1 ± 1.2	-0.8 ± 1.3	1.8 ± 1.8	-0.5 ± 1.2	0.9 ± 0.4
	10 min	-10.3 ± 6.6	-14.2 ± 7.6	0.9 ± 3.1	-12.6 ± 7.2	5.4 ± 2.0
	15 min	-29.4 ± 8.7	-35.6 ± 9.7	-12.1 ± 5.8	-32.7 ± 9.2	0.2 ± 3.6
	20 min	-45.5 ± 5.9	-52.5 ± 7.0	-25.1 ± 4.5	-49.1 ± 6.4	-7.1 ± 3.8
	25 min	-52.2 ± 6.0	-59.0 ± 7.5	-32.8 ± 4.6	-55.7 ± 6.8	-14.6 ± 4.0
	30 min	-51.9 ± 5.3	-58.3 ± 6.7	-34.0 ± 3.7	-55.2 ± 6.0	-19.7 ± 3.4
	35 min	-50.4 ± 5.1	-56.7 ± 6.0	-32.9 ± 5.9	-53.9 ± 5.6	-21.3 ± 3.4
	40 min	-49.7 ± 5.2	-55.7 ± 6.0	-33.3 ± 6.6	-53.0 ± 5.6	-23.4 ± 3.3
	45 min	-47.1 ± 6.4	-52.6 ± 6.9	-32.0 ± 8.3	-50.3 ± 6.6	-21.9 ± 3.9
	50 min	-45.6 ± 6.0	-51.0 ± 6.4	-31.4 ± 8.8	-48.7 ± 6.1	-21.1 ± 3.1
	55 min	-42.1 ± 5.9	-47.4 ± 5.8	-27.7 ± 10.1	-45.1 ± 5.7	-21.3 ± 3.7
	60 min	-37.5 ± 6.5	-42.7 ± 5.4	-22.9 ± 11.3	-40.4 ± 5.9	-19.5 ± 4.3
Recovery	5 min	-30.5 ± 6.6	-34.1 ± 6.1	-20.2 ± 11.5	-32.6 ± 6.3	-16.1 ± 5.1
	10 min	-28.6 ± 7.2	-32.7 ± 6.5	-17.1 ± 11.8	-31.0 ± 6.7	-13.3 ± 5.8
	15 min	-28.4 ± 7.2	-33.4 ± 6.5	-14.1 ± 11.2	-31.4 ± 6.7	-12.1 ± 5.9
	20 min	-29.0 ± 7.0	-35.0 ± 6.3	-11.9 ± 10.8	-32.4 ± 6.6	-12.1 ± 6.0
	25 min	-28.2 ± 6.8	-35.0 ± 6.0	-9.1 ± 10.6	-32.0 ± 6.4	-11.8 ± 6.1
	30 min	-27.4 ± 6.6	-34.9 ± 6.0	-5.9 ± 10.2	-31.5 ± 6.2	-11.5 ± 6.2
	35 min	-25.9 ± 6.0	-33.3 ± 6.1	-4.3 ± 8.9	-29.9 ± 6.1	-11.1 ± 6.4
	40 min	-25.8 ± 5.2	-33.6 ± 5.4	-3.0 ± 8.6	-30.1 ± 5.3	-10.7 ± 6.3
	45 min	-25.6 ± 4.1	-34.3 ± 4.2	-0.2 ± 8.3	-30.3 ± 4.2	-10.8 ± 6.2
	50 min	-23.1 ± 2.5	-31.6 ± 2.9	2.1 ± 7.7	-27.6 ± 2.6	-10.4 ± 6.3
	55 min	-22.2 ± 2.1	-31.6 ± 2.9	6.0 ± 9.6	-27.1 ± 2.3	-11.2 ± 6.1
	60 min	-22.4 ± 2.4	-32.4 ± 2.6	8.2 ± 11.1	-27.7 ± 2.2	-10.5 ± 6.2

Table 42. Hemodynamic effects of imipramine in sedentary rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	172.8 ± 2.5	121.4 ± 2.3	51.4 ± 2.9	143.4 ± 1.5	388.9 ± 12.9
Imipramine	5 min	176.4 ± 2.8	123.5 ± 2.2	52.8 ± 2.9	146.0 ± 1.8	390.6 ± 12.8
	10 min	177.7 ± 3.2	121.8 ± 3.0	55.9 ± 3.2	144.8 ± 2.7	409.7 ± 15.6
	15 min	144.6 ± 11.2	94.7 ± 8.9	49.9 ± 3.3	115.0 ± 9.7	399.2 ± 16.9
	20 min	104.4 ± 12.1	65.6 ± 10.9	38.8 ± 1.3	81.2 ± 11.1	357.4 ± 21.7
	25 min	88.0 ± 8.5	55.4 ± 7.7	32.6 ± 2.4	68.7 ± 7.9	323.7 ± 16.2
	30 min	78.4 ± 5.3	49.1 ± 4.7	29.3 ± 2.6	60.8 ± 4.7	299.8 ± 9.4
	35 min	79.9 ± 5.3	51.0 ± 4.8	28.9 ± 1.8	62.4 ± 4.9	294.0 ± 9.0
	40 min	81.0 ± 4.6	52.5 ± 4.1	28.5 ± 1.5	63.7 ± 4.2	290.2 ± 8.8
	45 min	83.0 ± 4.8	53.1 ± 4.6	29.9 ± 1.2	64.6 ± 4.6	287.6 ± 9.7
	50 min	84.0 ± 5.4	54.4 ± 5.0	29.6 ± 1.2	65.9 ± 5.1	286.3 ± 11.5
	55 min	86.7 ± 6.0	56.6 ± 5.3	30.1 ± 1.6	68.2 ± 5.4	286.2 ± 11.6
	60 min	92.6 ± 6.5	61.0 ± 5.2	31.5 ± 2.1	73.0 ± 5.7	285.0 ± 10.5
Recovery	5 min	109.1 ± 6.7	76.5 ± 5.8	32.6 ± 2.2	89.1 ± 6.2	300.2 ± 15.5
	10 min	118.7 ± 7.4	84.2 ± 6.5	34.5 ± 3.4	98.1 ± 7.0	316.5 ± 21.2
	15 min	127.1 ± 7.5	90.6 ± 6.0	36.6 ± 4.0	105.6 ± 6.5	329.1 ± 17.6
	20 min	134.3 ± 7.6	94.2 ± 6.3	40.1 ± 3.7	110.9 ± 6.9	337.8 ± 16.2
	25 min	138.1 ± 9.4	95.6 ± 7.4	42.5 ± 4.1	113.4 ± 8.2	338.2 ± 12.9
	30 min	134.8 ± 8.7	92.4 ± 7.1	42.4 ± 3.6	110.1 ± 7.7	337.8 ± 14.6
	35 min	129.5 ± 7.6	87.4 ± 7.2	40.8 ± 2.9	104.9 ± 7.3	335.9 ± 15.6
	40 min	124.4 ± 7.7	82.5 ± 7.4	41.9 ± 2.8	99.8 ± 7.5	333.3 ± 15.3
	45 min	120.3 ± 14.0	79.3 ± 10.7	41.0 ± 4.6	96.2 ± 12.0	329.3 ± 17.3
	50 min	124.3 ± 13.5	82.8 ± 9.8	41.5 ± 4.9	99.8 ± 11.3	333.2 ± 16.9
	55 min	133.6 ± 10.8	88.2 ± 7.4	45.4 ± 4.4	106.9 ± 8.7	338.8 ± 16.5
	60 min	140.5 ± 10.9	93.1 ± 7.5	47.4 ± 4.4	113.0 ± 8.9	343.9 ± 17.4

Table 43. Hemodynamic effects of imipramine in exercise rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 6.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	2.1 ± 0.5	1.8 ± 0.7	2.9 ± 0.5	1.8 ± 0.6	0.4 ± 0.1
	10 min	2.8 ± 1.3	0.3 ± 1.4	8.8 ± 1.1	1.0 ± 1.4	5.3 ± 0.7
	15 min	-16.5 ± 5.9	-22.0 ± 6.9	-3.0 ± 3.2	-19.9 ± 6.3	2.6 ± 2.1
	20 min	-39.7 ± 6.6	-46.5 ± 8.0	-23.1 ± 5.9	-43.7 ± 7.2	-8.2 ± 4.0
	25 min	-49.0 ± 5.0	-54.7 ± 5.6	-34.5 ± 7.8	-52.2 ± 5.2	-16.7 ± 3.4
	30 min	-54.4 ± 3.6	-59.5 ± 4.0	-41.3 ± 7.3	-57.5 ± 3.5	-22.7 ± 2.3
	35 min	-53.5 ± 3.5	-57.9 ± 4.1	-42.3 ± 5.9	-56.4 ± 3.6	-24.3 ± 1.7
	40 min	-53.0 ± 3.2	-56.7 ± 3.7	-43.3 ± 5.1	-55.5 ± 3.2	-25.3 ± 1.5
	45 min	-51.8 ± 3.1	-56.1 ± 4.1	-41.0 ± 3.6	-54.9 ± 3.5	-26.0 ± 1.3
	50 min	-51.2 ± 3.5	-55.1 ± 4.5	-41.5 ± 3.8	-54.0 ± 3.8	-26.4 ± 1.1
	55 min	-49.7 ± 3.8	-53.2 ± 4.7	-40.8 ± 3.6	-52.3 ± 4.1	-26.5 ± 1.1
	60 min	-46.4 ± 4.0	-49.6 ± 4.7	-38.2 ± 4.0	-49.0 ± 4.2	-26.7 ± 0.7
Recovery	5 min	-36.9 ± 3.8	-36.8 ± 5.2	-36.1 ± 4.0	-37.8 ± 4.5	-23.0 ± 1.4
	10 min	-31.3 ± 4.1	-30.4 ± 5.8	-32.4 ± 5.9	-31.5 ± 5.1	-19.0 ± 2.5
	15 min	-26.4 ± 4.4	-25.0 ± 5.8	-28.3 ± 7.0	-26.2 ± 5.0	-15.6 ± 1.6
	20 min	-22.3 ± 4.3	-22.1 ± 6.0	-21.6 ± 6.1	-22.5 ± 5.1	-13.3 ± 1.4
	25 min	-20.2 ± 5.2	-21.0 ± 6.7	-17.1 ± 6.2	-20.9 ± 5.9	-13.0 ± 2.0
	30 min	-22.1 ± 4.7	-23.7 ± 6.3	-17.2 ± 5.6	-23.2 ± 5.5	-13.1 ± 2.8
	35 min	-25.1 ± 4.1	-27.8 ± 6.1	-19.9 ± 5.2	-26.8 ± 5.1	-13.6 ± 3.2
	40 min	-28.1 ± 4.3	-31.8 ± 6.5	-17.8 ± 4.8	-30.3 ± 5.4	-14.3 ± 2.8
	45 min	-30.6 ± 7.8	-34.4 ± 9.3	-20.1 ± 7.3	-32.8 ± 8.6	-15.5 ± 2.7
	50 min	-28.2 ± 7.5	-31.4 ± 8.6	-19.1 ± 8.0	-30.2 ± 8.1	-14.4 ± 2.6
	55 min	-22.8 ± 5.8	-27.0 ± 6.8	-11.8 ± 6.0	-25.3 ± 6.3	-13.0 ± 2.7
	60 min	-18.9 ± 5.8	-23.0 ± 6.9	-7.9 ± 5.5	-21.1 ± 6.3	-11.7 ± 2.9

Table 44. Hemodynamic effects of imipramine in exercise rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	160.4 ± 4.3	119.7 ± 1.8	40.8 ± 4.4	135.9 ± 2.4	380.1 ± 11.0
Imipramine	5 min	163.1 ± 3.7	121.5 ± 1.8	41.5 ± 4.1	137.9 ± 2.1	383.4 ± 11.2
	10 min	167.8 ± 3.5	125.5 ± 3.1	42.4 ± 3.5	142.3 ± 3.2	396.8 ± 15.7
	15 min	141.8 ± 6.7	104.4 ± 4.7	37.5 ± 4.2	119.5 ± 5.2	385.6 ± 14.9
	20 min	123.1 ± 11.1	85.5 ± 8.3	37.6 ± 4.5	100.5 ± 9.1	363.3 ± 8.8
	25 min	104.2 ± 11.8	68.3 ± 8.2	35.9 ± 4.8	82.4 ± 9.2	338.6 ± 9.3
	30 min	101.0 ± 13.2	66.5 ± 8.7	34.5 ± 5.2	79.9 ± 10.1	328.1 ± 8.8
	35 min	99.2 ± 13.8	65.8 ± 8.7	33.4 ± 5.6	78.7 ± 10.3	327.7 ± 9.2
	40 min	104.8 ± 15.6	71.8 ± 10.4	33.0 ± 6.2	84.6 ± 12.0	329.7 ± 9.7
	45 min	111.5 ± 17.5	78.2 ± 12.2	33.3 ± 6.4	91.3 ± 13.9	331.4 ± 11.5
	50 min	113.4 ± 16.7	80.2 ± 11.7	33.3 ± 6.1	93.5 ± 13.4	331.3 ± 14.4
	55 min	111.2 ± 15.9	78.3 ± 11.2	32.9 ± 5.8	91.5 ± 12.8	330.8 ± 14.2
	60 min	109.4 ± 15.2	74.1 ± 11.3	35.3 ± 4.9	88.2 ± 12.8	302.2 ± 33.1
Recovery	5 min	117.0 ± 15.1	79.8 ± 11.2	37.2 ± 4.8	94.6 ± 12.7	303.2 ± 32.6
	10 min	119.1 ± 12.9	82.2 ± 9.7	36.9 ± 5.1	96.9 ± 10.8	326.6 ± 10.6
	15 min	120.6 ± 10.8	82.3 ± 8.4	38.4 ± 4.5	97.6 ± 9.1	328.3 ± 11.2
	20 min	120.5 ± 10.3	80.5 ± 8.1	40.0 ± 4.6	96.4 ± 8.6	331.4 ± 10.1
	25 min	120.1 ± 10.6	79.6 ± 8.7	40.5 ± 4.7	95.7 ± 9.0	336.7 ± 10.0
	30 min	118.6 ± 11.0	77.5 ± 9.0	41.1 ± 4.7	94.0 ± 9.4	336.3 ± 10.1
	35 min	120.0 ± 10.6	78.0 ± 8.8	42.0 ± 4.7	94.7 ± 9.0	336.8 ± 9.7
	40 min	121.1 ± 10.1	78.6 ± 8.5	42.5 ± 4.8	95.6 ± 8.5	340.4 ± 11.0
	45 min	120.8 ± 10.2	78.0 ± 8.5	42.9 ± 4.8	95.1 ± 8.6	342.3 ± 11.5
	50 min	123.4 ± 9.1	79.4 ± 7.5	44.0 ± 4.9	97.1 ± 7.5	345.0 ± 12.5
	55 min	122.7 ± 9.0	78.6 ± 7.9	44.1 ± 4.8	96.5 ± 7.9	346.3 ± 12.7
	60 min	122.3 ± 9.1	78.5 ± 8.0	43.8 ± 4.6	96.3 ± 7.9	347.9 ± 13.0

Table 45. Hemodynamic effects of imipramine in carvedilol rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 4.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	1.7 ± 0.8	1.6 ± 0.7	2.6 ± 2.1	1.5 ± 0.7	0.9 ± 0.4
	10 min	4.8 ± 1.8	4.8 ± 1.5	5.6 ± 3.9	4.7 ± 1.7	4.2 ± 1.4
	15 min	-11.6 ± 3.4	-12.8 ± 3.8	-7.9 ± 3.6	-12.0 ± 3.6	1.3 ± 1.3
	20 min	-23.4 ± 6.1	-28.4 ± 7.0	-8.0 ± 3.5	-26.0 ± 6.4	-4.4 ± 1.1
	25 min	-35.1 ± 6.7	-42.6 ± 7.3	-12.2 ± 4.9	-39.2 ± 6.9	-10.8 ± 1.8
	30 min	-37.2 ± 7.4	-44.0 ± 7.8	-16.0 ± 6.0	-41.0 ± 7.5	-13.5 ± 2.1
	35 min	-38.4 ± 7.8	-44.6 ± 7.8	-19.3 ± 7.1	-41.9 ± 7.7	-13.7 ± 2.1
	40 min	-35.0 ± 9.0	-39.7 ± 9.1	-21.1 ± 8.1	-37.6 ± 8.9	-13.1 ± 2.4
	45 min	-30.8 ± 10.2	-34.3 ± 10.5	-20.4 ± 9.1	-32.7 ± 10.2	-12.7 ± 2.8
	50 min	-29.5 ± 9.8	-32.6 ± 10.2	-20.0 ± 9.3	-31.0 ± 9.9	-12.7 ± 3.5
	55 min	-30.9 ± 9.3	-34.2 ± 9.7	-20.5 ± 8.6	-32.6 ± 9.4	-12.9 ± 3.6
	60 min	-31.9 ± 8.9	-37.8 ± 9.6	-11.7 ± 9.9	-35.0 ± 9.2	-20.7 ± 8.5
Recovery	5 min	-27.1 ± 8.9	-33.0 ± 9.5	-6.5 ± 10.5	-30.3 ± 9.2	-20.4 ± 8.3
	10 min	-25.6 ± 7.7	-30.9 ± 8.4	-9.7 ± 6.2	-28.5 ± 8.0	-13.9 ± 2.7
	15 min	-24.7 ± 6.4	-30.9 ± 7.5	-5.8 ± 3.8	-27.9 ± 6.9	-13.6 ± 2.4
	20 min	-24.8 ± 6.1	-32.4 ± 7.3	-1.9 ± 3.4	-28.8 ± 6.6	-12.7 ± 1.9
	25 min	-25.0 ± 6.3	-33.2 ± 7.7	-0.7 ± 3.4	-29.3 ± 6.9	-11.4 ± 1.8
	30 min	-26.0 ± 6.6	-34.8 ± 8.0	0.8 ± 3.1	-30.6 ± 7.2	-11.5 ± 1.7
	35 min	-25.1 ± 6.3	-34.4 ± 7.9	3.0 ± 2.9	-30.1 ± 7.0	-11.3 ± 1.7
	40 min	-24.5 ± 5.9	-34.0 ± 7.6	4.1 ± 3.0	-29.5 ± 6.5	-10.5 ± 1.6
	45 min	-24.7 ± 5.9	-34.5 ± 7.6	5.0 ± 2.7	-29.9 ± 6.6	-10.0 ± 1.5
	50 min	-23.1 ± 5.2	-33.3 ± 6.8	7.8 ± 3.5	-28.4 ± 5.8	-9.3 ± 1.6
	55 min	-23.5 ± 5.3	-34.0 ± 7.1	8.2 ± 3.7	-28.8 ± 6.1	-8.9 ± 1.5
	60 min	-23.8 ± 5.3	-34.1 ± 7.3	7.8 ± 4.6	-29.0 ± 6.1	-8.5 ± 1.6

Table 46. Hemodynamic effects of imipramine in carvedilol rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	179.1 ± 8.3	129.4 ± 5.8	49.7 ± 4.9	149.8 ± 6.3	412.2 ± 9.9
Imipramine	5 min	180.0 ± 9.1	129.2 ± 6.0	50.8 ± 5.3	149.9 ± 6.8	415.4 ± 8.2
	10 min	165.4 ± 7.5	119.9 ± 5.8	45.5 ± 3.6	138.4 ± 6.4	422.2 ± 10.6
	15 min	129.6 ± 10.3	90.8 ± 8.9	38.8 ± 2.5	106.1 ± 9.8	383.5 ± 17.2
	20 min	102.9 ± 10.2	69.3 ± 9.1	33.6 ± 1.9	82.6 ± 9.6	350.1 ± 16.2
	25 min	89.8 ± 11.9	60.9 ± 9.5	28.8 ± 4.5	72.5 ± 10.2	325.6 ± 15.1
	30 min	87.6 ± 10.6	58.0 ± 8.6	29.6 ± 3.9	69.4 ± 9.2	316.3 ± 11.4
	35 min	88.3 ± 10.8	58.5 ± 8.7	29.9 ± 3.4	70.0 ± 9.3	312.5 ± 9.6
	40 min	91.2 ± 11.1	59.3 ± 8.2	31.8 ± 3.4	72.1 ± 9.4	315.1 ± 10.5
	45 min	92.8 ± 11.3	59.5 ± 9.1	33.3 ± 2.9	72.8 ± 10.0	314.4 ± 11.6
	50 min	91.9 ± 10.7	58.1 ± 8.9	33.8 ± 2.7	71.8 ± 9.5	314.0 ± 12.8
	55 min	91.2 ± 9.9	57.9 ± 8.3	33.3 ± 2.4	71.3 ± 8.7	310.7 ± 14.4
	60 min	90.9 ± 9.4	55.1 ± 7.7	35.8 ± 2.8	69.4 ± 8.1	305.5 ± 14.1
Recovery	5 min	99.6 ± 9.8	60.9 ± 8.4	38.7 ± 4.0	75.7 ± 8.8	306.7 ± 17.6
	10 min	104.7 ± 11.1	67.9 ± 8.2	36.8 ± 5.5	81.9 ± 9.3	320.7 ± 15.4
	15 min	106.9 ± 11.7	70.1 ± 10.2	36.7 ± 4.3	84.0 ± 10.3	331.4 ± 17.1
	20 min	113.6 ± 9.6	72.3 ± 8.0	41.3 ± 2.9	88.0 ± 8.4	330.4 ± 18.6
	25 min	115.5 ± 9.2	72.8 ± 7.3	42.7 ± 3.7	89.1 ± 7.8	335.6 ± 17.8
	30 min	116.3 ± 8.7	70.7 ± 6.6	45.6 ± 4.5	88.3 ± 7.1	335.7 ± 16.9
	35 min	117.6 ± 8.5	70.5 ± 6.4	47.1 ± 5.1	89.1 ± 6.7	336.9 ± 17.3
	40 min	118.4 ± 8.3	70.5 ± 6.3	47.8 ± 5.5	89.5 ± 6.5	339.4 ± 16.6
	45 min	121.0 ± 8.2	71.9 ± 6.6	49.1 ± 5.4	91.3 ± 6.6	339.6 ± 16.8
	50 min	121.0 ± 8.7	71.2 ± 6.2	49.8 ± 5.7	91.0 ± 6.5	340.1 ± 16.7
	55 min	120.5 ± 7.4	70.2 ± 5.3	50.4 ± 5.8	90.1 ± 5.3	336.4 ± 15.0
	60 min	122.2 ± 7.4	70.7 ± 4.7	51.5 ± 5.9	91.0 ± 4.9	334.9 ± 12.9

Table 47. Hemodynamic effects of imipramine in clenbuterol rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 6.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.4 ± 0.9	-0.2 ± 0.8	2.1 ± 1.2	0.0 ± 0.8	0.8 ± 0.6
	10 min	-7.5 ± 1.8	-7.3 ± 2.0	-7.0 ± 3.8	-7.6 ± 1.9	2.5 ± 1.9
	15 min	-28.0 ± 3.7	-30.2 ± 5.0	-19.7 ± 5.8	-29.7 ± 4.7	-6.9 ± 3.7
	20 min	-43.0 ± 3.7	-47.4 ± 4.5	-29.9 ± 5.5	-45.6 ± 4.2	-15.0 ± 3.5
	25 min	-50.5 ± 4.9	-54.0 ± 5.1	-40.2 ± 8.6	-52.5 ± 4.8	-20.9 ± 3.7
	30 min	-51.5 ± 4.5	-56.1 ± 4.6	-37.9 ± 8.9	-54.4 ± 4.4	-23.1 ± 3.0
	35 min	-51.1 ± 4.5	-55.8 ± 4.6	-37.4 ± 8.4	-54.0 ± 4.4	-24.0 ± 2.6
	40 min	-49.6 ± 4.5	-54.9 ± 4.4	-32.9 ± 9.2	-52.6 ± 4.4	-23.4 ± 2.9
	45 min	-48.6 ± 4.9	-54.8 ± 5.2	-28.6 ± 11.4	-52.1 ± 5.0	-23.5 ± 3.3
	50 min	-48.8 ± 5.0	-55.6 ± 5.4	-27.1 ± 12.4	-52.5 ± 5.0	-23.5 ± 4.0
	55 min	-49.1 ± 4.5	-55.6 ± 5.2	-29.0 ± 10.5	-52.7 ± 4.6	-24.2 ± 4.4
	60 min	-49.2 ± 4.5	-57.6 ± 4.8	-24.2 ± 10.6	-53.8 ± 4.4	-25.5 ± 4.4
Recovery	5 min	-44.5 ± 4.0	-53.1 ± 5.3	-19.7 ± 8.9	-49.7 ± 4.6	-25.2 ± 5.0
	10 min	-42.2 ± 4.0	-48.0 ± 4.7	-27.9 ± 6.5	-45.8 ± 4.4	-22.0 ± 4.0
	15 min	-40.5 ± 5.3	-46.3 ± 6.7	-26.1 ± 5.4	-44.2 ± 5.8	-19.4 ± 4.3
	20 min	-36.6 ± 4.4	-44.5 ± 4.7	-12.6 ± 11.9	-41.5 ± 4.3	-19.8 ± 4.4
	25 min	-35.6 ± 4.0	-44.1 ± 4.0	-10.4 ± 11.8	-40.8 ± 3.8	-18.5 ± 4.3
	30 min	-35.2 ± 3.6	-45.8 ± 3.3	-4.7 ± 12.4	-41.3 ± 3.1	-18.5 ± 3.9
	35 min	-34.4 ± 3.4	-45.9 ± 3.0	-1.8 ± 12.7	-40.8 ± 2.7	-18.2 ± 4.0
	40 min	-33.9 ± 3.4	-45.8 ± 3.1	-0.2 ± 13.2	-40.5 ± 2.6	-17.6 ± 3.8
	45 min	-32.4 ± 3.2	-44.8 ± 3.4	2.6 ± 13.1	-39.3 ± 2.6	-17.6 ± 3.7
	50 min	-32.4 ± 3.5	-45.3 ± 2.8	4.0 ± 13.5	-39.5 ± 2.5	-17.5 ± 3.5
	55 min	-32.6 ± 3.0	-46.0 ± 2.3	5.3 ± 14.1	-40.0 ± 1.7	-18.4 ± 3.0
	60 min	-31.7 ± 2.9	-45.5 ± 1.8	7.6 ± 14.4	-39.3 ± 1.2	-18.8 ± 2.5

Table 48. Hemodynamic effects of imipramine in exercise rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	SBP (mmHg)	DBP (mmHg)	PP (mmHg)	MBP (mmHg)	HR (bpm)
	Baseline	149.4 ± 6.2	116.8 ± 4.9	32.6 ± 2.6	129.3 ± 5.5	415.4 ± 14.4
Imipramine	5 min	149.9 ± 7.1	116.5 ± 5.8	33.4 ± 2.5	129.4 ± 6.3	416.3 ± 15.1
	10 min	151.1 ± 6.0	115.4 ± 5.1	35.6 ± 2.8	129.1 ± 5.5	429.2 ± 10.1
	15 min	112.4 ± 7.6	80.8 ± 7.5	31.6 ± 2.4	93.4 ± 7.6	412.1 ± 10.7
	20 min	78.1 ± 10.8	52.3 ± 9.1	25.9 ± 2.7	62.7 ± 10.0	374.4 ± 14.8
	25 min	71.8 ± 8.6	48.1 ± 7.0	23.7 ± 2.8	57.6 ± 7.8	347.0 ± 15.9
	30 min	68.7 ± 6.4	46.8 ± 5.5	21.9 ± 2.5	55.6 ± 6.0	335.2 ± 16.6
	35 min	67.4 ± 4.8	47.2 ± 4.8	20.3 ± 1.9	55.3 ± 4.8	329.4 ± 17.1
	40 min	71.9 ± 7.1	51.7 ± 6.6	20.2 ± 1.9	59.8 ± 6.7	326.4 ± 17.9
	45 min	73.5 ± 7.7	53.5 ± 6.8	20.0 ± 2.0	61.4 ± 7.1	327.0 ± 15.9
	50 min	74.8 ± 7.8	53.9 ± 6.9	20.8 ± 2.1	62.2 ± 7.2	319.2 ± 16.9
	55 min	80.6 ± 9.8	58.7 ± 8.3	21.9 ± 2.6	67.2 ± 8.9	320.8 ± 15.8
	60 min	83.2 ± 11.0	60.2 ± 8.8	23.0 ± 3.2	69.0 ± 9.7	321.4 ± 15.4
Recovery	5 min	94.2 ± 11.8	69.2 ± 9.9	25.0 ± 3.3	78.6 ± 10.8	332.1 ± 15.9
	10 min	103.2 ± 9.4	75.4 ± 7.6	27.8 ± 3.3	86.0 ± 8.4	346.6 ± 15.5
	15 min	106.3 ± 7.9	76.9 ± 6.5	29.4 ± 3.3	88.1 ± 7.1	358.6 ± 16.3
	20 min	110.3 ± 6.9	79.1 ± 5.3	31.2 ± 3.5	91.0 ± 6.0	366.5 ± 17.3
	25 min	113.8 ± 6.9	80.9 ± 4.5	32.8 ± 3.8	93.5 ± 5.4	372.4 ± 18.4
	30 min	117.2 ± 7.1	83.4 ± 4.9	33.8 ± 3.7	96.4 ± 5.9	375.5 ± 18.4
	35 min	119.8 ± 6.9	85.0 ± 4.6	34.8 ± 3.7	98.2 ± 5.6	380.2 ± 18.5
	40 min	121.1 ± 6.5	85.6 ± 4.0	35.5 ± 3.5	99.1 ± 5.0	381.1 ± 19.9
	45 min	120.4 ± 6.4	84.3 ± 3.7	36.1 ± 3.6	98.2 ± 4.8	385.1 ± 19.8
	50 min	122.3 ± 6.9	85.4 ± 4.3	36.9 ± 3.6	99.5 ± 5.3	389.3 ± 20.4
	55 min	124.5 ± 6.8	87.0 ± 4.2	37.5 ± 3.6	101.3 ± 5.1	391.4 ± 21.5
	60 min	126.0 ± 6.6	88.0 ± 4.1	38.0 ± 3.6	102.6 ± 4.9	393.3 ± 23.2

Table 49. Hemodynamic effects of imipramine in dobutamine rats measured by the Millar pressure catheter system at abdominal aorta. Values are means ± SE; n = 4.

	Time	SBP (%)	DBP (%)	PP (%)	MBP (%)	HR (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
imipramine	5 min	0.3 ± 1.1	-0.4 ± 0.9	3.0 ± 2.0	0.0 ± 1.0	0.2 ± 0.2
	10 min	1.2 ± 1.4	-1.1 ± 1.6	9.3 ± 1.3	-0.1 ± 1.5	3.6 ± 1.7
	15 min	-24.6 ± 4.4	-30.8 ± 5.5	-2.7 ± 1.7	-27.7 ± 5.1	-0.6 ± 1.4
	20 min	-47.3 ± 7.3	-54.9 ± 7.9	-19.8 ± 6.7	-51.2 ± 7.7	-9.8 ± 2.6
	25 min	-51.7 ± 5.6	-58.5 ± 6.0	-27.0 ± 6.3	-55.2 ± 5.9	-16.5 ± 2.4
	30 min	-53.6 ± 4.4	-59.6 ± 4.8	-32.4 ± 5.7	-56.6 ± 4.7	-19.4 ± 2.3
	35 min	-54.3 ± 3.9	-59.1 ± 4.5	-37.4 ± 4.6	-56.7 ± 4.3	-20.8 ± 2.7
	40 min	-51.0 ± 6.0	-54.9 ± 6.8	-37.3 ± 5.4	-52.9 ± 6.4	-21.5 ± 3.1
	45 min	-49.9 ± 6.5	-53.3 ± 7.0	-37.9 ± 6.0	-51.5 ± 6.8	-21.3 ± 2.7
	50 min	-49.1 ± 6.5	-53.0 ± 7.0	-35.5 ± 6.1	-51.0 ± 6.8	-23.1 ± 3.2
	55 min	-45.3 ± 7.3	-49.0 ± 7.8	-32.7 ± 6.6	-47.3 ± 7.6	-22.7 ± 3.2
	60 min	-43.7 ± 7.8	-47.8 ± 8.0	-29.5 ± 7.7	-46.0 ± 8.0	-22.5 ± 3.2
Recovery	5 min	-36.2 ± 8.6	-39.8 ± 9.4	-23.8 ± 6.8	-38.3 ± 9.1	-19.9 ± 3.5
	10 min	-30.2 ± 7.0	-34.5 ± 7.8	-15.5 ± 5.5	-32.6 ± 7.5	-16.5 ± 3.0
	15 min	-28.0 ± 6.2	-33.1 ± 7.0	-10.5 ± 4.8	-30.9 ± 6.7	-13.7 ± 2.6
	20 min	-25.4 ± 5.7	-31.1 ± 6.4	-5.4 ± 4.3	-28.6 ± 6.1	-11.8 ± 2.6
	25 min	-23.3 ± 5.2	-29.7 ± 5.7	-0.6 ± 4.1	-26.8 ± 5.5	-10.4 ± 2.7
	30 min	-21.0 ± 5.3	-27.7 ± 5.9	2.8 ± 3.7	-24.6 ± 5.7	-9.7 ± 2.7
	35 min	-19.3 ± 5.0	-26.3 ± 5.6	5.8 ± 3.6	-23.3 ± 5.4	-8.6 ± 2.6
	40 min	-18.5 ± 4.5	-25.9 ± 5.1	8.4 ± 3.4	-22.7 ± 4.9	-8.4 ± 2.9
	45 min	-19.1 ± 4.1	-27.1 ± 4.6	10.1 ± 3.2	-23.5 ± 4.4	-7.4 ± 2.8
	50 min	-17.8 ± 4.3	-26.1 ± 4.9	12.8 ± 3.4	-22.5 ± 4.6	-6.4 ± 3.0
	55 min	-16.4 ± 4.3	-24.7 ± 5.2	14.6 ± 2.7	-21.1 ± 4.8	-5.9 ± 3.3
	60 min	-15.3 ± 4.1	-23.8 ± 5.2	16.2 ± 3.2	-20.0 ± 4.7	-5.5 ± 3.7

Table 50. Hemodynamic effects of imipramine in dobutamine rats measured by the Millar pressure catheter system at abdominal aorta as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	5.3 ± 1.3	139.8 ± 7.6	5,996 ± 546	-6,446 ± 819	83.3 ± 4.5	9.5 ± 0.9
Vehicle	5 min	6.5 ± 1.6	146.0 ± 7.9	6,302 ± 480	-6,829 ± 788	85.7 ± 4.5	9.3 ± 0.9
	10 min	5.7 ± 2.0	147.0 ± 8.0	6,307 ± 498	-6,956 ± 792	84.8 ± 4.8	9.3 ± 0.9
	15 min	6.3 ± 2.0	151.5 ± 9.8	6,581 ± 486	-7,211 ± 849	86.5 ± 4.6	9.3 ± 0.6
	20 min	5.3 ± 1.9	149.9 ± 8.9	6,579 ± 452	-7,090 ± 809	85.8 ± 4.8	9.3 ± 0.6
	25 min	5.8 ± 2.2	147.3 ± 8.4	6,542 ± 370	-7,009 ± 778	85.3 ± 4.8	9.0 ± 0.7
	30 min	5.9 ± 1.9	148.5 ± 9.0	6,459 ± 353	-7,012 ± 643	85.2 ± 4.3	9.0 ± 0.9
	35 min	5.9 ± 1.9	149.6 ± 9.2	6,475 ± 358	-7,023 ± 636	85.1 ± 4.3	9.3 ± 0.8
	40 min	6.1 ± 1.6	152.1 ± 8.7	6,575 ± 341	-7,106 ± 657	86.2 ± 4.0	9.0 ± 0.9
	45 min	5.6 ± 2.0	153.7 ± 9.0	6,552 ± 384	-7,180 ± 665	86.5 ± 3.9	9.1 ± 1.0
	50 min	5.8 ± 1.9	155.6 ± 8.0	6,589 ± 454	-7,233 ± 731	85.6 ± 4.2	9.3 ± 1.1
	55 min	5.9 ± 1.9	159.3 ± 9.1	6,734 ± 503	-7,339 ± 758	86.4 ± 3.9	9.4 ± 1.1
	60 min	5.6 ± 2.3	160.5 ± 9.5	6,938 ± 529	-7,495 ± 802	87.0 ± 4.1	9.3 ± 1.0
Recovery	5 min	5.9 ± 2.2	161.1 ± 9.2	6,937 ± 479	-7,492 ± 752	87.3 ± 4.3	9.4 ± 1.0
	10 min	5.5 ± 2.1	160.4 ± 9.4	6,972 ± 440	-7,516 ± 724	88.2 ± 4.5	9.1 ± 1.0
	15 min	5.6 ± 2.0	159.0 ± 8.8	6,940 ± 426	-7,496 ± 722	87.9 ± 4.8	9.0 ± 0.9
	20 min	5.4 ± 1.9	160.7 ± 8.3	7,073 ± 350	-7,632 ± 678	87.9 ± 5.2	9.0 ± 0.9
	25 min	5.3 ± 1.9	159.7 ± 7.7	7,086 ± 343	-7,664 ± 680	88.4 ± 5.3	9.0 ± 0.9
	30 min	5.0 ± 2.1	157.8 ± 9.2	7,048 ± 357	-7,671 ± 701	87.8 ± 5.5	8.8 ± 0.9
	35 min	5.0 ± 2.1	158.8 ± 10.2	7,108 ± 403	-7,743 ± 731	88.7 ± 5.2	8.8 ± 0.6
	40 min	4.9 ± 1.6	157.5 ± 6.5	7,167 ± 313	-7,666 ± 658	89.2 ± 5.4	8.8 ± 0.8
	45 min	4.8 ± 1.6	158.7 ± 7.5	7,268 ± 293	-7,786 ± 701	89.5 ± 5.2	8.7 ± 0.8
	50 min	3.7 ± 1.7	153.6 ± 7.9	7,019 ± 338	-7,532 ± 674	88.5 ± 5.5	8.9 ± 0.8
	55 min	3.4 ± 1.9	149.6 ± 9.0	6,947 ± 349	-7,365 ± 698	89.2 ± 5.3	8.7 ± 0.7
	60 min	3.5 ± 1.8	152.7 ± 8.1	6,918 ± 442	-7,624 ± 688	88.5 ± 5.6	8.5 ± 0.7

Continued

Table 51. Hemodynamic effects of matched-volume vehicle (sterile water) in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 4.

Table 51. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Baseline		21.4 ± 0.6	18.3 ± 0.7	3.4 ± 0.6	1,252 ± 254	280.3 ± 26.5
Vehicle	5 min	21.3 ± 0.5	18.6 ± 0.5	3.2 ± 0.5	1,185 ± 217	295.5 ± 21.6
	10 min	21.6 ± 0.6	18.3 ± 0.3	3.7 ± 0.8	1,379 ± 327	293.1 ± 23.8
	15 min	21.6 ± 0.6	18.2 ± 0.4	3.6 ± 0.7	1,377 ± 300	305.6 ± 23.1
	20 min	21.5 ± 0.6	18.1 ± 0.3	3.6 ± 0.7	1,360 ± 294	307.1 ± 21.8
	25 min	21.1 ± 0.5	18.3 ± 0.5	3.2 ± 0.6	1,226 ± 245	310.5 ± 18.8
	30 min	21.3 ± 0.6	18.5 ± 0.5	3.0 ± 0.5	1,125 ± 222	304.3 ± 19.4
	35 min	21.4 ± 0.6	18.6 ± 0.5	3.1 ± 0.5	1,168 ± 239	302.9 ± 19.2
	40 min	21.4 ± 0.5	18.8 ± 0.4	3.0 ± 0.5	1,112 ± 210	307.6 ± 16.7
	45 min	21.6 ± 0.7	18.9 ± 0.4	3.0 ± 0.5	1,098 ± 203	303.3 ± 17.9
	50 min	21.7 ± 0.7	18.9 ± 0.4	3.0 ± 0.5	1,082 ± 185	304.6 ± 20.2
	55 min	21.7 ± 0.7	19.0 ± 0.4	2.8 ± 0.4	1,041 ± 181	310.2 ± 21.5
	60 min	21.8 ± 0.8	19.2 ± 0.4	2.9 ± 0.5	1,035 ± 184	318.1 ± 22.3
Recovery	5 min	21.8 ± 0.7	19.2 ± 0.4	2.9 ± 0.5	1,069 ± 206	318.5 ± 20.7
	10 min	21.6 ± 0.7	18.9 ± 0.4	2.9 ± 0.5	1,096 ± 223	323.2 ± 19.7
	15 min	21.4 ± 0.6	19.0 ± 0.4	2.9 ± 0.5	1,111 ± 223	324.0 ± 16.7
	20 min	21.4 ± 0.6	18.9 ± 0.4	3.0 ± 0.5	1,135 ± 234	330.6 ± 15.2
	25 min	21.3 ± 0.6	18.8 ± 0.4	3.0 ± 0.5	1,156 ± 229	332.2 ± 13.9
	30 min	21.3 ± 0.6	18.7 ± 0.4	3.1 ± 0.5	1,168 ± 222	330.8 ± 13.8
	35 min	21.3 ± 0.6	18.6 ± 0.4	3.2 ± 0.5	1,208 ± 233	333.4 ± 17.0
	40 min	21.4 ± 0.6	18.8 ± 0.4	3.1 ± 0.5	1,194 ± 236	335.1 ± 13.5
	45 min	21.6 ± 0.3	19.1 ± 0.4	3.0 ± 0.6	1,151 ± 262	337.0 ± 13.8
	50 min	21.3 ± 0.5	18.3 ± 0.3	3.3 ± 0.6	1,229 ± 261	329.9 ± 14.3
	55 min	21.1 ± 0.5	18.1 ± 0.3	3.5 ± 0.7	1,255 ± 270	330.0 ± 14.7
	60 min	20.9 ± 0.5	18.2 ± 0.6	3.3 ± 0.6	1,242 ± 267	331.6 ± 18.5

Values are means ± SE; n = 4.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	31.9 ± 42.8	4.5 ± 1.3	5.6 ± 2.7	-6.5 ± 3.2	2.9 ± 1.9	-3.0 ± 2.4
	10 min	1.7 ± 42.6	5.2 ± 1.0	5.5 ± 1.4	-8.5 ± 2.8	1.7 ± 1.5	-2.6 ± 2.0
	15 min	13.4 ± 34.3	8.3 ± 3.1	10.3 ± 2.1	-12.3 ± 3.7	3.9 ± 1.8	-2.0 ± 4.6
	20 min	-8.8 ± 27.1	7.2 ± 2.4	10.4 ± 2.5	-10.6 ± 3.1	3.0 ± 1.4	-1.6 ± 4.4
	25 min	-0.5 ± 35.5	5.4 ± 1.0	10.2 ± 3.9	-9.4 ± 2.2	2.4 ± 1.6	-4.6 ± 2.7
	30 min	5.7 ± 14.0	6.2 ± 2.4	9.0 ± 5.5	-10.4 ± 5.2	2.4 ± 2.2	-5.7 ± 3.5
	35 min	4.5 ± 14.1	7.0 ± 2.4	9.3 ± 5.6	-10.7 ± 5.1	2.2 ± 2.3	-2.6 ± 2.0
	40 min	13.8 ± 8.5	8.8 ± 1.4	10.9 ± 4.9	-11.8 ± 4.8	3.7 ± 3.3	-5.3 ± 3.4
	45 min	-3.1 ± 16.7	9.9 ± 1.6	10.3 ± 3.6	-13.0 ± 5.1	4.1 ± 3.4	-4.6 ± 3.4
	50 min	5.5 ± 15.8	11.4 ± 0.6	10.6 ± 2.5	-13.4 ± 3.6	2.9 ± 2.1	-3.6 ± 3.6
	55 min	6.7 ± 14.8	13.9 ± 0.6	12.8 ± 2.0	-15.0 ± 4.3	3.9 ± 2.0	-1.5 ± 4.7
	60 min	-6.3 ± 24.2	14.7 ± 0.8	16.2 ± 2.0	-17.3 ± 3.2	4.6 ± 1.8	-2.5 ± 4.7
Recovery	5 min	3.6 ± 20.5	15.3 ± 0.5	16.4 ± 2.5	-17.5 ± 3.9	4.9 ± 2.0	-1.1 ± 5.5
	10 min	-6.3 ± 18.6	14.7 ± 1.3	17.2 ± 3.3	-18.1 ± 4.7	6.0 ± 2.8	-5.0 ± 3.4
	15 min	-2.7 ± 16.5	13.8 ± 0.2	16.7 ± 3.4	-17.8 ± 4.4	5.6 ± 2.9	-5.3 ± 3.4
	20 min	-8.3 ± 16.8	15.1 ± 1.6	19.3 ± 5.1	-20.3 ± 5.7	5.6 ± 2.9	-5.7 ± 3.5
	25 min	-9.7 ± 15.6	14.4 ± 1.9	19.6 ± 5.0	-20.8 ± 5.7	6.2 ± 3.2	-6.1 ± 3.3
	30 min	-18.2 ± 22.2	12.9 ± 2.8	18.8 ± 4.7	-20.8 ± 5.6	5.3 ± 2.6	-7.7 ± 2.9
	35 min	-18.2 ± 22.2	13.6 ± 3.8	19.7 ± 4.1	-21.8 ± 5.7	6.5 ± 2.8	-6.6 ± 2.8
	40 min	-14.4 ± 16.1	13.0 ± 2.8	21.1 ± 5.9	-20.9 ± 5.6	7.1 ± 3.3	-7.6 ± 3.5
	45 min	-15.9 ± 27.1	13.8 ± 3.4	23.0 ± 6.9	-22.7 ± 5.9	7.6 ± 3.7	-8.5 ± 3.0
	50 min	-41.2 ± 16.3	10.1 ± 3.1	18.5 ± 5.4	-18.7 ± 5.6	6.3 ± 4.0	-6.1 ± 5.0
	55 min	-53.6 ± 23.6	7.0 ± 3.0	17.2 ± 5.3	-15.9 ± 5.2	7.3 ± 5.0	-8.0 ± 4.8
	60 min	-47.8 ± 21.6	9.4 ± 3.4	16.4 ± 4.4	-20.2 ± 5.9	6.4 ± 4.2	-9.9 ± 3.5

Continued

Table 52. Hemodynamic effects of matched-volume vehicle (sterile water) in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

Table 52. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	-0.5 ± 1.1	1.4 ± 1.1	-2.3 ± 4.8	-2.8 ± 4.6	6.2 ± 3.9
	10 min	0.6 ± 0.6	-0.2 ± 1.7	9.3 ± 10.3	10.0 ± 10.2	5.0 ± 1.6
	15 min	0.6 ± 0.6	-0.5 ± 1.7	8.2 ± 6.9	10.5 ± 7.4	9.6 ± 2.1
	20 min	0.1 ± 0.2	-0.9 ± 1.8	7.7 ± 8.3	9.8 ± 8.7	10.3 ± 2.6
	25 min	-1.5 ± 0.6	-0.2 ± 1.9	-0.9 ± 7.9	0.5 ± 8.1	11.9 ± 4.1
	30 min	-0.7 ± 0.6	1.3 ± 2.7	-7.0 ± 9.8	-6.1 ± 10.3	9.8 ± 5.5
	35 min	0.0 ± 0.5	1.8 ± 2.6	-5.8 ± 8.5	-3.8 ± 9.3	9.4 ± 6.1
	40 min	-0.1 ± 0.9	2.6 ± 2.9	-5.8 ± 11.2	-6.2 ± 11.4	11.2 ± 5.7
	45 min	0.9 ± 1.0	3.4 ± 3.0	-6.7 ± 10.6	-7.3 ± 10.9	9.4 ± 4.5
	50 min	1.0 ± 1.1	3.5 ± 3.3	-5.7 ± 12.1	-7.2 ± 12.4	9.6 ± 3.4
	55 min	1.3 ± 1.3	4.2 ± 3.6	-9.7 ± 12.3	-10.6 ± 12.6	11.5 ± 2.9
	60 min	1.8 ± 1.8	5.1 ± 3.8	-9.9 ± 11.8	-11.6 ± 11.7	14.3 ± 3.0
Recovery	5 min	1.7 ± 1.7	4.9 ± 3.8	-9.0 ± 12.6	-8.9 ± 12.9	14.6 ± 3.8
	10 min	0.7 ± 1.0	3.5 ± 3.6	-7.8 ± 13.2	-6.8 ± 13.6	16.5 ± 4.3
	15 min	-0.1 ± 1.9	4.0 ± 3.6	-8.2 ± 12.3	-5.6 ± 13.3	17.1 ± 5.4
	20 min	-0.1 ± 1.6	3.5 ± 3.3	-8.0 ± 10.7	-5.0 ± 11.7	19.7 ± 6.8
	25 min	-0.4 ± 1.6	2.6 ± 3.1	-6.3 ± 9.3	-3.9 ± 10.0	20.4 ± 6.9
	30 min	-0.6 ± 1.7	2.3 ± 2.9	-5.4 ± 8.5	-2.8 ± 9.3	19.8 ± 6.7
	35 min	-0.5 ± 1.7	1.5 ± 2.6	-3.1 ± 7.8	-0.2 ± 8.5	20.5 ± 6.0
	40 min	-0.1 ± 1.8	2.5 ± 2.5	-5.1 ± 6.3	-2.4 ± 6.9	21.6 ± 7.6
	45 min	0.8 ± 1.8	4.4 ± 1.7	-11.5 ± 6.0	-9.4 ± 6.0	22.2 ± 7.2
	50 min	-0.7 ± 1.4	0.0 ± 2.1	0.0 ± 4.0	-0.9 ± 6.1	19.5 ± 6.7
	55 min	-1.7 ± 1.2	-1.3 ± 2.1	4.2 ± 7.5	0.6 ± 5.8	19.5 ± 6.4
	60 min	-2.7 ± 1.3	-0.9 ± 1.2	-2.2 ± 4.6	-0.5 ± 5.4	19.6 ± 5.0

Values are means ± SE; n = 4.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	7.0 ± 1.8	158.7 ± 7.3	6,627 ± 191	-6,821 ± 399	89.5 ± 3.4	7.7 ± 0.9
Imipramine	5 min	6.9 ± 1.9	158.6 ± 7.7	6,669 ± 208	-6,881 ± 423	90.5 ± 3.4	7.7 ± 0.9
	10 min	6.2 ± 1.7	143.1 ± 11.5	6,439 ± 549	-6,520 ± 692	93.7 ± 3.6	6.8 ± 0.8
	15 min	6.2 ± 1.6	116.6 ± 13.7	5,025 ± 713	-4,962 ± 693	90.8 ± 4.9	7.2 ± 0.7
	20 min	6.5 ± 1.5	94.9 ± 10.8	3,780 ± 585	-3,645 ± 511	88.9 ± 4.8	7.5 ± 0.8
	25 min	6.7 ± 1.5	85.5 ± 10.0	3,225 ± 548	-3,103 ± 499	86.7 ± 4.9	8.1 ± 0.9
	30 min	7.0 ± 1.5	85.0 ± 8.4	3,096 ± 423	-3,051 ± 417	84.4 ± 3.8	8.0 ± 0.8
	35 min	7.3 ± 1.6	86.4 ± 8.2	3,138 ± 421	-3,126 ± 414	84.0 ± 3.6	8.2 ± 0.9
	40 min	7.4 ± 1.5	87.0 ± 8.5	3,138 ± 439	-3,121 ± 426	83.2 ± 3.5	8.2 ± 0.9
	45 min	7.4 ± 1.5	90.7 ± 10.8	3,312 ± 566	-3,290 ± 544	84.5 ± 4.5	8.3 ± 1.0
	50 min	7.3 ± 1.5	92.2 ± 9.8	3,370 ± 541	-3,365 ± 512	83.2 ± 4.0	8.2 ± 1.0
	55 min	7.1 ± 1.5	96.5 ± 9.9	3,554 ± 565	-3,618 ± 549	82.2 ± 5.2	8.3 ± 1.0
	60 min	7.1 ± 1.7	102.2 ± 10.6	3,859 ± 626	-3,924 ± 610	83.5 ± 6.0	8.2 ± 1.1
Recovery	5 min	7.3 ± 1.7	112.3 ± 10.3	4,282 ± 635	-4,474 ± 688	81.9 ± 5.8	8.2 ± 1.2
	10 min	6.7 ± 1.9	114.8 ± 11.1	4,461 ± 678	-4,663 ± 746	83.5 ± 6.2	8.0 ± 1.2
	15 min	6.5 ± 1.8	114.4 ± 11.3	4,500 ± 672	-4,694 ± 731	84.6 ± 6.2	7.7 ± 1.1
	20 min	5.6 ± 2.0	113.2 ± 11.1	4,486 ± 659	-4,641 ± 701	84.8 ± 5.9	7.7 ± 1.1
	25 min	5.8 ± 2.1	114.3 ± 11.0	4,548 ± 645	-4,702 ± 693	84.8 ± 5.9	7.8 ± 1.1
	30 min	5.9 ± 2.0	115.5 ± 11.0	4,600 ± 636	-4,755 ± 692	84.8 ± 6.3	7.7 ± 1.1
	35 min	5.9 ± 2.1	117.4 ± 9.8	4,711 ± 598	-4,872 ± 687	85.1 ± 6.0	7.8 ± 1.1
	40 min	5.7 ± 1.9	117.6 ± 9.2	4,720 ± 566	-4,875 ± 645	85.6 ± 6.1	7.7 ± 1.1
	45 min	5.5 ± 1.9	117.7 ± 8.7	4,726 ± 531	-4,871 ± 596	85.4 ± 6.2	7.6 ± 1.1
	50 min	5.6 ± 1.8	121.3 ± 8.0	4,919 ± 487	-5,088 ± 555	86.0 ± 6.1	7.5 ± 1.0
	55 min	5.8 ± 1.9	122.5 ± 7.6	4,995 ± 435	-5,190 ± 538	85.5 ± 5.1	7.7 ± 1.0
	60 min	5.4 ± 1.8	122.6 ± 8.3	5,020 ± 454	-5,207 ± 537	86.0 ± 5.3	7.6 ± 1.0

Continued

Table 53. Hemodynamic effects of imipramine in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 6.

Table 53 Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Baseline		20.4 ± 1.2	18.9 ± 1.3	1.5 ± 0.3	605 ± 111	332.4 ± 27.0
Imipramine	5 min	20.3 ± 1.3	18.8 ± 1.3	1.5 ± 0.3	627 ± 107	336.8 ± 27.7
	10 min	19.2 ± 1.2	17.7 ± 1.2	1.5 ± 0.3	623 ± 112	343.2 ± 39.7
	15 min	19.3 ± 1.4	17.6 ± 1.4	1.7 ± 0.5	690 ± 169	274.2 ± 52.4
	20 min	19.7 ± 1.6	18.1 ± 1.6	1.7 ± 0.5	622 ± 163	207.1 ± 48.4
	25 min	20.2 ± 1.7	18.6 ± 1.7	1.6 ± 0.5	556 ± 166	172.4 ± 43.2
	30 min	20.4 ± 1.7	19.0 ± 1.7	1.4 ± 0.4	472 ± 123	160.8 ± 33.4
	35 min	20.6 ± 1.7	19.2 ± 1.7	1.5 ± 0.4	475 ± 134	160.7 ± 32.1
	40 min	20.7 ± 1.7	19.2 ± 1.8	1.5 ± 0.4	473 ± 138	160.3 ± 33.2
	45 min	20.8 ± 1.7	19.2 ± 1.8	1.6 ± 0.5	540 ± 186	169.2 ± 40.1
	50 min	20.9 ± 1.8	19.2 ± 1.8	1.7 ± 0.5	546 ± 181	172.1 ± 39.9
	55 min	20.9 ± 1.7	19.2 ± 1.8	1.7 ± 0.5	553 ± 193	181.1 ± 41.3
	60 min	20.8 ± 1.7	19.1 ± 1.7	1.7 ± 0.5	570 ± 196	195.8 ± 42.3
Recovery	5 min	20.7 ± 1.6	19.1 ± 1.7	1.6 ± 0.5	550 ± 199	216.5 ± 41.6
	10 min	20.3 ± 1.6	18.6 ± 1.6	1.6 ± 0.5	585 ± 193	230.7 ± 44.6
	15 min	20.1 ± 1.5	18.5 ± 1.6	1.6 ± 0.5	584 ± 191	235.4 ± 45.4
	20 min	20.1 ± 1.5	18.5 ± 1.6	1.6 ± 0.5	602 ± 190	234.3 ± 44.7
	25 min	20.2 ± 1.5	18.6 ± 1.6	1.6 ± 0.4	603 ± 189	236.7 ± 44.0
	30 min	20.3 ± 1.6	18.5 ± 1.5	1.8 ± 0.5	648 ± 193	238.4 ± 43.9
	35 min	20.3 ± 1.5	18.5 ± 1.5	1.8 ± 0.5	657 ± 188	242.8 ± 41.9
	40 min	20.4 ± 1.5	18.6 ± 1.5	1.8 ± 0.5	663 ± 192	242.6 ± 41.0
	45 min	20.3 ± 1.5	18.5 ± 1.5	1.8 ± 0.5	660 ± 193	243.3 ± 39.9
	50 min	20.3 ± 1.5	18.5 ± 1.5	1.8 ± 0.5	651 ± 183	252.8 ± 39.0
	55 min	20.3 ± 1.5	18.6 ± 1.5	1.7 ± 0.4	707 ± 192	255.3 ± 34.6
	60 min	20.3 ± 1.4	18.5 ± 1.5	1.8 ± 0.4	652 ± 181	256.8 ± 35.6

Values are means ± SE; n = 6.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-1.1 ± 2.8	-0.1 ± 1.3	0.6 ± 1.5	-0.9 ± 1.7	1.1 ± 0.9	-0.4 ± 0.4
	10 min	-15.0 ± 4.0	-9.8 ± 5.7	-3.1 ± 7.5	4.8 ± 8.1	4.9 ± 2.6	-11.3 ± 3.5
	15 min	-10.0 ± 5.1	-27.0 ± 6.7	-24.6 ± 9.7	26.7 ± 10.2	1.4 ± 3.6	-4.9 ± 6.2
	20 min	3.8 ± 12.2	-40.9 ± 4.1	-43.7 ± 7.1	46.3 ± 6.9	-0.5 ± 4.3	-1.5 ± 5.3
	25 min	6.0 ± 12.0	-46.7 ± 4.0	-52.1 ± 6.5	54.7 ± 6.3	-3.0 ± 5.0	6.0 ± 5.7
	30 min	16.1 ± 20.7	-46.7 ± 3.6	-53.8 ± 5.0	55.3 ± 5.4	-5.5 ± 4.0	5.2 ± 5.8
	35 min	20.1 ± 20.1	-45.8 ± 3.6	-53.2 ± 4.9	54.3 ± 5.2	-5.9 ± 3.5	6.7 ± 5.7
	40 min	23.8 ± 19.7	-45.4 ± 3.7	-53.2 ± 5.2	54.3 ± 5.5	-6.9 ± 3.1	6.7 ± 5.7
	45 min	26.9 ± 27.6	-43.3 ± 4.8	-50.8 ± 6.8	51.8 ± 7.1	-5.5 ± 3.8	8.1 ± 6.1
	50 min	26.9 ± 29.2	-42.2 ± 4.4	-49.9 ± 6.5	50.9 ± 6.5	-7.0 ± 2.4	7.3 ± 5.7
	55 min	24.4 ± 29.8	-39.4 ± 4.5	-47.2 ± 6.7	47.6 ± 6.6	-8.4 ± 2.7	8.5 ± 5.6
	60 min	14.9 ± 21.1	-35.7 ± 5.4	-42.5 ± 8.1	43.0 ± 7.8	-7.1 ± 3.7	6.3 ± 5.5
Recovery	5 min	19.8 ± 20.3	-29.1 ± 5.8	-36.1 ± 8.3	35.5 ± 8.2	-8.9 ± 3.5	5.0 ± 6.8
	10 min	11.8 ± 23.1	-27.6 ± 6.1	-33.4 ± 9.0	32.9 ± 8.8	-7.2 ± 3.7	2.8 ± 6.9
	15 min	15.2 ± 33.0	-27.9 ± 6.1	-32.8 ± 8.9	32.3 ± 8.7	-6.1 ± 3.6	-0.6 ± 6.0
	20 min	-19.1 ± 17.0	-28.7 ± 5.7	-33.0 ± 8.7	32.9 ± 8.4	-5.7 ± 3.2	-0.6 ± 6.0
	25 min	-15.1 ± 17.0	-28.0 ± 5.6	-32.0 ± 8.4	32.0 ± 8.2	-5.7 ± 3.2	0.4 ± 6.2
	30 min	-7.8 ± 19.9	-27.3 ± 5.5	-31.3 ± 8.2	31.3 ± 8.0	-5.8 ± 3.5	-1.0 ± 6.0
	35 min	-8.2 ± 19.8	-25.9 ± 5.3	-29.6 ± 7.6	29.8 ± 7.3	-5.4 ± 3.2	0.0 ± 6.1
	40 min	-11.8 ± 19.2	-25.8 ± 4.7	-29.4 ± 7.0	29.6 ± 6.7	-4.9 ± 3.3	-0.7 ± 6.0
	45 min	-16.7 ± 20.4	-25.9 ± 3.9	-29.3 ± 6.3	29.5 ± 5.9	-5.2 ± 3.4	-1.9 ± 4.8
	50 min	-13.5 ± 18.9	-23.5 ± 3.4	-26.4 ± 5.5	26.3 ± 4.8	-4.4 ± 3.2	-3.9 ± 3.7
	55 min	-10.4 ± 18.3	-22.7 ± 3.5	-25.1 ± 4.9	24.7 ± 4.3	-4.8 ± 2.1	-1.1 ± 3.9
	60 min	-14.6 ± 19.8	-22.8 ± 3.5	-24.7 ± 5.1	24.4 ± 4.6	-4.3 ± 2.5	-2.6 ± 4.0

Continued

Table 54. Hemodynamic effects of imipramine in sedentary rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 54. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.6 ± 0.4	-0.8 ± 0.5	4.2 ± 4.6	5.2 ± 5.1	1.3 ± 1.7
	10 min	-5.7 ± 1.6	-5.9 ± 1.7	3.9 ± 13.8	10.3 ± 15.9	2.6 ± 7.4
	15 min	-5.8 ± 2.0	-7.3 ± 2.1	14.7 ± 16.3	17.0 ± 18.6	-19.9 ± 10.2
	20 min	-3.8 ± 2.5	-4.8 ± 3.0	11.4 ± 18.4	5.6 ± 19.2	-40.7 ± 8.6
	25 min	-1.9 ± 3.2	-2.3 ± 3.8	5.3 ± 19.3	-7.0 ± 19.3	-50.6 ± 7.7
	30 min	-0.6 ± 3.1	-0.1 ± 3.8	-0.2 ± 18.4	-17.1 ± 17.6	-53.2 ± 5.6
	35 min	0.5 ± 3.0	0.8 ± 3.8	0.3 ± 17.8	-18.3 ± 17.1	-53.2 ± 5.3
	40 min	1.0 ± 3.1	1.1 ± 3.9	1.8 ± 18.2	-19.3 ± 16.8	-53.4 ± 5.6
	45 min	1.3 ± 3.0	0.7 ± 4.0	8.5 ± 20.7	-11.6 ± 19.8	-51.2 ± 7.1
	50 min	1.6 ± 3.3	0.8 ± 4.0	7.8 ± 18.4	-12.4 ± 17.1	-50.3 ± 7.0
	55 min	1.7 ± 3.2	0.9 ± 4.0	7.6 ± 18.4	-12.6 ± 17.5	-47.6 ± 7.4
	60 min	1.2 ± 3.3	0.2 ± 4.1	9.3 ± 18.9	-8.6 ± 18.7	-42.8 ± 8.4
Recovery	5 min	1.0 ± 2.9	0.6 ± 3.5	-1.0 ± 18.0	-13.9 ± 18.3	-36.2 ± 8.8
	10 min	-0.9 ± 2.9	-1.7 ± 3.4	7.0 ± 21.2	-3.2 ± 22.7	-32.0 ± 9.8
	15 min	-1.9 ± 2.8	-2.6 ± 3.5	6.4 ± 21.1	-2.1 ± 23.7	-30.7 ± 9.8
	20 min	-1.7 ± 2.9	-2.6 ± 3.6	12.7 ± 23.6	4.3 ± 27.3	-31.0 ± 9.6
	25 min	-1.4 ± 3.0	-2.1 ± 3.9	13.1 ± 23.5	5.6 ± 27.8	-30.2 ± 9.4
	30 min	-1.0 ± 3.1	-2.5 ± 3.6	20.8 ± 23.8	12.4 ± 28.1	-29.8 ± 9.2
	35 min	-0.6 ± 2.9	-2.2 ± 3.5	23.3 ± 24.7	15.4 ± 29.6	-28.2 ± 8.9
	40 min	-0.4 ± 2.9	-2.0 ± 3.6	23.4 ± 24.4	16.2 ± 29.5	-28.2 ± 8.3
	45 min	-0.6 ± 3.0	-2.3 ± 3.7	22.1 ± 22.4	13.9 ± 27.0	-28.0 ± 7.7
	50 min	-0.6 ± 3.1	-2.1 ± 3.9	21.3 ± 22.1	13.9 ± 26.9	-25.0 ± 7.3
	55 min	-0.6 ± 2.9	-1.8 ± 3.9	20.5 ± 21.0	18.5 ± 21.5	-23.8 ± 6.6
	60 min	-0.7 ± 2.8	-2.2 ± 3.7	22.6 ± 20.6	14.5 ± 25.4	-23.4 ± 6.6

Values are means ± SE; n = 6.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	5.5 ± 1.5	165.2 ± 1.6	6,560 ± 86	-6,372 ± 171	95.6 ± 1.0	7.8 ± 0.3
Imipramine	5 min	6.1 ± 1.6	169.2 ± 2.1	6,715 ± 83	-6,548 ± 159	96.4 ± 1.0	7.7 ± 0.3
	10 min	5.9 ± 1.8	167.6 ± 3.3	7,020 ± 100	-6,810 ± 125	101.0 ± 1.1	7.0 ± 0.2
	15 min	6.3 ± 1.6	135.4 ± 8.4	5,730 ± 456	-5,373 ± 444	96.0 ± 3.7	7.0 ± 0.3
	20 min	6.6 ± 1.7	101.7 ± 10.8	3,944 ± 577	-3,647 ± 543	86.3 ± 4.0	7.9 ± 0.5
	25 min	6.7 ± 1.5	90.3 ± 7.0	3,280 ± 374	-3,074 ± 342	84.4 ± 2.1	8.0 ± 0.4
	30 min	6.7 ± 1.4	82.3 ± 3.8	2,812 ± 156	-2,647 ± 181	82.1 ± 1.1	8.3 ± 0.2
	35 min	7.0 ± 1.6	82.1 ± 4.0	2,816 ± 171	-2,650 ± 198	82.6 ± 1.0	8.2 ± 0.3
	40 min	6.7 ± 1.3	82.1 ± 3.2	2,827 ± 150	-2,648 ± 178	82.5 ± 1.1	8.3 ± 0.2
	45 min	6.6 ± 1.2	82.1 ± 3.6	2,855 ± 167	-2,670 ± 201	82.4 ± 1.2	8.3 ± 0.3
	50 min	6.5 ± 1.2	82.5 ± 4.3	2,879 ± 196	-2,677 ± 236	82.1 ± 1.4	8.5 ± 0.3
	55 min	6.5 ± 1.0	84.4 ± 4.9	2,949 ± 219	-2,740 ± 267	81.5 ± 1.6	8.5 ± 0.3
	60 min	6.5 ± 0.9	88.5 ± 5.6	3,133 ± 248	-2,929 ± 302	82.1 ± 1.8	8.2 ± 0.5
Recovery	5 min	6.6 ± 0.8	105.1 ± 7.7	3,759 ± 294	-3,593 ± 357	83.5 ± 1.2	8.3 ± 0.3
	10 min	5.8 ± 1.0	115.0 ± 9.5	4,285 ± 391	-4,121 ± 454	86.6 ± 1.0	7.9 ± 0.3
	15 min	5.1 ± 1.0	123.5 ± 8.5	4,689 ± 347	-4,515 ± 431	88.4 ± 1.0	8.1 ± 0.3
	20 min	5.0 ± 1.1	129.4 ± 8.3	4,941 ± 311	-4,762 ± 392	89.3 ± 0.6	8.0 ± 0.4
	25 min	4.9 ± 0.9	132.6 ± 9.1	5,083 ± 332	-4,929 ± 393	89.8 ± 0.4	8.1 ± 0.3
	30 min	4.3 ± 1.0	129.2 ± 8.7	4,971 ± 338	-4,830 ± 392	89.3 ± 0.7	8.0 ± 0.3
	35 min	4.2 ± 1.0	123.8 ± 8.5	4,750 ± 342	-4,618 ± 392	88.4 ± 1.0	8.0 ± 0.3
	40 min	4.0 ± 1.0	118.2 ± 8.7	4,552 ± 344	-4,418 ± 416	87.4 ± 1.0	7.9 ± 0.3
	45 min	3.8 ± 1.2	116.2 ± 13.1	4,440 ± 525	-4,338 ± 632	86.4 ± 1.6	7.8 ± 0.2
	50 min	3.8 ± 1.2	119.7 ± 12.7	4,601 ± 515	-4,507 ± 622	87.3 ± 1.7	7.8 ± 0.3
	55 min	4.0 ± 1.5	126.6 ± 9.9	4,910 ± 409	-4,804 ± 510	88.8 ± 1.1	7.4 ± 0.3
	60 min	3.8 ± 1.6	133.2 ± 10.3	5,192 ± 419	-5,104 ± 520	89.9 ± 1.1	7.5 ± 0.4

Continued

Table 55. Hemodynamic effects of imipramine in exercise rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 6.

Table 55. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/dt)/EDV (mmHg/s* RVU)
Baseline		19.9 ± 0.4	18.3 ± 0.6	1.6 ± 0.3	613 ± 118	330.8 ± 10.0
Imipramine	5 min	19.9 ± 0.4	18.3 ± 0.6	1.6 ± 0.3	606 ± 124	338.6 ± 9.3
	10 min	19.4 ± 0.4	17.6 ± 0.6	1.8 ± 0.3	749 ± 111	362.3 ± 11.5
	15 min	19.4 ± 0.4	17.8 ± 0.8	1.6 ± 0.4	637 ± 164	297.2 ± 28.1
	20 min	20.1 ± 0.8	18.2 ± 1.0	1.8 ± 0.4	673 ± 169	203.2 ± 37.2
	25 min	20.6 ± 0.8	18.7 ± 1.0	1.9 ± 0.4	614 ± 137	164.0 ± 26.1
	30 min	20.9 ± 0.9	19.2 ± 1.0	1.7 ± 0.3	512 ± 101	136.8 ± 11.9
	35 min	21.1 ± 0.9	19.4 ± 1.0	1.7 ± 0.3	494 ± 92	135.4 ± 11.5
	40 min	21.3 ± 0.9	19.6 ± 1.0	1.7 ± 0.3	488 ± 92	134.9 ± 10.5
	45 min	21.4 ± 1.0	19.7 ± 1.0	1.7 ± 0.4	504 ± 107	135.6 ± 11.3
	50 min	21.6 ± 1.1	19.8 ± 1.1	1.8 ± 0.4	503 ± 102	136.2 ± 12.6
	55 min	21.5 ± 1.0	19.8 ± 1.1	1.7 ± 0.4	497 ± 101	139.3 ± 12.8
	60 min	21.5 ± 1.0	19.8 ± 1.1	1.7 ± 0.3	500 ± 99	147.4 ± 13.2
Recovery	5 min	21.2 ± 0.8	19.7 ± 1.0	1.4 ± 0.3	417 ± 83	178.3 ± 14.0
	10 min	20.7 ± 0.7	19.4 ± 1.0	1.3 ± 0.3	419 ± 100	207.2 ± 18.8
	15 min	20.6 ± 0.7	19.2 ± 0.9	1.4 ± 0.3	456 ± 97	227.7 ± 15.1
	20 min	20.6 ± 0.5	19.2 ± 0.9	1.4 ± 0.3	468 ± 108	240.5 ± 14.3
	25 min	20.6 ± 0.5	19.1 ± 0.8	1.5 ± 0.3	498 ± 113	247.4 ± 16.7
	30 min	20.4 ± 0.5	19.0 ± 0.8	1.4 ± 0.3	487 ± 124	244.1 ± 18.0
	35 min	20.5 ± 0.6	19.0 ± 0.8	1.5 ± 0.3	518 ± 124	232.9 ± 18.8
	40 min	20.5 ± 0.7	18.9 ± 0.9	1.6 ± 0.3	528 ± 110	223.2 ± 17.6
	45 min	20.4 ± 0.7	18.8 ± 1.0	1.6 ± 0.3	511 ± 99	216.0 ± 21.2
	50 min	20.3 ± 0.7	18.8 ± 1.0	1.5 ± 0.3	507 ± 103	224.4 ± 20.4
	55 min	20.6 ± 0.6	19.1 ± 0.9	1.5 ± 0.3	510 ± 111	237.6 ± 17.2
	60 min	20.6 ± 0.6	19.3 ± 0.9	1.4 ± 0.3	481 ± 113	251.5 ± 18.8

Values are means ± SE; n = 6.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	8.2 ± 4.8	2.4 ± 0.8	2.4 ± 0.6	-2.8 ± 0.7	0.8 ± 0.3	-2.2 ± 2.2
	10 min	-5.7 ± 15.0	1.4 ± 1.5	7.0 ± 1.1	-7.0 ± 1.4	5.6 ± 0.3	-10.2 ± 1.4
	15 min	15.6 ± 10.3	-18.1 ± 4.8	-12.8 ± 6.5	15.7 ± 6.8	0.3 ± 2.9	-10.5 ± 2.6
	20 min	27.2 ± 18.0	-38.6 ± 6.2	-40.2 ± 8.3	43.0 ± 8.2	-9.8 ± 4.0	0.5 ± 5.9
	25 min	38.8 ± 20.5	-45.4 ± 4.0	-50.1 ± 5.5	51.7 ± 5.5	-11.7 ± 2.3	2.3 ± 3.9
	30 min	43.0 ± 24.3	-50.2 ± 2.4	-57.1 ± 2.5	58.4 ± 3.0	-14.1 ± 1.9	6.9 ± 3.8
	35 min	48.6 ± 24.0	-50.2 ± 2.6	-57.0 ± 2.8	58.3 ± 3.3	-13.5 ± 1.9	4.8 ± 5.0
	40 min	44.9 ± 23.9	-50.3 ± 2.2	-56.8 ± 2.5	58.3 ± 2.9	-13.6 ± 2.0	6.2 ± 4.1
	45 min	43.6 ± 23.5	-50.2 ± 2.4	-56.4 ± 2.7	58.0 ± 3.1	-13.8 ± 2.0	5.8 ± 4.3
	50 min	47.8 ± 27.8	-50.0 ± 2.8	-56.1 ± 3.1	58.0 ± 3.6	-14.1 ± 2.2	9.0 ± 5.3
	55 min	52.7 ± 29.8	-48.8 ± 3.2	-55.0 ± 3.4	57.0 ± 4.0	-14.7 ± 2.3	9.0 ± 5.3
	60 min	53.6 ± 30.4	-46.3 ± 3.7	-52.2 ± 3.7	54.2 ± 4.3	-14.0 ± 2.5	4.8 ± 5.6
Recovery	5 min	59.8 ± 35.8	-36.3 ± 4.9	-42.8 ± 4.1	44.0 ± 4.3	-12.6 ± 2.1	6.5 ± 4.8
	10 min	27.1 ± 21.1	-30.2 ± 6.0	-34.9 ± 5.3	35.9 ± 5.3	-9.4 ± 1.8	1.3 ± 3.2
	15 min	13.3 ± 23.7	-25.1 ± 5.5	-28.6 ± 4.7	29.6 ± 5.0	-7.4 ± 1.9	3.2 ± 2.5
	20 min	13.6 ± 24.6	-21.6 ± 5.4	-24.8 ± 4.1	25.7 ± 4.3	-6.5 ± 1.3	2.5 ± 3.1
	25 min	15.0 ± 25.4	-19.6 ± 5.9	-22.6 ± 4.7	23.0 ± 4.8	-6.1 ± 0.7	2.9 ± 2.8
	30 min	-3.0 ± 19.3	-21.7 ± 5.6	-24.4 ± 4.6	24.6 ± 4.7	-6.6 ± 0.6	2.0 ± 2.8
	35 min	-2.2 ± 21.2	-25.0 ± 5.4	-27.8 ± 4.5	27.9 ± 4.5	-7.5 ± 0.9	2.4 ± 2.7
	40 min	-2.6 ± 25.9	-28.4 ± 5.6	-30.8 ± 4.5	31.2 ± 4.7	-8.5 ± 1.1	1.7 ± 2.9
	45 min	-9.7 ± 29.2	-29.4 ± 8.3	-32.4 ± 7.8	32.6 ± 8.6	-9.6 ± 2.1	-0.4 ± 2.9
	50 min	-9.8 ± 29.0	-27.3 ± 8.1	-29.9 ± 7.6	29.9 ± 8.5	-8.6 ± 2.2	-0.9 ± 3.4
	55 min	-8.4 ± 30.7	-23.3 ± 6.3	-25.3 ± 5.9	25.1 ± 6.7	-7.1 ± 1.3	-6.1 ± 2.1
	60 min	-15.0 ± 32.6	-19.3 ± 6.4	-21.0 ± 6.0	20.3 ± 6.9	-6.0 ± 1.0	-4.6 ± 2.7

Continued

Table 56. Hemodynamic effects of imipramine in exercise rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 56. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.0 ± 0.5	0.1 ± 0.5	-2.1 ± 2.0	-1.7 ± 2.0	2.4 ± 0.6
	10 min	-2.3 ± 0.4	-3.8 ± 0.6	20.6 ± 10.0	27.1 ± 11.0	9.6 ± 1.3
	15 min	-2.4 ± 1.1	-2.7 ± 1.7	-0.9 ± 12.7	2.5 ± 14.3	-10.3 ± 7.4
	20 min	0.8 ± 2.7	-0.7 ± 3.2	14.1 ± 11.2	5.6 ± 12.1	-39.7 ± 9.6
	25 min	3.3 ± 2.7	2.1 ± 3.2	17.7 ± 11.7	-1.9 ± 10.4	-51.1 ± 6.6
	30 min	4.9 ± 3.2	4.8 ± 3.0	8.8 ± 14.1	-15.9 ± 11.3	-58.8 ± 3.0
	35 min	6.0 ± 3.2	6.1 ± 2.9	8.9 ± 14.6	-17.8 ± 11.0	-59.2 ± 3.1
	40 min	6.7 ± 3.2	6.9 ± 2.9	9.2 ± 16.2	-18.3 ± 12.3	-59.3 ± 2.8
	45 min	7.5 ± 3.7	7.3 ± 3.2	12.8 ± 19.1	-16.3 ± 14.4	-59.1 ± 3.1
	50 min	8.2 ± 4.0	8.0 ± 3.4	14.2 ± 19.8	-15.6 ± 14.8	-58.9 ± 3.5
	55 min	8.1 ± 3.9	8.0 ± 3.3	13.5 ± 20.5	-16.3 ± 15.3	-58.0 ± 3.6
	60 min	8.2 ± 3.9	7.9 ± 3.4	16.1 ± 22.6	-14.8 ± 16.7	-55.6 ± 3.7
Recovery	5 min	6.5 ± 3.0	7.6 ± 2.9	-11.6 ± 5.0	-31.9 ± 4.5	-46.3 ± 3.3
	10 min	4.2 ± 2.5	5.9 ± 2.7	-15.6 ± 11.5	-30.4 ± 12.1	-37.6 ± 4.5
	15 min	3.4 ± 2.2	4.7 ± 2.3	-10.6 ± 12.1	-23.7 ± 12.0	-31.2 ± 3.8
	20 min	3.4 ± 1.9	4.7 ± 2.0	-10.8 ± 13.4	-22.1 ± 12.8	-27.2 ± 3.7
	25 min	3.6 ± 2.0	4.5 ± 2.1	-4.4 ± 15.6	-16.9 ± 13.7	-25.1 ± 4.8
	30 min	2.9 ± 2.4	3.9 ± 2.4	-8.5 ± 14.5	-20.6 ± 12.6	-26.2 ± 4.9
	35 min	3.2 ± 2.5	3.7 ± 2.4	-2.8 ± 13.9	-16.1 ± 12.1	-29.8 ± 4.5
	40 min	3.0 ± 2.7	3.3 ± 2.6	1.8 ± 15.1	-12.6 ± 13.4	-32.7 ± 4.2
	45 min	2.5 ± 2.9	2.8 ± 3.4	4.7 ± 18.5	-11.9 ± 16.1	-34.5 ± 6.4
	50 min	2.3 ± 2.8	2.7 ± 2.9	1.1 ± 17.3	-13.7 ± 15.5	-31.9 ± 6.4
	55 min	3.7 ± 2.0	4.3 ± 2.1	-0.6 ± 18.2	-13.8 ± 16.2	-27.9 ± 5.4
	60 min	3.8 ± 1.7	5.0 ± 1.7	-9.5 ± 15.3	-20.3 ± 13.9	-23.7 ± 5.8

Values are means ± SE; n = 6.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	4.7 ± 0.8	147.9 ± 4.1	6,180 ± 385	-6,334 ± 637	89.0 ± 2.6	8.3 ± 0.8
Imipramine	5 min	5.0 ± 0.8	150.5 ± 3.6	6,303 ± 401	-6,416 ± 666	89.0 ± 2.3	8.3 ± 0.7
	10 min	4.7 ± 0.8	155.4 ± 3.3	6,562 ± 426	-6,630 ± 673	90.1 ± 2.7	8.2 ± 0.8
	15 min	4.6 ± 1.0	132.9 ± 4.4	5,542 ± 327	-5,725 ± 482	87.2 ± 2.8	7.8 ± 0.7
	20 min	5.0 ± 1.2	114.1 ± 8.8	4,521 ± 433	-4,705 ± 578	86.2 ± 1.5	8.0 ± 0.6
	25 min	5.0 ± 1.2	97.2 ± 9.4	3,711 ± 403	-3,813 ± 534	85.6 ± 2.3	8.3 ± 0.8
	30 min	5.1 ± 1.3	94.1 ± 10.1	3,495 ± 389	-3,590 ± 493	84.9 ± 2.6	8.6 ± 0.7
	35 min	4.9 ± 1.5	92.3 ± 10.8	3,416 ± 382	-3,466 ± 475	85.3 ± 3.7	8.6 ± 0.7
	40 min	5.0 ± 1.5	97.3 ± 12.7	3,598 ± 438	-3,678 ± 566	84.9 ± 4.7	8.6 ± 0.7
	45 min	5.3 ± 1.5	103.8 ± 14.5	3,819 ± 510	-3,961 ± 676	84.5 ± 4.9	8.8 ± 0.7
	50 min	5.2 ± 1.5	105.6 ± 14.0	3,906 ± 530	-4,089 ± 729	85.3 ± 5.3	8.8 ± 0.7
	55 min	5.0 ± 1.4	103.6 ± 13.4	3,793 ± 516	-3,995 ± 723	84.1 ± 4.7	8.8 ± 0.7
	60 min	5.5 ± 1.6	101.9 ± 12.8	3,665 ± 529	-3,923 ± 719	77.4 ± 2.3	8.8 ± 0.5
Recovery	5 min	5.5 ± 1.3	108.2 ± 12.3	3,934 ± 538	-4,247 ± 730	78.2 ± 2.8	8.9 ± 0.7
	10 min	5.7 ± 1.6	110.7 ± 9.8	4,069 ± 501	-4,305 ± 695	84.6 ± 3.7	8.8 ± 0.9
	15 min	5.4 ± 1.6	111.3 ± 8.4	4,145 ± 462	-4,403 ± 651	81.8 ± 2.1	8.7 ± 0.9
	20 min	5.4 ± 1.6	111.5 ± 7.9	4,199 ± 450	-4,455 ± 626	83.3 ± 1.7	8.6 ± 0.8
	25 min	5.5 ± 1.7	111.3 ± 8.2	4,224 ± 462	-4,475 ± 635	84.3 ± 1.5	8.3 ± 0.8
	30 min	5.3 ± 1.7	109.9 ± 8.6	4,206 ± 480	-4,429 ± 643	84.4 ± 1.7	8.3 ± 0.8
	35 min	4.9 ± 1.5	110.2 ± 8.6	4,273 ± 482	-4,498 ± 637	85.2 ± 1.7	8.2 ± 0.8
	40 min	4.7 ± 1.3	111.6 ± 8.5	4,332 ± 472	-4,557 ± 642	85.7 ± 1.4	8.1 ± 0.8
	45 min	4.9 ± 1.5	111.4 ± 8.7	4,357 ± 486	-4,544 ± 638	85.8 ± 1.5	8.3 ± 0.8
	50 min	4.7 ± 1.3	113.2 ± 7.8	4,476 ± 471	-4,696 ± 615	86.3 ± 1.7	7.9 ± 0.8
	55 min	4.6 ± 1.4	113.0 ± 8.0	4,479 ± 473	-4,689 ± 623	85.7 ± 2.2	8.0 ± 0.8
	60 min	5.4 ± 1.7	114.0 ± 8.7	4,512 ± 479	-4,706 ± 620	85.8 ± 2.1	7.9 ± 0.7

Continued

Table 57. Hemodynamic effects of imipramine in carvedilol rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 6.

Table 57. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Baseline		20.0 ± 1.0	17.9 ± 1.1	2.1 ± 0.5	805 ± 215	310.5 ± 17.9
Imipramine	5 min	20.2 ± 1.0	18.1 ± 1.1	2.1 ± 0.6	794 ± 220	314.2 ± 17.8
	10 min	20.1 ± 1.0	18.3 ± 1.0	1.9 ± 0.4	746 ± 188	328.1 ± 19.4
	15 min	19.6 ± 1.0	17.8 ± 1.1	1.8 ± 0.4	701 ± 164	285.7 ± 20.4
	20 min	19.8 ± 1.1	18.1 ± 1.2	1.7 ± 0.3	614 ± 116	231.8 ± 25.2
	25 min	19.9 ± 1.3	18.2 ± 1.3	1.7 ± 0.3	574 ± 109	189.0 ± 20.5
	30 min	20.2 ± 1.4	18.5 ± 1.4	1.7 ± 0.3	570 ± 102	175.6 ± 19.4
	35 min	20.4 ± 1.5	18.6 ± 1.5	1.8 ± 0.3	575 ± 111	170.5 ± 18.7
	40 min	20.7 ± 1.4	18.8 ± 1.4	1.8 ± 0.4	608 ± 124	177.5 ± 22.6
	45 min	21.1 ± 1.3	19.1 ± 1.3	2.0 ± 0.4	653 ± 142	183.5 ± 25.5
	50 min	21.4 ± 1.3	19.2 ± 1.2	2.2 ± 0.7	703 ± 206	184.9 ± 24.6
	55 min	21.3 ± 1.4	19.1 ± 1.2	2.2 ± 0.8	719 ± 242	179.9 ± 22.7
	60 min	21.6 ± 1.4	19.2 ± 1.3	2.4 ± 0.8	692 ± 246	171.2 ± 21.9
Recovery	5 min	21.4 ± 1.2	19.2 ± 1.1	2.2 ± 0.7	645 ± 208	185.2 ± 23.3
	10 min	20.9 ± 1.1	19.1 ± 1.1	1.8 ± 0.5	596 ± 162	196.5 ± 23.5
	15 min	20.7 ± 1.1	19.0 ± 1.1	1.7 ± 0.4	566 ± 141	202.3 ± 22.1
	20 min	20.8 ± 1.2	19.1 ± 1.2	1.7 ± 0.4	579 ± 138	203.0 ± 21.0
	25 min	20.8 ± 1.1	19.1 ± 1.1	1.7 ± 0.4	577 ± 130	204.9 ± 21.8
	30 min	20.8 ± 1.1	19.0 ± 1.1	1.8 ± 0.4	590 ± 142	202.6 ± 20.9
	35 min	20.9 ± 1.1	19.0 ± 1.1	1.9 ± 0.5	629 ± 166	204.9 ± 20.4
	40 min	20.9 ± 1.0	19.0 ± 1.1	1.9 ± 0.5	653 ± 166	206.5 ± 18.6
	45 min	21.0 ± 1.1	19.0 ± 1.1	1.9 ± 0.5	663 ± 164	206.8 ± 18.8
	50 min	21.1 ± 1.0	19.1 ± 1.1	2.0 ± 0.5	693 ± 174	211.3 ± 18.1
	55 min	21.0 ± 1.0	19.0 ± 1.1	2.1 ± 0.5	715 ± 174	212.0 ± 18.3
	60 min	21.0 ± 1.0	19.0 ± 1.1	2.0 ± 0.5	706 ± 168	214.1 ± 19.2

Values are means ± SE; n = 6.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	8.6 ± 5.7	1.8 ± 0.8	2.0 ± 1.2	-1.2 ± 0.6	0.0 ± 0.8	-0.2 ± 0.7
	10 min	1.2 ± 5.2	5.2 ± 1.8	6.2 ± 2.1	-4.7 ± 1.4	1.2 ± 1.3	-2.4 ± 2.4
	15 min	-5.5 ± 9.1	-10.0 ± 2.5	-10.2 ± 1.3	8.9 ± 2.5	-2.1 ± 0.4	-6.2 ± 2.6
	20 min	4.1 ± 10.7	-22.9 ± 5.5	-26.7 ± 5.6	25.4 ± 6.2	-2.7 ± 3.4	-3.5 ± 2.3
	25 min	3.3 ± 11.8	-34.3 ± 5.9	-39.6 ± 5.9	39.4 ± 6.6	-3.1 ± 5.2	0.3 ± 3.5
	30 min	5.8 ± 12.5	-36.4 ± 6.4	-42.9 ± 6.3	42.5 ± 7.2	-3.8 ± 5.7	4.3 ± 5.2
	35 min	-3.3 ± 16.4	-37.7 ± 6.8	-44.1 ± 6.5	44.2 ± 7.5	-3.2 ± 7.3	3.6 ± 5.0
	40 min	-1.6 ± 17.0	-34.4 ± 8.2	-41.2 ± 7.3	41.1 ± 8.7	-3.5 ± 8.6	3.6 ± 5.0
	45 min	7.0 ± 12.4	-30.0 ± 9.5	-37.8 ± 8.2	37.1 ± 9.9	-3.9 ± 8.8	6.8 ± 5.8
	50 min	3.5 ± 10.9	-28.8 ± 9.1	-36.6 ± 7.9	35.6 ± 9.4	-2.9 ± 9.5	6.7 ± 5.6
	55 min	0.3 ± 15.6	-30.1 ± 8.5	-38.6 ± 7.2	37.4 ± 8.6	-4.3 ± 8.7	7.1 ± 5.9
	60 min	10.5 ± 15.9	-31.3 ± 8.0	-41.0 ± 6.8	38.7 ± 7.9	-13.0 ± 2.1	7.0 ± 5.7
Recovery	5 min	16.0 ± 14.3	-26.9 ± 7.7	-36.5 ± 6.9	33.3 ± 8.0	-12.1 ± 2.0	7.8 ± 5.4
	10 min	22.1 ± 32.1	-25.1 ± 6.2	-34.2 ± 6.3	32.4 ± 7.2	-4.0 ± 7.2	6.2 ± 4.3
	15 min	12.2 ± 23.4	-24.7 ± 5.4	-33.0 ± 5.5	30.9 ± 6.0	-7.9 ± 2.4	4.1 ± 4.2
	20 min	16.6 ± 33.1	-24.6 ± 5.0	-32.1 ± 5.4	29.9 ± 5.7	-6.1 ± 2.6	2.9 ± 4.3
	25 min	18.3 ± 39.5	-24.7 ± 5.2	-31.7 ± 5.6	29.6 ± 5.9	-5.0 ± 3.1	0.6 ± 4.9
	30 min	11.5 ± 35.1	-25.7 ± 5.5	-32.0 ± 5.9	30.4 ± 6.1	-4.9 ± 2.7	0.6 ± 4.9
	35 min	3.7 ± 29.8	-25.5 ± 5.3	-31.0 ± 5.8	29.3 ± 5.8	-4.0 ± 2.8	-1.8 ± 4.1
	40 min	-0.7 ± 24.4	-24.7 ± 5.1	-30.2 ± 5.4	28.6 ± 5.4	-3.4 ± 2.9	-2.6 ± 3.5
	45 min	1.6 ± 25.6	-24.8 ± 5.2	-29.8 ± 5.5	28.8 ± 5.1	-3.3 ± 2.4	-0.2 ± 5.4
	50 min	-1.4 ± 25.0	-23.6 ± 4.5	-28.0 ± 4.8	26.3 ± 4.6	-2.8 ± 2.0	-4.6 ± 2.5
	55 min	-3.9 ± 26.2	-23.7 ± 4.7	-27.9 ± 5.0	26.4 ± 4.8	-3.6 ± 1.8	-4.2 ± 2.6
	60 min	9.2 ± 29.1	-23.1 ± 5.0	-27.4 ± 5.2	26.1 ± 5.0	-3.4 ± 1.7	-4.9 ± 2.5

Continued

Table 58. Hemodynamic effects of imipramine in carvedilol rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 58. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.8 ± 0.5	1.2 ± 0.5	-2.7 ± 2.4	-1.9 ± 2.4	1.2 ± 1.2
	10 min	0.5 ± 0.6	2.1 ± 1.3	-9.8 ± 4.3	-6.0 ± 4.4	5.6 ± 1.7
	15 min	-2.0 ± 1.3	-0.8 ± 0.7	-12.2 ± 6.4	-11.3 ± 6.0	-8.3 ± 1.4
	20 min	-1.3 ± 1.7	0.7 ± 0.7	-13.6 ± 7.1	-17.3 ± 6.8	-25.7 ± 5.6
	25 min	-0.8 ± 2.5	1.2 ± 1.9	-10.3 ± 7.1	-19.9 ± 7.0	-38.9 ± 6.0
	30 min	0.9 ± 3.2	2.8 ± 2.8	-5.9 ± 9.3	-18.3 ± 9.2	-43.1 ± 6.1
	35 min	1.6 ± 3.7	3.5 ± 3.2	-7.8 ± 7.5	-20.2 ± 7.2	-44.6 ± 6.1
	40 min	2.9 ± 3.2	4.5 ± 3.2	-4.9 ± 6.1	-17.2 ± 6.4	-42.5 ± 7.1
	45 min	5.3 ± 2.2	6.7 ± 2.6	1.5 ± 6.7	-10.9 ± 7.9	-40.5 ± 8.0
	50 min	6.6 ± 2.2	7.1 ± 2.9	3.8 ± 7.4	-9.1 ± 8.1	-39.9 ± 8.0
	55 min	6.2 ± 2.8	6.4 ± 3.1	1.5 ± 9.4	-12.1 ± 7.7	-41.5 ± 7.5
	60 min	7.4 ± 2.8	6.9 ± 3.0	10.1 ± 13.9	-17.1 ± 9.0	-44.5 ± 6.9
Recovery	5 min	6.8 ± 2.2	7.3 ± 2.3	3.3 ± 10.1	-20.6 ± 8.2	-40.1 ± 7.0
	10 min	4.4 ± 2.1	6.5 ± 2.5	-11.6 ± 7.0	-24.0 ± 6.5	-36.6 ± 6.6
	15 min	3.3 ± 2.2	5.9 ± 2.3	-15.4 ± 4.1	-27.0 ± 3.8	-34.7 ± 6.1
	20 min	4.1 ± 1.9	6.6 ± 1.9	-13.7 ± 3.1	-24.8 ± 3.0	-34.4 ± 5.9
	25 min	3.8 ± 1.8	6.4 ± 1.5	-13.9 ± 4.3	-23.7 ± 4.0	-33.8 ± 6.0
	30 min	4.0 ± 1.2	6.3 ± 1.2	-13.2 ± 3.2	-23.2 ± 3.0	-34.4 ± 6.1
	35 min	4.2 ± 1.0	6.0 ± 1.2	-10.2 ± 2.4	-20.4 ± 2.0	-33.6 ± 5.9
	40 min	4.6 ± 0.6	6.1 ± 0.6	-7.4 ± 2.4	-17.2 ± 1.7	-33.1 ± 5.4
	45 min	4.9 ± 0.7	6.3 ± 0.5	-3.7 ± 4.5	-13.2 ± 4.8	-33.1 ± 5.2
	50 min	5.5 ± 0.8	6.7 ± 0.7	-1.4 ± 3.3	-10.5 ± 3.8	-31.7 ± 4.7
	55 min	5.3 ± 1.1	6.1 ± 1.1	2.1 ± 4.0	-7.0 ± 4.3	-31.5 ± 4.8
	60 min	5.1 ± 1.4	6.0 ± 1.2	-0.2 ± 3.4	-8.8 ± 3.0	-30.8 ± 5.1

Values are means ± SE; n = 6.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	2.8 ± 0.5	171.5 ± 7.4	7,471 ± 622	-6,316 ± 287	96.0 ± 3.5	9.3 ± 0.8
Imipramine	5 min	2.9 ± 0.6	172.5 ± 8.4	7,534 ± 696	-6,158 ± 216	96.4 ± 4.0	9.3 ± 0.8
	10 min	1.7 ± 0.6	154.2 ± 7.0	7,497 ± 870	-6,961 ± 719	99.8 ± 5.7	7.8 ± 0.5
	15 min	1.9 ± 0.4	119.6 ± 10.2	5,691 ± 847	-5,545 ± 928	91.6 ± 5.6	7.4 ± 0.4
	20 min	2.5 ± 0.3	98.2 ± 9.0	4,024 ± 483	-4,086 ± 620	83.6 ± 2.3	8.0 ± 0.4
	25 min	2.7 ± 0.3	89.3 ± 9.5	3,437 ± 446	-3,511 ± 571	84.1 ± 3.6	8.2 ± 0.3
	30 min	3.0 ± 0.4	87.4 ± 8.5	3,280 ± 382	-3,360 ± 499	84.4 ± 4.7	8.4 ± 0.3
	35 min	3.0 ± 0.4	87.9 ± 8.5	3,262 ± 357	-3,354 ± 458	84.0 ± 4.8	8.5 ± 0.5
	40 min	3.3 ± 0.6	90.6 ± 8.7	3,411 ± 410	-3,427 ± 447	84.6 ± 3.4	8.4 ± 0.3
	45 min	3.3 ± 0.5	91.2 ± 9.3	3,394 ± 397	-3,387 ± 414	84.4 ± 4.2	8.5 ± 0.3
	50 min	3.1 ± 0.5	90.0 ± 9.0	3,327 ± 348	-3,294 ± 353	85.2 ± 4.9	8.5 ± 0.3
	55 min	3.3 ± 0.5	89.6 ± 8.3	3,286 ± 314	-3,242 ± 316	85.1 ± 4.8	8.4 ± 0.3
	60 min	3.8 ± 0.7	89.1 ± 8.1	3,248 ± 289	-3,201 ± 305	84.8 ± 4.4	8.4 ± 0.4
Recovery	5 min	5.1 ± 1.2	95.6 ± 9.5	3,511 ± 326	-3,427 ± 335	84.0 ± 2.7	8.8 ± 0.5
	10 min	4.9 ± 1.1	101.1 ± 9.3	3,873 ± 389	-3,795 ± 401	84.3 ± 2.0	8.7 ± 0.4
	15 min	4.6 ± 1.4	100.5 ± 10.4	3,891 ± 437	-3,747 ± 418	88.3 ± 4.4	8.5 ± 0.4
	20 min	4.7 ± 1.5	104.0 ± 9.0	4,079 ± 403	-3,981 ± 407	86.2 ± 2.2	8.4 ± 0.4
	25 min	4.9 ± 1.6	104.9 ± 8.6	4,160 ± 409	-4,067 ± 436	87.2 ± 2.5	8.3 ± 0.4
	30 min	5.0 ± 1.7	105.0 ± 7.8	4,189 ± 401	-4,069 ± 409	87.5 ± 2.6	8.4 ± 0.4
	35 min	5.2 ± 1.8	106.3 ± 7.4	4,258 ± 408	-4,124 ± 397	87.9 ± 2.7	8.3 ± 0.5
	40 min	5.1 ± 1.7	107.0 ± 6.6	4,311 ± 400	-4,170 ± 367	88.4 ± 2.9	8.1 ± 0.5
	45 min	5.5 ± 1.8	109.5 ± 6.4	4,414 ± 414	-4,258 ± 354	88.4 ± 2.9	8.1 ± 0.5
	50 min	5.7 ± 1.6	109.7 ± 6.3	4,446 ± 454	-4,263 ± 363	88.7 ± 3.2	8.2 ± 0.7
	55 min	5.7 ± 1.5	109.3 ± 5.1	4,427 ± 395	-4,291 ± 354	88.6 ± 3.0	7.9 ± 0.6
	60 min	6.2 ± 1.5	110.7 ± 4.9	4,512 ± 412	-4,389 ± 385	89.1 ± 3.2	7.8 ± 0.6

Continued

Table 59. Hemodynamic effects of imipramine in clenbuterol rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 6.

Table 59. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Baseline		22.1 ± 1.5	21.0 ± 1.4	1.0 ± 0.2	407 ± 91	353.5 ± 50.5
Imipramine	5 min	22.1 ± 1.5	21.1 ± 1.4	1.1 ± 0.2	441 ± 92	354.9 ± 52.3
	10 min	21.8 ± 1.4	20.8 ± 1.4	1.0 ± 0.2	438 ± 74	359.0 ± 57.6
	15 min	22.3 ± 1.6	20.7 ± 1.4	1.6 ± 0.4	569 ± 132	270.9 ± 52.6
	20 min	23.1 ± 1.7	21.2 ± 1.4	1.8 ± 0.5	605 ± 141	187.9 ± 39.3
	25 min	23.8 ± 1.8	21.9 ± 1.5	1.9 ± 0.5	588 ± 162	157.7 ± 36.7
	30 min	24.1 ± 1.9	22.2 ± 1.5	1.8 ± 0.5	565 ± 145	148.4 ± 32.9
	35 min	24.3 ± 1.9	22.4 ± 1.6	1.9 ± 0.5	565 ± 146	145.3 ± 29.5
	40 min	24.5 ± 1.9	22.6 ± 1.6	1.9 ± 0.5	584 ± 141	151.5 ± 32.8
	45 min	24.6 ± 2.0	22.7 ± 1.7	1.9 ± 0.5	570 ± 140	150.0 ± 30.8
	50 min	24.5 ± 2.0	22.7 ± 1.7	1.9 ± 0.5	583 ± 163	145.2 ± 25.6
	55 min	24.6 ± 2.0	22.6 ± 1.7	2.0 ± 0.6	626 ± 178	142.1 ± 23.3
	60 min	24.7 ± 2.0	22.8 ± 1.6	1.9 ± 0.5	593 ± 168	138.9 ± 21.3
Recovery	5 min	24.7 ± 1.8	22.7 ± 1.5	2.0 ± 0.5	597 ± 167	149.3 ± 21.9
	10 min	24.5 ± 1.7	22.6 ± 1.5	1.9 ± 0.5	592 ± 142	166.6 ± 26.6
	15 min	24.3 ± 1.7	22.5 ± 1.4	1.9 ± 0.5	602 ± 141	168.4 ± 28.7
	20 min	24.4 ± 1.7	22.4 ± 1.4	1.9 ± 0.5	614 ± 147	175.9 ± 27.7
	25 min	24.4 ± 1.6	22.5 ± 1.3	1.9 ± 0.5	612 ± 152	178.8 ± 28.0
	30 min	24.3 ± 1.6	22.4 ± 1.3	1.9 ± 0.5	605 ± 140	181.2 ± 29.7
	35 min	24.3 ± 1.6	22.4 ± 1.3	1.9 ± 0.5	617 ± 147	184.6 ± 31.6
	40 min	24.3 ± 1.5	22.4 ± 1.3	2.0 ± 0.5	633 ± 144	187.1 ± 32.2
	45 min	24.3 ± 1.5	22.4 ± 1.3	2.0 ± 0.5	640 ± 145	191.4 ± 33.0
	50 min	24.4 ± 1.4	22.4 ± 1.2	2.0 ± 0.4	656 ± 129	191.3 ± 33.5
	55 min	24.4 ± 1.4	22.3 ± 1.1	2.1 ± 0.5	673 ± 153	189.9 ± 30.1
	60 min	24.4 ± 1.4	22.3 ± 1.1	2.1 ± 0.5	676 ± 146	192.5 ± 29.4

Values are means ± SE; n = 6.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.4 ± 9.8	0.5 ± 1.4	0.5 ± 0.9	2.3 ± 1.3	0.3 ± 0.5	0.3 ± 0.3
	10 min	-49.9 ± 12.1	-10.0 ± 2.3	-0.7 ± 3.7	-9.4 ± 7.9	3.6 ± 2.0	-14.9 ± 3.4
	15 min	-28.2 ± 9.5	-30.5 ± 4.4	-25.6 ± 6.0	13.3 ± 12.5	-4.9 ± 2.5	-18.8 ± 5.5
	20 min	13.8 ± 38.3	-43.2 ± 3.2	-46.4 ± 4.1	35.3 ± 9.7	-12.7 ± 1.8	-11.4 ± 7.3
	25 min	20.4 ± 37.0	-48.5 ± 3.6	-54.2 ± 4.2	44.3 ± 9.2	-12.4 ± 1.5	-9.3 ± 6.3
	30 min	41.5 ± 53.2	-49.5 ± 3.1	-56.1 ± 3.5	46.7 ± 8.0	-12.3 ± 2.0	-7.9 ± 6.2
	35 min	41.5 ± 53.2	-49.2 ± 3.1	-56.3 ± 3.6	46.9 ± 7.2	-12.8 ± 2.1	-6.7 ± 7.4
	40 min	48.2 ± 51.5	-47.6 ± 3.2	-54.3 ± 4.2	45.7 ± 7.1	-11.9 ± 1.3	-7.9 ± 6.2
	45 min	50.8 ± 51.7	-47.3 ± 3.7	-54.2 ± 4.6	46.2 ± 6.7	-12.2 ± 1.5	-6.6 ± 5.5
	50 min	46.5 ± 52.8	-47.7 ± 3.9	-54.7 ± 4.7	47.6 ± 5.7	-11.5 ± 2.1	-6.6 ± 5.5
	55 min	49.6 ± 52.0	-47.9 ± 3.7	-55.2 ± 4.4	48.4 ± 5.1	-11.6 ± 2.3	-7.1 ± 5.6
	60 min	69.9 ± 54.8	-48.1 ± 3.7	-55.7 ± 4.1	49.2 ± 4.8	-11.8 ± 2.3	-7.2 ± 6.7
Recovery	5 min	109.7 ± 56.3	-44.4 ± 4.4	-52.3 ± 4.3	45.7 ± 4.9	-12.3 ± 2.6	-3.8 ± 5.8
	10 min	98.9 ± 54.1	-41.3 ± 3.9	-47.8 ± 4.4	40.0 ± 5.8	-11.9 ± 2.1	-5.2 ± 4.7
	15 min	91.7 ± 64.7	-41.6 ± 4.9	-47.1 ± 5.9	40.3 ± 7.0	-8.1 ± 1.7	-6.8 ± 5.3
	20 min	92.7 ± 65.0	-39.5 ± 4.0	-44.9 ± 4.8	37.0 ± 6.2	-10.0 ± 1.9	-7.4 ± 5.5
	25 min	96.0 ± 65.3	-39.1 ± 3.7	-44.0 ± 4.4	35.8 ± 6.2	-9.0 ± 1.7	-8.4 ± 6.0
	30 min	98.2 ± 66.8	-39.0 ± 3.1	-43.7 ± 4.0	35.7 ± 5.8	-8.6 ± 1.9	-8.3 ± 5.7
	35 min	103.4 ± 68.5	-38.2 ± 2.8	-42.8 ± 3.8	34.8 ± 5.7	-8.3 ± 1.8	-9.6 ± 5.8
	40 min	103.2 ± 66.0	-37.7 ± 2.4	-42.0 ± 3.7	33.9 ± 5.3	-7.7 ± 1.9	-12.1 ± 5.4
	45 min	115.0 ± 64.9	-36.2 ± 2.2	-40.6 ± 3.9	32.5 ± 5.2	-7.7 ± 2.0	-11.8 ± 5.5
	50 min	125.1 ± 58.5	-36.1 ± 2.0	-40.4 ± 3.8	32.5 ± 5.1	-7.5 ± 2.3	-11.1 ± 5.4
	55 min	130.8 ± 57.9	-36.2 ± 1.7	-40.6 ± 3.0	32.1 ± 4.7	-7.7 ± 1.6	-14.3 ± 5.5
	60 min	150.6 ± 59.2	-35.4 ± 1.4	-39.6 ± 2.8	30.7 ± 4.9	-7.0 ± 2.2	-14.9 ± 5.8

Continued

Table 60. Hemodynamic effects of imipramine in clenbuterol rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 60. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.5 ± 0.2	0.1 ± 0.1	10.9 ± 5.3	11.8 ± 5.5	0.0 ± 0.8
	10 min	-1.0 ± 0.4	-1.4 ± 0.6	18.4 ± 20.3	20.4 ± 19.2	0.3 ± 3.6
	15 min	1.1 ± 1.7	-1.3 ± 1.6	57.2 ± 27.1	42.5 ± 21.9	-26.1 ± 6.2
	20 min	4.6 ± 2.8	1.0 ± 2.4	81.9 ± 31.1	51.6 ± 25.2	-48.4 ± 4.7
	25 min	7.8 ± 4.0	4.3 ± 3.0	76.1 ± 30.6	37.7 ± 24.5	-56.9 ± 4.8
	30 min	9.0 ± 4.1	5.7 ± 3.4	79.0 ± 28.1	36.7 ± 21.9	-59.1 ± 4.3
	35 min	10.0 ± 4.4	6.7 ± 3.7	82.0 ± 29.3	37.2 ± 22.2	-59.5 ± 4.4
	40 min	11.0 ± 4.4	7.3 ± 3.6	98.2 ± 37.3	50.0 ± 28.4	-58.0 ± 5.1
	45 min	11.2 ± 4.7	7.8 ± 3.8	89.6 ± 31.0	42.7 ± 23.1	-57.9 ± 5.6
	50 min	11.1 ± 4.9	7.7 ± 3.8	82.3 ± 32.1	37.4 ± 25.0	-58.3 ± 5.9
	55 min	11.5 ± 5.0	7.3 ± 3.7	97.3 ± 35.8	47.6 ± 28.1	-58.7 ± 5.8
	60 min	12.1 ± 4.9	8.4 ± 3.7	92.4 ± 35.7	41.1 ± 27.0	-59.5 ± 5.4
Recovery	5 min	12.0 ± 4.3	8.1 ± 3.1	96.1 ± 36.0	43.7 ± 26.8	-56.5 ± 5.6
	10 min	11.2 ± 3.6	7.5 ± 2.6	96.9 ± 33.6	50.8 ± 24.5	-52.2 ± 5.7
	15 min	10.6 ± 3.4	7.0 ± 2.4	89.6 ± 25.7	49.4 ± 17.8	-51.3 ± 6.7
	20 min	10.7 ± 3.5	6.9 ± 2.6	97.9 ± 30.1	55.8 ± 22.3	-49.4 ± 6.0
	25 min	10.9 ± 3.3	7.3 ± 2.5	91.1 ± 28.9	53.2 ± 22.8	-48.8 ± 5.6
	30 min	10.7 ± 3.4	7.1 ± 2.5	90.6 ± 29.6	52.4 ± 22.6	-48.4 ± 5.2
	35 min	10.8 ± 3.4	7.0 ± 2.4	90.2 ± 29.0	52.2 ± 22.0	-47.7 ± 4.9
	40 min	10.7 ± 3.1	6.7 ± 2.1	97.6 ± 30.3	59.8 ± 23.4	-47.0 ± 4.6
	45 min	10.8 ± 3.1	6.7 ± 2.1	98.5 ± 29.0	60.5 ± 22.2	-45.8 ± 4.7
	50 min	11.4 ± 3.4	7.0 ± 2.4	115.5 ± 38.7	75.6 ± 32.3	-46.1 ± 4.0
	55 min	11.3 ± 3.4	6.5 ± 2.4	113.2 ± 35.9	71.6 ± 29.0	-46.1 ± 3.8
	60 min	11.5 ± 3.2	6.7 ± 2.3	115.9 ± 34.6	73.0 ± 27.3	-45.4 ± 3.5

Values are means ± SE; n = 6.

	Time	LVEDP (mmHg)	LVESP (mmHg)	+dP/d*t* (mmHg/s)	-dP/d*t* (mmHg/s)	CI (s^{-1})	tau (ms)
	Baseline	5.5 ± 1.6	141.0 ± 5.7	5,286 ± 317	-5,237 ± 344	83.2 ± 2.4	7.8 ± 0.4
Imipramine	5 min	5.3 ± 1.5	141.5 ± 6.6	5,314 ± 319	-5,259 ± 339	83.4 ± 2.2	8.0 ± 0.4
	10 min	5.1 ± 1.4	142.3 ± 4.9	5,600 ± 308	-5,563 ± 342	86.3 ± 2.5	7.1 ± 0.3
	15 min	5.0 ± 1.5	108.5 ± 4.8	4,070 ± 306	-4,012 ± 322	82.1 ± 2.9	7.5 ± 0.5
	20 min	4.8 ± 1.4	80.2 ± 7.8	2,825 ± 367	-2,661 ± 418	79.9 ± 2.3	8.2 ± 0.5
	25 min	5.3 ± 1.3	74.3 ± 6.4	2,520 ± 271	-2,354 ± 336	80.1 ± 2.0	8.6 ± 0.5
	30 min	5.3 ± 1.3	71.4 ± 4.8	2,372 ± 178	-2,198 ± 234	79.5 ± 1.8	8.8 ± 0.4
	35 min	5.2 ± 1.3	69.9 ± 4.3	2,292 ± 136	-2,102 ± 175	78.5 ± 1.9	8.9 ± 0.4
	40 min	5.0 ± 1.3	72.9 ± 7.3	2,402 ± 239	-2,239 ± 301	77.5 ± 1.8	9.0 ± 0.5
	45 min	4.9 ± 1.3	74.0 ± 7.7	2,451 ± 268	-2,303 ± 340	77.5 ± 1.9	9.0 ± 0.5
	50 min	5.0 ± 1.3	74.8 ± 7.7	2,465 ± 278	-2,336 ± 355	76.9 ± 1.9	8.9 ± 0.5
	55 min	4.9 ± 1.1	79.2 ± 8.9	2,641 ± 330	-2,536 ± 421	76.5 ± 1.9	8.9 ± 0.5
	60 min	4.9 ± 1.1	81.0 ± 9.8	2,718 ± 380	-2,623 ± 476	76.8 ± 2.3	8.8 ± 0.5
Recovery	5 min	4.8 ± 1.1	90.3 ± 11.0	3,065 ± 441	-3,002 ± 546	77.1 ± 2.4	8.6 ± 0.6
	10 min	4.5 ± 1.2	97.4 ± 9.0	3,354 ± 396	-3,349 ± 482	78.7 ± 3.0	8.3 ± 0.6
	15 min	4.0 ± 1.1	99.9 ± 7.6	3,485 ± 342	-3,492 ± 416	80.0 ± 3.1	8.0 ± 0.5
	20 min	3.8 ± 1.1	103.4 ± 6.8	3,667 ± 316	-3,681 ± 384	81.4 ± 2.8	7.8 ± 0.5
	25 min	3.9 ± 1.1	106.7 ± 6.5	3,835 ± 319	-3,849 ± 382	82.4 ± 2.7	7.7 ± 0.4
	30 min	3.7 ± 1.0	109.7 ± 6.6	3,985 ± 329	-4,008 ± 386	83.0 ± 2.6	7.4 ± 0.5
	35 min	3.8 ± 1.0	112.1 ± 6.4	4,110 ± 342	-4,140 ± 390	83.5 ± 2.5	7.4 ± 0.5
	40 min	3.5 ± 0.9	113.1 ± 5.9	4,157 ± 337	-4,192 ± 376	83.6 ± 2.4	7.3 ± 0.6
	45 min	3.6 ± 0.9	112.4 ± 5.7	4,141 ± 333	-4,171 ± 369	83.6 ± 2.4	7.3 ± 0.6
	50 min	3.5 ± 0.9	114.1 ± 6.1	4,225 ± 361	-4,271 ± 398	83.7 ± 2.4	7.3 ± 0.6
	55 min	3.7 ± 1.1	116.2 ± 6.2	4,337 ± 376	-4,397 ± 414	84.4 ± 2.4	7.3 ± 0.6
	60 min	3.4 ± 1.2	117.6 ± 6.2	4,418 ± 395	-4,479 ± 426	84.5 ± 2.4	7.3 ± 0.6

Continued

Table 61. Hemodynamic effects of imipramine in dobutamine rats measured by the Millar pressure-volume conductance catheter system at LV chamber. Values are means ± SE; n = 6.

Table 61. Continued.

	Time	LVEDV (RVU)	LVESV (RVU)	SV (RVU)	CO (RVU /min)	(+dP/d*t*)/EDV (mmHg/s* RVU)
Baseline		19.8 ± 1.6	18.5 ± 1.4	1.3 ± 0.3	509 ± 122	278.3 ± 32.5
Imipramine	5 min	19.8 ± 1.6	18.5 ± 1.4	1.2 ± 0.3	495 ± 114	278.5 ± 29.3
	10 min	19.5 ± 1.5	18.3 ± 1.3	1.2 ± 0.3	516 ± 128	297.7 ± 32.0
	15 min	19.7 ± 1.5	18.3 ± 1.3	1.5 ± 0.4	579 ± 157	214.9 ± 26.1
	20 min	20.2 ± 1.7	18.7 ± 1.5	1.5 ± 0.4	544 ± 128	144.2 ± 19.7
	25 min	20.9 ± 1.8	19.4 ± 1.6	1.6 ± 0.4	516 ± 123	125.4 ± 16.8
	30 min	21.4 ± 1.9	19.8 ± 1.6	1.6 ± 0.4	495 ± 117	116.7 ± 16.1
	35 min	21.6 ± 1.9	20.1 ± 1.7	1.5 ± 0.4	454 ± 111	112.1 ± 14.9
	40 min	21.7 ± 1.9	20.2 ± 1.7	1.5 ± 0.4	463 ± 111	116.0 ± 16.0
	45 min	21.7 ± 1.9	20.3 ± 1.7	1.3 ± 0.3	423 ± 81	118.6 ± 17.0
	50 min	21.7 ± 1.9	20.2 ± 1.7	1.5 ± 0.3	446 ± 96	119.1 ± 17.1
	55 min	21.6 ± 1.9	20.3 ± 1.7	1.3 ± 0.3	401 ± 71	126.8 ± 17.2
	60 min	21.5 ± 1.8	20.0 ± 1.6	1.5 ± 0.4	456 ± 100	130.8 ± 18.5
Recovery	5 min	21.1 ± 1.8	19.7 ± 1.6	1.4 ± 0.4	462 ± 104	150.9 ± 23.6
	10 min	20.8 ± 1.7	19.5 ± 1.5	1.4 ± 0.3	450 ± 94	169.3 ± 26.3
	15 min	20.6 ± 1.6	19.2 ± 1.4	1.4 ± 0.3	474 ± 94	178.2 ± 26.9
	20 min	20.5 ± 1.5	19.1 ± 1.3	1.4 ± 0.3	479 ± 91	186.4 ± 24.8
	25 min	20.5 ± 1.4	19.1 ± 1.2	1.4 ± 0.3	483 ± 97	194.3 ± 23.8
	30 min	20.3 ± 1.3	18.9 ± 1.1	1.4 ± 0.4	508 ± 103	202.3 ± 23.1
	35 min	20.3 ± 1.3	18.9 ± 1.1	1.4 ± 0.3	497 ± 103	208.8 ± 24.3
	40 min	20.4 ± 1.2	19.0 ± 1.0	1.4 ± 0.4	503 ± 105	209.7 ± 23.6
	45 min	20.4 ± 1.2	19.0 ± 1.0	1.4 ± 0.4	515 ± 111	207.8 ± 21.6
	50 min	20.3 ± 1.2	19.0 ± 0.9	1.4 ± 0.4	502 ± 109	212.0 ± 21.9
	55 min	20.3 ± 1.1	18.9 ± 0.9	1.5 ± 0.4	536 ± 116	217.8 ± 23.5
	60 min	20.3 ± 1.1	18.9 ± 0.8	1.4 ± 0.4	527 ± 118	222.2 ± 24.7

Values are means ± SE; n = 6.

	Time	LVEDP (%)	LVESP (%)	+dP/d*t* (%)	-dP/d*t* (%)	CI (%)	tau (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	9.6 ± 14.9	0.3 ± 1.3	0.6 ± 1.6	-0.5 ± 1.5	0.2 ± 0.5	2.3 ± 1.9
	10 min	-0.9 ± 11.6	1.1 ± 1.6	6.1 ± 1.5	-6.4 ± 1.8	3.7 ± 1.0	-9.1 ± 2.0
	15 min	3.0 ± 17.6	-22.5 ± 3.9	-22.3 ± 5.4	22.7 ± 5.5	-1.4 ± 2.2	-4.3 ± 3.8
	20 min	3.3 ± 20.3	-42.4 ± 6.3	-45.5 ± 7.2	48.2 ± 7.9	-3.9 ± 1.9	5.4 ± 6.9
	25 min	32.8 ± 35.4	-46.8 ± 4.9	-51.6 ± 5.2	54.5 ± 5.9	-3.6 ± 1.7	10.0 ± 4.9
	30 min	32.4 ± 35.6	-48.9 ± 4.0	-54.4 ± 3.8	57.4 ± 4.3	-4.3 ± 1.9	13.1 ± 3.1
	35 min	31.7 ± 35.8	-49.9 ± 3.8	-55.8 ± 3.6	59.1 ± 3.7	-5.5 ± 2.3	13.5 ± 3.4
	40 min	34.0 ± 39.8	-47.7 ± 5.7	-53.6 ± 5.3	56.4 ± 6.0	-6.7 ± 2.2	15.7 ± 5.7
	45 min	34.3 ± 40.8	-46.9 ± 5.9	-52.7 ± 5.8	55.2 ± 6.7	-6.7 ± 2.3	15.3 ± 5.5
	50 min	40.3 ± 44.1	-46.4 ± 5.9	-52.4 ± 5.9	54.6 ± 6.9	-7.4 ± 2.4	14.6 ± 5.8
	55 min	42.8 ± 43.8	-43.4 ± 6.4	-49.3 ± 6.4	51.0 ± 7.7	-7.9 ± 2.1	13.9 ± 5.3
	60 min	46.6 ± 49.4	-42.2 ± 6.9	-47.9 ± 7.1	49.4 ± 8.5	-7.6 ± 2.2	12.0 ± 5.4
Recovery	5 min	45.7 ± 49.7	-35.5 ± 7.8	-41.3 ± 8.2	42.2 ± 9.8	-7.2 ± 2.1	9.8 ± 5.5
	10 min	23.9 ± 38.5	-30.4 ± 6.5	-36.1 ± 7.1	35.8 ± 8.2	-5.4 ± 2.4	6.2 ± 3.9
	15 min	13.8 ± 37.1	-28.6 ± 5.9	-33.5 ± 6.2	32.9 ± 7.1	-3.9 ± 2.2	2.3 ± 3.4
	20 min	9.8 ± 38.1	-26.1 ± 5.3	-30.2 ± 5.5	29.5 ± 6.2	-2.3 ± 1.7	-1.2 ± 2.2
	25 min	25.3 ± 48.7	-24.0 ± 4.7	-27.3 ± 4.6	26.6 ± 5.3	-1.0 ± 1.3	-2.2 ± 1.7
	30 min	23.7 ± 49.0	-21.8 ± 4.7	-24.5 ± 4.5	23.6 ± 5.2	-0.3 ± 1.1	-5.7 ± 2.8
	35 min	39.8 ± 62.2	-20.1 ± 4.4	-22.3 ± 4.2	21.1 ± 4.8	0.3 ± 1.2	-6.5 ± 3.0
	40 min	20.4 ± 49.8	-19.5 ± 3.9	-21.4 ± 3.8	20.1 ± 4.2	0.5 ± 1.2	-6.9 ± 3.2
	45 min	35.1 ± 63.5	-20.1 ± 3.4	-21.8 ± 3.4	20.6 ± 3.8	0.4 ± 1.0	-6.9 ± 3.2
	50 min	35.0 ± 63.6	-19.0 ± 3.3	-20.3 ± 3.7	18.8 ± 4.1	0.6 ± 0.7	-6.9 ± 3.2
	55 min	58.2 ± 81.1	-17.5 ± 3.3	-18.3 ± 3.8	16.5 ± 4.0	1.5 ± 1.0	-6.9 ± 3.2
	60 min	51.5 ± 83.3	-16.5 ± 3.2	-16.8 ± 4.0	15.0 ± 4.0	1.5 ± 0.8	-6.9 ± 3.2

Continued

Table 62. Hemodynamic effects of imipramine in dobutamine rats measured by the Millar pressure-volume conductance catheter system at LV chamber as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 62. Continued.

	Time	LVEDV (%)	LVESV (%)	SV (%)	CO (%)	(+dP/d*t*)/EDV (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.1 ± 0.3	0.1 ± 0.4	1.2 ± 4.3	1.4 ± 4.4	0.6 ± 1.5
	10 min	-1.3 ± 0.6	-1.2 ± 1.2	5.2 ± 11.6	8.2 ± 10.6	7.5 ± 1.7
	15 min	-0.2 ± 2.1	-1.1 ± 3.0	27.6 ± 21.3	25.9 ± 19.6	-22.1 ± 5.4
	20 min	2.2 ± 3.1	1.2 ± 3.8	35.3 ± 21.9	22.8 ± 21.4	-47.0 ± 6.4
	25 min	5.6 ± 3.3	4.6 ± 4.0	38.9 ± 23.1	17.1 ± 21.6	-54.4 ± 4.2
	30 min	7.9 ± 3.2	7.1 ± 3.9	41.8 ± 25.1	15.4 ± 22.2	-57.9 ± 2.9
	35 min	8.6 ± 3.0	8.3 ± 3.7	37.1 ± 28.5	9.1 ± 24.0	-59.5 ± 2.6
	40 min	9.3 ± 3.1	8.8 ± 3.9	46.1 ± 32.8	14.1 ± 26.1	-57.8 ± 4.2
	45 min	9.1 ± 3.0	9.3 ± 3.4	41.6 ± 36.6	10.6 ± 28.2	-56.8 ± 4.9
	50 min	9.2 ± 2.9	8.9 ± 3.4	50.8 ± 39.3	14.8 ± 29.8	-56.6 ± 5.1
	55 min	8.6 ± 2.5	9.1 ± 3.1	44.9 ± 43.8	10.5 ± 32.9	-53.6 ± 5.5
	60 min	8.1 ± 2.3	7.7 ± 3.1	53.7 ± 41.2	17.4 ± 30.4	-52.0 ± 6.2
Recovery	5 min	6.7 ± 2.2	6.3 ± 3.1	53.3 ± 44.5	20.3 ± 32.9	-44.9 ± 7.9
	10 min	5.4 ± 2.2	5.3 ± 2.9	44.3 ± 42.2	17.8 ± 32.1	-39.1 ± 7.2
	15 min	4.2 ± 2.5	3.8 ± 2.9	47.9 ± 42.9	25.0 ± 34.0	-36.2 ± 5.9
	20 min	4.2 ± 2.7	3.9 ± 2.9	47.1 ± 42.7	27.1 ± 34.8	-33.1 ± 4.9
	25 min	4.2 ± 3.1	3.8 ± 3.2	44.8 ± 41.9	27.1 ± 34.8	-30.2 ± 4.4
	30 min	3.7 ± 3.6	3.0 ± 3.6	46.8 ± 39.1	30.0 ± 32.2	-27.0 ± 4.7
	35 min	3.8 ± 3.9	3.3 ± 3.9	41.9 ± 38.4	27.4 ± 32.4	-24.7 ± 4.6
	40 min	4.4 ± 4.2	3.7 ± 3.9	47.2 ± 43.5	32.3 ± 36.9	-24.2 ± 4.6
	45 min	4.5 ± 4.3	3.8 ± 4.2	46.1 ± 40.8	33.0 ± 35.1	-24.5 ± 4.6
	50 min	4.4 ± 4.8	3.9 ± 4.5	43.2 ± 42.5	31.4 ± 36.9	-22.7 ± 5.6
	55 min	4.6 ± 5.0	3.6 ± 4.8	49.6 ± 41.5	38.0 ± 36.1	-20.9 ± 5.7
	60 min	4.6 ± 5.3	3.7 ± 5.0	48.8 ± 43.2	37.2 ± 37.6	-19.2 ± 6.3

Values are means ± SE; n = 6.

Appendix C: ECG raw data from Lead I during imipramine or vehicle infusion

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.176 ± 0.049	0.012 ± 0.014	0.043 ± 0.009	-0.0030 ± 0.0049	-0.097 ± 0.024
Vehicle	5 min	0.185 ± 0.051	0.011 ± 0.014	0.038 ± 0.012	-0.0070 ± 0.0038	-0.098 ± 0.024
	10 min	0.185 ± 0.051	0.012 ± 0.015	0.039 ± 0.013	-0.0068 ± 0.0036	-0.095 ± 0.027
	15 min	0.184 ± 0.052	0.013 ± 0.016	0.039 ± 0.013	-0.0070 ± 0.0034	-0.092 ± 0.024
	20 min	0.185 ± 0.051	0.013 ± 0.016	0.039 ± 0.013	-0.0083 ± 0.0042	-0.088 ± 0.024
	25 min	0.188 ± 0.050	0.013 ± 0.015	0.038 ± 0.012	-0.0078 ± 0.0041	-0.087 ± 0.023
	30 min	0.190 ± 0.049	0.013 ± 0.015	0.037 ± 0.012	-0.0080 ± 0.0040	-0.086 ± 0.024
	35 min	0.194 ± 0.049	0.013 ± 0.015	0.038 ± 0.012	-0.0075 ± 0.0041	-0.082 ± 0.025
	40 min	0.198 ± 0.050	0.014 ± 0.015	0.036 ± 0.012	-0.0068 ± 0.0036	-0.082 ± 0.023
	45 min	0.197 ± 0.048	0.014 ± 0.015	0.036 ± 0.012	-0.0065 ± 0.0041	-0.081 ± 0.023
	50 min	0.202 ± 0.048	0.013 ± 0.014	0.033 ± 0.010	-0.0070 ± 0.0036	-0.082 ± 0.021
	55 min	0.207 ± 0.049	0.013 ± 0.015	0.037 ± 0.013	-0.0065 ± 0.0037	-0.081 ± 0.022
	60 min	0.199 ± 0.046	0.014 ± 0.015	0.036 ± 0.013	-0.0060 ± 0.0034	-0.083 ± 0.020
Recovery	5 min	0.201 ± 0.045	0.011 ± 0.015	0.033 ± 0.012	-0.0005 ± 0.0039	-0.084 ± 0.018
	10 min	0.195 ± 0.042	0.012 ± 0.015	0.034 ± 0.013	-0.0008 ± 0.0043	-0.088 ± 0.018
	15 min	0.197 ± 0.042	0.012 ± 0.015	0.034 ± 0.013	-0.0005 ± 0.0040	-0.086 ± 0.016
	20 min	0.190 ± 0.043	0.013 ± 0.016	0.033 ± 0.013	-0.0010 ± 0.0041	-0.087 ± 0.016
	25 min	0.196 ± 0.043	0.014 ± 0.017	0.036 ± 0.013	-0.0013 ± 0.0040	-0.089 ± 0.017
	30 min	0.194 ± 0.042	0.014 ± 0.017	0.034 ± 0.013	-0.0010 ± 0.0041	-0.091 ± 0.022
	35 min	0.193 ± 0.043	0.014 ± 0.017	0.034 ± 0.011	-0.0013 ± 0.0037	-0.094 ± 0.024
	40 min	0.193 ± 0.043	0.014 ± 0.017	0.034 ± 0.012	-0.0008 ± 0.0036	-0.095 ± 0.023
	45 min	0.177 ± 0.040	0.014 ± 0.019	0.037 ± 0.013	-0.0003 ± 0.0038	-0.099 ± 0.028
	50 min	0.188 ± 0.039	0.017 ± 0.019	0.037 ± 0.012	-0.0008 ± 0.0045	-0.099 ± 0.031
	55 min	0.186 ± 0.039	0.014 ± 0.018	0.033 ± 0.010	0.0003 ± 0.0039	-0.100 ± 0.033
	60 min	0.182 ± 0.037	0.014 ± 0.016	0.033 ± 0.009	-0.0015 ± 0.0036	-0.099 ± 0.031

Table 63. Effects of matched-volume vehicle (sterile water) on ECG form lead I in sedentary rats. Values are means ± SE; n = 4.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	5.3 ± 0.4	-10.7 ± 20.5	-11.4 ± 18.7	-82.5 ± 66.9	-2.7 ± 7.4
	10 min	4.9 ± 1.8	-1.7 ± 22.3	-8.5 ± 19.4	-80.9 ± 67.5	2.3 ± 6.8
	15 min	2.9 ± 4.3	6.4 ± 18.8	-9.0 ± 20.1	-87.2 ± 66.9	4.1 ± 8.5
	20 min	4.7 ± 3.6	2.8 ± 25.6	-8.8 ± 19.5	-98.4 ± 69.1	9.5 ± 5.2
	25 min	7.2 ± 4.2	2.4 ± 20.3	-11.4 ± 19.2	-91.9 ± 72.1	9.6 ± 6.5
	30 min	8.2 ± 4.9	9.5 ± 23.6	-12.8 ± 18.2	-96.9 ± 69.7	11.8 ± 7.1
	35 min	12.1 ± 4.3	9.5 ± 23.6	-11.2 ± 19.9	-86.9 ± 67.3	18.6 ± 6.7
	40 min	14.2 ± 5.1	13.1 ± 21.1	-16.8 ± 18.5	-82.2 ± 76.5	16.5 ± 5.8
	45 min	15.2 ± 5.1	17.6 ± 18.8	-17.2 ± 18.9	-69.1 ± 66.2	17.4 ± 7.4
	50 min	19.4 ± 6.0	17.9 ± 17.9	-22.9 ± 15.8	-83.8 ± 68.5	14.9 ± 6.7
	55 min	22.0 ± 6.7	12.1 ± 15.6	-13.6 ± 20.1	-73.8 ± 66.5	15.8 ± 7.8
	60 min	17.5 ± 7.8	16.2 ± 19.0	-18.3 ± 19.1	-67.2 ± 62.5	11.6 ± 8.9
Recovery	5 min	20.1 ± 8.2	-12.9 ± 17.9	-22.8 ± 19.1	36.3 ± 28.5	7.5 ± 13.9
	10 min	18.2 ± 9.7	-5.7 ± 9.7	-20.8 ± 19.8	35.9 ± 22.0	1.8 ± 17.1
	15 min	19.8 ± 10.3	-9.3 ± 11.3	-19.2 ± 21.1	37.5 ± 21.7	3.5 ± 17.7
	20 min	14.2 ± 7.4	-3.4 ± 10.8	-22.3 ± 19.4	30.9 ± 25.1	2.5 ± 18.7
	25 min	18.4 ± 9.1	-2.4 ± 11.4	-15.5 ± 20.8	24.7 ± 26.3	1.6 ± 16.5
	30 min	16.8 ± 8.8	-1.5 ± 12.0	-19.6 ± 19.7	30.9 ± 25.1	1.8 ± 14.5
	35 min	15.6 ± 7.7	-2.0 ± 11.7	-19.1 ± 19.8	21.3 ± 29.5	-1.2 ± 15.6
	40 min	15.6 ± 7.7	2.1 ± 11.2	-18.5 ± 19.8	29.1 ± 28.6	-1.6 ± 15.3
	45 min	6.7 ± 7.7	-20.6 ± 32.7	-11.8 ± 23.0	37.8 ± 21.7	-4.3 ± 16.8
	50 min	14.8 ± 9.9	16.1 ± 9.4	-12.6 ± 21.1	39.4 ± 27.4	-2.9 ± 16.0
	55 min	12.7 ± 9.1	-1.0 ± 14.8	-16.8 ± 22.3	49.1 ± 23.8	-1.2 ± 13.9
	60 min	12.3 ± 11.3	11.4 ± 3.8	-16.2 ± 22.5	15.0 ± 31.6	-1.1 ± 13.1

Table 64. Effects of matched-volume vehicle (sterile water) on ECG from lead I in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.254 ± 0.066	0.006 ± 0.004	0.039 ± 0.004	-0.0028 ± 0.0027	-0.128 ± 0.035
Imipramine	5 min	0.252 ± 0.065	0.006 ± 0.004	0.039 ± 0.004	-0.0030 ± 0.0026	-0.128 ± 0.036
	10 min	0.193 ± 0.066	0.006 ± 0.005	0.038 ± 0.006	-0.0050 ± 0.0027	-0.160 ± 0.049
	15 min	0.156 ± 0.061	0.009 ± 0.006	0.036 ± 0.005	-0.0048 ± 0.0035	-0.228 ± 0.072
	20 min	0.108 ± 0.051	0.011 ± 0.010	0.040 ± 0.007	-0.0048 ± 0.0041	-0.281 ± 0.084
	25 min	0.097 ± 0.038	0.013 ± 0.011	0.041 ± 0.006	0.0013 ± 0.0027	-0.329 ± 0.093
	30 min	0.080 ± 0.021	0.011 ± 0.011	0.039 ± 0.006	0.0018 ± 0.0039	-0.331 ± 0.094
	35 min	0.066 ± 0.017	0.010 ± 0.012	0.037 ± 0.006	-0.0018 ± 0.0044	-0.344 ± 0.094
	40 min	0.064 ± 0.018	0.010 ± 0.013	0.036 ± 0.006	0.0002 ± 0.0045	-0.354 ± 0.095
	45 min	0.058 ± 0.017	0.011 ± 0.013	0.037 ± 0.007	-0.0018 ± 0.0042	-0.355 ± 0.091
	50 min	0.052 ± 0.020	0.011 ± 0.013	0.036 ± 0.007	-0.0052 ± 0.0072	-0.356 ± 0.091
	55 min	0.058 ± 0.016	0.010 ± 0.012	0.038 ± 0.007	-0.0017 ± 0.0053	-0.345 ± 0.095
	60 min	0.063 ± 0.014	0.011 ± 0.012	0.035 ± 0.007	-0.0030 ± 0.0065	-0.338 ± 0.093
Recovery	5 min	0.076 ± 0.037	0.006 ± 0.008	0.037 ± 0.008	-0.0290 ± 0.0233	-0.247 ± 0.074
	10 min	0.112 ± 0.039	0.003 ± 0.008	0.035 ± 0.009	-0.0280 ± 0.0201	-0.204 ± 0.074
	15 min	0.142 ± 0.049	0.002 ± 0.005	0.037 ± 0.008	-0.0263 ± 0.0191	-0.191 ± 0.068
	20 min	0.156 ± 0.052	0.003 ± 0.005	0.036 ± 0.007	-0.0228 ± 0.0173	-0.176 ± 0.064
	25 min	0.164 ± 0.054	0.004 ± 0.006	0.037 ± 0.007	-0.0202 ± 0.0161	-0.178 ± 0.064
	30 min	0.166 ± 0.055	0.003 ± 0.005	0.036 ± 0.007	-0.0190 ± 0.0150	-0.182 ± 0.064
	35 min	0.170 ± 0.056	0.003 ± 0.005	0.036 ± 0.007	-0.0168 ± 0.0135	-0.177 ± 0.064
	40 min	0.172 ± 0.055	0.005 ± 0.005	0.036 ± 0.007	-0.0155 ± 0.0125	-0.177 ± 0.063
	45 min	0.173 ± 0.057	0.007 ± 0.006	0.037 ± 0.007	-0.0143 ± 0.0113	-0.179 ± 0.060
	50 min	0.179 ± 0.056	0.006 ± 0.006	0.037 ± 0.008	-0.0113 ± 0.0093	-0.179 ± 0.059
	55 min	0.183 ± 0.055	0.005 ± 0.006	0.038 ± 0.007	-0.0102 ± 0.0092	-0.180 ± 0.059
	60 min	0.181 ± 0.054	0.006 ± 0.007	0.037 ± 0.007	-0.0092 ± 0.0080	-0.180 ± 0.057

Table 65. Effects of imipramine on ECG from lead I in sedentary rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.3 ± 1.4	-2.8 ± 10.9	1.2 ± 1.0	-17.1 ± 31.3	1.4 ± 2.6
	10 min	-20.9 ± 12.9	-40.2 ± 56.2	-3.7 ± 8.5	-129.7 ± 80.4	-26.3 ± 14.3
	15 min	-41.8 ± 11.2	-26.3 ± 74.0	-6.9 ± 7.6	-243.0 ± 260.2	-92.6 ± 48.8
	20 min	-57.4 ± 11.7	-64.4 ± 88.3	0.7 ± 11.7	-89.0 ± 124.9	-151.3 ± 74.3
	25 min	-52.4 ± 15.0	-40.4 ± 81.9	5.1 ± 7.5	162.9 ± 189.2	-194.1 ± 81.3
	30 min	-50.3 ± 19.7	-75.8 ± 92.1	0.0 ± 7.3	56.2 ± 291.4	-196.4 ± 84.8
	35 min	-51.9 ± 22.2	-125.7 ± 98.7	-6.1 ± 7.9	-78.1 ± 394.5	-207.5 ± 82.6
	40 min	-54.1 ± 20.5	-133.1 ± 103.0	-7.3 ± 9.8	-61.1 ± 410.7	-222.5 ± 91.5
	45 min	-57.5 ± 18.9	-115.1 ± 115.3	-4.4 ± 11.3	-46.9 ± 350.8	-231.1 ± 97.2
	50 min	-57.0 ± 21.2	-102.0 ± 142.1	-7.5 ± 12.9	-23.2 ± 388.2	-223.3 ± 83.8
	55 min	-56.2 ± 20.0	-115.3 ± 114.1	-3.5 ± 11.4	29.3 ± 299.4	-203.0 ± 75.2
	60 min	-48.0 ± 26.9	-70.9 ± 126.2	-7.3 ± 16.6	-209.2 ± 540.5	-197.6 ± 73.7
Recovery	5 min	-45.4 ± 30.4	-141.7 ± 95.2	-7.6 ± 14.3	-2,298.8 ± 2,363.5	-104.0 ± 43.2
	10 min	-43.5 ± 16.5	-218.2 ± 113.1	-12.5 ± 16.2	-2,256.4 ± 2,044.9	-40.2 ± 17.7
	15 min	-37.5 ± 13.3	-163.8 ± 87.4	-8.9 ± 13.7	-2,085.7 ± 1,915.7	-31.2 ± 14.3
	20 min	-34.0 ± 12.0	-129.0 ± 83.9	-8.4 ± 10.5	-1,888.4 ± 1,742.7	-19.6 ± 15.1
	25 min	-28.1 ± 14.2	-121.3 ± 98.1	-5.9 ± 11.0	-1,803.5 ± 1,609.0	-20.8 ± 14.5
	30 min	-26.6 ± 14.8	-121.5 ± 111.4	-10.7 ± 10.6	-1,701.4 ± 1,495.3	-25.9 ± 13.1
	35 min	-24.0 ± 16.1	-111.2 ± 98.8	-9.0 ± 11.3	-1,575.5 ± 1,332.2	-19.1 ± 16.7
	40 min	-21.7 ± 16.8	-79.1 ± 111.2	-9.0 ± 11.3	-1,470.1 ± 1,223.1	-20.1 ± 15.3
	45 min	-21.5 ± 17.0	-47.7 ± 118.9	-5.8 ± 12.0	-1,341.2 ± 1,103.1	-26.2 ± 13.3
	50 min	-17.8 ± 17.4	-82.4 ± 123.3	-8.1 ± 14.1	-1,066.4 ± 851.1	-27.5 ± 13.8
	55 min	-15.0 ± 18.3	-84.5 ± 112.9	-3.5 ± 12.5	-1,022.9 ± 836.2	-30.4 ± 13.6
	60 min	-15.1 ± 18.8	-106.6 ± 99.9	-5.9 ± 12.7	-924.9 ± 706.4	-32.0 ± 15.2

Table 66. Effects of imipramine on ECG from lead I in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.179 ± 0.023	0.014 ± 0.007	0.039 ± 0.009	-0.0095 ± 0.0048	-0.146 ± 0.047
Imipramine	5 min	0.179 ± 0.022	0.019 ± 0.007	0.045 ± 0.009	-0.0118 ± 0.0062	-0.147 ± 0.048
	10 min	0.124 ± 0.031	0.018 ± 0.008	0.050 ± 0.010	-0.0122 ± 0.0057	-0.208 ± 0.044
	15 min	0.071 ± 0.037	0.019 ± 0.007	0.056 ± 0.010	-0.0310 ± 0.0166	-0.258 ± 0.036
	20 min	0.058 ± 0.049	0.023 ± 0.010	0.054 ± 0.010	-0.0352 ± 0.0229	-0.295 ± 0.028
	25 min	0.071 ± 0.039	0.023 ± 0.009	0.052 ± 0.009	-0.0295 ± 0.0130	-0.345 ± 0.041
	30 min	0.071 ± 0.037	0.026 ± 0.009	0.053 ± 0.006	-0.0273 ± 0.0112	-0.371 ± 0.049
	35 min	0.056 ± 0.043	0.032 ± 0.013	0.051 ± 0.009	-0.0333 ± 0.0166	-0.377 ± 0.051
	40 min	0.049 ± 0.044	0.034 ± 0.012	0.054 ± 0.009	-0.0340 ± 0.0179	-0.382 ± 0.055
	45 min	0.047 ± 0.043	0.037 ± 0.013	0.055 ± 0.009	-0.0327 ± 0.0184	-0.389 ± 0.056
	50 min	0.046 ± 0.041	0.039 ± 0.014	0.055 ± 0.009	-0.0283 ± 0.0193	-0.407 ± 0.057
	55 min	0.049 ± 0.039	0.038 ± 0.014	0.054 ± 0.008	-0.0272 ± 0.0174	-0.400 ± 0.067
	60 min	0.051 ± 0.038	0.036 ± 0.010	0.053 ± 0.007	-0.0232 ± 0.0152	-0.397 ± 0.078
Recovery	5 min	0.072 ± 0.044	0.005 ± 0.004	0.045 ± 0.009	-0.0282 ± 0.0208	-0.235 ± 0.067
	10 min	0.103 ± 0.042	0.001 ± 0.004	0.040 ± 0.008	-0.0227 ± 0.0191	-0.208 ± 0.061
	15 min	0.113 ± 0.042	-0.001 ± 0.003	0.038 ± 0.009	-0.0213 ± 0.0187	-0.204 ± 0.057
	20 min	0.127 ± 0.041	-0.001 ± 0.003	0.038 ± 0.009	-0.0197 ± 0.0176	-0.197 ± 0.058
	25 min	0.137 ± 0.040	0.001 ± 0.004	0.039 ± 0.009	-0.0175 ± 0.0158	-0.194 ± 0.059
	30 min	0.139 ± 0.040	0.002 ± 0.004	0.040 ± 0.009	-0.0158 ± 0.0147	-0.197 ± 0.060
	35 min	0.142 ± 0.040	0.003 ± 0.004	0.039 ± 0.008	-0.0157 ± 0.0150	-0.195 ± 0.059
	40 min	0.141 ± 0.041	0.003 ± 0.004	0.039 ± 0.009	-0.0158 ± 0.0152	-0.195 ± 0.060
	45 min	0.136 ± 0.048	0.002 ± 0.004	0.038 ± 0.008	-0.0150 ± 0.0149	-0.194 ± 0.060
	50 min	0.138 ± 0.049	0.002 ± 0.004	0.040 ± 0.007	-0.0148 ± 0.0145	-0.202 ± 0.058
	55 min	0.140 ± 0.048	0.003 ± 0.004	0.040 ± 0.008	-0.0113 ± 0.0121	-0.212 ± 0.058
	60 min	0.142 ± 0.044	0.004 ± 0.004	0.038 ± 0.008	-0.0140 ± 0.0135	-0.203 ± 0.059

Table 67. Effects of imipramine on ECG from lead I in exercise rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	1.4 ± 3.9	88.2 ± 63.4	21.2 ± 6.7	3.4 ± 16.2	1.4 ± 3.4
	10 min	-36.1 ± 13.7	59.0 ± 42.4	42.2 ± 12.9	16.5 ± 49.1	-73.2 ± 22.6
	15 min	-73.0 ± 27.8	69.8 ± 42.4	68.8 ± 23.0	-93.7 ± 91.6	-161.8 ± 62.7
	20 min	-88.2 ± 41.4	86.3 ± 54.9	55.8 ± 14.8	-145.3 ± 77.1	-258.9 ± 132.4
	25 min	-70.6 ± 26.0	143.6 ± 103.2	56.3 ± 19.0	-175.5 ± 27.9	-328.9 ± 156.4
	30 min	-70.3 ± 25.4	190.3 ± 130.1	92.8 ± 56.4	-219.8 ± 64.9	-360.0 ± 170.9
	35 min	-76.5 ± 27.3	247.6 ± 149.9	45.5 ± 17.0	-215.6 ± 88.8	-340.7 ± 148.2
	40 min	-79.5 ± 27.2	312.0 ± 197.9	56.1 ± 18.3	-203.6 ± 102.1	-339.9 ± 146.4
	45 min	-79.6 ± 26.8	383.1 ± 248.4	69.1 ± 24.7	-193.4 ± 113.5	-356.7 ± 156.3
	50 min	-77.8 ± 24.2	420.9 ± 293.5	68.6 ± 23.7	-147.8 ± 131.8	-412.2 ± 191.7
	55 min	-75.2 ± 22.6	436.1 ± 321.7	69.3 ± 27.9	-158.6 ± 114.4	-393.7 ± 187.6
	60 min	-73.2 ± 21.6	436.3 ± 323.9	88.0 ± 47.8	-155.8 ± 103.4	-346.4 ± 166.3
Recovery	5 min	-77.2 ± 36.4	-33.7 ± 15.1	22.8 ± 9.7	-55.5 ± 98.0	-87.4 ± 60.4
	10 min	-55.6 ± 28.3	-101.2 ± 40.7	14.4 ± 16.8	-34.1 ± 76.7	-51.3 ± 43.5
	15 min	-49.8 ± 27.2	-106.4 ± 40.5	4.4 ± 14.5	-37.3 ± 75.8	-58.2 ± 37.9
	20 min	-40.4 ± 24.2	-105.8 ± 39.8	-1.2 ± 12.8	-45.8 ± 76.5	-48.0 ± 32.6
	25 min	-34.1 ± 22.4	-98.5 ± 34.8	3.7 ± 7.5	-28.5 ± 74.2	-42.3 ± 25.5
	30 min	-32.6 ± 22.5	-87.3 ± 30.5	7.6 ± 9.0	-34.8 ± 73.8	-45.2 ± 22.6
	35 min	-31.3 ± 23.2	-82.6 ± 31.5	9.2 ± 10.7	-43.7 ± 92.1	-48.3 ± 22.7
	40 min	-32.3 ± 24.8	-87.4 ± 36.9	5.2 ± 9.5	-37.0 ± 85.0	-46.5 ± 22.4
	45 min	-39.2 ± 32.1	-75.8 ± 18.7	8.3 ± 10.0	-18.3 ± 71.2	-41.1 ± 33.7
	50 min	-38.8 ± 32.6	-71.8 ± 13.5	16.8 ± 11.6	-26.9 ± 75.3	-57.7 ± 34.9
	55 min	-37.1 ± 31.3	-52.6 ± 9.0	19.4 ± 16.7	-3.3 ± 73.1	-74.1 ± 42.6
	60 min	-33.2 ± 26.7	-59.7 ± 15.3	9.6 ± 16.2	-18.3 ± 74.7	-56.9 ± 30.6

Table 68. Effects of imipramine on ECG from lead I in exercise rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.250 ± 0.040	-0.002 ± 0.004	0.028 ± 0.007	-0.0240 ± 0.0146	-0.082 ± 0.008
Imipramine	5 min	0.244 ± 0.040	-0.001 ± 0.006	0.027 ± 0.008	-0.0217 ± 0.0119	-0.079 ± 0.008
	10 min	0.151 ± 0.032	-0.001 ± 0.005	0.021 ± 0.011	-0.0370 ± 0.0172	-0.079 ± 0.010
	15 min	0.103 ± 0.012	0.000 ± 0.007	0.022 ± 0.010	-0.0535 ± 0.0236	-0.133 ± 0.048
	20 min	0.067 ± 0.021	0.000 ± 0.006	0.024 ± 0.009	-0.0543 ± 0.0243	-0.175 ± 0.058
	25 min	0.068 ± 0.018	0.003 ± 0.006	0.042 ± 0.009	-0.0540 ± 0.0293	-0.189 ± 0.065
	30 min	0.050 ± 0.026	0.001 ± 0.008	0.034 ± 0.009	-0.0543 ± 0.0335	-0.244 ± 0.078
	35 min	0.049 ± 0.026	-0.003 ± 0.007	0.029 ± 0.008	-0.0612 ± 0.0325	-0.253 ± 0.089
	40 min	0.060 ± 0.024	-0.003 ± 0.008	0.027 ± 0.006	-0.0512 ± 0.0276	-0.256 ± 0.090
	45 min	0.071 ± 0.017	-0.002 ± 0.006	0.031 ± 0.006	-0.0483 ± 0.0227	-0.237 ± 0.105
	50 min	0.069 ± 0.023	-0.002 ± 0.007	0.032 ± 0.008	-0.0527 ± 0.0242	-0.225 ± 0.096
	55 min	0.044 ± 0.036	-0.002 ± 0.006	0.030 ± 0.009	-0.0655 ± 0.0332	-0.250 ± 0.085
	60 min	0.008 ± 0.064	0.012 ± 0.012	0.033 ± 0.009	-0.0710 ± 0.0477	-0.268 ± 0.079
Recovery	5 min	0.085 ± 0.015	-0.003 ± 0.003	0.034 ± 0.009	-0.0692 ± 0.0316	-0.082 ± 0.028
	10 min	0.117 ± 0.022	-0.005 ± 0.004	0.034 ± 0.009	-0.0643 ± 0.0269	-0.066 ± 0.013
	15 min	0.116 ± 0.026	-0.004 ± 0.004	0.035 ± 0.006	-0.0568 ± 0.0273	-0.069 ± 0.015
	20 min	0.112 ± 0.032	-0.004 ± 0.004	0.033 ± 0.007	-0.0540 ± 0.0255	-0.071 ± 0.018
	25 min	0.127 ± 0.029	-0.004 ± 0.004	0.034 ± 0.008	-0.0477 ± 0.0253	-0.061 ± 0.011
	30 min	0.124 ± 0.030	-0.004 ± 0.004	0.034 ± 0.009	-0.0472 ± 0.0257	-0.057 ± 0.011
	35 min	0.119 ± 0.030	-0.005 ± 0.003	0.034 ± 0.008	-0.0468 ± 0.0239	-0.062 ± 0.014
	40 min	0.113 ± 0.032	-0.005 ± 0.003	0.023 ± 0.013	-0.0478 ± 0.0239	-0.064 ± 0.014
	45 min	0.122 ± 0.031	-0.004 ± 0.003	0.022 ± 0.013	-0.0463 ± 0.0241	-0.058 ± 0.013
	50 min	0.123 ± 0.032	-0.006 ± 0.003	0.021 ± 0.013	-0.0473 ± 0.0237	-0.063 ± 0.014
	55 min	0.125 ± 0.033	-0.006 ± 0.003	0.023 ± 0.014	-0.0460 ± 0.0241	-0.066 ± 0.017
	60 min	0.127 ± 0.032	-0.006 ± 0.004	0.023 ± 0.014	-0.0458 ± 0.0249	-0.060 ± 0.015

Table 69. Effects of imipramine on ECG from lead I in carvedilol rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-2.7 ± 1.1	42.7 ± 22.8	-8.1 ± 7.4	-25.7 ± 20.8	4.6 ± 2.3
	10 min	-44.0 ± 10.3	-42.8 ± 72.8	-37.7 ± 24.5	-50.6 ± 26.6	-3.3 ± 21.5
	15 min	-51.4 ± 9.9	-40.3 ± 105.9	-38.3 ± 16.3	-195.6 ± 102.2	-83.7 ± 80.6
	20 min	-64.0 ± 15.9	-19.5 ± 65.4	-24.3 ± 11.7	-209.8 ± 101.7	-144.1 ± 97.8
	25 min	-62.9 ± 15.8	73.1 ± 79.1	66.7 ± 40.3	-81.8 ± 38.6	-167.1 ± 107.1
	30 min	-73.3 ± 15.8	98.0 ± 91.8	19.6 ± 9.7	-30.9 ± 61.8	-241.5 ± 130.8
	35 min	-73.2 ± 16.5	-50.7 ± 64.5	9.8 ± 16.8	-4.7 ± 106.5	-257.0 ± 145.7
	40 min	-69.2 ± 15.0	-47.0 ± 71.2	14.0 ± 31.8	-153.4 ± 76.5	-263.9 ± 148.0
	45 min	-61.9 ± 15.4	-14.2 ± 48.4	40.1 ± 39.0	-179.1 ± 88.3	-244.2 ± 168.6
	50 min	-64.0 ± 14.6	-19.2 ± 40.6	26.7 ± 28.8	-229.6 ± 156.4	-226.2 ± 154.4
	55 min	-73.6 ± 22.0	-46.1 ± 64.1	7.8 ± 30.7	-201.7 ± 85.9	-255.7 ± 136.3
	60 min	-93.1 ± 30.5	324.6 ± 347.8	26.9 ± 42.2	-196.3 ± 120.6	-262.5 ± 110.9
Recovery	5 min	-62.9 ± 5.8	-18.2 ± 43.6	36.5 ± 40.4	-41.3 ± 110.1	-11.0 ± 41.5
	10 min	-48.0 ± 10.1	-38.2 ± 53.0	26.2 ± 36.2	-105.6 ± 46.0	13.3 ± 22.3
	15 min	-45.9 ± 13.8	-29.7 ± 62.2	46.1 ± 30.2	-117.3 ± 28.6	8.1 ± 26.7
	20 min	-45.8 ± 16.8	-30.2 ± 40.4	37.5 ± 34.2	-115.4 ± 29.6	5.0 ± 29.4
	25 min	-41.5 ± 14.5	-14.9 ± 53.4	42.4 ± 42.1	-88.4 ± 33.1	21.4 ± 18.7
	30 min	-46.0 ± 13.0	-22.4 ± 60.2	54.6 ± 53.8	-67.6 ± 26.7	27.1 ± 15.6
	35 min	-48.2 ± 13.4	-51.2 ± 43.1	63.3 ± 60.6	-66.5 ± 32.5	18.6 ± 20.0
	40 min	-51.3 ± 14.0	-54.9 ± 43.0	15.4 ± 80.3	-64.8 ± 29.6	17.4 ± 20.2
	45 min	-47.4 ± 13.2	-2.9 ± 57.4	8.6 ± 74.3	-57.8 ± 30.4	25.5 ± 18.6
	50 min	-47.8 ± 13.4	-100.2 ± 78.5	2.6 ± 76.5	-98.3 ± 37.0	17.9 ± 19.7
	55 min	-46.5 ± 13.8	-94.1 ± 100.7	20.1 ± 86.4	-72.7 ± 28.7	14.6 ± 23.2
	60 min	-45.9 ± 13.5	-88.3 ± 94.9	12.5 ± 81.3	-67.6 ± 27.4	21.9 ± 21.0

Table 70. Effects of imipramine on ECG from lead I in carvedilol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.295 ± 0.043	0.013 ± 0.005	0.051 ± 0.003	-0.0090 ± 0.0049	-0.063 ± 0.022
Imipramine	5 min	0.304 ± 0.041	0.015 ± 0.005	0.051 ± 0.003	-0.0120 ± 0.0060	-0.066 ± 0.024
	10 min	0.252 ± 0.041	0.010 ± 0.005	0.050 ± 0.006	-0.0117 ± 0.0046	-0.069 ± 0.016
	15 min	0.226 ± 0.035	0.010 ± 0.004	0.057 ± 0.007	-0.0080 ± 0.0038	-0.064 ± 0.016
	20 min	0.211 ± 0.034	0.008 ± 0.003	0.047 ± 0.009	-0.0062 ± 0.0031	-0.076 ± 0.021
	25 min	0.192 ± 0.032	0.011 ± 0.003	0.046 ± 0.009	-0.0062 ± 0.0037	-0.075 ± 0.022
	30 min	0.167 ± 0.018	0.010 ± 0.003	0.050 ± 0.011	-0.0033 ± 0.0032	-0.089 ± 0.025
	35 min	0.152 ± 0.017	0.013 ± 0.003	0.052 ± 0.009	-0.0023 ± 0.0034	-0.097 ± 0.030
	40 min	0.136 ± 0.023	0.017 ± 0.004	0.052 ± 0.008	0.0007 ± 0.0038	-0.119 ± 0.037
	45 min	0.124 ± 0.024	0.016 ± 0.005	0.046 ± 0.009	-0.0083 ± 0.0081	-0.130 ± 0.035
	50 min	0.114 ± 0.019	0.013 ± 0.005	0.043 ± 0.008	-0.0043 ± 0.0087	-0.137 ± 0.041
	55 min	0.121 ± 0.018	0.015 ± 0.005	0.043 ± 0.007	-0.0060 ± 0.0096	-0.170 ± 0.056
	60 min	0.112 ± 0.018	0.015 ± 0.006	0.045 ± 0.006	-0.0072 ± 0.0108	-0.186 ± 0.063
Recovery	5 min	0.136 ± 0.027	0.005 ± 0.004	0.041 ± 0.008	-0.0057 ± 0.0094	-0.043 ± 0.020
	10 min	0.164 ± 0.025	0.003 ± 0.004	0.035 ± 0.007	-0.0043 ± 0.0041	-0.053 ± 0.017
	15 min	0.188 ± 0.022	0.003 ± 0.004	0.035 ± 0.007	-0.0032 ± 0.0031	-0.058 ± 0.015
	20 min	0.206 ± 0.024	0.004 ± 0.003	0.040 ± 0.007	-0.0038 ± 0.0036	-0.055 ± 0.016
	25 min	0.217 ± 0.026	0.005 ± 0.002	0.037 ± 0.009	-0.0052 ± 0.0032	-0.055 ± 0.014
	30 min	0.221 ± 0.022	0.007 ± 0.003	0.038 ± 0.009	-0.0060 ± 0.0039	-0.057 ± 0.014
	35 min	0.226 ± 0.021	0.008 ± 0.003	0.040 ± 0.008	-0.0060 ± 0.0041	-0.057 ± 0.013
	40 min	0.227 ± 0.020	0.006 ± 0.003	0.039 ± 0.008	-0.0070 ± 0.0042	-0.057 ± 0.012
	45 min	0.229 ± 0.021	0.006 ± 0.003	0.040 ± 0.008	-0.0080 ± 0.0049	-0.057 ± 0.012
	50 min	0.229 ± 0.021	0.008 ± 0.003	0.041 ± 0.007	-0.0073 ± 0.0053	-0.058 ± 0.014
	55 min	0.227 ± 0.022	0.007 ± 0.003	0.040 ± 0.008	-0.0090 ± 0.0056	-0.056 ± 0.012
	60 min	0.226 ± 0.021	0.007 ± 0.004	0.040 ± 0.008	-0.0087 ± 0.0053	-0.057 ± 0.013

Table 71. Effects of imipramine on ECG from lead I in clenbuterol rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	4.4 ± 2.8	34.0 ± 30.3	0.3 ± 1.1	-29.0 ± 25.5	-0.6 ± 8.4
	10 min	-14.7 ± 5.2	-31.4 ± 32.1	-1.5 ± 10.7	-47.0 ± 26.1	-27.3 ± 23.7
	15 min	-21.4 ± 8.2	19.8 ± 61.9	12.7 ± 17.3	-27.3 ± 40.0	-26.9 ± 32.2
	20 min	-25.3 ± 10.1	23.8 ± 68.8	-7.4 ± 16.5	-17.3 ± 40.5	-45.2 ± 40.9
	25 min	-32.5 ± 8.5	28.3 ± 51.3	-11.3 ± 14.5	-3.3 ± 40.7	-44.7 ± 46.4
	30 min	-40.1 ± 6.2	23.3 ± 42.8	-2.3 ± 21.4	41.0 ± 24.1	-74.4 ± 58.0
	35 min	-45.3 ± 5.4	26.9 ± 32.3	2.4 ± 18.3	54.0 ± 17.4	-97.1 ± 75.8
	40 min	-50.7 ± 7.2	65.8 ± 36.4	2.8 ± 17.0	75.7 ± 29.5	-116.4 ± 68.1
	45 min	-56.0 ± 8.2	17.3 ± 58.6	-9.5 ± 18.4	79.7 ± 43.2	-157.4 ± 82.7
	50 min	-58.1 ± 7.9	-21.8 ± 38.0	-16.8 ± 13.7	116.7 ± 54.3	-179.2 ± 101.8
	55 min	-55.4 ± 7.0	19.9 ± 90.6	-17.1 ± 11.3	86.7 ± 67.1	-242.8 ± 143.7
	60 min	-59.2 ± 7.4	30.7 ± 122.3	-12.6 ± 11.0	74.7 ± 89.0	-281.8 ± 168.5
Recovery	5 min	-47.9 ± 15.5	-101.1 ± 67.7	-20.6 ± 14.4	-186.7 ± 298.2	27.4 ± 16.6
	10 min	-40.3 ± 12.5	-134.0 ± 66.5	-32.1 ± 11.6	-64.7 ± 147.1	4.1 ± 15.6
	15 min	-32.7 ± 8.4	-126.0 ± 53.9	-32.6 ± 11.1	21.3 ± 27.6	-9.9 ± 19.5
	20 min	-26.3 ± 8.0	-95.6 ± 38.1	-23.4 ± 11.6	27.7 ± 29.7	-3.5 ± 18.7
	25 min	-23.2 ± 6.7	-62.8 ± 25.9	-28.7 ± 15.1	16.7 ± 17.9	-5.5 ± 18.7
	30 min	-21.1 ± 6.7	-60.9 ± 22.3	-27.1 ± 15.4	20.3 ± 8.6	-9.0 ± 20.6
	35 min	-19.1 ± 6.7	-36.3 ± 25.1	-22.1 ± 12.2	21.7 ± 8.4	-11.3 ± 22.6
	40 min	-18.3 ± 7.8	-52.2 ± 24.7	-26.2 ± 12.4	13.3 ± 9.7	-11.3 ± 22.4
	45 min	-17.8 ± 8.0	-46.7 ± 34.9	-23.6 ± 12.2	5.0 ± 9.7	-11.7 ± 22.9
	50 min	-17.4 ± 8.2	-30.2 ± 38.8	-21.6 ± 11.8	13.0 ± 11.6	-11.0 ± 21.6
	55 min	-18.9 ± 6.7	-31.9 ± 44.0	-22.3 ± 11.8	1.7 ± 10.7	-12.1 ± 25.2
	60 min	-19.0 ± 7.1	-47.2 ± 44.7	-24.2 ± 11.5	-1.7 ± 14.9	-12.3 ± 24.9

Table 72. Effects of imipramine on ECG from lead I in clenbuterol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.302 ± 0.070	0.003 ± 0.005	0.035 ± 0.005	-0.0203 ± 0.0137	-0.073 ± 0.019
Imipramine	5 min	0.308 ± 0.067	0.004 ± 0.005	0.036 ± 0.004	-0.0198 ± 0.0138	-0.072 ± 0.022
	10 min	0.186 ± 0.060	0.002 ± 0.004	0.039 ± 0.006	-0.0300 ± 0.0176	-0.102 ± 0.026
	15 min	0.088 ± 0.057	0.006 ± 0.005	0.045 ± 0.005	-0.0397 ± 0.0227	-0.152 ± 0.027
	20 min	0.109 ± 0.037	0.010 ± 0.006	0.049 ± 0.004	-0.0037 ± 0.0025	-0.206 ± 0.056
	25 min	0.099 ± 0.030	0.007 ± 0.006	0.048 ± 0.002	-0.0075 ± 0.0033	-0.234 ± 0.061
	30 min	0.074 ± 0.020	0.004 ± 0.006	0.042 ± 0.006	-0.0258 ± 0.0188	-0.264 ± 0.066
	35 min	0.085 ± 0.011	0.002 ± 0.006	0.044 ± 0.007	-0.0225 ± 0.0183	-0.247 ± 0.061
	40 min	0.079 ± 0.010	0.004 ± 0.007	0.039 ± 0.009	-0.0218 ± 0.0188	-0.248 ± 0.060
	45 min	0.056 ± 0.009	0.009 ± 0.010	0.038 ± 0.009	-0.0202 ± 0.0193	-0.260 ± 0.055
	50 min	0.058 ± 0.011	0.009 ± 0.010	0.039 ± 0.008	-0.0032 ± 0.0037	-0.303 ± 0.043
	55 min	0.062 ± 0.014	0.024 ± 0.015	0.039 ± 0.007	-0.0070 ± 0.0046	-0.353 ± 0.060
	60 min	0.052 ± 0.012	0.024 ± 0.016	0.040 ± 0.007	-0.0057 ± 0.0034	-0.339 ± 0.084
Recovery	5 min	0.108 ± 0.056	-0.003 ± 0.003	0.041 ± 0.007	-0.0753 ± 0.0159	-0.113 ± 0.025
	10 min	0.147 ± 0.065	-0.002 ± 0.003	0.042 ± 0.006	-0.0760 ± 0.0143	-0.095 ± 0.016
	15 min	0.127 ± 0.071	-0.004 ± 0.002	0.039 ± 0.006	-0.0810 ± 0.0222	-0.100 ± 0.019
	20 min	0.149 ± 0.062	-0.002 ± 0.004	0.039 ± 0.009	-0.0583 ± 0.0211	-0.104 ± 0.021
	25 min	0.153 ± 0.061	-0.002 ± 0.004	0.038 ± 0.008	-0.0505 ± 0.0199	-0.099 ± 0.019
	30 min	0.157 ± 0.059	-0.002 ± 0.004	0.039 ± 0.009	-0.0457 ± 0.0180	-0.098 ± 0.019
	35 min	0.163 ± 0.059	-0.002 ± 0.004	0.039 ± 0.010	-0.0422 ± 0.0168	-0.099 ± 0.021
	40 min	0.167 ± 0.055	-0.001 ± 0.005	0.040 ± 0.010	-0.0410 ± 0.0159	-0.097 ± 0.022
	45 min	0.162 ± 0.054	-0.002 ± 0.005	0.039 ± 0.009	-0.0392 ± 0.0157	-0.096 ± 0.023
	50 min	0.171 ± 0.054	-0.002 ± 0.006	0.039 ± 0.009	-0.0353 ± 0.0146	-0.099 ± 0.026
	55 min	0.170 ± 0.054	-0.002 ± 0.006	0.038 ± 0.010	-0.0343 ± 0.0148	-0.097 ± 0.024
	60 min	0.169 ± 0.056	-0.004 ± 0.005	0.035 ± 0.010	-0.0350 ± 0.0155	-0.101 ± 0.025

Table 73. Effects of imipramine on ECG from lead I in dobutamine rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	4.5 ± 2.7	21.3 ± 15.7	2.3 ± 4.9	14.6 ± 26.7	6.2 ± 6.6
	10 min	-40.5 ± 7.1	-58.7 ± 61.1	15.8 ± 18.1	-25.8 ± 80.1	-48.0 ± 23.3
	15 min	-79.5 ± 16.8	-18.8 ± 71.5	37.0 ± 22.0	-79.8 ± 12.0	-143.9 ± 54.5
	20 min	-62.4 ± 6.1	129.8 ± 41.2	50.9 ± 21.8	23.0 ± 79.2	-241.8 ± 107.9
	25 min	-63.4 ± 6.5	130.8 ± 111.8	46.6 ± 18.1	-8.4 ± 119.4	-290.5 ± 117.0
	30 min	-68.4 ± 8.0	94.5 ± 109.9	33.7 ± 24.0	-71.1 ± 84.8	-328.6 ± 103.8
	35 min	-64.5 ± 6.5	32.8 ± 46.3	37.6 ± 25.3	-33.0 ± 66.8	-305.7 ± 101.6
	40 min	-66.0 ± 7.0	49.3 ± 45.8	17.8 ± 29.0	42.9 ± 120.9	-307.4 ± 98.3
	45 min	-70.3 ± 10.0	65.2 ± 42.2	13.7 ± 29.3	63.5 ± 118.6	-338.8 ± 106.1
	50 min	-69.3 ± 10.3	103.9 ± 43.4	14.2 ± 26.9	47.7 ± 50.9	-392.7 ± 76.0
	55 min	-66.7 ± 11.6	479.8 ± 173.1	13.7 ± 24.7	-59.3 ± 122.3	-517.4 ± 139.3
	60 min	-69.0 ± 12.9	516.2 ± 244.6	16.9 ± 24.4	5.3 ± 56.6	-520.5 ± 190.2
Recovery	5 min	-81.3 ± 23.9	-79.0 ± 18.8	19.1 ± 19.9	-1,977.0 ± 1,241.9	-84.0 ± 44.2
	10 min	-69.3 ± 17.4	-112.9 ± 76.1	22.6 ± 20.6	-1,213.5 ± 660.5	-53.8 ± 33.7
	15 min	-76.0 ± 19.4	-137.7 ± 91.7	11.5 ± 17.3	-883.6 ± 388.4	-61.7 ± 37.1
	20 min	-58.1 ± 13.0	-130.0 ± 93.0	12.2 ± 28.4	-875.2 ± 434.1	-67.9 ± 38.7
	25 min	-54.4 ± 12.4	-126.0 ± 94.0	8.0 ± 26.5	-628.3 ± 364.3	-59.8 ± 34.0
	30 min	-51.1 ± 11.5	-141.2 ± 114.9	11.2 ± 32.3	-461.3 ± 314.2	-53.0 ± 29.0
	35 min	-48.6 ± 11.6	-127.5 ± 93.2	10.2 ± 35.0	-405.8 ± 296.3	-50.6 ± 26.9
	40 min	-46.0 ± 10.5	-123.9 ± 94.6	14.4 ± 34.0	-395.7 ± 265.5	-43.8 ± 24.0
	45 min	-48.1 ± 9.6	-120.0 ± 96.2	12.7 ± 32.1	-351.2 ± 257.6	-39.4 ± 22.2
	50 min	-44.9 ± 9.6	-93.9 ± 54.6	11.5 ± 31.1	-304.1 ± 235.6	-41.0 ± 21.2
	55 min	-45.4 ± 9.4	-113.9 ± 74.3	11.7 ± 33.6	-292.7 ± 232.9	-38.4 ± 20.7
	60 min	-46.7 ± 9.8	-133.0 ± 68.9	1.8 ± 35.5	-285.6 ± 248.6	-46.0 ± 21.5

Table 74. Effects of imipramine on ECG from lead I in dobutamine rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Appendix D: ECG raw data from Lead AVF during imipramine or vehicle infusion

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.222 ± 0.041	0.088 ± 0.012	0.052 ± 0.042	-0.0075 ± 0.0018	-0.311 ± 0.116
Vehicle	5 min	0.229 ± 0.040	0.088 ± 0.011	0.052 ± 0.045	-0.0085 ± 0.0033	-0.306 ± 0.114
	10 min	0.225 ± 0.038	0.086 ± 0.011	0.052 ± 0.046	-0.0083 ± 0.0034	-0.303 ± 0.114
	15 min	0.227 ± 0.040	0.085 ± 0.009	0.051 ± 0.045	-0.0093 ± 0.0031	-0.307 ± 0.115
	20 min	0.225 ± 0.040	0.084 ± 0.010	0.051 ± 0.046	-0.0090 ± 0.0031	-0.306 ± 0.113
	25 min	0.229 ± 0.037	0.083 ± 0.009	0.053 ± 0.046	-0.0085 ± 0.0033	-0.304 ± 0.111
	30 min	0.233 ± 0.038	0.085 ± 0.010	0.052 ± 0.046	-0.0085 ± 0.0029	-0.301 ± 0.112
	35 min	0.241 ± 0.036	0.086 ± 0.009	0.051 ± 0.047	-0.0088 ± 0.0028	-0.302 ± 0.112
	40 min	0.244 ± 0.036	0.084 ± 0.009	0.051 ± 0.047	-0.0093 ± 0.0030	-0.304 ± 0.112
	45 min	0.243 ± 0.037	0.086 ± 0.010	0.053 ± 0.047	-0.0093 ± 0.0029	-0.306 ± 0.114
	50 min	0.249 ± 0.036	0.085 ± 0.011	0.050 ± 0.047	-0.0083 ± 0.0030	-0.300 ± 0.117
	55 min	0.255 ± 0.035	0.084 ± 0.010	0.055 ± 0.048	-0.0095 ± 0.0029	-0.305 ± 0.114
	60 min	0.253 ± 0.033	0.087 ± 0.010	0.059 ± 0.049	-0.0100 ± 0.0034	-0.306 ± 0.113
Recovery	5 min	0.258 ± 0.031	0.089 ± 0.011	0.059 ± 0.048	-0.0065 ± 0.0026	-0.309 ± 0.115
	10 min	0.261 ± 0.033	0.091 ± 0.012	0.060 ± 0.048	-0.0055 ± 0.0032	-0.310 ± 0.118
	15 min	0.261 ± 0.030	0.093 ± 0.011	0.062 ± 0.049	-0.0058 ± 0.0030	-0.315 ± 0.118
	20 min	0.259 ± 0.029	0.094 ± 0.012	0.062 ± 0.049	-0.0058 ± 0.0030	-0.315 ± 0.117
	25 min	0.262 ± 0.030	0.093 ± 0.010	0.065 ± 0.049	-0.0050 ± 0.0029	-0.317 ± 0.117
	30 min	0.265 ± 0.031	0.096 ± 0.010	0.065 ± 0.048	-0.0055 ± 0.0035	-0.315 ± 0.120
	35 min	0.263 ± 0.032	0.096 ± 0.010	0.063 ± 0.048	-0.0058 ± 0.0034	-0.319 ± 0.120
	40 min	0.266 ± 0.030	0.095 ± 0.010	0.062 ± 0.048	-0.0055 ± 0.0030	-0.321 ± 0.121
	45 min	0.257 ± 0.024	0.099 ± 0.012	0.058 ± 0.047	-0.0058 ± 0.0034	-0.321 ± 0.123
	50 min	0.259 ± 0.031	0.097 ± 0.010	0.060 ± 0.046	-0.0058 ± 0.0033	-0.325 ± 0.123
	55 min	0.259 ± 0.030	0.094 ± 0.010	0.056 ± 0.045	-0.0050 ± 0.0027	-0.327 ± 0.121
	60 min	0.262 ± 0.033	0.096 ± 0.010	0.054 ± 0.045	-0.0045 ± 0.0027	-0.328 ± 0.124

Table 75. Effects of matched-volume vehicle (sterile water) on ECG from lead AVF in sedentary rats. Values are means ± SE; n = 4.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	3.8 ± 2.0	1.6 ± 3.5	0.0 ± 4.9	-14.9 ± 27.9	1.0 ± 1.0
	10 min	2.5 ± 3.5	-1.0 ± 4.4	-1.1 ± 5.7	-1.8 ± 19.0	2.8 ± 1.4
	15 min	3.1 ± 3.9	-1.7 ± 5.2	-0.8 ± 5.7	-25.1 ± 21.2	1.1 ± 1.3
	20 min	2.4 ± 3.6	-2.7 ± 5.3	-2.2 ± 6.7	-22.0 ± 22.0	0.6 ± 2.3
	25 min	5.2 ± 4.6	-4.0 ± 4.4	0.1 ± 7.1	-10.1 ± 20.5	0.3 ± 3.1
	30 min	7.3 ± 5.8	-1.6 ± 5.5	-0.9 ± 7.4	-16.8 ± 22.4	1.8 ± 3.4
	35 min	11.9 ± 7.8	-0.2 ± 6.6	-2.0 ± 8.9	-20.4 ± 20.2	1.3 ± 3.2
	40 min	13.3 ± 8.0	-2.7 ± 6.1	-1.4 ± 9.6	-25.6 ± 19.4	0.7 ± 2.7
	45 min	12.4 ± 6.6	-0.5 ± 7.7	1.0 ± 9.3	-21.4 ± 12.4	0.3 ± 3.0
	50 min	16.6 ± 10.3	-1.4 ± 8.5	-2.8 ± 13.4	-8.9 ± 16.7	4.8 ± 4.7
	55 min	19.9 ± 10.8	-2.0 ± 7.1	2.5 ± 10.6	-24.6 ± 13.1	1.0 ± 2.9
	60 min	20.0 ± 13.2	1.9 ± 8.7	8.1 ± 12.2	-24.0 ± 14.5	-0.7 ± 4.0
Recovery	5 min	23.2 ± 14.4	3.6 ± 9.0	7.9 ± 11.7	19.9 ± 20.9	-1.2 ± 3.8
	10 min	24.3 ± 15.5	5.3 ± 6.8	9.0 ± 11.5	43.8 ± 32.9	-0.5 ± 3.9
	15 min	25.1 ± 16.0	7.7 ± 8.8	12.9 ± 14.0	39.1 ± 32.5	-3.7 ± 5.1
	20 min	24.2 ± 15.2	8.3 ± 8.0	12.0 ± 12.6	34.4 ± 30.5	-3.8 ± 5.1
	25 min	25.2 ± 14.3	8.3 ± 8.9	15.8 ± 15.2	42.1 ± 32.2	-4.8 ± 4.4
	30 min	26.7 ± 15.4	12.5 ± 8.3	17.2 ± 16.4	44.2 ± 37.3	-2.5 ± 4.2
	35 min	25.4 ± 14.0	12.0 ± 7.9	14.5 ± 15.1	41.7 ± 33.9	-4.8 ± 4.9
	40 min	27.2 ± 14.5	10.2 ± 6.3	13.2 ± 14.0	38.5 ± 26.9	-5.5 ± 5.6
	45 min	23.9 ± 15.7	14.3 ± 6.6	6.2 ± 6.1	36.9 ± 32.6	-5.1 ± 6.1
	50 min	23.7 ± 15.5	12.7 ± 5.7	9.6 ± 8.5	40.6 ± 35.1	-6.9 ± 6.9
	55 min	24.0 ± 15.3	9.0 ± 7.6	6.7 ± 12.4	43.8 ± 23.9	-9.4 ± 8.4
	60 min	24.9 ± 14.5	11.1 ± 6.6	2.8 ± 11.8	55.2 ± 25.9	-8.4 ± 6.7

Table 76. Effects of matched-volume vehicle (sterile water) on ECG from lead AVF in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.313 ± 0.025	0.099 ± 0.016	0.113 ± 0.007	-0.0053 ± 0.0058	-0.101 ± 0.043
Imipramine	5 min	0.312 ± 0.023	0.102 ± 0.016	0.115 ± 0.007	-0.0048 ± 0.0065	-0.101 ± 0.044
	10 min	0.277 ± 0.023	0.108 ± 0.018	0.125 ± 0.007	-0.0025 ± 0.0077	-0.138 ± 0.048
	15 min	0.257 ± 0.021	0.113 ± 0.020	0.116 ± 0.009	-0.0035 ± 0.0037	-0.137 ± 0.044
	20 min	0.245 ± 0.017	0.118 ± 0.020	0.105 ± 0.010	-0.0013 ± 0.0028	-0.148 ± 0.048
	25 min	0.238 ± 0.017	0.109 ± 0.017	0.091 ± 0.015	-0.0022 ± 0.0014	-0.154 ± 0.050
	30 min	0.239 ± 0.018	0.102 ± 0.015	0.083 ± 0.018	-0.0038 ± 0.0021	-0.161 ± 0.050
	35 min	0.244 ± 0.019	0.098 ± 0.015	0.084 ± 0.018	-0.0038 ± 0.0017	-0.161 ± 0.051
	40 min	0.258 ± 0.019	0.096 ± 0.014	0.081 ± 0.018	-0.0047 ± 0.0020	-0.163 ± 0.049
	45 min	0.264 ± 0.020	0.093 ± 0.016	0.082 ± 0.018	-0.0067 ± 0.0025	-0.168 ± 0.047
	50 min	0.263 ± 0.019	0.101 ± 0.015	0.084 ± 0.017	-0.0063 ± 0.0032	-0.194 ± 0.069
	55 min	0.272 ± 0.019	0.102 ± 0.014	0.087 ± 0.018	-0.0048 ± 0.0030	-0.204 ± 0.081
	60 min	0.282 ± 0.017	0.101 ± 0.015	0.093 ± 0.020	-0.0038 ± 0.0035	-0.193 ± 0.084
Recovery	5 min	0.322 ± 0.016	0.091 ± 0.020	0.100 ± 0.023	-0.0003 ± 0.0027	-0.136 ± 0.042
	10 min	0.326 ± 0.015	0.092 ± 0.022	0.101 ± 0.023	-0.0015 ± 0.0028	-0.099 ± 0.030
	15 min	0.336 ± 0.019	0.093 ± 0.022	0.107 ± 0.019	-0.0035 ± 0.0040	-0.089 ± 0.026
	20 min	0.334 ± 0.019	0.095 ± 0.021	0.107 ± 0.018	-0.0033 ± 0.0049	-0.084 ± 0.028
	25 min	0.334 ± 0.018	0.095 ± 0.020	0.107 ± 0.018	-0.0035 ± 0.0045	-0.085 ± 0.027
	30 min	0.335 ± 0.018	0.094 ± 0.021	0.105 ± 0.018	-0.0038 ± 0.0048	-0.086 ± 0.024
	35 min	0.341 ± 0.019	0.095 ± 0.021	0.107 ± 0.019	-0.0040 ± 0.0049	-0.089 ± 0.023
	40 min	0.340 ± 0.019	0.095 ± 0.020	0.107 ± 0.021	-0.0045 ± 0.0049	-0.088 ± 0.022
	45 min	0.345 ± 0.020	0.094 ± 0.020	0.103 ± 0.023	-0.0040 ± 0.0053	-0.091 ± 0.023
	50 min	0.348 ± 0.019	0.097 ± 0.019	0.102 ± 0.024	-0.0047 ± 0.0048	-0.092 ± 0.025
	55 min	0.347 ± 0.019	0.099 ± 0.017	0.107 ± 0.023	-0.0055 ± 0.0049	-0.096 ± 0.028
	60 min	0.352 ± 0.020	0.100 ± 0.017	0.109 ± 0.022	-0.0052 ± 0.0053	-0.101 ± 0.032

Table 77. Effects of imipramine on ECG from lead AVF in sedentary rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.1 ± 1.0	3.3 ± 1.0	1.7 ± 0.9	6.3 ± 8.4	1.2 ± 2.7
	10 min	-10.0 ± 7.6	8.5 ± 3.3	11.2 ± 3.5	27.5 ± 37.7	-49.8 ± 20.2
	15 min	-17.5 ± 3.2	12.4 ± 4.3	2.4 ± 6.9	15.9 ± 27.7	-59.1 ± 33.3
	20 min	-20.7 ± 4.1	18.3 ± 4.3	-5.9 ± 10.6	28.6 ± 34.9	-83.5 ± 47.1
	25 min	-23.4 ± 3.7	11.5 ± 6.0	-17.2 ± 14.8	16.3 ± 39.1	-100.6 ± 58.6
	30 min	-22.8 ± 5.0	5.4 ± 7.4	-24.5 ± 17.0	2.7 ± 36.8	-110.2 ± 60.2
	35 min	-20.9 ± 5.7	0.9 ± 7.2	-23.7 ± 17.5	-1.5 ± 46.6	-112.6 ± 62.1
	40 min	-16.4 ± 5.6	-0.6 ± 8.5	-26.9 ± 16.3	-7.9 ± 50.5	-117.9 ± 61.4
	45 min	-13.8 ± 7.8	-4.5 ± 8.3	-25.8 ± 16.9	-31.2 ± 54.0	-122.9 ± 55.5
	50 min	-14.1 ± 8.2	4.8 ± 8.5	-23.5 ± 16.8	-29.3 ± 54.2	-124.7 ± 51.2
	55 min	-10.6 ± 9.5	5.7 ± 8.9	-21.2 ± 16.8	-12.5 ± 51.1	-120.2 ± 47.5
	60 min	-7.8 ± 7.4	3.0 ± 5.9	-17.0 ± 18.5	-2.3 ± 60.1	-104.2 ± 45.1
Recovery	5 min	5.4 ± 8.4	-8.4 ± 11.3	-11.0 ± 20.2	31.5 ± 33.7	-67.0 ± 35.4
	10 min	7.0 ± 8.3	-8.9 ± 14.5	-9.6 ± 20.7	15.5 ± 34.4	-30.5 ± 31.2
	15 min	10.5 ± 10.1	-7.5 ± 13.5	-5.2 ± 17.1	3.3 ± 27.0	-16.8 ± 23.8
	20 min	10.1 ± 10.8	-4.6 ± 12.7	-5.4 ± 15.3	0.3 ± 24.8	-7.1 ± 21.6
	25 min	10.5 ± 11.5	-3.5 ± 13.0	-5.3 ± 15.1	0.1 ± 20.4	-7.5 ± 18.9
	30 min	10.9 ± 11.3	-5.2 ± 13.3	-7.4 ± 15.6	-5.9 ± 23.3	-8.3 ± 16.8
	35 min	12.6 ± 11.8	-4.0 ± 13.6	-5.0 ± 16.0	-9.0 ± 28.6	-16.4 ± 18.7
	40 min	12.6 ± 12.0	-3.7 ± 13.4	-5.6 ± 17.9	-5.1 ± 18.1	-15.9 ± 18.8
	45 min	14.0 ± 11.8	-4.3 ± 12.4	-9.3 ± 19.6	-7.3 ± 24.3	-14.2 ± 17.8
	50 min	14.8 ± 11.5	-1.4 ± 11.5	-10.1 ± 20.3	-9.6 ± 21.3	-15.3 ± 17.9
	55 min	14.2 ± 10.9	1.1 ± 9.1	-5.6 ± 19.2	-20.5 ± 29.9	-18.3 ± 19.3
	60 min	16.0 ± 11.5	2.4 ± 7.9	-4.0 ± 18.5	-24.2 ± 39.9	-19.4 ± 17.1

Table 78. Effects of imipramine on ECG from lead AVF in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.282 ± 0.019	0.092 ± 0.011	0.062 ± 0.029	-0.0123 ± 0.0023	-0.150 ± 0.033
Imipramine	5 min	0.281 ± 0.020	0.094 ± 0.010	0.065 ± 0.028	-0.0108 ± 0.0025	-0.152 ± 0.033
	10 min	0.262 ± 0.017	0.109 ± 0.010	0.110 ± 0.006	-0.0070 ± 0.0015	-0.158 ± 0.029
	15 min	0.252 ± 0.019	0.115 ± 0.010	0.097 ± 0.008	-0.0043 ± 0.0014	-0.167 ± 0.031
	20 min	0.238 ± 0.022	0.115 ± 0.009	0.089 ± 0.011	0.0020 ± 0.0019	-0.153 ± 0.021
	25 min	0.241 ± 0.027	0.106 ± 0.009	0.074 ± 0.013	-0.0012 ± 0.0030	-0.145 ± 0.018
	30 min	0.242 ± 0.031	0.102 ± 0.009	0.062 ± 0.008	0.0003 ± 0.0030	-0.153 ± 0.024
	35 min	0.242 ± 0.031	0.102 ± 0.013	0.028 ± 0.023	-0.0038 ± 0.0032	-0.185 ± 0.046
	40 min	0.242 ± 0.029	0.100 ± 0.013	0.025 ± 0.022	-0.0050 ± 0.0015	-0.189 ± 0.054
	45 min	0.244 ± 0.029	0.099 ± 0.015	0.023 ± 0.021	-0.0042 ± 0.0016	-0.184 ± 0.053
	50 min	0.251 ± 0.027	0.093 ± 0.015	0.023 ± 0.021	-0.0045 ± 0.0016	-0.175 ± 0.047
	55 min	0.258 ± 0.029	0.090 ± 0.016	0.024 ± 0.022	-0.0030 ± 0.0021	-0.173 ± 0.046
	60 min	0.263 ± 0.029	0.094 ± 0.017	0.027 ± 0.022	-0.0022 ± 0.0030	-0.198 ± 0.063
Recovery	5 min	0.290 ± 0.027	0.081 ± 0.009	0.067 ± 0.020	-0.0015 ± 0.0017	-0.163 ± 0.046
	10 min	0.307 ± 0.019	0.084 ± 0.008	0.093 ± 0.010	-0.0027 ± 0.0014	-0.144 ± 0.034
	15 min	0.316 ± 0.019	0.091 ± 0.007	0.097 ± 0.007	-0.0022 ± 0.0024	-0.139 ± 0.029
	20 min	0.318 ± 0.022	0.096 ± 0.007	0.100 ± 0.007	-0.0017 ± 0.0024	-0.137 ± 0.029
	25 min	0.320 ± 0.020	0.096 ± 0.007	0.098 ± 0.009	-0.0027 ± 0.0028	-0.128 ± 0.026
	30 min	0.316 ± 0.022	0.095 ± 0.007	0.092 ± 0.011	-0.0028 ± 0.0027	-0.127 ± 0.026
	35 min	0.312 ± 0.022	0.091 ± 0.008	0.076 ± 0.021	-0.0042 ± 0.0024	-0.126 ± 0.025
	40 min	0.306 ± 0.023	0.089 ± 0.008	0.073 ± 0.020	-0.0035 ± 0.0024	-0.125 ± 0.025
	45 min	0.303 ± 0.016	0.086 ± 0.009	0.072 ± 0.021	-0.0035 ± 0.0030	-0.122 ± 0.024
	50 min	0.305 ± 0.015	0.086 ± 0.012	0.058 ± 0.026	-0.0048 ± 0.0031	-0.124 ± 0.025
	55 min	0.313 ± 0.020	0.089 ± 0.009	0.073 ± 0.020	-0.0035 ± 0.0028	-0.127 ± 0.026
	60 min	0.316 ± 0.020	0.090 ± 0.009	0.076 ± 0.021	-0.0037 ± 0.0027	-0.129 ± 0.026

Table 79. Effects of imipramine on ECG from lead AVF in exercise rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.6 ± 0.6	4.5 ± 5.6	34.0 ± 35.0	9.2 ± 13.7	-1.4 ± 1.8
	10 min	-7.0 ± 1.2	22.7 ± 9.9	181.8 ± 124.8	34.1 ± 16.1	-9.4 ± 8.0
	15 min	-10.9 ± 1.4	30.1 ± 12.7	145.9 ± 102.0	45.6 ± 30.8	-15.2 ± 6.9
	20 min	-16.4 ± 2.9	32.5 ± 17.4	126.0 ± 93.3	118.2 ± 19.2	-11.7 ± 9.8
	25 min	-15.5 ± 4.8	21.6 ± 17.2	63.1 ± 55.3	86.5 ± 29.3	-7.2 ± 12.1
	30 min	-15.7 ± 5.9	19.3 ± 21.7	49.4 ± 53.0	98.1 ± 31.1	-12.9 ± 12.4
	35 min	-15.8 ± 6.2	23.9 ± 32.0	-21.6 ± 31.2	57.9 ± 35.9	-27.7 ± 14.3
	40 min	-15.5 ± 5.6	21.0 ± 32.2	-30.6 ± 25.2	50.8 ± 13.8	-30.4 ± 18.5
	45 min	-14.7 ± 5.8	20.9 ± 35.1	-30.8 ± 25.3	50.9 ± 21.0	-28.2 ± 19.2
	50 min	-12.0 ± 6.0	11.5 ± 31.5	-35.6 ± 21.5	48.7 ± 20.8	-21.5 ± 15.8
	55 min	-9.6 ± 6.9	9.6 ± 33.0	-36.0 ± 20.3	65.3 ± 26.3	-19.5 ± 14.6
	60 min	-7.7 ± 7.1	14.1 ± 35.1	-35.1 ± 19.6	78.1 ± 31.1	-35.5 ± 20.5
Recovery	5 min	2.4 ± 7.5	-7.2 ± 15.7	28.2 ± 51.9	73.1 ± 19.9	-6.6 ± 11.4
	10 min	9.2 ± 4.6	-5.7 ± 8.3	116.0 ± 80.5	69.0 ± 18.3	2.7 ± 8.8
	15 min	12.3 ± 3.5	4.8 ± 12.8	143.7 ± 101.7	72.8 ± 25.6	2.8 ± 9.2
	20 min	12.7 ± 3.1	10.4 ± 12.4	146.5 ± 100.5	81.5 ± 23.6	5.3 ± 8.7
	25 min	13.5 ± 2.7	10.0 ± 11.5	148.9 ± 106.3	71.6 ± 28.8	11.3 ± 8.7
	30 min	12.0 ± 2.7	8.3 ± 11.7	135.8 ± 101.3	68.9 ± 27.2	11.8 ± 9.5
	35 min	10.5 ± 2.6	3.9 ± 10.0	112.3 ± 98.3	41.6 ± 40.2	12.3 ± 9.2
	40 min	8.1 ± 2.6	1.3 ± 9.6	107.8 ± 96.3	55.1 ± 32.1	12.6 ± 9.5
	45 min	7.9 ± 2.0	-3.7 ± 6.7	110.4 ± 100.9	52.1 ± 40.0	15.5 ± 8.3
	50 min	8.8 ± 2.3	-5.3 ± 8.7	94.5 ± 110.2	47.2 ± 35.5	13.4 ± 9.0
	55 min	11.3 ± 3.0	0.4 ± 9.7	116.3 ± 105.4	56.0 ± 34.8	12.3 ± 8.8
	60 min	12.5 ± 3.4	2.0 ± 10.1	123.1 ± 108.5	50.6 ± 38.3	10.8 ± 8.8

Table 80. Effects of imipramine on ECG from lead AVF in exercise rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.337 ± 0.036	0.101 ± 0.010	0.094 ± 0.016	-0.0005 ± 0.0049	-0.128 ± 0.061
Imipramine	5 min	0.338 ± 0.033	0.106 ± 0.009	0.095 ± 0.012	0.0002 ± 0.0039	-0.122 ± 0.061
	10 min	0.320 ± 0.036	0.100 ± 0.012	0.064 ± 0.033	0.0035 ± 0.0055	-0.135 ± 0.059
	15 min	0.300 ± 0.034	0.100 ± 0.013	0.056 ± 0.030	0.0038 ± 0.0040	-0.181 ± 0.069
	20 min	0.301 ± 0.036	0.099 ± 0.014	0.055 ± 0.039	-0.0018 ± 0.0034	-0.195 ± 0.071
	25 min	0.286 ± 0.038	0.090 ± 0.014	0.017 ± 0.026	-0.0087 ± 0.0032	-0.198 ± 0.070
	30 min	0.279 ± 0.038	0.087 ± 0.014	0.011 ± 0.030	-0.0070 ± 0.0041	-0.203 ± 0.070
	35 min	0.276 ± 0.034	0.089 ± 0.013	0.024 ± 0.033	-0.0032 ± 0.0045	-0.212 ± 0.072
	40 min	0.283 ± 0.032	0.088 ± 0.013	0.024 ± 0.032	-0.0022 ± 0.0043	-0.223 ± 0.069
	45 min	0.283 ± 0.028	0.087 ± 0.013	0.028 ± 0.030	0.0042 ± 0.0037	-0.217 ± 0.069
	50 min	0.296 ± 0.035	0.089 ± 0.011	0.031 ± 0.030	0.0028 ± 0.0030	-0.234 ± 0.063
	55 min	0.286 ± 0.033	0.090 ± 0.010	0.030 ± 0.029	-0.0018 ± 0.0032	-0.230 ± 0.070
	60 min	0.284 ± 0.037	0.094 ± 0.012	0.016 ± 0.034	-0.0017 ± 0.0047	-0.222 ± 0.069
Recovery	5 min	0.301 ± 0.038	0.078 ± 0.013	0.025 ± 0.033	-0.0012 ± 0.0037	-0.214 ± 0.069
	10 min	0.300 ± 0.036	0.076 ± 0.014	0.024 ± 0.034	0.0000 ± 0.0025	-0.179 ± 0.070
	15 min	0.310 ± 0.039	0.078 ± 0.014	0.024 ± 0.034	-0.0033 ± 0.0026	-0.184 ± 0.064
	20 min	0.315 ± 0.036	0.080 ± 0.012	0.058 ± 0.025	-0.0035 ± 0.0015	-0.175 ± 0.066
	25 min	0.312 ± 0.033	0.080 ± 0.013	0.054 ± 0.024	-0.0013 ± 0.0025	-0.167 ± 0.067
	30 min	0.309 ± 0.033	0.080 ± 0.013	0.058 ± 0.025	-0.0015 ± 0.0025	-0.161 ± 0.065
	35 min	0.311 ± 0.033	0.079 ± 0.014	0.059 ± 0.024	-0.0032 ± 0.0027	-0.159 ± 0.065
	40 min	0.308 ± 0.034	0.083 ± 0.013	0.081 ± 0.013	-0.0005 ± 0.0026	-0.161 ± 0.066
	45 min	0.309 ± 0.035	0.084 ± 0.013	0.081 ± 0.013	-0.0007 ± 0.0022	-0.161 ± 0.067
	50 min	0.310 ± 0.034	0.084 ± 0.013	0.080 ± 0.014	-0.0012 ± 0.0030	-0.159 ± 0.067
	55 min	0.311 ± 0.033	0.083 ± 0.013	0.081 ± 0.014	0.0003 ± 0.0037	-0.160 ± 0.068
	60 min	0.310 ± 0.033	0.083 ± 0.013	0.080 ± 0.014	-0.0005 ± 0.0034	-0.161 ± 0.069

Table 81. Effects of imipramine on ECG from lead AVF in carvedilol rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	0.6 ± 1.0	6.5 ± 6.6	21.2 ± 24.8	15.9 ± 25.3	5.4 ± 7.9
	10 min	-5.5 ± 1.3	-0.3 ± 9.3	-6.1 ± 37.6	51.9 ± 60.9	-18.7 ± 14.4
	15 min	-11.0 ± 2.8	-1.2 ± 8.4	-27.7 ± 27.1	91.6 ± 50.6	-93.1 ± 41.1
	20 min	-10.7 ± 3.3	-2.6 ± 4.2	-155.7 ± 141.1	4.7 ± 49.3	-112.2 ± 49.3
	25 min	-15.6 ± 4.2	-10.5 ± 9.5	-134.4 ± 70.0	-195.2 ± 77.6	-155.9 ± 103.9
	30 min	-17.9 ± 4.3	-13.9 ± 8.3	-163.5 ± 98.0	-207.8 ± 87.8	-171.9 ± 128.5
	35 min	-18.1 ± 4.2	-11.9 ± 7.7	-146.1 ± 92.1	-126.6 ± 75.2	-205.4 ± 160.2
	40 min	-15.6 ± 4.5	-12.9 ± 7.2	-138.2 ± 81.6	-95.5 ± 60.1	-239.5 ± 177.0
	45 min	-14.6 ± 5.3	-13.7 ± 7.6	-121.6 ± 66.7	20.4 ± 82.8	-229.8 ± 171.0
	50 min	-11.7 ± 5.6	-11.2 ± 6.8	-121.4 ± 70.8	8.1 ± 66.0	-283.8 ± 204.6
	55 min	-14.2 ± 6.3	-9.4 ± 5.4	-121.5 ± 69.5	-53.9 ± 51.7	-280.7 ± 208.6
	60 min	-15.4 ± 6.4	-6.8 ± 5.3	-128.9 ± 63.7	-99.0 ± 101.1	-272.4 ± 210.4
Recovery	5 min	-9.5 ± 7.6	-23.4 ± 7.4	-105.0 ± 47.9	-60.9 ± 52.1	-282.0 ± 232.9
	10 min	-9.9 ± 7.2	-26.2 ± 9.0	-102.8 ± 46.3	-18.0 ± 35.9	-184.1 ± 157.7
	15 min	-7.7 ± 6.0	-23.5 ± 9.0	-104.2 ± 47.9	-73.9 ± 41.2	-188.5 ± 144.8
	20 min	-5.6 ± 5.5	-21.3 ± 6.7	-18.4 ± 30.9	-59.1 ± 35.9	-166.3 ± 129.8
	25 min	-6.5 ± 5.2	-20.6 ± 7.8	-23.6 ± 30.3	-1.1 ± 59.2	-135.4 ± 104.8
	30 min	-7.4 ± 5.4	-20.7 ± 8.5	-18.7 ± 31.7	-12.5 ± 55.3	-111.3 ± 76.9
	35 min	-6.7 ± 5.5	-21.9 ± 9.3	-18.0 ± 30.1	-52.4 ± 68.6	-94.4 ± 60.1
	40 min	-7.6 ± 5.6	-18.0 ± 7.9	1.8 ± 21.6	6.3 ± 37.9	-86.3 ± 44.0
	45 min	-7.4 ± 5.5	-16.3 ± 8.4	2.5 ± 22.2	3.3 ± 31.7	-80.3 ± 39.6
	50 min	-7.1 ± 5.0	-16.7 ± 9.0	1.2 ± 21.7	12.3 ± 63.3	-74.4 ± 37.2
	55 min	-6.8 ± 5.0	-17.2 ± 8.5	1.4 ± 21.6	30.6 ± 78.4	-72.6 ± 33.9
	60 min	-7.0 ± 4.8	-16.9 ± 8.7	1.1 ± 21.8	12.2 ± 62.5	-70.3 ± 32.0

Table 82. Effects of imipramine on ECG from lead AVF in carvedilol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.286 ± 0.045	0.128 ± 0.012	0.109 ± 0.006	-0.0038 ± 0.0045	-0.249 ± 0.066
Imipramine	5 min	0.288 ± 0.044	0.131 ± 0.011	0.111 ± 0.005	-0.0028 ± 0.0042	-0.247 ± 0.065
	10 min	0.254 ± 0.044	0.139 ± 0.012	0.114 ± 0.009	0.0015 ± 0.0040	-0.282 ± 0.062
	15 min	0.246 ± 0.037	0.146 ± 0.015	0.089 ± 0.011	-0.0017 ± 0.0039	-0.322 ± 0.060
	20 min	0.235 ± 0.031	0.143 ± 0.014	0.056 ± 0.022	-0.0033 ± 0.0090	-0.302 ± 0.054
	25 min	0.224 ± 0.030	0.140 ± 0.014	0.064 ± 0.016	-0.0023 ± 0.0050	-0.276 ± 0.049
	30 min	0.215 ± 0.030	0.136 ± 0.013	0.069 ± 0.012	-0.0023 ± 0.0057	-0.277 ± 0.041
	35 min	0.219 ± 0.026	0.134 ± 0.014	0.070 ± 0.012	-0.0023 ± 0.0059	-0.257 ± 0.044
	40 min	0.218 ± 0.025	0.130 ± 0.016	0.070 ± 0.009	-0.0057 ± 0.0107	-0.255 ± 0.039
	45 min	0.214 ± 0.029	0.122 ± 0.015	0.072 ± 0.011	-0.0032 ± 0.0090	-0.257 ± 0.041
	50 min	0.213 ± 0.032	0.109 ± 0.018	0.050 ± 0.022	-0.0068 ± 0.0076	-0.249 ± 0.043
	55 min	0.213 ± 0.033	0.103 ± 0.017	0.044 ± 0.021	-0.0063 ± 0.0067	-0.238 ± 0.042
	60 min	0.214 ± 0.034	0.102 ± 0.017	0.043 ± 0.019	-0.0037 ± 0.0055	-0.230 ± 0.042
Recovery	5 min	0.232 ± 0.030	0.101 ± 0.019	0.054 ± 0.021	-0.0040 ± 0.0066	-0.223 ± 0.054
	10 min	0.219 ± 0.031	0.096 ± 0.018	0.054 ± 0.021	-0.0037 ± 0.0073	-0.225 ± 0.056
	15 min	0.215 ± 0.034	0.088 ± 0.020	0.049 ± 0.024	0.0002 ± 0.0042	-0.214 ± 0.056
	20 min	0.215 ± 0.035	0.092 ± 0.019	0.046 ± 0.024	-0.0005 ± 0.0053	-0.214 ± 0.051
	25 min	0.219 ± 0.033	0.095 ± 0.019	0.053 ± 0.021	-0.0015 ± 0.0064	-0.203 ± 0.052
	30 min	0.225 ± 0.034	0.095 ± 0.020	0.051 ± 0.021	-0.0013 ± 0.0061	-0.191 ± 0.051
	35 min	0.226 ± 0.034	0.093 ± 0.019	0.056 ± 0.020	-0.0023 ± 0.0062	-0.199 ± 0.050
	40 min	0.225 ± 0.037	0.089 ± 0.018	0.054 ± 0.020	0.0000 ± 0.0047	-0.191 ± 0.049
	45 min	0.225 ± 0.037	0.089 ± 0.018	0.053 ± 0.021	-0.0007 ± 0.0054	-0.189 ± 0.049
	50 min	0.225 ± 0.038	0.089 ± 0.018	0.053 ± 0.023	-0.0002 ± 0.0041	-0.189 ± 0.050
	55 min	0.222 ± 0.040	0.091 ± 0.017	0.055 ± 0.022	-0.0023 ± 0.0052	-0.197 ± 0.047
	60 min	0.224 ± 0.039	0.091 ± 0.017	0.053 ± 0.023	-0.0028 ± 0.0047	-0.198 ± 0.047

Table 83. Effects of imipramine on ECG from lead AVF in clenbuterol rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	1.5 ± 1.9	2.1 ± 1.1	2.6 ± 2.5	9.5 ± 6.5	0.3 ± 3.2
	10 min	-12.2 ± 4.5	8.8 ± 5.7	4.3 ± 4.4	23.5 ± 56.7	-18.8 ± 14.3
	15 min	-13.4 ± 4.4	13.7 ± 7.7	-18.3 ± 9.0	-12.7 ± 58.6	-39.5 ± 20.6
	20 min	-12.6 ± 9.2	11.4 ± 7.4	-49.8 ± 20.9	250.4 ± 257.3	-32.8 ± 20.4
	25 min	-16.6 ± 9.7	10.1 ± 8.2	-40.1 ± 14.7	-38.7 ± 93.1	-22.9 ± 18.8
	30 min	-19.1 ± 10.9	7.3 ± 8.7	-36.6 ± 10.4	8.9 ± 52.7	-26.9 ± 17.6
	35 min	-15.6 ± 12.0	5.7 ± 10.7	-34.9 ± 10.4	8.0 ± 51.0	-15.3 ± 17.4
	40 min	-14.6 ± 13.4	3.1 ± 13.2	-34.3 ± 9.0	77.6 ± 86.1	-17.7 ± 18.0
	45 min	-17.3 ± 13.1	-4.1 ± 11.5	-33.5 ± 10.1	126.3 ± 111.2	-18.0 ± 18.3
	50 min	-17.4 ± 13.6	-15.3 ± 12.6	-51.2 ± 19.6	-135.6 ± 151.1	-13.5 ± 18.8
	55 min	-17.9 ± 13.7	-19.5 ± 12.8	-56.3 ± 18.8	-110.5 ± 121.3	-12.1 ± 21.0
	60 min	-18.2 ± 13.2	-20.0 ± 12.5	-56.8 ± 17.1	42.5 ± 84.4	-8.3 ± 21.2
Recovery	5 min	-10.6 ± 13.6	-22.1 ± 12.6	-47.3 ± 18.4	-52.2 ± 92.8	-0.6 ± 22.1
	10 min	-16.9 ± 11.9	-26.1 ± 10.5	-48.8 ± 18.3	-31.8 ± 92.8	1.5 ± 18.4
	15 min	-20.5 ± 10.8	-33.3 ± 11.8	-52.8 ± 20.4	-37.0 ± 124.4	9.7 ± 15.7
	20 min	-19.9 ± 11.3	-29.8 ± 10.9	-54.6 ± 20.1	51.3 ± 52.9	7.0 ± 14.0
	25 min	-19.4 ± 9.4	-27.0 ± 11.6	-49.4 ± 17.4	28.8 ± 76.8	13.0 ± 13.4
	30 min	-17.4 ± 9.5	-27.3 ± 12.3	-51.0 ± 17.9	51.1 ± 49.7	18.7 ± 13.6
	35 min	-16.4 ± 9.7	-29.4 ± 10.5	-45.9 ± 17.3	-4.1 ± 76.6	14.2 ± 14.5
	40 min	-17.6 ± 9.8	-32.7 ± 9.7	-48.0 ± 17.5	53.8 ± 45.2	17.9 ± 12.3
	45 min	-17.5 ± 9.5	-32.2 ± 10.0	-48.5 ± 17.6	34.7 ± 49.1	19.4 ± 11.2
	50 min	-17.8 ± 10.1	-32.5 ± 9.2	-48.7 ± 19.2	69.8 ± 45.7	19.1 ± 12.5
	55 min	-19.3 ± 9.1	-30.7 ± 8.9	-46.6 ± 18.6	-16.1 ± 68.6	16.3 ± 9.9
	60 min	-18.4 ± 9.2	-30.7 ± 9.1	-48.2 ± 19.6	-36.9 ± 66.5	15.5 ± 10.8

Table 84. Effects of imipramine on ECG from lead AVF in clenbuterol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

	Time	R_a (mV)	T_a (mV)	P_a (mV)	Q_a (mV)	S_a (mV)
Baseline		0.362 ± 0.033	0.089 ± 0.007	0.088 ± 0.014	-0.0012 ± 0.0031	-0.064 ± 0.028
Imipramine	5 min	0.372 ± 0.033	0.090 ± 0.007	0.091 ± 0.015	-0.0013 ± 0.0029	-0.060 ± 0.027
	10 min	0.329 ± 0.033	0.100 ± 0.006	0.115 ± 0.007	-0.0030 ± 0.0011	-0.104 ± 0.046
	15 min	0.282 ± 0.024	0.104 ± 0.009	0.097 ± 0.008	0.0007 ± 0.0042	-0.152 ± 0.048
	20 min	0.267 ± 0.021	0.101 ± 0.011	0.077 ± 0.007	0.0005 ± 0.0024	-0.164 ± 0.052
	25 min	0.265 ± 0.019	0.099 ± 0.013	0.067 ± 0.010	-0.0018 ± 0.0016	-0.183 ± 0.058
	30 min	0.268 ± 0.021	0.099 ± 0.013	0.048 ± 0.017	-0.0032 ± 0.0023	-0.192 ± 0.058
	35 min	0.264 ± 0.018	0.100 ± 0.014	0.050 ± 0.018	-0.0012 ± 0.0007	-0.202 ± 0.063
	40 min	0.274 ± 0.022	0.102 ± 0.015	0.047 ± 0.022	-0.0005 ± 0.0019	-0.221 ± 0.072
	45 min	0.276 ± 0.022	0.098 ± 0.015	0.040 ± 0.023	-0.0003 ± 0.0027	-0.224 ± 0.072
	50 min	0.277 ± 0.022	0.093 ± 0.014	0.038 ± 0.023	-0.0047 ± 0.0043	-0.216 ± 0.069
	55 min	0.288 ± 0.029	0.090 ± 0.014	0.046 ± 0.020	-0.0015 ± 0.0019	-0.195 ± 0.066
	60 min	0.298 ± 0.031	0.091 ± 0.015	0.060 ± 0.020	0.0003 ± 0.0017	-0.183 ± 0.062
Recovery	5 min	0.322 ± 0.033	0.086 ± 0.014	0.060 ± 0.019	0.0005 ± 0.0018	-0.177 ± 0.063
	10 min	0.330 ± 0.032	0.082 ± 0.015	0.064 ± 0.020	0.0003 ± 0.0025	-0.145 ± 0.048
	15 min	0.340 ± 0.033	0.080 ± 0.015	0.071 ± 0.021	0.0005 ± 0.0021	-0.102 ± 0.032
	20 min	0.348 ± 0.038	0.081 ± 0.014	0.066 ± 0.021	-0.0007 ± 0.0025	-0.097 ± 0.033
	25 min	0.345 ± 0.038	0.082 ± 0.014	0.065 ± 0.021	-0.0012 ± 0.0026	-0.088 ± 0.030
	30 min	0.343 ± 0.038	0.082 ± 0.014	0.066 ± 0.021	-0.0025 ± 0.0027	-0.086 ± 0.031
	35 min	0.342 ± 0.039	0.082 ± 0.014	0.066 ± 0.021	-0.0018 ± 0.0033	-0.084 ± 0.030
	40 min	0.341 ± 0.038	0.081 ± 0.014	0.066 ± 0.021	-0.0020 ± 0.0036	-0.080 ± 0.027
	45 min	0.341 ± 0.038	0.081 ± 0.013	0.067 ± 0.021	-0.0023 ± 0.0037	-0.082 ± 0.027
	50 min	0.339 ± 0.039	0.084 ± 0.012	0.068 ± 0.022	-0.0032 ± 0.0042	-0.084 ± 0.028
	55 min	0.336 ± 0.038	0.085 ± 0.012	0.068 ± 0.022	-0.0020 ± 0.0040	-0.081 ± 0.028
	60 min	0.333 ± 0.036	0.089 ± 0.013	0.092 ± 0.007	-0.0023 ± 0.0041	-0.079 ± 0.028

Table 85. Effects of imipramine on ECG from lead AVF in dobutamine rats. Values are means ± SE; n = 6.

	Time	R_a (%)	T_a (%)	P_a (%)	Q_a (%)	S_a (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	2.8 ± 1.4	0.9 ± 1.9	2.4 ± 2.8	10.0 ± 18.4	9.4 ± 4.2
	10 min	-9.4 ± 3.3	13.2 ± 5.0	82.5 ± 68.6	-16.5 ± 31.1	-56.3 ± 28.6
	15 min	-21.9 ± 3.3	17.6 ± 9.7	32.7 ± 28.6	37.1 ± 73.4	-212.1 ± 111.6
	20 min	-25.4 ± 3.4	13.8 ± 11.9	9.4 ± 27.8	44.5 ± 56.4	-227.4 ± 105.9
	25 min	-25.7 ± 3.1	12.5 ± 14.3	-0.2 ± 32.2	-16.3 ± 47.4	-274.1 ± 141.0
	30 min	-25.1 ± 3.5	13.8 ± 17.9	-14.0 ± 40.4	-19.1 ± 43.5	-307.5 ± 146.3
	35 min	-26.0 ± 3.3	15.7 ± 19.3	-11.9 ± 40.4	-3.1 ± 34.8	-336.9 ± 180.1
	40 min	-23.4 ± 3.1	17.7 ± 21.5	-18.9 ± 41.6	-14.4 ± 40.5	-373.9 ± 201.1
	45 min	-22.9 ± 3.1	13.0 ± 20.6	-28.5 ± 41.5	-21.8 ± 45.9	-392.5 ± 214.8
	50 min	-22.7 ± 3.1	6.4 ± 18.4	-31.7 ± 39.9	-85.5 ± 53.7	-363.8 ± 168.9
	55 min	-19.7 ± 4.7	2.9 ± 17.9	-23.6 ± 38.3	-39.2 ± 62.2	-271.9 ± 104.0
	60 min	-17.4 ± 4.4	2.5 ± 16.0	-14.7 ± 33.0	4.6 ± 43.8	-248.5 ± 101.8
Recovery	5 min	-10.8 ± 3.8	-3.0 ± 13.8	-10.1 ± 37.5	3.0 ± 43.1	-252.3 ± 138.3
	10 min	-8.2 ± 4.2	-9.7 ± 12.4	-3.9 ± 39.2	-12.4 ± 64.5	-237.3 ± 163.5
	15 min	-5.5 ± 4.0	-13.0 ± 11.3	16.6 ± 55.9	11.3 ± 40.8	-163.6 ± 132.3
	20 min	-4.1 ± 3.9	-11.0 ± 11.5	0.5 ± 42.3	-14.4 ± 58.9	-161.9 ± 143.1
	25 min	-5.2 ± 3.6	-10.2 ± 12.0	-2.7 ± 40.8	-33.5 ± 71.3	-131.5 ± 115.6
	30 min	-5.6 ± 3.9	-9.1 ± 12.3	-1.3 ± 40.6	-37.4 ± 64.4	-120.1 ± 111.3
	35 min	-5.9 ± 4.1	-8.9 ± 11.6	-1.1 ± 40.8	-13.8 ± 62.6	-105.3 ± 96.2
	40 min	-6.2 ± 3.9	-10.1 ± 11.6	-3.2 ± 38.6	7.8 ± 64.7	-85.0 ± 73.6
	45 min	-6.4 ± 4.2	-9.8 ± 10.8	-0.6 ± 40.7	16.0 ± 72.5	-86.1 ± 71.3
	50 min	-7.0 ± 4.1	-6.0 ± 10.7	-1.0 ± 39.5	9.3 ± 80.9	-84.1 ± 63.6
	55 min	-7.7 ± 4.0	-5.2 ± 10.8	-0.8 ± 39.6	33.9 ± 88.0	-72.0 ± 59.3
	60 min	-8.4 ± 3.3	-0.2 ± 11.7	26.8 ± 27.6	26.2 ± 84.3	-61.4 ± 49.4

Table 86. Effects of imipramine on ECG from lead AVF in dobutamine rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Appendix E: ECG raw data from Lead V3 during imipramine or vehicle infusion

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		166 ± 6	362 ± 12	16.5 ± 0.7	41.0 ± 2.7	24.5 ± 2.2	21.0 ± 1.3
Vehicle	5 min	165 ± 6	365 ± 13	16.2 ± 0.7	40.3 ± 3.2	24.1 ± 2.7	20.9 ± 1.0
	10 min	164 ± 6	368 ± 13	16.1 ± 0.7	40.2 ± 3.2	24.0 ± 2.7	20.9 ± 1.0
	15 min	163 ± 6	371 ± 13	16.1 ± 0.7	39.9 ± 3.2	23.8 ± 2.7	21.0 ± 0.9
	20 min	162 ± 6	372 ± 13	16.1 ± 0.8	39.8 ± 3.2	23.7 ± 2.6	21.0 ± 1.0
	25 min	163 ± 6	370 ± 13	16.0 ± 0.7	39.7 ± 3.1	23.7 ± 2.6	21.0 ± 1.0
	30 min	164 ± 6	367 ± 12	16.0 ± 0.7	39.5 ± 3.1	23.5 ± 2.5	21.1 ± 1.0
	35 min	164 ± 5	367 ± 11	16.1 ± 0.7	39.5 ± 3.1	23.4 ± 2.5	21.2 ± 1.1
	40 min	165 ± 6	366 ± 12	16.2 ± 0.8	39.4 ± 3.1	23.3 ± 2.5	21.3 ± 1.0
	45 min	164 ± 6	367 ± 12	16.2 ± 0.8	39.5 ± 3.0	23.3 ± 2.5	21.3 ± 1.0
	50 min	165 ± 5	366 ± 11	16.2 ± 0.8	39.0 ± 3.2	22.9 ± 2.5	21.6 ± 1.0
	55 min	165 ± 5	365 ± 11	16.2 ± 0.7	39.5 ± 3.0	23.3 ± 2.5	21.5 ± 1.0
	60 min	163 ± 6	369 ± 12	16.1 ± 0.8	39.2 ± 3.1	23.1 ± 2.6	21.5 ± 1.0
Recovery	5 min	163 ± 6	370 ± 12	16.4 ± 0.9	39.3 ± 3.1	22.9 ± 2.5	21.9 ± 1.1
	10 min	162 ± 5	371 ± 12	16.4 ± 0.9	39.2 ± 3.1	22.8 ± 2.6	21.8 ± 1.2
	15 min	163 ± 5	370 ± 11	16.3 ± 0.9	39.3 ± 3.1	22.9 ± 2.6	21.9 ± 1.1
	20 min	162 ± 5	370 ± 11	16.4 ± 0.9	39.3 ± 3.2	22.9 ± 2.6	21.7 ± 1.1
	25 min	162 ± 5	370 ± 11	16.3 ± 0.9	39.3 ± 3.1	22.9 ± 2.5	21.7 ± 1.2
	30 min	162 ± 5	371 ± 11	16.3 ± 0.9	39.2 ± 3.1	22.8 ± 2.6	21.8 ± 1.1
	35 min	162 ± 5	371 ± 10	16.4 ± 0.9	39.2 ± 3.2	22.8 ± 2.6	21.6 ± 1.1
	40 min	161 ± 5	373 ± 11	16.3 ± 0.9	39.0 ± 3.1	22.7 ± 2.5	21.7 ± 1.1
	45 min	164 ± 8	368 ± 16	16.5 ± 0.9	39.3 ± 3.2	22.9 ± 2.6	21.7 ± 1.2
	50 min	162 ± 7	372 ± 14	16.4 ± 0.9	39.2 ± 3.1	22.8 ± 2.5	21.6 ± 1.1
	55 min	161 ± 6	373 ± 14	16.4 ± 0.9	38.9 ± 3.3	22.5 ± 2.7	21.6 ± 1.2
	60 min	161 ± 6	374 ± 13	16.4 ± 0.9	38.6 ± 3.3	22.2 ± 2.6	21.5 ± 1.2

Continued

Table 87. Effects of matched-volume vehicle (sterile water) on ECG from lead V3 in sedentary rats. Values are means ± SE; n = 4.

Table 87. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		71.5 ± 0.9	175.4 ± 3.0	130.0 ± 1.8	10.6 ± 1.2	44.8 ± 2.3	39.6 ± 2.1
Vehicle	5 min	72.6 ± 0.7	178.9 ± 3.5	132.4 ± 2.0	11.0 ± 1.2	43.9 ± 1.9	40.4 ± 2.4
	10 min	72.2 ± 1.1	178.7 ± 3.7	132.1 ± 2.3	11.2 ± 1.2	44.0 ± 1.8	39.8 ± 2.6
	15 min	72.5 ± 1.0	180.2 ± 3.4	133.0 ± 2.0	11.5 ± 1.3	43.7 ± 1.9	39.6 ± 2.5
	20 min	72.6 ± 0.9	180.4 ± 4.0	133.2 ± 2.4	11.3 ± 1.3	43.8 ± 1.9	40.0 ± 2.7
	25 min	73.1 ± 0.6	181.4 ± 3.6	134.0 ± 2.0	11.3 ± 1.3	43.8 ± 1.8	40.5 ± 2.6
	30 min	73.1 ± 0.6	180.9 ± 3.5	133.7 ± 2.0	11.3 ± 1.4	43.9 ± 1.8	40.3 ± 2.5
	35 min	73.0 ± 0.6	180.5 ± 3.6	133.4 ± 2.1	11.2 ± 1.4	44.0 ± 1.7	40.2 ± 2.7
	40 min	72.3 ± 0.6	178.6 ± 3.8	132.2 ± 2.1	11.2 ± 1.3	44.0 ± 1.6	39.7 ± 2.5
	45 min	71.6 ± 1.0	176.9 ± 3.2	130.8 ± 1.9	11.2 ± 1.3	44.1 ± 1.6	38.8 ± 2.4
	50 min	72.4 ± 0.6	178.9 ± 3.2	132.3 ± 1.8	11.4 ± 1.4	44.2 ± 1.7	39.4 ± 2.5
	55 min	72.2 ± 0.8	178.0 ± 4.0	131.7 ± 2.4	11.3 ± 1.3	43.9 ± 1.8	39.2 ± 2.7
	60 min	73.1 ± 1.1	181.2 ± 5.1	133.9 ± 3.1	11.4 ± 1.3	43.7 ± 1.6	39.9 ± 3.0
Recovery	5 min	72.3 ± 1.4	179.5 ± 4.9	132.5 ± 3.1	11.6 ± 1.4	43.9 ± 1.4	38.7 ± 2.3
	10 min	72.1 ± 1.1	179.1 ± 3.6	132.2 ± 2.3	11.5 ± 1.2	43.7 ± 1.4	38.6 ± 1.9
	15 min	72.9 ± 1.6	181.0 ± 4.4	133.7 ± 3.0	11.7 ± 1.3	43.9 ± 1.4	39.2 ± 1.9
	20 min	72.8 ± 1.4	180.8 ± 3.1	133.5 ± 2.2	11.8 ± 1.3	43.7 ± 1.2	39.2 ± 1.5
	25 min	72.0 ± 1.4	178.7 ± 3.3	131.9 ± 2.3	11.9 ± 1.5	43.5 ± 1.2	38.3 ± 2.0
	30 min	72.1 ± 1.6	179.2 ± 3.4	132.3 ± 2.5	11.9 ± 1.3	43.5 ± 1.2	38.3 ± 1.5
	35 min	72.4 ± 1.5	180.2 ± 3.6	133.0 ± 2.6	11.8 ± 1.4	43.5 ± 1.1	39.0 ± 1.6
	40 min	72.7 ± 1.5	181.0 ± 3.4	133.5 ± 2.4	12.0 ± 1.5	43.2 ± 1.1	38.9 ± 1.6
	45 min	70.5 ± 1.3	174.4 ± 5.8	128.9 ± 3.6	11.5 ± 1.2	42.4 ± 0.6	37.3 ± 2.4
	50 min	72.2 ± 1.6	179.8 ± 3.4	132.7 ± 2.4	12.0 ± 1.5	43.5 ± 0.7	38.4 ± 1.4
	55 min	72.6 ± 1.4	181.1 ± 4.7	133.5 ± 3.0	12.0 ± 1.4	43.7 ± 0.5	38.9 ± 2.0
	60 min	72.7 ± 1.6	181.5 ± 3.7	133.8 ± 2.5	12.1 ± 1.7	43.4 ± 0.7	38.8 ± 1.6

Values are means ± SE. n = 4.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	-0.9 ± 0.6	0.9 ± 0.6	-1.8 ± 0.5	-2.0 ± 1.6	-2.2 ± 2.5	-0.3 ± 1.1
	10 min	-1.7 ± 0.8	1.7 ± 0.8	-2.0 ± 0.5	-2.2 ± 1.8	-2.6 ± 2.8	-0.3 ± 1.5
	15 min	-2.3 ± 0.6	2.3 ± 0.7	-2.3 ± 0.5	-2.9 ± 1.8	-3.6 ± 2.9	0.2 ± 1.9
	20 min	-2.5 ± 0.8	2.6 ± 0.8	-2.3 ± 0.5	-3.1 ± 1.8	-3.9 ± 2.7	0.5 ± 1.7
	25 min	-2.1 ± 0.8	2.1 ± 0.8	-2.7 ± 0.5	-3.4 ± 1.8	-3.9 ± 2.7	0.6 ± 1.6
	30 min	-1.4 ± 1.1	1.4 ± 1.1	-2.6 ± 0.5	-3.8 ± 1.7	-4.8 ± 2.5	1.0 ± 1.3
	35 min	-1.3 ± 1.1	1.3 ± 1.2	-2.4 ± 0.5	-3.8 ± 1.6	-4.8 ± 2.4	1.4 ± 1.1
	40 min	-1.0 ± 1.0	1.1 ± 1.1	-2.0 ± 0.7	-4.0 ± 1.8	-5.4 ± 2.6	1.6 ± 1.4
	45 min	-1.3 ± 1.1	1.3 ± 1.1	-1.8 ± 0.5	-3.9 ± 1.5	-5.3 ± 2.2	1.9 ± 1.4
	50 min	-1.0 ± 0.6	1.0 ± 0.6	-1.9 ± 0.9	-4.9 ± 2.3	-7.0 ± 3.2	3.1 ± 1.4
	55 min	-0.9 ± 0.4	0.9 ± 0.4	-1.8 ± 0.3	-3.8 ± 1.5	-5.4 ± 2.4	2.7 ± 1.5
	60 min	-1.9 ± 0.6	2.0 ± 0.6	-2.3 ± 0.6	-4.5 ± 1.8	-6.1 ± 2.8	2.7 ± 1.4
Recovery	5 min	-2.2 ± 0.7	2.3 ± 0.7	-0.5 ± 1.1	-4.4 ± 1.8	-7.2 ± 2.8	4.6 ± 1.0
	10 min	-2.3 ± 0.7	2.4 ± 0.7	-0.6 ± 1.4	-4.5 ± 2.0	-7.3 ± 3.0	4.2 ± 0.8
	15 min	-2.2 ± 0.9	2.2 ± 0.9	-1.0 ± 1.4	-4.4 ± 2.0	-6.9 ± 3.1	4.4 ± 1.0
	20 min	-2.2 ± 1.0	2.3 ± 1.0	-0.6 ± 1.3	-4.2 ± 2.0	-6.9 ± 3.2	3.7 ± 1.1
	25 min	-2.3 ± 0.7	2.3 ± 0.8	-0.8 ± 1.3	-4.4 ± 1.9	-7.0 ± 3.0	3.8 ± 0.8
	30 min	-2.6 ± 0.7	2.7 ± 0.8	-0.9 ± 1.5	-4.6 ± 2.1	-7.3 ± 3.2	3.9 ± 0.9
	35 min	-2.5 ± 0.6	2.6 ± 0.6	-0.8 ± 1.3	-4.6 ± 2.3	-7.3 ± 3.6	3.4 ± 1.1
	40 min	-2.9 ± 0.4	3.0 ± 0.5	-0.8 ± 1.5	-4.9 ± 2.1	-7.9 ± 3.1	3.5 ± 0.9
	45 min	-1.4 ± 1.1	1.4 ± 1.1	-0.1 ± 1.2	-4.3 ± 2.3	-7.3 ± 3.4	3.4 ± 0.7
	50 min	-2.7 ± 0.5	2.7 ± 0.6	-0.3 ± 1.3	-4.5 ± 1.8	-7.5 ± 2.8	3.0 ± 0.9
	55 min	-3.0 ± 0.4	3.0 ± 0.4	-0.6 ± 1.2	-5.4 ± 2.7	-8.7 ± 4.1	3.1 ± 0.6
	60 min	-3.2 ± 0.1	3.3 ± 0.1	-0.4 ± 1.4	-6.0 ± 2.8	-10.0 ± 4.0	2.8 ± 0.7

Continued

Table 88. Effects of matched-volume vehicle (sterile water) on ECG from lead V3 in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 4.

Table 88. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Vehicle	5 min	1.6 ± 2.0	2.0 ± 2.0	1.9 ± 2.0	4.8 ± 3.8	-2.0 ± 1.1	2.0 ± 3.9
	10 min	1.1 ± 2.2	1.9 ± 2.0	1.6 ± 2.1	6.5 ± 5.5	-1.7 ± 1.1	0.6 ± 5.0
	15 min	1.5 ± 1.9	2.8 ± 1.7	2.4 ± 1.7	9.9 ± 7.0	-2.5 ± 1.0	0.4 ± 5.2
	20 min	1.6 ± 2.1	2.9 ± 1.9	2.5 ± 1.9	7.6 ± 6.6	-2.0 ± 1.0	1.1 ± 4.8
	25 min	2.3 ± 2.0	3.4 ± 1.8	3.1 ± 1.9	7.6 ± 6.6	-2.0 ± 1.0	2.3 ± 4.5
	30 min	2.4 ± 2.1	3.2 ± 2.0	2.9 ± 2.0	7.3 ± 6.4	-1.9 ± 1.2	1.8 ± 4.3
	35 min	2.2 ± 2.1	2.9 ± 1.9	2.7 ± 2.0	5.9 ± 5.9	-1.6 ± 1.4	1.5 ± 4.4
	40 min	1.3 ± 1.6	1.9 ± 1.4	1.7 ± 1.4	6.1 ± 6.0	-1.5 ± 1.6	0.1 ± 3.4
	45 min	0.2 ± 1.7	0.9 ± 1.2	0.6 ± 1.4	5.9 ± 5.4	-1.3 ± 1.7	-1.9 ± 4.1
	50 min	1.4 ± 1.5	2.0 ± 1.2	1.8 ± 1.3	7.5 ± 5.2	-1.1 ± 1.5	-0.6 ± 3.5
	55 min	1.0 ± 2.0	1.5 ± 1.9	1.3 ± 1.9	6.9 ± 5.3	-1.9 ± 1.3	-1.0 ± 4.4
	60 min	2.3 ± 2.0	3.3 ± 1.8	3.0 ± 1.9	8.3 ± 5.9	-2.3 ± 1.6	0.7 ± 4.6
Recovery	5 min	1.1 ± 0.9	2.3 ± 1.1	1.9 ± 1.0	9.4 ± 6.0	-1.7 ± 2.0	-2.4 ± 1.7
	10 min	0.9 ± 0.4	2.1 ± 0.5	1.7 ± 0.5	9.8 ± 6.0	-2.1 ± 2.1	-2.2 ± 1.9
	15 min	2.0 ± 1.0	3.2 ± 1.3	2.8 ± 1.2	11.2 ± 7.2	-1.8 ± 2.1	-0.7 ± 2.5
	20 min	1.8 ± 0.9	3.1 ± 1.1	2.7 ± 1.0	11.8 ± 7.2	-2.2 ± 2.4	-0.6 ± 3.2
	25 min	0.7 ± 1.3	1.9 ± 1.1	1.5 ± 1.2	12.5 ± 7.7	-2.5 ± 2.6	-3.0 ± 3.9
	30 min	0.8 ± 1.1	2.2 ± 1.3	1.7 ± 1.2	13.0 ± 7.1	-2.5 ± 2.6	-2.8 ± 3.3
	35 min	1.3 ± 0.9	2.7 ± 1.2	2.2 ± 1.1	11.9 ± 6.3	-2.6 ± 2.7	-1.3 ± 2.0
	40 min	1.7 ± 1.0	3.2 ± 1.2	2.7 ± 1.1	13.3 ± 6.6	-3.1 ± 2.8	-1.5 ± 2.3
	45 min	-1.4 ± 1.4	-0.6 ± 1.8	-0.9 ± 1.7	10.2 ± 8.3	-4.7 ± 4.2	-5.8 ± 2.6
	50 min	1.0 ± 1.2	2.5 ± 1.1	2.0 ± 1.1	13.9 ± 6.0	-2.4 ± 3.7	-2.5 ± 3.0
	55 min	1.5 ± 1.1	3.2 ± 1.2	2.6 ± 1.2	13.6 ± 7.3	-1.8 ± 4.3	-1.8 ± 0.5
	60 min	1.7 ± 1.1	3.5 ± 1.0	2.9 ± 1.0	14.5 ± 8.1	-2.5 ± 4.0	-1.7 ± 2.1

Values are means ± SE. n = 4.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		147 ± 8	413 ± 21	15.3 ± 0.7	40.4 ± 1.2	25.0 ± 1.4	19.7 ± 0.7
Imipramine	5 min	146 ± 8	416 ± 22	15.3 ± 0.7	40.2 ± 1.1	24.9 ± 1.4	19.6 ± 0.7
	10 min	140 ± 8	433 ± 20	15.4 ± 0.7	41.1 ± 1.0	25.7 ± 1.2	19.6 ± 0.6
	15 min	148 ± 8	411 ± 21	15.3 ± 0.6	41.7 ± 0.9	26.3 ± 1.0	20.5 ± 0.8
	20 min	160 ± 11	383 ± 24	15.9 ± 0.5	43.3 ± 1.3	27.4 ± 1.2	21.3 ± 0.9
	25 min	175 ± 12	352 ± 25	16.5 ± 0.5	44.5 ± 1.8	28.0 ± 1.6	22.2 ± 0.9
	30 min	185 ± 13	332 ± 21	17.0 ± 0.7	45.5 ± 1.7	28.4 ± 1.5	22.9 ± 0.9
	35 min	190 ± 14	324 ± 22	17.2 ± 0.7	46.3 ± 1.7	29.1 ± 1.4	23.5 ± 0.9
	40 min	194 ± 14	316 ± 21	17.7 ± 0.9	47.2 ± 1.4	29.5 ± 1.1	23.8 ± 1.0
	45 min	192 ± 15	322 ± 25	17.5 ± 0.6	48.1 ± 1.3	30.6 ± 1.0	24.0 ± 1.2
	50 min	189 ± 14	326 ± 23	17.7 ± 0.8	49.2 ± 1.6	31.5 ± 1.3	24.2 ± 1.2
	55 min	190 ± 15	326 ± 25	17.4 ± 0.6	49.1 ± 1.5	31.7 ± 1.1	24.0 ± 1.2
	60 min	186 ± 15	333 ± 27	17.7 ± 0.7	50.0 ± 1.3	32.3 ± 0.9	24.1 ± 1.1
Recovery	5 min	179 ± 16	347 ± 29	16.9 ± 0.9	47.8 ± 1.2	30.9 ± 0.7	23.8 ± 1.3
	10 min	174 ± 16	359 ± 31	16.9 ± 1.1	46.1 ± 1.4	29.2 ± 1.0	23.7 ± 1.1
	15 min	172 ± 16	363 ± 32	16.8 ± 1.0	45.3 ± 1.4	28.5 ± 1.1	23.0 ± 0.9
	20 min	173 ± 17	364 ± 34	16.8 ± 1.1	45.2 ± 1.6	28.4 ± 1.0	22.4 ± 0.8
	25 min	172 ± 17	366 ± 34	16.8 ± 1.1	44.8 ± 1.5	28.0 ± 1.0	22.0 ± 0.8
	30 min	172 ± 18	367 ± 35	16.8 ± 1.1	44.1 ± 1.3	27.3 ± 1.0	22.2 ± 0.9
	35 min	171 ± 17	368 ± 35	16.7 ± 1.1	44.2 ± 1.5	27.5 ± 0.9	21.7 ± 0.8
	40 min	170 ± 17	369 ± 35	16.7 ± 1.1	43.9 ± 1.4	27.2 ± 0.9	21.6 ± 0.8
	45 min	171 ± 18	369 ± 36	16.7 ± 1.1	43.4 ± 1.2	26.7 ± 1.0	21.5 ± 0.8
	50 min	170 ± 18	371 ± 36	16.7 ± 1.1	43.1 ± 1.2	26.5 ± 1.0	21.5 ± 0.8
	55 min	171 ± 18	368 ± 34	16.6 ± 1.1	43.1 ± 1.2	26.5 ± 0.9	21.7 ± 0.9
	60 min	170 ± 18	371 ± 35	16.5 ± 1.1	43.2 ± 1.3	26.8 ± 0.9	21.2 ± 0.7

Continued

Table 89. Effects of imipramine on ECG from lead V3 in sedentary rats. Values are means ± SE; n = 6.

Table 89. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		71.6 ± 2.5	187.1 ± 6.0	135.8 ± 4.2	9.1 ± 0.9	48.9 ± 1.7	42.5 ± 2.9
Imipramine	5 min	71.3 ± 2.3	187.1 ± 5.5	135.6 ± 3.8	9.2 ± 0.9	48.7 ± 1.6	41.9 ± 2.7
	10 min	70.9 ± 1.7	190.3 ± 5.8	136.9 ± 3.6	9.2 ± 0.7	48.9 ± 2.6	41.6 ± 2.2
	15 min	72.6 ± 3.6	189.1 ± 8.4	137.4 ± 6.2	9.1 ± 0.7	50.2 ± 3.1	42.6 ± 3.8
	20 min	75.5 ± 4.0	189.3 ± 8.4	139.2 ± 6.4	8.7 ± 0.7	51.9 ± 3.1	45.5 ± 4.0
	25 min	78.8 ± 3.9	189.6 ± 8.6	141.4 ± 6.3	8.2 ± 0.7	52.6 ± 3.4	48.8 ± 3.5
	30 min	80.8 ± 4.3	189.0 ± 10.7	142.3 ± 7.7	8.1 ± 0.8	54.3 ± 3.5	49.6 ± 4.0
	35 min	82.2 ± 3.9	190.1 ± 10.5	143.6 ± 7.3	8.2 ± 0.8	55.6 ± 3.8	50.0 ± 3.8
	40 min	82.4 ± 4.4	188.1 ± 10.5	142.7 ± 7.6	8.4 ± 0.8	56.3 ± 3.8	50.4 ± 4.2
	45 min	82.0 ± 4.5	188.5 ± 10.0	142.8 ± 7.3	8.7 ± 0.9	56.3 ± 4.2	49.9 ± 4.5
	50 min	81.8 ± 4.2	189.2 ± 9.6	143.0 ± 7.0	9.3 ± 0.9	57.1 ± 4.3	48.9 ± 4.2
	55 min	81.2 ± 4.6	187.8 ± 10.6	141.9 ± 7.8	9.4 ± 1.0	56.8 ± 4.5	48.8 ± 4.4
	60 min	81.5 ± 4.6	190.3 ± 10.1	143.3 ± 7.4	9.5 ± 1.0	56.3 ± 4.5	48.5 ± 4.8
Recovery	5 min	80.3 ± 4.4	191.0 ± 9.0	143.0 ± 6.7	9.2 ± 1.0	55.6 ± 4.3	47.1 ± 4.8
	10 min	77.9 ± 4.3	188.2 ± 8.7	140.1 ± 6.4	9.1 ± 0.9	55.2 ± 4.3	44.7 ± 4.6
	15 min	77.8 ± 4.6	188.7 ± 9.2	140.3 ± 6.9	9.2 ± 1.0	54.3 ± 4.2	45.0 ± 5.0
	20 min	77.8 ± 4.9	188.7 ± 10.2	140.3 ± 7.5	9.3 ± 1.1	53.5 ± 4.1	45.3 ± 5.3
	25 min	76.1 ± 4.6	185.3 ± 10.7	137.5 ± 7.5	9.5 ± 1.1	52.9 ± 4.0	43.7 ± 5.2
	30 min	75.3 ± 3.7	183.8 ± 8.5	136.4 ± 5.7	9.3 ± 1.2	52.6 ± 3.9	43.5 ± 4.6
	35 min	74.8 ± 4.1	182.8 ± 9.0	135.6 ± 6.3	9.5 ± 1.2	52.3 ± 3.7	42.9 ± 4.9
	40 min	75.8 ± 4.5	184.9 ± 9.1	137.2 ± 6.7	9.6 ± 1.2	51.9 ± 3.7	43.3 ± 5.2
	45 min	75.2 ± 4.2	184.3 ± 10.3	136.5 ± 7.1	9.5 ± 1.3	51.5 ± 3.5	43.3 ± 5.1
	50 min	74.4 ± 4.0	182.5 ± 9.7	135.1 ± 6.6	9.5 ± 1.3	51.0 ± 3.2	42.5 ± 4.9
	55 min	75.5 ± 3.1	184.4 ± 7.5	136.7 ± 4.6	9.5 ± 1.4	50.8 ± 3.0	43.6 ± 4.2
	60 min	73.7 ± 3.2	181.2 ± 8.6	134.1 ± 5.4	9.6 ± 1.3	50.4 ± 3.0	41.9 ± 4.2

Values are means ± SE. n = 6.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-7.2 ± 3.0	0.7 ± 0.5	-0.1 ± 0.5	-0.4 ± 0.3	-0.6 ± 0.3	-0.7 ± 0.1
	10 min	-4.6 ± 1.7	5.0 ± 1.9	0.2 ± 0.9	1.9 ± 0.7	3.0 ± 1.4	-0.3 ± 1.1
	15 min	0.8 ± 4.1	-0.1 ± 3.5	0.1 ± 1.6	3.4 ± 1.4	5.8 ± 2.1	4.2 ± 4.0
	20 min	8.8 ± 5.0	-7.2 ± 3.8	3.7 ± 1.6	7.4 ± 2.3	10.4 ± 4.2	8.6 ± 4.7
	25 min	18.6 ± 5.6	-14.8 ± 3.8	8.3 ± 2.1	10.3 ± 2.5	12.2 ± 5.1	13.3 ± 5.0
	30 min	25.7 ± 5.5	-19.7 ± 3.3	11.3 ± 2.8	12.6 ± 2.5	14.2 ± 4.9	16.8 ± 5.4
	35 min	28.7 ± 5.7	-21.5 ± 3.4	12.4 ± 3.2	14.6 ± 2.4	16.9 ± 4.8	20.2 ± 5.9
	40 min	31.9 ± 5.7	-23.5 ± 3.2	15.4 ± 3.8	17.1 ± 2.3	18.9 ± 4.2	21.6 ± 6.5
	45 min	30.0 ± 6.6	-22.1 ± 3.9	14.2 ± 2.5	19.3 ± 2.5	23.5 ± 4.8	22.7 ± 7.6
	50 min	28.2 ± 5.0	-21.4 ± 3.1	15.4 ± 3.2	22.0 ± 2.6	27.0 ± 5.1	23.7 ± 7.8
	55 min	28.5 ± 5.8	-21.3 ± 3.7	13.6 ± 2.4	21.8 ± 2.6	28.0 ± 5.1	22.8 ± 8.2
	60 min	26.3 ± 6.8	-19.7 ± 4.3	15.4 ± 2.3	24.1 ± 3.7	30.6 ± 6.1	23.5 ± 7.9
Recovery	5 min	21.4 ± 7.6	-16.0 ± 5.1	10.0 ± 2.5	18.5 ± 2.7	24.7 ± 5.1	22.0 ± 8.6
	10 min	18.1 ± 8.0	-13.3 ± 5.7	10.3 ± 3.9	14.3 ± 1.9	17.4 ± 4.0	21.2 ± 7.2
	15 min	16.7 ± 8.0	-12.3 ± 5.8	9.3 ± 3.9	12.3 ± 1.6	14.7 ± 3.4	17.3 ± 6.3
	20 min	16.7 ± 8.0	-12.3 ± 5.9	9.2 ± 4.4	11.9 ± 2.3	14.1 ± 2.9	14.3 ± 5.7
	25 min	16.3 ± 8.1	-11.9 ± 6.1	9.4 ± 4.4	10.9 ± 2.1	12.4 ± 2.6	12.6 ± 5.6
	30 min	15.9 ± 8.2	-11.5 ± 6.2	9.3 ± 4.5	9.2 ± 1.4	9.6 ± 2.4	13.2 ± 6.0
	35 min	15.6 ± 8.4	-11.2 ± 6.3	8.8 ± 4.2	9.6 ± 2.0	10.6 ± 2.7	11.1 ± 5.7
	40 min	15.3 ± 8.4	-11.0 ± 6.3	8.5 ± 4.4	8.6 ± 1.7	9.2 ± 2.8	10.2 ± 5.6
	45 min	15.4 ± 8.5	-11.1 ± 6.3	8.5 ± 4.4	7.5 ± 1.3	7.3 ± 2.8	9.8 ± 5.5
	50 min	14.8 ± 8.6	-10.5 ± 6.3	8.3 ± 4.3	6.9 ± 1.1	6.5 ± 3.0	9.9 ± 5.7
	55 min	15.6 ± 8.4	-11.3 ± 6.1	8.0 ± 4.4	6.7 ± 1.4	6.4 ± 2.6	10.5 ± 5.4
	60 min	14.9 ± 8.6	-10.7 ± 6.2	7.0 ± 4.1	7.1 ± 1.7	7.6 ± 2.8	8.4 ± 5.0

Continued

Table 90. Effects of imipramine on ECG from lead V3 in sedentary rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 90. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
	Baseline	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.4 ± 0.5	0.1 ± 0.5	-0.1 ± 0.5	2.0 ± 1.2	-0.4 ± 0.5	-1.2 ± 1.0
	10 min	-0.7 ± 1.4	1.8 ± 0.6	0.9 ± 0.9	4.2 ± 6.2	-0.2 ± 3.2	-1.6 ± 2.4
	15 min	1.2 ± 3.1	0.9 ± 1.7	1.0 ± 2.0	4.0 ± 7.9	2.2 ± 3.8	-0.5 ± 4.8
	20 min	5.3 ± 3.7	1.0 ± 1.6	2.4 ± 2.2	0.0 ± 9.9	5.6 ± 3.8	6.4 ± 5.3
	25 min	10.0 ± 3.6	1.2 ± 2.0	4.0 ± 2.3	-5.5 ± 11.8	7.2 ± 4.7	15.0 ± 5.0
	30 min	12.7 ± 4.0	0.7 ± 3.1	4.5 ± 3.2	-5.8 ± 12.2	10.7 ± 5.0	16.6 ± 5.9
	35 min	14.8 ± 4.0	1.3 ± 3.2	5.6 ± 3.2	-4.7 ± 12.4	13.2 ± 5.1	17.8 ± 6.8
	40 min	15.0 ± 4.3	0.2 ± 3.0	4.9 ± 3.2	-2.5 ± 12.3	14.6 ± 5.2	18.4 ± 5.7
	45 min	14.4 ± 4.3	0.5 ± 2.7	4.9 ± 3.0	0.2 ± 13.0	14.6 ± 5.9	16.8 ± 7.1
	50 min	14.1 ± 4.1	1.0 ± 2.8	5.1 ± 3.1	7.2 ± 11.9	16.0 ± 6.2	14.8 ± 6.7
	55 min	13.3 ± 5.2	0.1 ± 3.4	4.3 ± 3.9	7.2 ± 12.2	15.4 ± 6.6	14.4 ± 7.5
	60 min	13.7 ± 4.5	1.4 ± 2.8	5.3 ± 3.1	8.6 ± 11.0	14.4 ± 7.0	13.2 ± 7.6
Recovery	5 min	12.1 ± 4.7	1.9 ± 2.3	5.1 ± 2.8	4.6 ± 10.6	13.1 ± 6.9	9.8 ± 6.7
	10 min	8.8 ± 5.0	0.5 ± 2.6	3.1 ± 3.1	2.8 ± 9.7	12.4 ± 6.8	4.2 ± 7.0
	15 min	8.7 ± 5.7	0.8 ± 3.3	3.3 ± 3.8	3.6 ± 8.8	10.4 ± 6.6	4.8 ± 8.7
	20 min	8.6 ± 6.0	0.7 ± 3.9	3.2 ± 4.3	3.9 ± 7.6	8.8 ± 6.4	5.6 ± 9.3
	25 min	6.1 ± 5.1	-1.2 ± 3.5	1.1 ± 3.7	6.0 ± 7.9	7.6 ± 6.1	1.4 ± 8.4
	30 min	5.1 ± 3.0	-1.9 ± 2.2	0.3 ± 1.9	3.2 ± 7.8	7.1 ± 6.0	1.1 ± 5.7
	35 min	4.4 ± 4.1	-2.4 ± 2.7	-0.3 ± 2.7	5.5 ± 8.0	6.4 ± 5.5	-0.4 ± 7.3
	40 min	5.6 ± 4.7	-1.2 ± 3.2	0.9 ± 3.3	6.9 ± 8.4	5.6 ± 5.2	0.2 ± 7.7
	45 min	4.9 ± 4.2	-1.7 ± 3.3	0.4 ± 3.3	6.1 ± 8.9	4.8 ± 4.7	0.3 ± 7.8
	50 min	3.7 ± 3.7	-2.7 ± 2.9	-0.7 ± 2.6	5.2 ± 9.0	3.7 ± 4.2	-1.5 ± 7.1
	55 min	5.4 ± 2.5	-1.4 ± 2.2	0.7 ± 1.6	4.3 ± 8.9	3.4 ± 3.8	1.6 ± 4.9
	60 min	2.9 ± 2.0	-3.3 ± 2.4	-1.4 ± 1.6	6.8 ± 8.8	2.6 ± 3.7	-2.6 ± 4.5

Values are means ± SE. n= 6.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		155 ± 5	389 ± 13	15.0 ± 0.7	38.5 ± 2.4	23.5 ± 1.7	19.9 ± 0.3
Imipramine	5 min	154 ± 4	391 ± 13	15.6 ± 0.8	38.8 ± 2.4	23.2 ± 1.8	19.7 ± 0.4
	10 min	147 ± 5	410 ± 16	15.6 ± 0.4	41.0 ± 1.3	25.4 ± 1.0	20.1 ± 0.4
	15 min	152 ± 6	398 ± 17	15.9 ± 0.5	42.3 ± 1.2	26.4 ± 1.0	20.5 ± 0.4
	20 min	172 ± 10	356 ± 22	16.6 ± 0.6	44.1 ± 1.3	27.6 ± 1.0	21.3 ± 0.4
	25 min	188 ± 9	323 ± 16	17.4 ± 0.5	46.2 ± 1.2	28.9 ± 1.3	22.5 ± 0.3
	30 min	201 ± 6	299 ± 9	18.2 ± 0.7	47.6 ± 1.2	29.4 ± 1.2	23.6 ± 0.4
	35 min	205 ± 6	294 ± 9	18.3 ± 1.0	46.8 ± 1.6	28.5 ± 0.9	24.5 ± 0.6
	40 min	208 ± 6	290 ± 9	18.8 ± 1.3	49.2 ± 2.8	30.5 ± 1.7	24.8 ± 0.8
	45 min	210 ± 7	288 ± 10	18.9 ± 1.2	49.8 ± 3.2	30.9 ± 2.1	25.4 ± 0.9
	50 min	211 ± 8	286 ± 12	19.0 ± 1.2	50.4 ± 3.3	31.4 ± 2.2	25.6 ± 0.9
	55 min	211 ± 8	286 ± 11	19.2 ± 1.2	51.2 ± 3.4	32.0 ± 2.2	26.1 ± 1.2
	60 min	212 ± 7	285 ± 10	19.1 ± 1.2	50.7 ± 2.9	31.6 ± 1.8	26.6 ± 1.7
Recovery	5 min	202 ± 9	301 ± 16	18.1 ± 0.8	50.5 ± 2.0	32.4 ± 1.3	24.1 ± 1.0
	10 min	193 ± 10	317 ± 21	17.4 ± 0.6	47.8 ± 1.1	30.4 ± 1.1	23.1 ± 0.8
	15 min	184 ± 8	330 ± 17	16.3 ± 0.6	45.2 ± 1.0	28.9 ± 1.0	22.7 ± 0.6
	20 min	179 ± 7	338 ± 16	16.2 ± 0.6	44.0 ± 1.2	27.8 ± 1.1	22.4 ± 0.5
	25 min	179 ± 7	338 ± 13	16.0 ± 0.5	43.2 ± 1.1	27.1 ± 1.0	22.2 ± 0.5
	30 min	179 ± 8	338 ± 15	16.2 ± 0.6	42.7 ± 1.1	26.6 ± 0.9	22.0 ± 0.5
	35 min	181 ± 9	336 ± 16	16.6 ± 1.1	42.6 ± 1.0	25.9 ± 1.1	21.8 ± 0.5
	40 min	182 ± 9	333 ± 15	16.7 ± 1.2	42.6 ± 0.9	25.9 ± 1.1	21.8 ± 0.6
	45 min	186 ± 10	328 ± 18	16.6 ± 1.1	42.5 ± 0.9	25.9 ± 1.0	21.7 ± 0.6
	50 min	182 ± 9	333 ± 17	16.7 ± 1.1	41.3 ± 0.9	24.6 ± 0.8	21.7 ± 0.6
	55 min	179 ± 9	339 ± 16	16.7 ± 1.1	42.3 ± 0.9	25.6 ± 1.1	21.6 ± 0.5
	60 min	177 ± 9	344 ± 18	16.7 ± 1.1	42.0 ± 0.9	25.3 ± 1.0	21.7 ± 0.5

Continued

Table 91. Effects of imipramine on ECG from lead V3 in exercise rats. Values are means ± SE; n = 6.

Table 91. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		67.5 ± 1.1	171.7 ± 4.5	125.8 ± 2.8	10.4 ± 0.6	49.8 ± 1.3	37.1 ± 1.6
Imipramine	5 min	68.2 ± 1.1	174.2 ± 5.2	127.5 ± 3.2	10.5 ± 0.6	49.1 ± 1.4	38.3 ± 1.4
	10 min	66.1 ± 0.5	172.5 ± 3.2	125.3 ± 1.6	10.6 ± 0.8	47.1 ± 1.3	36.1 ± 1.1
	15 min	67.1 ± 1.2	173.2 ± 4.8	126.2 ± 2.8	10.4 ± 0.7	50.2 ± 2.0	36.7 ± 1.5
	20 min	70.0 ± 0.6	170.0 ± 4.6	126.4 ± 2.2	10.2 ± 0.4	53.9 ± 2.6	38.7 ± 0.2
	25 min	72.5 ± 0.7	168.3 ± 5.3	127.1 ± 2.9	9.8 ± 0.5	56.4 ± 2.5	40.1 ± 0.4
	30 min	74.6 ± 1.1	166.7 ± 4.3	127.5 ± 2.7	9.2 ± 0.5	58.5 ± 2.6	41.6 ± 1.3
	35 min	75.5 ± 0.9	166.9 ± 3.4	128.1 ± 2.1	9.5 ± 0.4	60.5 ± 3.2	42.0 ± 1.2
	40 min	77.1 ± 1.7	169.7 ± 5.0	130.5 ± 3.4	9.8 ± 0.4	61.6 ± 3.1	42.5 ± 2.1
	45 min	78.0 ± 1.6	171.0 ± 4.3	131.6 ± 2.9	10.0 ± 0.4	62.1 ± 3.1	43.1 ± 1.9
	50 min	77.2 ± 2.1	168.2 ± 4.5	129.7 ± 3.3	10.1 ± 0.4	62.2 ± 3.0	41.8 ± 2.5
	55 min	76.9 ± 2.3	167.8 ± 4.3	129.4 ± 3.3	10.3 ± 0.5	62.6 ± 2.6	40.6 ± 2.5
	60 min	77.0 ± 1.7	167.5 ± 3.2	129.3 ± 2.4	10.5 ± 0.5	62.5 ± 2.1	41.1 ± 2.1
Recovery	5 min	76.7 ± 2.6	170.8 ± 4.4	130.8 ± 3.5	12.3 ± 0.7	60.6 ± 1.5	41.2 ± 2.9
	10 min	75.0 ± 2.5	171.2 ± 4.6	130.0 ± 3.4	12.6 ± 0.9	58.5 ± 1.4	39.6 ± 2.5
	15 min	72.0 ± 1.3	168.6 ± 3.3	126.9 ± 2.0	12.0 ± 0.7	56.8 ± 1.3	37.6 ± 1.2
	20 min	70.9 ± 1.6	167.8 ± 3.2	125.9 ± 2.2	11.8 ± 0.7	55.5 ± 1.2	37.2 ± 1.8
	25 min	71.6 ± 1.5	169.4 ± 2.8	127.1 ± 2.0	11.7 ± 0.7	54.7 ± 1.3	38.1 ± 1.8
	30 min	70.9 ± 1.7	167.5 ± 1.7	125.7 ± 1.5	11.5 ± 0.6	54.8 ± 1.2	37.7 ± 2.0
	35 min	70.3 ± 1.6	165.6 ± 2.5	124.4 ± 1.7	11.4 ± 0.4	55.1 ± 1.1	37.2 ± 1.8
	40 min	70.1 ± 1.7	164.3 ± 3.1	123.7 ± 2.2	11.3 ± 0.4	55.2 ± 1.1	37.4 ± 1.6
	45 min	69.8 ± 1.5	161.9 ± 2.9	122.2 ± 1.5	11.6 ± 0.4	54.7 ± 1.4	37.0 ± 1.8
	50 min	70.5 ± 1.5	165.6 ± 2.7	124.5 ± 1.8	11.7 ± 0.3	55.1 ± 1.5	37.5 ± 1.3
	55 min	70.4 ± 1.7	166.9 ± 4.1	125.2 ± 2.7	11.9 ± 0.4	54.4 ± 1.6	37.4 ± 1.6
	60 min	69.9 ± 1.9	166.5 ± 2.9	124.6 ± 2.2	12.0 ± 0.4	53.7 ± 1.5	36.3 ± 1.9

Values are means ± SE. n = 6.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-3.4 ± 2.7	0.4 ± 0.1	4.8 ± 3.8	0.9 ± 1.1	-1.5 ± 0.8	-1.4 ± 1.0
	10 min	-5.1 ± 0.7	5.4 ± 0.7	5.2 ± 3.5	8.3 ± 6.5	10.9 ± 9.7	0.8 ± 1.0
	15 min	-2.1 ± 2.1	2.4 ± 2.1	6.8 ± 4.7	11.8 ± 7.3	15.8 ± 10.9	2.8 ± 2.0
	20 min	10.4 ± 4.8	-8.6 ± 4.0	11.6 ± 4.6	16.7 ± 7.5	20.8 ± 11.6	6.8 ± 2.1
	25 min	21.4 ± 4.5	-17.0 ± 3.4	16.8 ± 4.1	22.4 ± 8.3	27.1 ± 14.0	13.0 ± 1.5
	30 min	30.2 ± 3.7	-22.9 ± 2.3	22.5 ± 5.4	25.7 ± 7.5	28.8 ± 12.5	18.5 ± 2.5
	35 min	32.6 ± 2.8	-24.4 ± 1.7	22.8 ± 6.3	23.0 ± 5.5	24.2 ± 9.2	23.0 ± 2.8
	40 min	34.2 ± 2.7	-25.3 ± 1.5	26.1 ± 9.3	29.5 ± 8.6	32.7 ± 11.0	24.6 ± 4.1
	45 min	35.4 ± 2.3	-26.0 ± 1.3	27.0 ± 9.2	31.2 ± 9.7	34.7 ± 12.1	27.3 ± 4.3
	50 min	36.0 ± 2.2	-26.4 ± 1.1	28.0 ± 9.6	32.8 ± 9.8	36.6 ± 11.7	28.2 ± 4.1
	55 min	36.3 ± 2.0	-26.5 ± 1.1	29.4 ± 9.2	34.6 ± 9.8	38.9 ± 11.9	30.7 ± 5.8
	60 min	36.5 ± 1.3	-26.7 ± 0.7	28.6 ± 8.9	33.2 ± 8.1	37.0 ± 9.8	33.3 ± 8.2
Recovery	5 min	29.8 ± 2.4	-22.8 ± 1.5	22.3 ± 8.1	34.5 ± 11.5	43.4 ± 15.8	20.9 ± 4.0
	10 min	23.7 ± 3.4	-18.8 ± 2.5	17.3 ± 6.5	26.8 ± 9.1	33.7 ± 13.2	15.9 ± 2.7
	15 min	18.4 ± 2.0	-15.4 ± 1.5	9.2 ± 2.5	19.4 ± 7.2	26.9 ± 12.5	13.8 ± 1.9
	20 min	15.5 ± 1.8	-13.3 ± 1.4	8.4 ± 2.7	16.2 ± 7.0	22.2 ± 12.1	12.5 ± 1.6
	25 min	15.3 ± 2.9	-13.0 ± 2.0	7.5 ± 2.6	13.9 ± 6.7	19.0 ± 11.5	11.4 ± 1.4
	30 min	15.8 ± 4.2	-13.1 ± 2.8	8.3 ± 2.3	12.9 ± 6.6	16.6 ± 11.3	10.4 ± 1.5
	35 min	16.7 ± 4.9	-13.6 ± 3.2	10.9 ± 2.9	12.5 ± 6.7	14.3 ± 12.3	9.4 ± 1.5
	40 min	17.6 ± 4.3	-14.5 ± 2.8	11.1 ± 3.0	12.5 ± 6.5	14.2 ± 12.0	9.1 ± 1.7
	45 min	19.5 ± 4.6	-15.8 ± 2.9	10.5 ± 2.5	12.2 ± 6.4	14.0 ± 11.6	8.8 ± 1.9
	50 min	17.4 ± 3.8	-14.4 ± 2.6	11.1 ± 2.8	9.4 ± 7.3	9.3 ± 12.7	9.0 ± 1.8
	55 min	15.5 ± 3.8	-13.0 ± 2.7	11.2 ± 2.6	11.6 ± 5.9	12.5 ± 10.9	8.4 ± 1.6
	60 min	13.7 ± 4.0	-11.5 ± 2.9	11.2 ± 2.9	11.0 ± 6.3	11.7 ± 11.6	8.8 ± 1.5

Continued

Table 92. Effects of imipramine on ECG from lead V3 in exercise rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 92. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	1.1 ± 0.7	1.4 ± 0.7	1.3 ± 0.7	0.8 ± 0.5	-1.5 ± 0.3	3.3 ± 1.2
	10 min	-2.0 ± 1.1	0.6 ± 1.0	-0.3 ± 1.0	2.2 ± 3.8	-5.4 ± 0.4	-2.5 ± 2.4
	15 min	-0.5 ± 1.3	0.9 ± 1.2	0.4 ± 1.2	0.1 ± 4.8	0.7 ± 2.2	-1.1 ± 1.8
	20 min	3.8 ± 1.8	-0.8 ± 2.4	0.7 ± 2.0	0.4 ± 9.4	8.0 ± 3.7	5.4 ± 5.1
	25 min	7.6 ± 1.5	-1.9 ± 2.6	1.2 ± 2.1	-3.4 ± 10.2	13.1 ± 2.9	9.0 ± 5.1
	30 min	10.7 ± 2.7	-2.7 ± 3.2	1.6 ± 3.0	-8.7 ± 10.3	17.1 ± 2.9	13.6 ± 7.6
	35 min	12.0 ± 2.5	-2.6 ± 2.6	2.1 ± 2.5	-6.3 ± 9.7	21.1 ± 3.7	14.6 ± 7.2
	40 min	14.5 ± 3.9	-0.8 ± 4.0	4.1 ± 3.9	-3.7 ± 9.0	23.4 ± 3.5	16.7 ± 10.7
	45 min	15.8 ± 3.3	-0.1 ± 3.4	4.9 ± 3.3	-2.2 ± 9.4	24.3 ± 3.3	17.8 ± 9.5
	50 min	14.6 ± 3.8	-1.7 ± 3.7	3.4 ± 3.7	-1.1 ± 9.8	24.5 ± 3.2	14.3 ± 10.0
	55 min	14.2 ± 3.8	-2.0 ± 3.5	3.1 ± 3.6	0.8 ± 8.9	25.5 ± 2.5	10.8 ± 9.1
	60 min	14.3 ± 3.2	-2.1 ± 2.9	3.1 ± 3.0	2.5 ± 9.4	25.3 ± 2.2	11.9 ± 8.2
Recovery	5 min	14.0 ± 4.8	-0.1 ± 4.0	4.4 ± 4.2	18.2 ± 5.5	21.6 ± 2.5	12.7 ± 10.9
	10 min	11.4 ± 4.9	0.0 ± 3.6	3.7 ± 4.0	20.8 ± 5.6	17.6 ± 2.6	8.4 ± 10.3
	15 min	6.9 ± 2.9	-1.6 ± 2.4	1.2 ± 2.5	15.0 ± 3.2	14.1 ± 2.1	2.5 ± 6.1
	20 min	5.3 ± 3.1	-2.0 ± 2.6	0.3 ± 2.7	13.7 ± 2.1	11.5 ± 1.4	0.9 ± 6.0
	25 min	6.2 ± 2.8	-1.1 ± 2.5	1.3 ± 2.5	12.0 ± 2.5	9.8 ± 0.9	3.4 ± 5.6
	30 min	5.2 ± 3.0	-2.1 ± 2.6	0.2 ± 2.6	10.6 ± 2.2	10.1 ± 0.9	2.3 ± 6.2
	35 min	4.3 ± 3.0	-3.2 ± 3.0	-0.8 ± 2.8	10.7 ± 4.4	10.6 ± 0.9	1.2 ± 6.3
	40 min	4.1 ± 3.1	-4.0 ± 3.0	-1.4 ± 2.9	9.4 ± 4.3	10.8 ± 1.1	1.7 ± 6.5
	45 min	3.6 ± 2.8	-5.5 ± 2.4	-2.6 ± 2.3	12.3 ± 5.1	9.7 ± 1.7	0.7 ± 7.2
	50 min	4.6 ± 3.0	-3.3 ± 2.4	-0.7 ± 2.5	13.7 ± 4.9	10.7 ± 2.2	2.1 ± 6.7
	55 min	4.5 ± 2.4	-2.6 ± 2.4	-0.3 ± 2.3	15.4 ± 4.4	9.2 ± 1.9	1.4 ± 5.0
	60 min	3.6 ± 2.8	-2.8 ± 2.5	-0.7 ± 2.5	16.2 ± 4.0	7.8 ± 1.7	-1.5 ± 5.7

Values are means ± SE. n= 6.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		159 ± 4	380 ± 11	15.5 ± 0.9	38.8 ± 1.3	23.3 ± 0.9	20.8 ± 1.1
Imipramine	5 min	157 ± 4	383 ± 11	15.0 ± 0.9	37.9 ± 1.5	22.9 ± 0.9	21.3 ± 1.1
	10 min	152 ± 6	397 ± 16	15.6 ± 1.2	39.1 ± 1.9	23.5 ± 1.3	21.0 ± 1.3
	15 min	156 ± 6	387 ± 16	15.9 ± 0.8	41.4 ± 1.6	25.4 ± 1.2	21.6 ± 1.5
	20 min	166 ± 4	363 ± 9	16.0 ± 0.9	42.7 ± 1.6	26.7 ± 0.9	23.1 ± 1.0
	25 min	178 ± 5	338 ± 9	17.3 ± 1.1	41.4 ± 1.9	24.3 ± 1.4	22.8 ± 0.7
	30 min	184 ± 5	328 ± 9	17.2 ± 1.2	43.4 ± 1.6	26.3 ± 1.5	23.6 ± 0.9
	35 min	184 ± 5	328 ± 9	17.1 ± 0.8	45.7 ± 0.7	28.6 ± 0.9	24.0 ± 0.8
	40 min	183 ± 6	330 ± 10	17.5 ± 0.6	45.1 ± 1.2	27.6 ± 1.0	24.2 ± 0.7
	45 min	182 ± 7	331 ± 12	17.2 ± 0.5	45.0 ± 1.6	27.8 ± 1.4	24.8 ± 0.7
	50 min	183 ± 8	332 ± 14	17.2 ± 0.6	47.0 ± 1.9	29.8 ± 1.8	25.0 ± 0.9
	55 min	183 ± 8	331 ± 14	17.4 ± 0.7	48.4 ± 2.4	30.9 ± 2.2	25.8 ± 1.0
	60 min	221 ± 41	302 ± 33	17.9 ± 0.9	50.3 ± 1.8	32.3 ± 2.2	25.8 ± 1.0
Recovery	5 min	219 ± 39	303 ± 33	16.9 ± 1.5	50.2 ± 1.7	33.4 ± 2.0	25.5 ± 1.0
	10 min	185 ± 6	327 ± 11	17.1 ± 1.2	47.6 ± 1.8	30.5 ± 1.5	24.3 ± 0.3
	15 min	184 ± 7	328 ± 11	17.3 ± 1.5	44.6 ± 1.4	27.3 ± 1.4	23.8 ± 0.4
	20 min	182 ± 6	331 ± 10	17.7 ± 1.5	45.8 ± 1.7	28.2 ± 0.8	22.7 ± 0.5
	25 min	179 ± 5	337 ± 10	18.1 ± 1.4	44.1 ± 1.7	26.0 ± 1.0	22.2 ± 0.6
	30 min	179 ± 5	336 ± 10	17.8 ± 1.4	43.2 ± 1.9	25.4 ± 1.4	21.7 ± 0.7
	35 min	179 ± 5	337 ± 10	17.9 ± 1.4	42.7 ± 1.8	24.8 ± 1.4	21.8 ± 0.7
	40 min	177 ± 6	341 ± 11	17.9 ± 1.1	43.5 ± 1.0	25.5 ± 1.3	22.0 ± 0.7
	45 min	176 ± 6	343 ± 12	17.8 ± 1.0	43.1 ± 0.9	25.3 ± 1.3	21.8 ± 0.8
	50 min	175 ± 6	345 ± 12	17.7 ± 1.0	42.7 ± 0.9	25.0 ± 1.3	21.8 ± 0.8
	55 min	174 ± 6	347 ± 13	17.8 ± 1.0	42.8 ± 0.8	25.0 ± 1.3	21.6 ± 0.9
	60 min	174 ± 6	348 ± 13	17.7 ± 1.1	42.6 ± 0.8	24.9 ± 1.3	21.3 ± 1.0

Continued

Table 93. Effects of imipramine on ECG from lead V3 in carvedilol rats. Values are means ± SE; n = 6.

Table 93. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		69.4 ± 1.1	174.5 ± 2.3	128.3 ± 1.6	10.2 ± 1.0	51.8 ± 2.9	38.9 ± 1.3
Imipramine	5 min	68.8 ± 1.4	174.1 ± 2.9	127.7 ± 2.1	10.7 ± 1.2	51.8 ± 3.0	38.1 ± 1.7
	10 min	68.2 ± 1.6	174.9 ± 2.6	127.7 ± 2.0	10.6 ± 1.1	51.0 ± 3.0	37.1 ± 2.0
	15 min	68.2 ± 1.4	172.9 ± 2.8	126.8 ± 1.9	9.6 ± 0.8	53.4 ± 3.3	37.1 ± 1.3
	20 min	70.9 ± 1.7	174.5 ± 3.6	129.3 ± 2.7	9.5 ± 0.9	55.0 ± 3.7	38.5 ± 1.4
	25 min	71.8 ± 1.9	170.6 ± 4.5	127.8 ± 3.3	9.4 ± 0.7	54.7 ± 4.3	39.8 ± 1.6
	30 min	73.0 ± 2.1	170.5 ± 5.0	128.5 ± 3.6	9.4 ± 0.7	55.6 ± 4.4	40.3 ± 1.7
	35 min	72.7 ± 1.6	169.8 ± 3.8	128.0 ± 2.7	9.7 ± 0.8	56.1 ± 4.3	39.0 ± 1.2
	40 min	73.2 ± 1.5	171.6 ± 3.9	129.2 ± 2.7	10.1 ± 0.7	56.2 ± 3.7	39.0 ± 1.7
	45 min	74.1 ± 1.3	174.1 ± 4.5	131.0 ± 2.9	10.8 ± 0.5	56.8 ± 3.4	38.7 ± 1.4
	50 min	74.1 ± 1.1	174.0 ± 5.1	130.9 ± 3.0	11.1 ± 0.6	57.3 ± 3.5	38.7 ± 1.7
	55 min	74.8 ± 1.1	175.5 ± 5.5	132.1 ± 3.2	11.3 ± 0.7	58.2 ± 3.6	38.7 ± 1.3
	60 min	74.6 ± 1.0	166.0 ± 11.4	126.8 ± 6.3	11.6 ± 0.6	57.1 ± 3.8	38.1 ± 1.9
Recovery	5 min	74.4 ± 1.3	165.5 ± 10.7	126.5 ± 5.9	12.6 ± 1.7	56.7 ± 3.6	37.1 ± 2.2
	10 min	73.0 ± 1.7	170.2 ± 4.3	128.4 ± 3.0	12.5 ± 1.7	56.9 ± 3.9	36.7 ± 2.1
	15 min	72.9 ± 1.3	170.5 ± 4.0	128.5 ± 2.6	12.5 ± 1.4	56.3 ± 3.8	36.7 ± 1.7
	20 min	71.8 ± 1.7	168.4 ± 3.6	126.7 ± 2.7	12.5 ± 1.3	54.8 ± 3.7	36.4 ± 2.0
	25 min	70.9 ± 2.0	167.8 ± 4.5	125.9 ± 3.3	12.0 ± 1.3	54.4 ± 3.6	37.0 ± 2.4
	30 min	70.7 ± 1.7	167.3 ± 4.0	125.6 ± 2.8	12.1 ± 1.3	53.8 ± 3.6	36.9 ± 2.3
	35 min	70.9 ± 1.8	167.9 ± 4.4	126.0 ± 3.2	12.1 ± 1.2	53.6 ± 3.6	36.8 ± 2.2
	40 min	70.6 ± 1.4	168.1 ± 3.4	125.9 ± 2.4	12.5 ± 1.2	53.8 ± 3.3	36.0 ± 1.9
	45 min	70.6 ± 1.6	168.6 ± 3.9	126.1 ± 2.7	12.6 ± 1.2	53.5 ± 3.4	36.5 ± 2.4
	50 min	71.6 ± 1.5	171.6 ± 4.5	128.2 ± 2.9	12.9 ± 1.1	53.6 ± 3.3	37.3 ± 2.4
	55 min	71.5 ± 1.4	171.5 ± 3.8	128.1 ± 2.5	12.8 ± 1.1	53.4 ± 3.3	37.6 ± 2.7
	60 min	72.5 ± 1.6	174.3 ± 4.1	130.1 ± 2.8	13.0 ± 1.1	53.0 ± 3.2	38.5 ± 3.1

Values are means ± SE. n = 6.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.8 ± 0.2	0.8 ± 0.2	-2.7 ± 2.6	-2.4 ± 1.2	-2.0 ± 1.0	2.4 ± 1.4
	10 min	-4.1 ± 1.2	4.3 ± 1.4	0.6 ± 3.6	0.6 ± 2.0	0.6 ± 2.4	0.6 ± 2.4
	15 min	-1.6 ± 1.4	1.7 ± 1.5	3.6 ± 4.5	6.6 ± 2.0	9.3 ± 4.0	4.1 ± 5.3
	20 min	4.6 ± 1.2	-4.3 ± 1.1	4.3 ± 5.6	10.1 ± 2.1	14.9 ± 2.8	12.1 ± 6.4
	25 min	12.4 ± 2.3	-10.8 ± 1.8	12.5 ± 6.4	6.8 ± 4.3	4.5 ± 5.8	11.2 ± 6.5
	30 min	16.1 ± 2.8	-13.6 ± 2.1	12.0 ± 5.5	12.3 ± 5.1	13.7 ± 8.6	15.0 ± 7.1
	35 min	16.1 ± 2.9	-13.6 ± 2.1	11.3 ± 4.6	18.3 ± 4.2	23.9 ± 7.2	17.0 ± 7.0
	40 min	15.4 ± 3.2	-13.0 ± 2.4	14.2 ± 5.5	16.6 ± 3.7	19.4 ± 6.5	17.5 ± 5.9
	45 min	15.1 ± 3.8	-12.6 ± 2.9	13.1 ± 6.4	16.9 ± 6.2	20.4 ± 8.2	20.5 ± 5.9
	50 min	15.3 ± 4.5	-12.6 ± 3.5	13.1 ± 6.8	22.3 ± 7.4	29.1 ± 9.4	21.4 ± 5.2
	55 min	15.7 ± 4.6	-12.8 ± 3.6	14.4 ± 7.7	26.1 ± 9.6	34.5 ± 12.4	25.0 ± 5.4
	60 min	38.4 ± 23.4	-20.7 ± 8.6	18.0 ± 9.4	30.7 ± 7.4	40.4 ± 12.2	25.0 ± 6.3
Recovery	5 min	37.1 ± 22.4	-20.4 ± 8.3	11.2 ± 12.3	30.6 ± 7.6	45.1 ± 13.1	24.0 ± 7.1
	10 min	16.6 ± 3.6	-13.8 ± 2.7	12.7 ± 10.7	23.9 ± 8.1	32.5 ± 10.6	18.5 ± 6.6
	15 min	16.0 ± 3.1	-13.5 ± 2.4	14.0 ± 12.9	15.8 ± 6.4	18.1 ± 7.9	15.8 ± 6.1
	20 min	14.8 ± 2.4	-12.7 ± 1.8	16.7 ± 13.1	18.7 ± 5.7	21.1 ± 2.7	10.7 ± 5.8
	25 min	12.9 ± 2.3	-11.3 ± 1.8	20.1 ± 14.0	14.0 ± 5.1	11.7 ± 3.7	8.0 ± 5.3
	30 min	13.1 ± 2.2	-11.4 ± 1.7	18.5 ± 14.1	11.7 ± 5.1	9.3 ± 6.0	5.3 ± 4.8
	35 min	12.9 ± 2.2	-11.3 ± 1.7	19.6 ± 15.3	10.3 ± 5.1	6.7 ± 6.5	5.5 ± 4.9
	40 min	11.7 ± 1.9	-10.3 ± 1.6	19.4 ± 13.1	12.6 ± 4.4	10.3 ± 7.5	6.5 ± 3.8
	45 min	11.0 ± 1.9	-9.8 ± 1.5	18.4 ± 12.8	11.7 ± 4.1	9.3 ± 7.2	5.6 ± 3.5
	50 min	10.3 ± 1.9	-9.2 ± 1.5	17.7 ± 12.5	10.7 ± 3.8	8.0 ± 6.9	5.4 ± 3.7
	55 min	9.8 ± 1.8	-8.8 ± 1.5	18.3 ± 12.9	10.8 ± 3.9	7.9 ± 6.9	4.2 ± 3.6
	60 min	9.4 ± 1.9	-8.5 ± 1.6	17.8 ± 12.8	10.4 ± 4.1	7.3 ± 6.6	2.9 ± 3.3

Continued

Table 94. Effects of imipramine on ECG from lead V3 in carvedilol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 94. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.9 ± 0.7	-0.2 ± 0.7	-0.5 ± 0.7	3.3 ± 2.2	-0.1 ± 1.0	-2.3 ± 1.4
	10 min	-1.9 ± 1.1	0.3 ± 1.1	-0.4 ± 1.0	3.7 ± 2.9	-1.6 ± 1.2	-4.8 ± 2.2
	15 min	-1.8 ± 0.9	-0.9 ± 1.0	-1.2 ± 0.9	-3.2 ± 9.4	2.8 ± 1.5	-4.3 ± 3.0
	20 min	2.2 ± 2.3	0.1 ± 2.8	0.8 ± 2.6	-4.0 ± 10.4	5.7 ± 2.1	-0.8 ± 2.8
	25 min	3.5 ± 2.7	-2.1 ± 3.3	-0.3 ± 3.1	-4.3 ± 10.8	5.1 ± 3.8	2.5 ± 3.1
	30 min	5.3 ± 3.1	-2.1 ± 3.8	0.3 ± 3.5	-3.7 ± 12.6	6.7 ± 3.5	3.7 ± 4.1
	35 min	4.8 ± 2.2	-2.6 ± 2.9	-0.2 ± 2.6	-0.6 ± 12.3	7.6 ± 3.5	0.5 ± 3.4
	40 min	5.6 ± 2.3	-1.5 ± 3.0	0.8 ± 2.7	3.7 ± 12.0	8.3 ± 2.7	0.4 ± 4.2
	45 min	6.8 ± 2.0	-0.1 ± 3.3	2.2 ± 2.9	9.8 ± 10.2	9.6 ± 2.3	-0.3 ± 3.1
	50 min	6.8 ± 2.1	-0.1 ± 3.8	2.1 ± 3.2	13.5 ± 12.1	10.3 ± 2.0	-0.3 ± 4.4
	55 min	7.9 ± 2.4	0.8 ± 4.0	3.1 ± 3.4	15.3 ± 13.3	12.2 ± 2.3	-0.2 ± 4.0
	60 min	7.7 ± 2.8	-4.6 ± 7.1	-0.9 ± 5.7	19.7 ± 14.7	10.1 ± 3.8	-1.8 ± 5.0
Recovery	5 min	7.3 ± 2.7	-4.9 ± 6.6	-1.2 ± 5.3	26.7 ± 16.6	9.3 ± 3.0	-4.6 ± 5.0
	10 min	5.2 ± 2.3	-2.3 ± 3.0	0.1 ± 2.7	24.6 ± 14.5	9.4 ± 2.4	-5.9 ± 3.7
	15 min	5.2 ± 2.1	-2.2 ± 2.7	0.2 ± 2.5	25.2 ± 12.6	8.4 ± 2.2	-5.6 ± 2.4
	20 min	3.4 ± 2.5	-3.3 ± 2.8	-1.1 ± 2.7	24.8 ± 12.1	5.5 ± 2.6	-6.5 ± 3.4
	25 min	2.2 ± 3.0	-3.7 ± 3.4	-1.8 ± 3.2	20.3 ± 11.5	4.7 ± 2.8	-5.2 ± 4.0
	30 min	2.0 ± 2.5	-4.0 ± 3.0	-2.0 ± 2.8	20.9 ± 12.1	3.5 ± 2.5	-5.4 ± 3.4
	35 min	2.2 ± 2.7	-3.6 ± 3.2	-1.7 ± 3.0	21.6 ± 11.7	3.3 ± 2.8	-5.6 ± 3.7
	40 min	1.8 ± 2.4	-3.5 ± 2.8	-1.8 ± 2.7	25.3 ± 10.8	3.7 ± 2.6	-7.6 ± 2.9
	45 min	1.8 ± 2.4	-3.3 ± 2.8	-1.6 ± 2.6	26.2 ± 10.0	3.1 ± 2.4	-6.4 ± 4.2
	50 min	3.2 ± 2.7	-1.5 ± 3.1	0.0 ± 2.9	28.6 ± 9.9	3.4 ± 2.5	-4.4 ± 4.7
	55 min	3.1 ± 2.5	-1.6 ± 2.7	-0.1 ± 2.6	28.1 ± 10.1	3.0 ± 2.8	-3.7 ± 5.2
	60 min	4.5 ± 2.5	0.0 ± 2.7	1.5 ± 2.6	29.7 ± 9.7	2.2 ± 2.6	-1.4 ± 5.4

Values are means ± SE. n= 6.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		146 ± 4	412 ± 10	16.2 ± 0.9	42.5 ± 1.3	26.3 ± 0.6	18.2 ± 0.3
Imipramine	5 min	145 ± 3	416 ± 8	16.2 ± 0.9	42.6 ± 1.3	26.4 ± 0.6	18.2 ± 0.3
	10 min	143 ± 4	422 ± 10	16.2 ± 0.9	43.3 ± 1.4	27.2 ± 0.7	18.2 ± 0.4
	15 min	158 ± 8	383 ± 17	16.6 ± 0.7	42.4 ± 2.2	25.8 ± 1.9	18.8 ± 0.6
	20 min	174 ± 9	350 ± 16	16.8 ± 0.6	43.2 ± 1.6	26.5 ± 1.6	19.2 ± 0.6
	25 min	186 ± 9	327 ± 15	17.3 ± 0.8	46.4 ± 2.1	29.2 ± 1.6	20.0 ± 0.6
	30 min	191 ± 7	316 ± 11	17.6 ± 0.7	48.4 ± 2.5	30.8 ± 1.9	20.9 ± 0.5
	35 min	193 ± 6	312 ± 9	17.9 ± 0.7	49.2 ± 2.5	31.4 ± 2.0	21.4 ± 0.6
	40 min	192 ± 6	315 ± 10	17.8 ± 0.6	51.1 ± 2.2	33.3 ± 1.6	22.0 ± 0.6
	45 min	192 ± 7	314 ± 12	17.9 ± 0.6	53.3 ± 2.8	35.2 ± 2.2	22.7 ± 0.6
	50 min	193 ± 8	314 ± 13	18.1 ± 0.7	54.8 ± 4.8	36.7 ± 4.3	22.9 ± 0.5
	55 min	195 ± 9	310 ± 15	19.0 ± 0.9	58.1 ± 7.1	39.2 ± 6.5	23.2 ± 0.8
	60 min	198 ± 9	306 ± 14	19.0 ± 0.9	60.0 ± 8.5	41.0 ± 7.8	23.2 ± 0.7
Recovery	5 min	199 ± 11	307 ± 18	18.2 ± 0.9	56.6 ± 5.6	38.4 ± 5.2	22.5 ± 0.7
	10 min	188 ± 9	323 ± 16	17.9 ± 0.9	55.2 ± 4.6	37.3 ± 4.3	22.4 ± 0.9
	15 min	184 ± 9	331 ± 17	17.5 ± 0.8	53.1 ± 3.8	35.6 ± 3.6	23.2 ± 1.7
	20 min	184 ± 10	330 ± 19	17.6 ± 0.8	51.6 ± 3.2	34.0 ± 2.7	21.9 ± 0.9
	25 min	181 ± 9	335 ± 18	17.8 ± 0.9	52.2 ± 3.8	34.4 ± 3.3	21.6 ± 0.8
	30 min	181 ± 9	336 ± 17	17.7 ± 0.9	50.8 ± 3.2	33.1 ± 2.6	21.5 ± 0.8
	35 min	180 ± 9	337 ± 17	17.6 ± 0.9	49.8 ± 2.8	32.2 ± 2.2	21.3 ± 0.8
	40 min	179 ± 9	339 ± 17	17.6 ± 0.9	49.1 ± 2.6	31.5 ± 2.0	21.2 ± 0.7
	45 min	179 ± 9	340 ± 17	17.5 ± 0.9	48.8 ± 2.6	31.2 ± 1.9	21.0 ± 0.7
	50 min	179 ± 8	340 ± 17	17.7 ± 0.9	48.4 ± 2.7	30.8 ± 2.0	20.7 ± 0.7
	55 min	180 ± 8	336 ± 15	17.6 ± 0.9	48.2 ± 2.6	30.5 ± 1.9	20.5 ± 0.7
	60 min	180 ± 7	335 ± 13	17.6 ± 1.0	47.8 ± 2.9	30.2 ± 2.1	20.3 ± 0.7

Continued

Table 95. Effects of imipramine on ECG from lead V3 in clenbuterol rats. Values are means ± SE; n = 6.

Table 95. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		74.0 ± 2.3	193.6 ± 4.9	140.5 ± 3.7	11.1 ± 0.4	42.5 ± 4.7	44.8 ± 2.5
Imipramine	5 min	73.1 ± 1.9	192.2 ± 4.4	139.3 ± 3.3	11.3 ± 0.4	42.3 ± 4.7	43.6 ± 2.2
	10 min	72.3 ± 1.6	191.6 ± 4.4	138.5 ± 3.1	11.5 ± 0.4	43.7 ± 5.5	42.8 ± 1.8
	15 min	76.2 ± 2.1	192.5 ± 6.3	141.3 ± 4.1	11.1 ± 0.4	51.4 ± 7.3	46.2 ± 2.2
	20 min	77.8 ± 2.7	187.9 ± 8.9	140.0 ± 5.9	10.6 ± 0.5	55.0 ± 7.8	48.0 ± 2.7
	25 min	79.8 ± 2.0	186.6 ± 7.9	140.5 ± 5.1	10.6 ± 0.7	56.8 ± 9.0	48.8 ± 2.5
	30 min	82.7 ± 2.0	189.8 ± 7.6	143.9 ± 5.0	10.7 ± 0.7	57.8 ± 9.1	50.5 ± 2.8
	35 min	84.2 ± 2.7	192.4 ± 8.5	146.1 ± 5.8	11.1 ± 0.7	58.1 ± 8.8	51.1 ± 3.6
	40 min	84.5 ± 3.0	193.7 ± 8.8	146.9 ± 6.1	11.5 ± 0.6	57.9 ± 8.7	50.2 ± 3.5
	45 min	86.0 ± 2.9	197.1 ± 9.1	149.5 ± 6.2	11.6 ± 0.7	57.5 ± 8.1	51.1 ± 3.4
	50 min	83.3 ± 2.3	190.2 ± 5.8	144.4 ± 4.0	11.7 ± 0.7	56.8 ± 7.5	48.4 ± 2.6
	55 min	83.7 ± 2.0	189.9 ± 4.8	144.4 ± 3.2	11.5 ± 1.0	53.5 ± 8.3	48.4 ± 2.4
	60 min	84.3 ± 2.4	189.8 ± 5.5	144.8 ± 3.9	11.7 ± 1.0	56.5 ± 7.4	49.0 ± 2.6
Recovery	5 min	84.4 ± 2.8	190.2 ± 6.8	145.0 ± 4.7	12.6 ± 0.7	55.5 ± 7.2	49.0 ± 3.0
	10 min	84.8 ± 4.4	196.0 ± 9.1	148.2 ± 7.0	12.3 ± 0.8	56.6 ± 8.3	50.1 ± 4.4
	15 min	85.2 ± 5.1	199.2 ± 11.0	150.0 ± 8.3	13.1 ± 0.9	48.5 ± 6.0	49.3 ± 4.9
	20 min	83.7 ± 4.7	195.2 ± 9.3	147.1 ± 7.3	12.3 ± 0.8	49.0 ± 4.9	50.1 ± 4.5
	25 min	83.4 ± 4.0	196.2 ± 8.1	147.5 ± 6.2	12.3 ± 0.8	48.6 ± 4.9	50.2 ± 4.0
	30 min	83.2 ± 4.3	196.1 ± 8.9	147.4 ± 6.8	12.4 ± 0.9	48.6 ± 5.0	49.6 ± 4.4
	35 min	83.0 ± 4.5	195.7 ± 9.3	147.0 ± 7.1	12.3 ± 0.8	48.4 ± 5.1	50.1 ± 4.2
	40 min	82.2 ± 4.4	194.5 ± 9.1	145.9 ± 7.0	12.4 ± 0.8	48.2 ± 5.1	48.9 ± 4.3
	45 min	82.4 ± 4.4	195.2 ± 9.1	146.4 ± 6.9	12.4 ± 0.8	47.8 ± 5.0	49.2 ± 4.4
	50 min	81.6 ± 3.8	193.2 ± 6.7	144.9 ± 5.4	12.3 ± 0.8	48.0 ± 5.2	47.8 ± 4.1
	55 min	80.3 ± 3.7	189.5 ± 7.0	142.3 ± 5.5	11.9 ± 0.6	47.7 ± 5.2	47.4 ± 4.1
	60 min	80.0 ± 3.6	188.7 ± 7.0	141.7 ± 5.5	12.2 ± 0.7	47.5 ± 5.1	47.3 ± 4.0

Values are means ± SE. n = 6.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.9 ± 0.6	0.9 ± 0.6	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.2	0.5 ± 0.4
	10 min	-2.2 ± 1.8	2.4 ± 1.9	-0.1 ± 0.4	1.9 ± 0.8	3.1 ± 1.2	0.4 ± 0.6
	15 min	8.5 ± 4.9	-7.0 ± 3.7	3.0 ± 1.9	-0.4 ± 3.6	-2.3 ± 6.4	3.4 ± 2.1
	20 min	18.9 ± 5.4	-15.1 ± 3.5	4.6 ± 4.9	2.2 ± 5.0	0.7 ± 6.2	5.8 ± 3.4
	25 min	27.4 ± 6.0	-20.7 ± 3.5	8.0 ± 6.1	10.0 ± 7.0	11.3 ± 7.8	10.5 ± 3.8
	30 min	31.2 ± 5.3	-23.2 ± 3.0	9.8 ± 6.1	14.5 ± 7.6	17.6 ± 8.9	15.2 ± 2.6
	35 min	32.5 ± 4.8	-24.1 ± 2.6	11.4 ± 5.5	16.5 ± 7.7	19.8 ± 9.3	17.9 ± 2.8
	40 min	31.6 ± 5.3	-23.4 ± 2.9	11.3 ± 5.3	20.8 ± 6.6	27.0 ± 7.9	21.2 ± 3.2
	45 min	32.0 ± 5.9	-23.5 ± 3.3	11.5 ± 5.4	25.5 ± 6.7	33.9 ± 9.5	25.4 ± 3.3
	50 min	32.8 ± 7.2	-23.6 ± 4.0	12.8 ± 4.9	28.9 ± 10.2	39.8 ± 16.6	26.5 ± 3.2
	55 min	34.5 ± 8.2	-24.3 ± 4.4	17.6 ± 3.1	36.2 ± 14.4	48.9 ± 24.1	27.8 ± 5.0
	60 min	36.7 ± 8.4	-25.5 ± 4.4	17.7 ± 3.5	40.3 ± 17.2	55.7 ± 28.9	28.0 ± 4.7
Recovery	5 min	36.9 ± 9.2	-25.3 ± 5.0	13.1 ± 5.4	33.0 ± 11.5	46.2 ± 19.5	23.9 ± 4.1
	10 min	28.9 ± 6.6	-21.3 ± 4.2	11.5 ± 5.9	29.9 ± 9.9	41.9 ± 16.2	23.7 ± 4.5
	15 min	25.9 ± 6.3	-19.5 ± 4.2	9.3 ± 7.0	25.0 ± 8.6	35.5 ± 13.9	27.7 ± 8.9
	20 min	26.3 ± 6.4	-19.7 ± 4.4	9.9 ± 6.4	21.8 ± 8.0	29.5 ± 10.8	20.7 ± 4.1
	25 min	24.3 ± 6.1	-18.5 ± 4.3	10.6 ± 5.8	23.0 ± 8.7	31.1 ± 12.7	19.1 ± 4.1
	30 min	23.9 ± 5.7	-18.4 ± 3.9	10.0 ± 5.7	19.9 ± 7.8	26.3 ± 10.7	18.4 ± 3.8
	35 min	23.7 ± 5.8	-18.2 ± 4.0	9.2 ± 5.6	17.6 ± 7.6	23.0 ± 9.7	17.3 ± 3.9
	40 min	22.6 ± 5.4	-17.6 ± 3.8	9.5 ± 5.7	16.2 ± 7.5	20.4 ± 9.1	16.7 ± 3.7
	45 min	22.5 ± 5.2	-17.6 ± 3.7	9.1 ± 5.7	15.3 ± 7.4	19.3 ± 8.9	15.7 ± 3.8
	50 min	22.3 ± 4.9	-17.5 ± 3.5	10.0 ± 5.8	14.6 ± 7.7	17.5 ± 9.2	14.4 ± 4.0
	55 min	23.4 ± 4.3	-18.4 ± 3.0	9.8 ± 6.1	14.0 ± 7.7	16.6 ± 9.0	13.0 ± 4.0
	60 min	23.4 ± 3.4	-18.6 ± 2.4	9.3 ± 6.4	13.2 ± 8.4	15.5 ± 9.9	12.1 ± 4.1

Continued

Table 96. Effects of imipramine on ECG from lead V3 in clenbuterol rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 96. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-1.1 ± 0.6	-0.7 ± 0.5	-0.8 ± 0.5	1.3 ± 1.0	-0.4 ± 0.6	-2.4 ± 0.9
	10 min	-2.1 ± 0.8	-1.0 ± 1.0	-1.4 ± 0.8	3.1 ± 2.8	1.8 ± 2.1	-4.0 ± 1.5
	15 min	3.2 ± 1.4	-0.6 ± 1.5	0.6 ± 1.1	-0.4 ± 2.6	19.2 ± 5.4	3.5 ± 2.3
	20 min	5.3 ± 3.0	-3.0 ± 3.7	-0.3 ± 3.3	-4.9 ± 3.3	27.8 ± 6.6	7.7 ± 4.5
	25 min	8.1 ± 2.3	-3.7 ± 3.0	0.1 ± 2.6	-5.1 ± 4.1	30.6 ± 9.1	9.6 ± 4.7
	30 min	12.0 ± 2.8	-2.0 ± 3.1	2.5 ± 2.9	-4.1 ± 3.4	33.0 ± 9.1	13.2 ± 4.9
	35 min	14.0 ± 2.9	-0.6 ± 3.3	4.0 ± 3.1	-0.8 ± 3.0	34.2 ± 8.6	14.3 ± 5.9
	40 min	14.4 ± 3.3	0.0 ± 3.6	4.6 ± 3.4	2.5 ± 1.8	34.7 ± 9.0	12.3 ± 6.0
	45 min	16.5 ± 3.5	1.8 ± 4.0	6.5 ± 3.8	3.6 ± 3.7	34.5 ± 8.1	14.5 ± 5.8
	50 min	12.8 ± 1.9	-1.6 ± 3.0	2.9 ± 2.4	5.0 ± 3.3	33.6 ± 7.9	8.4 ± 3.3
	55 min	13.3 ± 2.3	-1.6 ± 3.5	3.1 ± 2.8	2.8 ± 5.8	29.9 ± 8.4	8.5 ± 3.7
	60 min	14.2 ± 3.2	-1.6 ± 3.8	3.3 ± 3.3	3.9 ± 5.9	33.2 ± 8.0	10.1 ± 5.1
Recovery	5 min	14.3 ± 2.8	-1.4 ± 4.5	3.5 ± 3.8	12.5 ± 3.9	31.1 ± 7.5	9.6 ± 4.8
	10 min	14.5 ± 4.4	1.3 ± 4.0	5.5 ± 3.9	10.2 ± 4.9	32.6 ± 8.6	11.5 ± 6.4
	15 min	15.0 ± 5.3	2.8 ± 4.8	6.7 ± 4.8	17.4 ± 7.9	22.4 ± 6.7	9.8 ± 8.3
	20 min	12.9 ± 4.4	0.8 ± 3.9	4.6 ± 3.9	9.9 ± 5.1	17.7 ± 6.6	11.3 ± 6.4
	25 min	12.6 ± 3.3	1.4 ± 3.5	5.0 ± 3.2	9.7 ± 4.9	16.6 ± 6.4	11.7 ± 5.1
	30 min	12.4 ± 3.8	1.3 ± 3.7	4.8 ± 3.5	11.1 ± 5.8	16.3 ± 6.5	10.2 ± 5.4
	35 min	12.0 ± 4.0	1.0 ± 3.7	4.5 ± 3.6	10.1 ± 6.1	15.8 ± 6.6	11.4 ± 5.1
	40 min	10.9 ± 4.1	0.4 ± 3.7	3.8 ± 3.6	11.1 ± 5.9	15.2 ± 6.6	8.7 ± 5.7
	45 min	11.2 ± 3.7	0.8 ± 3.6	4.1 ± 3.5	11.2 ± 6.3	14.3 ± 6.5	9.2 ± 5.5
	50 min	10.2 ± 2.6	-0.2 ± 2.4	3.1 ± 2.3	10.1 ± 7.0	14.7 ± 6.6	6.3 ± 5.0
	55 min	8.4 ± 2.5	-2.1 ± 2.7	1.3 ± 2.5	6.8 ± 5.0	13.8 ± 6.4	5.6 ± 5.2
	60 min	8.1 ± 2.4	-2.6 ± 2.4	0.9 ± 2.3	9.3 ± 5.5	13.5 ± 6.3	5.4 ± 5.5

Values are means ± SE. n= 6.

	Time	RR (ms)	HR (bpm)	P_d (ms)	PR (ms)	PR_{sect} (ms)	QRS (ms)
Baseline		145 ± 5	416 ± 14	14.7 ± 0.4	36.4 ± 0.7	21.7 ± 0.8	18.1 ± 0.6
Imipramine	5 min	145 ± 5	417 ± 15	14.8 ± 0.4	36.4 ± 0.8	21.7 ± 0.8	18.0 ± 0.6
	10 min	140 ± 3	429 ± 10	14.7 ± 0.5	38.5 ± 1.6	23.8 ± 1.5	18.2 ± 0.6
	15 min	146 ± 4	412 ± 11	15.4 ± 0.6	39.9 ± 1.8	24.5 ± 1.3	19.6 ± 1.2
	20 min	162 ± 7	374 ± 15	16.9 ± 0.8	42.1 ± 1.9	25.2 ± 1.3	21.3 ± 1.2
	25 min	175 ± 8	346 ± 16	17.6 ± 0.7	44.5 ± 1.7	27.0 ± 1.2	22.0 ± 1.2
	30 min	181 ± 9	335 ± 17	17.4 ± 1.0	44.9 ± 2.0	27.5 ± 1.2	22.9 ± 1.2
	35 min	185 ± 10	330 ± 17	17.6 ± 1.0	45.7 ± 1.9	28.1 ± 0.9	23.5 ± 1.2
	40 min	187 ± 10	326 ± 18	17.6 ± 1.0	46.8 ± 2.2	29.1 ± 1.3	24.1 ± 1.1
	45 min	186 ± 9	327 ± 16	17.7 ± 0.9	47.9 ± 2.4	30.2 ± 1.6	24.1 ± 1.2
	50 min	190 ± 9	319 ± 17	18.4 ± 1.0	49.5 ± 2.1	31.1 ± 1.3	24.3 ± 1.1
	55 min	189 ± 9	321 ± 16	18.7 ± 1.0	53.1 ± 2.0	34.4 ± 2.0	24.6 ± 1.2
	60 min	189 ± 9	322 ± 15	18.2 ± 1.1	56.8 ± 3.5	38.6 ± 3.8	25.1 ± 1.4
Recovery	5 min	183 ± 8	332 ± 16	19.3 ± 1.2	56.2 ± 3.2	36.9 ± 3.2	26.3 ± 1.8
	10 min	175 ± 8	347 ± 15	18.2 ± 0.9	52.0 ± 2.4	33.8 ± 2.1	24.1 ± 1.3
	15 min	169 ± 8	359 ± 16	17.2 ± 0.8	47.4 ± 1.4	30.2 ± 1.2	23.4 ± 1.2
	20 min	165 ± 8	367 ± 17	17.2 ± 0.8	44.9 ± 1.3	27.7 ± 1.4	22.9 ± 1.2
	25 min	163 ± 8	373 ± 18	16.9 ± 0.9	43.5 ± 1.2	26.6 ± 1.4	22.5 ± 1.1
	30 min	162 ± 8	376 ± 18	16.9 ± 0.8	42.4 ± 1.2	25.5 ± 1.5	21.9 ± 1.1
	35 min	160 ± 8	380 ± 18	16.7 ± 0.7	41.4 ± 1.2	24.8 ± 1.6	21.6 ± 1.0
	40 min	159 ± 8	382 ± 20	16.5 ± 0.6	40.6 ± 1.2	24.1 ± 1.5	21.3 ± 0.9
	45 min	158 ± 8	385 ± 20	16.5 ± 0.6	40.3 ± 1.2	23.8 ± 1.5	21.2 ± 0.8
	50 min	156 ± 8	389 ± 20	16.3 ± 0.6	39.9 ± 1.1	23.6 ± 1.5	21.1 ± 0.8
	55 min	155 ± 8	392 ± 22	16.2 ± 0.6	39.5 ± 1.2	23.2 ± 1.5	20.9 ± 0.8
	60 min	155 ± 9	394 ± 23	15.9 ± 0.5	40.5 ± 1.1	24.6 ± 1.3	20.8 ± 0.8

Continued

Table 97. Effects of imipramine on ECG from lead V3 in dobutamine rats. Values are means ± SE; n = 6.

Table 97. Continued.

	Time	QT (ms)	QTcB (ms_c)	QTcF (ms_c)	QT_1 (ms)	QA (ms)	T_d (ms)
Baseline		71.2 ± 3.1	187.0 ± 6.7	135.5 ± 5.1	10.6 ± 0.8	51.6 ± 1.6	42.2 ± 2.4
Imipramine	5 min	70.2 ± 2.5	184.7 ± 5.5	133.8 ± 4.1	10.5 ± 0.6	51.5 ± 1.5	41.3 ± 2.0
	10 min	68.9 ± 2.0	184.1 ± 4.0	132.7 ± 3.1	9.8 ± 0.6	49.8 ± 1.7	40.9 ± 1.6
	15 min	75.0 ± 1.7	196.0 ± 3.0	142.2 ± 2.3	9.9 ± 0.5	52.7 ± 2.7	45.6 ± 1.3
	20 min	79.9 ± 2.4	198.7 ± 3.4	146.6 ± 3.0	9.5 ± 0.5	51.0 ± 2.3	49.2 ± 1.8
	25 min	84.2 ± 3.9	201.4 ± 7.4	150.5 ± 5.9	9.6 ± 0.4	51.9 ± 2.1	52.6 ± 3.5
	30 min	87.4 ± 4.3	205.4 ± 8.4	154.4 ± 6.6	9.1 ± 0.7	53.6 ± 2.4	55.0 ± 3.8
	35 min	88.0 ± 3.8	205.2 ± 7.2	154.7 ± 5.6	9.8 ± 0.5	55.0 ± 2.6	54.9 ± 3.2
	40 min	88.5 ± 3.5	205.1 ± 5.4	154.9 ± 4.4	10.1 ± 0.5	56.5 ± 2.8	54.8 ± 2.4
	45 min	89.4 ± 3.5	207.3 ± 5.4	156.6 ± 4.6	10.5 ± 0.7	57.4 ± 2.7	55.2 ± 2.3
	50 min	91.5 ± 3.6	210.0 ± 6.3	159.2 ± 5.0	11.0 ± 0.8	58.1 ± 2.7	56.2 ± 2.5
	55 min	91.7 ± 4.3	210.8 ± 7.3	159.6 ± 6.0	11.1 ± 0.7	58.6 ± 2.5	56.0 ± 3.5
	60 min	89.2 ± 4.2	205.1 ± 7.0	155.3 ± 5.8	11.4 ± 0.6	58.6 ± 2.6	53.1 ± 2.9
Recovery	5 min	87.6 ± 2.7	205.2 ± 4.2	154.5 ± 3.4	13.0 ± 0.7	58.2 ± 2.7	48.8 ± 1.6
	10 min	82.0 ± 3.3	196.0 ± 4.6	146.5 ± 4.2	12.1 ± 0.5	57.6 ± 2.5	46.0 ± 2.5
	15 min	79.4 ± 3.8	192.9 ± 6.1	143.4 ± 5.2	11.9 ± 0.7	57.0 ± 2.6	44.5 ± 2.7
	20 min	79.1 ± 4.0	194.4 ± 6.3	144.0 ± 5.4	11.8 ± 0.7	55.8 ± 2.5	44.5 ± 2.8
	25 min	79.0 ± 3.8	195.5 ± 6.0	144.5 ± 5.1	12.0 ± 0.7	54.7 ± 2.4	44.7 ± 2.6
	30 min	78.6 ± 3.5	195.6 ± 5.3	144.3 ± 4.6	12.4 ± 0.8	54.1 ± 2.1	44.6 ± 2.4
	35 min	78.1 ± 3.2	195.5 ± 4.9	143.9 ± 4.1	12.5 ± 0.9	53.6 ± 2.0	44.3 ± 2.2
	40 min	77.1 ± 2.9	193.2 ± 4.7	142.2 ± 3.8	12.7 ± 0.9	53.2 ± 2.0	43.5 ± 2.0
	45 min	77.3 ± 3.0	195.1 ± 5.1	143.3 ± 4.1	12.7 ± 0.9	52.8 ± 2.0	43.5 ± 2.1
	50 min	76.6 ± 2.7	194.3 ± 4.7	142.4 ± 3.7	13.1 ± 1.0	52.4 ± 2.0	42.9 ± 1.9
	55 min	77.5 ± 3.0	196.6 ± 4.7	144.1 ± 3.9	13.3 ± 1.0	52.0 ± 2.1	43.5 ± 2.3
	60 min	77.2 ± 3.1	196.5 ± 4.1	143.9 ± 3.6	13.4 ± 1.0	51.9 ± 2.1	43.3 ± 2.3

Values are means ± SE. n = 6.

	Time	RR (%)	HR (%)	P_d (%)	PR (%)	PR_{sect} (%)	QRS (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-0.3 ± 0.2	0.3 ± 0.2	0.7 ± 0.7	0.2 ± 0.3	-0.2 ± 0.3	-0.3 ± 0.4
	10 min	-3.2 ± 1.6	3.4 ± 1.7	-0.1 ± 1.6	6.0 ± 4.9	10.3 ± 8.0	0.9 ± 0.8
	15 min	0.9 ± 1.4	-0.8 ± 1.4	5.2 ± 3.4	9.9 ± 5.2	13.3 ± 6.9	8.4 ± 3.7
	20 min	11.6 ± 3.2	-10.0 ± 2.5	15.5 ± 5.0	15.9 ± 5.6	16.6 ± 6.9	17.5 ± 3.8
	25 min	20.6 ± 3.5	-16.7 ± 2.4	20.0 ± 4.3	22.7 ± 5.5	25.0 ± 7.2	21.6 ± 3.9
	30 min	24.7 ± 3.6	-19.5 ± 2.3	18.9 ± 6.0	23.8 ± 6.5	27.5 ± 7.6	26.9 ± 3.9
	35 min	27.0 ± 4.2	-20.8 ± 2.7	19.8 ± 6.3	26.0 ± 6.1	30.5 ± 6.8	30.3 ± 4.1
	40 min	28.4 ± 4.7	-21.6 ± 3.1	20.3 ± 5.9	28.8 ± 6.2	35.0 ± 7.3	33.4 ± 4.8
	45 min	27.9 ± 4.0	-21.4 ± 2.7	20.9 ± 5.3	31.9 ± 6.6	39.8 ± 8.3	33.9 ± 6.1
	50 min	31.2 ± 4.9	-23.2 ± 3.2	25.3 ± 6.0	36.3 ± 6.0	44.1 ± 7.2	35.0 ± 5.0
	55 min	30.4 ± 5.1	-22.7 ± 3.3	27.8 ± 6.4	46.3 ± 6.2	59.0 ± 9.7	36.3 ± 4.9
	60 min	30.1 ± 5.0	-22.5 ± 3.2	24.3 ± 6.3	56.6 ± 10.5	78.6 ± 18.8	39.7 ± 8.9
Recovery	5 min	26.0 ± 5.0	-20.0 ± 3.5	31.5 ± 8.3	54.8 ± 9.6	70.4 ± 14.7	46.0 ± 9.2
	10 min	20.4 ± 4.0	-16.5 ± 3.0	23.7 ± 4.6	43.2 ± 7.2	56.5 ± 10.2	33.4 ± 6.9
	15 min	16.5 ± 3.4	-13.8 ± 2.6	17.3 ± 4.3	30.5 ± 3.9	39.4 ± 4.6	29.5 ± 5.5
	20 min	13.9 ± 3.2	-11.8 ± 2.6	17.0 ± 4.2	23.5 ± 2.7	27.6 ± 3.5	26.7 ± 4.5
	25 min	12.2 ± 3.3	-10.5 ± 2.7	15.2 ± 4.4	19.7 ± 2.0	22.4 ± 3.3	24.4 ± 4.1
	30 min	11.3 ± 3.2	-9.7 ± 2.7	15.0 ± 4.2	16.5 ± 1.8	17.1 ± 3.7	21.2 ± 3.4
	35 min	9.9 ± 3.0	-8.6 ± 2.6	13.7 ± 4.0	13.9 ± 1.7	13.7 ± 4.2	19.7 ± 3.1
	40 min	9.6 ± 3.3	-8.3 ± 2.9	12.5 ± 3.6	11.6 ± 1.6	10.7 ± 4.2	17.9 ± 2.6
	45 min	8.5 ± 3.1	-7.5 ± 2.8	12.7 ± 3.7	10.8 ± 1.4	9.2 ± 4.1	17.6 ± 2.6
	50 min	7.4 ± 3.2	-6.5 ± 3.0	11.5 ± 3.7	9.7 ± 1.5	8.2 ± 4.3	16.6 ± 2.5
	55 min	6.9 ± 3.5	-5.9 ± 3.3	10.6 ± 3.8	8.4 ± 1.7	6.8 ± 4.7	15.7 ± 2.4
	60 min	6.6 ± 3.9	-5.5 ± 3.7	8.2 ± 3.0	11.4 ± 3.2	13.7 ± 5.8	15.5 ± 2.2

Continued

Table 98. Effects of imipramine on ECG from lead V3 in dobutamine rats as percentage change from their baseline-instrumentation values. Values are means ± SE; n = 6.

Table 98. Continued.

	Time	QT (%)	QTcB (%)	QTcF (%)	QT_1 (%)	QA (%)	T_d (%)
Baseline		0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Imipramine	5 min	-1.1 ± 1.3	-1.1 ± 1.4	-1.1 ± 1.4	-0.4 ± 1.5	-0.1 ± 0.6	-1.7 ± 2.2
	10 min	-2.9 ± 1.6	-1.2 ± 1.6	-1.8 ± 1.6	-5.8 ± 6.2	-3.6 ± 0.9	-2.5 ± 2.6
	15 min	6.0 ± 3.2	5.4 ± 3.3	5.6 ± 3.3	-3.7 ± 8.2	1.9 ± 3.5	9.4 ± 5.4
	20 min	13.0 ± 4.9	7.0 ± 4.4	8.9 ± 4.5	-8.1 ± 7.1	-1.1 ± 2.6	18.1 ± 6.7
	25 min	19.1 ± 6.7	8.5 ± 5.8	11.9 ± 6.0	-6.8 ± 6.9	0.7 ± 2.4	25.7 ± 8.5
	30 min	23.8 ± 7.9	10.9 ± 7.4	15.1 ± 7.5	-13.2 ± 6.4	3.8 ± 2.4	31.7 ± 10.5
	35 min	24.6 ± 7.3	10.9 ± 7.2	15.3 ± 7.2	-6.0 ± 6.2	6.5 ± 2.8	31.6 ± 9.4
	40 min	25.1 ± 5.9	10.6 ± 6.0	15.3 ± 5.8	-2.6 ± 6.6	9.4 ± 3.3	31.2 ± 6.8
	45 min	26.0 ± 4.6	11.6 ± 4.7	16.2 ± 4.6	0.8 ± 6.4	11.2 ± 3.5	31.7 ± 4.5
	50 min	29.3 ± 5.8	13.0 ± 5.0	18.2 ± 5.1	5.9 ± 8.6	12.5 ± 3.3	34.5 ± 6.9
	55 min	29.4 ± 6.6	13.3 ± 4.8	18.4 ± 5.2	6.8 ± 8.1	13.6 ± 2.9	33.7 ± 7.7
	60 min	25.6 ± 5.1	10.0 ± 3.5	14.9 ± 3.9	11.7 ± 10.6	13.6 ± 3.0	26.1 ± 4.4
Recovery	5 min	23.7 ± 4.4	10.4 ± 4.1	14.7 ± 4.0	26.7 ± 13.1	12.8 ± 2.9	16.8 ± 4.8
	10 min	15.4 ± 2.8	5.2 ± 2.4	8.5 ± 2.3	17.4 ± 7.8	11.6 ± 2.9	9.8 ± 5.8
	15 min	11.6 ± 2.8	3.4 ± 2.3	6.0 ± 2.4	14.2 ± 6.0	10.3 ± 2.4	6.1 ± 6.3
	20 min	11.2 ± 3.0	4.2 ± 2.5	6.5 ± 2.6	12.9 ± 6.2	8.0 ± 2.1	6.2 ± 5.6
	25 min	11.0 ± 2.9	4.8 ± 2.5	6.8 ± 2.5	15.0 ± 7.0	5.9 ± 1.7	6.6 ± 5.2
	30 min	10.6 ± 2.6	4.9 ± 2.4	6.8 ± 2.3	19.0 ± 8.1	4.7 ± 1.1	6.4 ± 5.0
	35 min	9.9 ± 2.2	4.9 ± 2.1	6.5 ± 2.0	19.9 ± 8.5	3.8 ± 0.9	5.6 ± 4.5
	40 min	8.5 ± 2.5	3.7 ± 2.7	5.3 ± 2.5	21.8 ± 9.2	3.0 ± 1.1	3.9 ± 4.9
	45 min	8.9 ± 2.2	4.7 ± 2.2	6.0 ± 2.1	22.1 ± 9.1	2.2 ± 1.1	3.8 ± 4.5
	50 min	8.0 ± 2.4	4.3 ± 2.6	5.5 ± 2.4	25.9 ± 10.0	1.5 ± 1.2	2.5 ± 4.9
	55 min	9.0 ± 2.3	5.5 ± 2.3	6.7 ± 2.2	28.2 ± 10.3	0.6 ± 1.3	3.8 ± 4.9
	60 min	8.7 ± 2.2	5.5 ± 2.3	6.5 ± 2.1	29.0 ± 10.4	0.6 ± 1.4	3.2 ± 4.6

Values are means ± SE. n= 6.