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CARDIOVASCULAR EFFECTS OF DILTIAZEM ON THE DOGS WITH ATRIAL FIBRILLATION

DISSERTATION

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

By

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*****

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2001

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ABSTRACT

Atrial fibrillation (AF) is commonly associated with enlargement of the left atrium as produced by severe mitral regurgitation and dilated cardiomyopathy in dogs. The two main pathological features of AF which cause deterioration of the patients are a rapid ventricular response (VR) and absence of atrial contraction. Initially preload is decreased because of less end diastolic filling volume caused by less time to fill and no atrial contraction. Following this, the cardiac output declines. At rest, most patients can tolerate AF, however, exercise intolerance occurs.

The best way to treat AF patients in dogs is to control VR with drugs which prolong the refractory period and slow the conduction of the AV node. There are three main drugs used for this purpose in dogs: calcium channel blockers, β blockers, digitalis. Diltiazem is one of the calcium channel blockers which is the most commonly used in dogs with AF. This is because during AF, it is hard to control the VR when there is low parasympathetic and high sympathetic tone as in exercise, heart failure, excitement, and stress. Therefore, even though digitalis is used frequently, it is less effective than calcium channel blockers. Also β blockers and verapamil, one of the calcium channel blockers, have the ability to reduce the VR through effects on the AV node, but they have potent negative inotropic effects that might be injurious.
Variable doses of diltiazem are commonly used in dogs with AF. However, no research has been done exploring the dose of diltiazem based on the optimal VR. By studying acute, iatrogenic, AF in dogs, the optimal doses of intravenous and oral diltiazem were determined. The optimal dose is considered that dose which slows VR without reducing cardiac output or arterial pressure to levels below that during sinus rhythm. Results from studies on experimentally-induced AF in the dogs are difficult to apply to patients with the naturally-occurring arrhythmia, because patients have structural defects and more chronic consequences of the arrhythmia.

Because of the relative short half-life of regular release diltiazem, a sustained form of diltiazem was developed. The ability of sustained release diltiazem to slow the VR in dogs with naturally-occurring AF was determined. Sustained release diltiazem is superior when compared to the standard diltiazem because of its duration of the action and ease of administration (i.e., less frequent dosing). However, because of the limited number of the dogs with natural disease in this study, more cases are needed to investigate the pharmacodynamic effects of sustained release diltiazem in dogs with AF.
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   2000 ACVIM Meeting, Seattle, WA.


Papers


FIELDS OF STUDY

Major Field: Veterinary Biosciences
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CHAPTER 1

LITERATURE REVIEW

ATRIAL FIBRILLATION

Definition:

Normally the atria are stimulated by a wave of depolarization which originates in the SA node and travels through first the right atrium and then the left atrium. This wave generates the P wave of the ECG and stimulates the atria to contract and to eject into the ventricles from 15% to 35% of the blood which the ventricles ultimately eject into the great arteries. Atrial fibrillation (AF) is a disturbance of the heart’s rhythm in which the atria fail to beat, but merely “wiggle like a bag of worms”. This results because the SA node no longer controls the rhythm, but because hundreds of islets of tissue within the atria are stimulated independently and asynchronously.

Historical Background:

Harvey, in 1628, first observed peculiar waves traversing the atria in dogs dying during experimentation. This was no doubt about the first observation of AF. Adams, in the 19th century, was the first to describe the clinical features of auricular fibrillation, including the irregular arterial pulsations in patients. It took 200 years to realize that AF could be a clinically significant arrhythmia in patients. Early nineteenth-
century clinicians including Adams\textsuperscript{1,3}, identified the association between the irregular pulse and mitral valve disease. Marey\textsuperscript{1,3} depicted auricular (atrial) fibrillation graphically the first time in 1863 with a sphygmomanometer, and other physiologists almost at the same time identified it as well using the sphygmomanometer. However, none of them could propose a mechanism to explain the irregular pulse. In 1872, Vulpian\textsuperscript{1,4} noted rapid irregular motion of the atria in a dog, and named the condition “mouvement fibrillaire”. Later Cushny\textsuperscript{1,3,5} was convinced that the arrhythmia seen in human was the same as that seen in dogs. Mackenzie recognized the association between gross irregularity of the pulse and jugular pulse tracing. Originally he could identify atrial activity, but by 1907, he accepted that this condition as AF\textsuperscript{1,3,6}. After Hering and Einthoven\textsuperscript{7} first reported electrocardiograms of patients with irregular pulses in 1906,\textsuperscript{3} Rothberger and Winterberg\textsuperscript{7,8} used the new technique to prove that AF existed in human. They found the three distinctive features of AF: (1) an irregular ventricular rate, (2) the absence of P waves, (3) the presence of oscillations of the baseline (little “f” waves). In 1909, Lewis\textsuperscript{1,3,9,10} concluded that AF was the usual cause of the irregular arterial pulse, and declared that it was “a common clinical condition”. While a lot of experiments were conducted on auricular fibrillation in dogs, Roos\textsuperscript{11} reported the first clinical cases of spontaneous auricular fibrillation in dogs in 1924. In this paper, he reported that the pulse rate was increased to twice the normal and that all dogs afflicted with fibrillation have some kind of heart disease.\textsuperscript{11} At this time, little consideration was given to this arrhythmia, however, more cases were reported soon in dogs.\textsuperscript{12-19} Within the last 10 years, thousands of papers describing all features of AF in man are found in the literature.
Clinical Importance:

There is no question that AF is the most clinically important arrhythmia in men, dogs, and horses. Atrial fibrillation is the most common sustained arrhythmia observed in human cardiology. Because the prevalence of AF increases with advancing age, and patients are becoming older and older, and because of the increased prevalence of cerebral vascular accidents due to thrombosis originating within the fibrillating atria, AF constitutes enormous societal problem. The overall prevalence of AF was 1.5-6.2% in 4 major population-based studies (Cardiovascular Health Study, Framingham Heart Study, Western Australia study, and Rochester MN study). Of people over 65 years of age, about 6% have AF either sustained or paroxysmal. In addition to thromboembolism, the high ventricular rate (response, VR) observed in AF leads to heart failure. AF occurs also with relatively great prevalence post surgically, with diabetes mellitus, and with systemic arterial hypertension.

Enlargement of the left atrium as identified by echocardiography or radiography shows the importance of this anatomical observation in the genesis of AF. Atrial fibrillation was thought to be a benign arrhythmia because of a low incidence acute crisis or death. However, it is now well-known that AF is an independent risk factor for both stroke in humans and heart failure. About 15% of strokes occur in the setting of AF. Stroke in the setting of AF was nearly twice as likely to be fatal compared with stroke from other causes. Also survivors of stroke who had AF had longer hospital stays, increased disability, and were more likely to have recurrent strokes. Even though AF has been known to be a “bad arrhythmia”, and despite hundreds of clinical trials of tens of thousands of patients, it is often difficult to convert AF to sinus rhythms or to
control the VR.

Also AF is one of the most common arrhythmias seen in dogs. However, 0.6% of prevalence in dogs presented to a small animal clinic is low compared to the prevalence in humans.\textsuperscript{27} This is due, probably, to the relatively small atrial mass in dogs.\textsuperscript{27} Cessation of AF has been reported, in man, after surgical reduction of left atrial mass.\textsuperscript{28} Atrial fibrillation in dogs occurs in more prevalently in giant breeds (Great Dane, St. Bernard, Newfoundland, and Irish Wolfhound) and in dogs over eight years of age.\textsuperscript{27} No doubt the predilection to larger dogs is related to the larger atrial mass, and the increased prevalence in older dogs to more severe heart disease (i.e., mitral regurgitation, dilated cardiomyopathy).\textsuperscript{27} There is no question that AF is the most clinically important arrhythmia in men and dogs.

**Mechanism:**

The mechanisms of AF have been investigated exhaustively since the late 19th century. Many theories as to its genesis have been described and tested. One of the theories proposed a disturbance in a hypothetical "coordinating center" of the heart thought to be located in the proximal interventricular septum.\textsuperscript{1} However, this idea was proved false by MacWilliam and Porter.\textsuperscript{1} Engelmann, in 1895, advocated that AF was caused by multiple ectopic foci beating independently at their individual intrinsic rates.\textsuperscript{1} In 1905, Rothberger and Winterberg proposed the theory that fibrillation was due to the extremely rapid discharge of a single focus.\textsuperscript{1,29} In the middle of 1950s, Scherf and colleagues,\textsuperscript{30-32} and also Kimura\textsuperscript{31} demonstrated, by applying aconitine to the atria, that AF could be generated from a single, rapidly-firing focus. According to their
experiments, rapid activation of the atria was caused by application of aconitine on the atrial appendage, and the arrhythmia terminated after removal of the aconitine.

However, modern studies of the electogenesis of AF have lead to the concept of reentry. The basic principles of reentry were described by Cranefield, Mayer and Mines in 1914. They described an anatomical substrate with a central obstacle around which a reentrant wave front could circulate and unidirectional block. They demonstrated that a wave length of excitation shorter than the path length was required. Later Lewis developed the circus hypothesis with an anatomic center for the reentrant circuit. As invasive electrophysiological techniques emerged, other mechanisms, including the theory of intra-atrial reentry and the multiple wavelet hypotheses, were proposed.

In the 1960’s, Moe et al hypothesized the theory of “multiple wavelet reentry”, and later he developed a computer model of AF which was based on multiple reentrant wavelets in a two-dimensional sheet with realistic properties. With this model, the important clinical and experimental observations regarding AF were reproduced. According to his theory, the presence of a number of independent wavelets that wander “randomly” through the myocardium around islets or areas of refractory tissue maintained fibrillation. The overall probability of spontaneous termination of fibrillation depends on the average number of wavelets present. If many wavelets exist, the chance that all wavelets will be extinguished simultaneously is small. On the other hand, if only a small number of wandering wavelets are present, the waves may die or fuse into a broad single wavefront and thereby terminate fibrillation or produce atrial flutter. This hypothesis was tested experimentally by Allessie and coworkers in
the 1970s who established the "leading circle reentry". According to this, the center of a reentrant circuit need not be an anatomic obstacle but rather could be functionally determined as parallel pathways that conduct at different velocities. By this time, the mechanism of AF started to become clear though the mechanism of the actual initiation of AF was less obvious. Later, with the technique of high density mapping, the role of conduction inhomogeneities in the initiation of reentry and AF was established. These conduction inhomogeneities were caused by both anatomical and electrophysiological properties. The microarchitecture and the anisotropic properties of the myocardium may cause inhomogeneous and discontinuous propagation of the impulse. In addition, spatial dispersion in electrophysiological properties such as refractory period, excitability, and stimulating efficacy of the depolarization wave may lead to local conduction block of a premature depolarization. It is proposed that the conduction inhomogeneities are an initial requirement for the initiation of AF, while the length of the excitation wave constitutes a second requirement. This had already been pointed out by Lewis in 1925 and mathematically defined by Wiener and Rosenblueth as the distance traveled by the depolarization wave during the refractory period. And also in 1914, Garney already demonstrated very important fundamental concept about critical mass of tissues which is necessary to sustain fibrillation of any sort.

Based on this, AF is widely considered to be due to multiple reentrant wavelets. In the 1990s, it has been shown that AF itself causes the electrophysiologic changes in the atrium that favor both induction and maintenance of AF. These include shortened atrial refractory period and diminution of the rate-dependent change in refractoriness.
Physiological function of AV node:

Because elevation of VR occurs due to rapid bombardment of the AV node from the fibrillating atria, it is important to discuss, briefly, electrophysiology of the AV node—the region of specialized conductile tissue bridging the gap, electrically-speaking, between the atria and the ventricles. The AV node is located in the right atrium just above the origin of the tricuspid valve. The impulse from the atrium travels directly to the ventricles through the AV node, continues along the His bundle, enters the Purkinje fibers, and bursts through the ventricles producing the QRS complex of the ECG and stimulating the ventricles to contract. The AV node consists of atrial fibers (junctional) which fuse into the AV, the body of the node, and nodal-His bundle projections.

The AV junction serves as a subsidiary pacemaker, with a nominal rate of discharge of approximately 60 beats/minute, when the main pacemaker in the sinus node fails to function. The AV node, conducting at only 0.024 m/seconds, delays the impulse from the atria to the ventricles, giving the atria time to eject a portion of their contents into the ventricles before the ventricles contract. The AV node also can control the number and order of atrial impulses by acting as a filter and prevents the conduction of all of impulses from atrium to ventricle by all of these mechanisms.

The clinical hallmark of AF which is an irregular ventricular rhythm was described by Hering in 1903. In 1914, Hoffmann published the paper that auricular fibrillation was followed by a slightly irregular ventricular rhythm. The concept of "concealed conduction" was introduced by Scherf et al. in 1925. The change in refractoriness of the AV node was caused either by atrial activity that fails to propagate to the ventricles or by ventricular activity that fails to reach the atria. In 1990, Toivonen et
al.\textsuperscript{56} reported that the refractory periods and conductivity of the AV node are the best indicators of the potential of the node to transmit atrial impulses to the ventricles during AF. Therefore, the degree of concealed conduction in the AV node is less important determinant of the mean VR during AF.

**Hemodynamic consequence of AF:**

Rapid VR, loss of atrial contraction, and irregularity of the rhythm all participate in the reduction in the cardiac output with AF. This is exaggerated in the presence of heart disease in which myocardial function is already compromised either by altered atrial or ventricular function.\textsuperscript{57} After loss of atrial transport, cardiac index decreased by 20 %. The rate of closure of mitral and tricuspid valves is determined by the vigor and synchronization of atrial contraction and by the interval between atrial and ventricular contraction, which determine the position of the valvular leaflets. The absence of these contractions may be particularly deleterious in patients with dilated ventricles and may offer a plausible explanation for the increased severity of mitral and tricuspid regurgitation observed after the onset of AF. Intense debate on the cause/effect relation between AF and atrial enlargement has been going on.\textsuperscript{57} Whatever the mechanism, left atrial enlargement may predispose to systemic thromboembolism in human.\textsuperscript{22,24,25} Indeed, AF is one of the greatest risk factors of stroke due to thromboembolism in man.
Treatment:

Before the development of calcium channel blockers which slow AV conduction, digitalis was the most popular drug for slowing VR in patients with AF. As early as 1841, Blaine had briefly described the successful treatment of dropsy in dogs with foxglove, although he was unaware that digitalis acted primarily on the heart. The effect of digitalis is due to its vagomimetic and minimal antiadrenergic properties. Therefore, during periods of high sympathetic tone (as during exercise or excitement), slowing of VR is inadequate. Conversion of AF and maintenance of a normal sinus rhythm are rare in the dog with underlying heart disease. Ettinger reported defibrillating cases of AF treated with direct current synchronized shock after disappearance of the effect of digitalis. In some of the cases, defibrillation was successful, but AF returned in most of them no doubt because of the underlying heart disease (i.e., dramatic left atrial enlargement due to mitral regurgitation). In Uchino’s report, direct cardioversion was attempted in two cases of AF, but AF returned in both. Attempts to convert AF using quinidine have been reported, but the responses were in general inadequate in dogs with underlying heart disease.

It is generally agreed that in all patients with AF, control of VR is the main goal of treatment. With reduction and control of the VR, patient’s hemodynamic status is improved by extending the diastolic filling period and increasing left ventricular stroke volume, and cardiac output.

Attempts to control VR in dogs with AF have utilized 3 classes of drugs: digitalis, β-blockers, calcium channel blockers (CCBs). All drugs share the property of slowing
AV conduction and prolonging the refractory period of the AV node (thus producing greater concealment of atrial waves).\textsuperscript{68}

For over a century, digitalis (most recently digoxin) has been used as the mainstay for control of VR in the treatment of AF.\textsuperscript{58,60} Yet, in the early 1920s, Mackenzie\textsuperscript{69} and Lewis\textsuperscript{70} had already indicated that digitalis often failed to control the VR. As mentioned the mechanism by which digitalis slows VR is via its parasympathomimetic action, however, there is also a direct negative dromotropic effect of the glycoside. Digitalis alone may be used to control VR in some patients with AF, but its efficacy is quite limited in most patients for the following reasons.\textsuperscript{72} The first is that the onset of VR slowing is delayed until 4 to 9.5 hours after in initial dmg administration.\textsuperscript{68,73-75} Therefore, it is not ideal for an emergency setting of AF with very fast VR. But in patients with compromised cardiac function, digitalis is used to improve myocardial function, and it is used with addition of a β-blocker or calcium channel blocker.\textsuperscript{76} Because its mechanism is through the enhancement of vagal tone, the patients with high sympathetic tone (i.e., CHF, exercise, excitement, and thyrotoxicosis) have less response to the glycoside.\textsuperscript{58,68,73}

Lang et. al.\textsuperscript{71} compared the effects of verapamil with or without digoxin and digoxin alone in patients at rest and during exercise with AF patients. They found that verapamil is superior to digoxin in controlling the VR and in improving exercise capacity. Furthermore, the serum concentration of digoxin necessary to decrease VR was in the upper therapeutical — and close to the toxic — range.\textsuperscript{71,77,78} Because faster acting agents such as CCBs and β-blockers are now available, the use of digoxin as a first-line agent for VR control is questioned. β-blockers increase the refractoriness and conduction
time of AV node to reduce VR. They are particularly useful in patients with AF during exercise or after cardiac surgery, and in patients with hyperthyroidism or pericarditis, since increased adrenergic tone is a critical factor in the initiation and maintenance of these forms of AF. Esmolol — a β-blocker — has rapid onset of action after intravenous administration and the ability to titrate because of its short half-life (i.e., minutes). Therefore, it is preferred in the emergency situation. Propranolol—a mixed β-blocker with a significantly longer half life — is also used. CCBs slow VR by blocking the influx of calcium ion through the slow type of calcium channel. This results in an increase in the refractoriness and decrease in conduction of AV node. Many cellular functions, including electrical activity of the heart, contraction of cardiac, skeletal, and vascular muscle, and other metabolic and regulatory cellular processes require the separation and movement of calcium across membranes. Only surface calcium channels are sensitive to the CCBs and not all cellular events mediated by calcium are affected by administration of CCBs. Also not all tissues that are sensitive to CCBs are equally responsive to CCBs in clinical use. Verapamil and diltiazem are often used for this purpose, whereas nifedipine has little use for AF.

**DILTIAZEM**

**Historical Background:**

In 1963, the earliest research using CCBs was started in German. The Tanabe Seiyaku company began to work on the synthesis of 1,5-benzothiazepine derivatives as a central nervous system antidepressant in 1966. Following this, the company developed a series of 1,5-benzothiazepines that dilate coronary arteries, and the D-cis isomer of a
group of DL-cis 3-acetoxy-2-(4-methoxy phenyl) derivatives were finally selected. One was named CRD 401, which is now known as diltiazem.\textsuperscript{83,84} In 1973, diltiazem was approved as an antianginal drug in Japan, and as an antihypertensive drug in 1982. In the same year, this drug was approved for angina in the United States. In 1989, a sustained release formulation of diltiazem was approved by the FDA for use in patients with hypertension. In 1991, an injectable form of diltiazem was developed treatment of supraventricular arrhythmias, and once-daily formulation of diltiazem was approved for hypertension\textsuperscript{85} and subsequently in 1992 for angina in human.

**Pharmacokinetics and pharmacodynamics:**

Diltiazem is absorbed rapidly from the GI tract in the intact form.\textsuperscript{86} It first appears in the plasma 15 minutes after oral administration, and peak concentrations occur after 30 minutes in dogs.\textsuperscript{86} Mushi\textsuperscript{87} also reported rapid absorption and disappearance of approximately 95% of the administered dose from the GI tract within 120 minutes in rats. Piepho reported that a peak diltiazem plasma level was achieved in 1 hour after oral administration in dogs.\textsuperscript{88} Approximately 70-80% of the drug is bound to plasma proteins; about 60% of the drug is metabolized by the liver, and the remainder is excreted by the kidneys.\textsuperscript{86} In spite of high absorption in dogs after oral administration, bioavailability of diltiazem is less than 50% because of a high hepatic first-pass effect.\textsuperscript{88} A significant first-pass effect leads to large differences from individual to individual in absolute bioavailability, plasma concentration, and clearance.

The major metabolic pathways involve o-deacetylation or N-demethylation followed by o-demethylation, and finally, glucuronide or sulfate conjugation. Diltiazem
is metabolized to desmethyldiltiazem and desacetyldiltiazem, which have about 40% of
the activity of the parent compound. Occasionally diltiazem achieves two peaks in
plasma concentration, one occurs at 30 to 60 minutes and the other at 3 to 4 hours after
the administration of 20 mg/kg of diltiazem. Piepho suggested that enterohepatic
recycling of diltiazem occurs in dogs. The initial volume of distribution is about 7.5
l/kg and ultimately about 40 l/kg. This indicated "a large transfer of diltiazem into
tissues". The main route of excretion is in the liver. Diltiazem is rapidly eliminated
(t½ = 2.3-4 hours) and the relatively short half-life appears to be a result of the high
level of plasma clearance. Piepho compared the plasma diltiazem clearance with
hepatic blood flow in the dog, and concluded that the drug is eliminated at a rate
dependent on hepatic blood flow. Thus, even though the drug is apparently extensively
distributed in the body, the half-life of diltiazem in the beagle dog is relatively short
because of the highly efficient elimination process.

The peak effect of oral diltiazem occurs within 2 hours and there is a
physiological response for up to 6 hours. Immediately following the diltiazem bolus,
there is a pronounced decline in systemic arterial pressure which subsequently
plateaus. A small transient increase in heart rate was observed at the time of maximal
reduction in systemic arterial pressure. However, the increase in HR produced by a
decrease of 30 mmHg in systemic arterial pressure appeared to be less than what would
be expected by activating the baroreceptor reflex. This attenuation of the baroreceptor
reflex may have been modified by direct suppression of the SA node. Browne studied
the effect of oral diltiazem on normal conscious dogs. At a dose of 1 to 3 mg/kg
diltiazem produced a slight increased HR, and at a dose of 10 mg/kg, a slight decrease in
HR was seen. This also indicated that higher doses of diltiazem may possess a negative chronotropic effect. Direct systemic arteriolar dilatation produced by diltiazem caused the immediate decline in blood pressure, and this decline evokes a brief baroreceptor-mediated reflex increase in HR. Therefore, the balance between diltiazem's direct electrophysiologic effect which depresses the sinoatrial and atrioventricular nodes and the baroreceptor-mediated reflex response to peripheral vasodilatation determined the net overall chronotropic responses to diltiazem.\textsuperscript{89}

Diltiazem is used in the treatment of angina pectoris\textsuperscript{91-94} (due to coronary artery spasm or atherosclerosis), systemic hypertension\textsuperscript{91,95} and pulmonary hypertension because of its ability to relax vascular smooth muscle. It is also used to treat hypertrophic cardiomyopathy by virtue of its ability to promote ventricular relaxation—a positive lusitrope.\textsuperscript{96} Diltiazem also retards atrioventricular nodal conduction. Smith\textsuperscript{97} observed a 14 % prolongation of the PR interval after infusion of 20 mg over 10 minutes. This suggested that diltiazem can be used for the treatment of supraventricular arrhythmias.

MYOCARDIAL OXYGEN CONSUMPTION AND EFFICIENCY

Efficiency is defined as the ratio between the work done by a machine and the energy put into it. As early as 1895, Frank applied this concept to the heart and defined its efficiency as mean systolic pressure times cardiac output divided by myocardial oxygen consumption.\textsuperscript{98} The cardiac oxygen consumption is measured as the coronary blood flow times the difference in arterio-venous oxygen content. However, because of the necessity of the invasive technique involving coronary sinus catheterization (an
ethical limitation in patients with cardiovascular disease), this direct method is not practical.^{99} It has been shown that highly accurate cardiac oxygen consumption can be obtained by the indirect methods expressed as the tension-time index, the pressure rate product, and the triple product^{100—all methods used to estimate myocardial oxygen consumption. In 1958, Katz and Feinberg^{101} published the paper about pressure rate product as an indicator of myocardial oxygen consumption. In 1980, Baller et al.^{102} confirmed that there is a very good relationship between the pressure rate product and the direct measurement of myocardial oxygen consumption. They concluded that pressure rate product can be used as bedside indicator of myocardial oxygen consumption.
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CHAPTER 2

THE EFFECTS OF INTRAVENOUS DILTIAZEM ON THE DOGS
WITH INDUCED ATRIAL FIBRILLATION

Introduction:

Diltiazem blocks L type calcium channels,\footnote{1} and has proven useful in both humans\footnote{1-8} and dogs\footnote{9-12} for slowing the ventricular response (VR) in patients with atrial fibrillation (AF). Because of the dose-response relationship, it is possible to slow the VR to almost any degree, even to rates too low to sustain life. Although it is agreed that a VR of 250/minute in a patient with AF is too fast, there is little agreement on what range of VR minimizes myocardial oxygen consumption and right atrial pressure but sustains cardiac output and systemic arterial pressure at levels appropriate for optimal performance.

The purpose of this study is to report the effects of graded doses of diltiazem on parameters of cardiovascular function in dogs with AF produced by rapid atrial pacing. Our hypothesis was that diltiazem could produce a ventricular rate (termed optimal) at which the rate-pressure product (the prime determinant of myocardial oxygen consumption) and right atrial pressure are low and systemic arterial pressure is sustained.
at nearly normal levels (i.e., near values obtained during SR). Such a result should optimize ventricular efficiency (i.e., the ratio of useful work to myocardial oxygen consumption).
Material and methods:

ANIMALS: Twelve, young adult, healthy beagles of both sexes were anesthetized with thiopental (12 mg/kg IV) and alpha chloralose (Sigma C-9821) (100 mg/kg IV), and anesthesia was maintained with alpha chloralose (30 mg/kg/hour IV). The dogs were intubated, placed in lateral recumbency on a water-circulating heating blanket, and ventilated with room air using a volume of 15-20 ml · kg\(^{-1}\) and respiratory rate of 12 to 15 breaths per minute to sustain PaCO\(_2\) 35 to 45 mmHg. Arterial pH, PCO\(_2\), and PO\(_2\) were measured periodically during instrumentation and maintained within normal limits by adjusting tidal volume and ventilatory rate, and by intravenous administration of sodium bicarbonate. A solid state cathetertip micromanometer (Millar model SPC-350, 5F) was placed into the left ventricle, and fluid-filled catheters were placed in the thoracic portion of the descending aorta, in the right atrium, and in the pulmonary trunk. Pressures were recorded from the left ventricle, aorta, and right atrium, and cardiac output (CO) was measured by thermodilution (Baxter model COM-2) after injecting 5 ml of room temperature saline into the right atrium and sampling the temperature of blood in the pulmonary trunk. A fluid-filled catheter was placed into a femoral vein for injecting diltiazem, and a bipolar pacing catheter was placed in the high right atrium for pacing (50 Hz, 2 V, 2 ms pulses) into AF. Myocardial oxygen consumption (MVO\(_2\)) was not measured directly, but was estimated by the product of heart rate (HR) and mean systemic arterial pressure (P\(_{Ao}\)), termed the rate-pressure-product (RPP).\(^{13-17}\)

\[
\text{MVO}_2 = \text{HR} \times \text{P}_{Ao}
\]

Although the prime determinants of myocardial oxygen consumption are HR,\(^{18}\) myocardial contractility,\(^{19}\) and peak tension,\(^{20}\) RPP is commonly used for clinical
As an estimate of left ventricular efficiency ($E$), we calculated useful work (i.e., $CO \times PA_o$) and divided that product by an estimate of myocardial oxygen demand (i.e., $HR \times PA_o \times dP/dt_{max}$). \cite{21}

$$E \equiv (CO \times PA_o) / (HR \times PA_o \times dP/dt_{max})$$

This equation simplifies to:

$$E \equiv CO / (HR \times dP/dt_{max})$$

d$P/dt_{max}$ is determined also by preload, but contractility is a much more powerful determinant of $dP/dt_{max}$ than is preload. \cite{22, 23}

**PROTOCOL:** Control measurements of all physiological parameters were made from all dogs. The vagus nerves were cut so that high ventricular responses could occur without significant block in the atrioventricular (AV) node, and physiological measurements were repeated. All dogs then were paced into sustained AF as described above. Half of the dogs received saline in volumes comparable with the volume of diltiazem (Sigma D 2521), and half received total cumulative doses of diltiazem of 0.063, 0.188, 0.438, 0.938, and 1.938 mg/kg. The initial dose was chosen because, in preliminary studies, we found this to be a no-effect dose. Doses were given every 15 minutes, and physiological recordings were made in triplicate during the last minute of each dose. The half-life of diltiazem is approximately 3 h (2.5 to 4 h), \cite{24-26} and the duration of dosing in this study was 75 minutes. Thus, the amount of diltiazem metabolized or excreted was inconsequential in estimating the cumulative dose. That is, if 50% of the initial dose was metabolized and/or excreted in 3 h, then almost 96% of that dose was present during the measurements 15 minutes after the last dose was given.
Just before each physiological measurement in 4 of the 6 dogs, arterial blood samples were drawn for analysis of plasma concentration of diltiazem. These samples were analyzed in the Analytical Toxicology Laboratory, College of Veterinary Medicine, The Ohio State University (Dr. Richard Sams) using high pressure liquid chromatography. The lower limit of quantitation was 10 ng/ml.

STATISTICS: Means and standard deviations of the means, for both vehicle controls and for dogs receiving diltiazem, were calculated for all parameters at all recordings. Means were compared by a 2-way ANOVA with repeated measure design. When indicated by a significant F-statistic, specific means were compared by Student Neuman-Kuhls multiple comparison requiring a $p < 0.05$ for significance. We determined after which dose the values did not differ significantly from the value obtained when the dogs were in SR (statement of the hypothesis). In all graphs, values for means followed by the same letter did not differ ($p > 0.05$).
Results:

Figure 2.1 shows a plot of blood level of diltiazem (ordinate) vs total cumulative dose (abscissa) obtained during incremental dosing. It can be observed that plasma concentration increased linearly with the geometrical dosing, giving a regression equation of plasma concentration in ng/ml:

\[
(\text{plasma concentration of diltiazem}) = 2.8 + 128.9 \times (\text{cumulative dose of diltiazem})
\]

\(r^2\) is 0.83 with \(p < 0.001\)

Figure 2.2 shows plots of HR, dP/dt_{max}, CO, and \(P_{Ao}\), (ordinates) vs cumulative dose of diltiazem (abscissa). When dogs were put into AF, both HR and dP/dt_{max} increased, while CO and \(P_{Ao}\) did not change. In response to graded doses of diltiazem, but not in the controls, both HR and dP/dt_{max} decreased in a dose-dependent fashion. At doses higher than 0.938 mg/kg, both CO and \(P_{Ao}\) decreased, and fell below values obtained during SR at a dose of 1.938 mg/kg. Even at the highest dose, dP/dt_{max} did not fall below the value measured during the period of SR. Ventricular response at doses of 0.938 and 1.939 mg/kg fell below VR during SR.

Figure 2.3 shows plots of left ventricular end diastolic pressure (LVEDP) and right atrial pressure (RAP) (estimates of ventricular filling forces) vs cumulative dose of diltiazem. RAP (but not LVEDP) increased when dogs were put into AF. In response to incremental doses of diltiazem, RAP initially decreased then increased to same level as during AF at a dose of 0.938 mg/kg and LVEDP showed no change until after at a dose of 0.438 mg/kg dose, after which both LVEDP and RAP increased.

Figure 2.4 shows plots of RPP (an estimate of myocardial oxygen consumption) and efficiency (an estimate of the ratio of useful work to oxygen consumption) vs the
cumulative dose of diltiazem. RPP increased and efficiency decreased from SR to AF, whereas remained constant for the controls, and both returned to values not different from those obtained during SR at a dose of diltiazem of 0.938 mg/kg. At a dose of diltiazem of 1.938 mg/kg, RPP fell below and efficiency increased above values obtained during SR.
Fig 2.1 Relationship, including regression equation, between plasma concentration (ng/ml) and dose (mg/kg) of diltiazem.
Fig 2.2 Plots of hemodynamic parameters compared versus doses of diltiazem (mg/kg) obtained during atrial fibrillation (AF). SR refers to baseline obtained during sinus rhythm. HR, dP/dt_max, CO, and P_Ao stand for, respectively, heart rate, maximal rate of rise of intraventricular pressure, cardiac output and mean systemic arterial pressure. Values for means followed by the same letter did not differ (p > 0.05). Controls are open squares, and dogs receiving diltiazem are closed circles. Notice that values for HR and dP/dt_max tended to return to values close to those during SR, but that values for both CO and P_Ao fell, after the highest dose, to levels below that during SR.
Fig 2.3 Plots of LVEDP and RAP-estimates of ventricular preload – versus dose of diltiazem (mg/kg). LVEDP and RAP stand for, respectively, left ventricular end diastolic pressure and right atrial pressure. Values for means followed by the same letter did not differ (p > 0.05). Notice both increase at doses of diltiazem at or greater than 0.938 mg/kg.
Fig. 2.4 Plots of rate pressure product (RPP) and an estimate of left ventricular efficiency versus dose of diltiazem. Values for means followed by the same letter did not differ (p > 0.05). Notice that RPP increased and efficiency decreased between SR and AF, that both remained constant in controls, but that both returned towards that during SR at a dose of 0.938 mg/kg.
Fig. 2.5 Plots of percent change in HR (compared with that during AF) and diltiazem plasma concentration in dogs and humans.

Discussion:

This study supported the hypothesis for dogs with iatrogenic AF that diltiazem could be used to slow VR such that physiological function did not differ from that observed during SR. A cumulative dose of diltiazem of 0.438 mg/kg, producing a plasma concentration of 67.8 (SD 36.5) ng/ml, satisfied this hypothesis. This plasma concentration is considered slightly lower than that used in humans with naturally-occurring AF to slow VR onse comparably. In our study, a plasma concentration of 67.8 ng/ml reduced VR approximately 30% from that during AF, whereas in humans, a plasma concentration of 172 ng/ml was required (Fig. 2.5). A species difference could be due to the fact that our dogs with AF had much higher VR than humans with AF. Alternatively, the difference could have resulted from greater potency of diltiazem in dogs than in humans.

Diltiazem exerts Ca\textsuperscript{2+} blockade by affecting voltage-gated channels, and to a lesser degree by affecting ligand-gated channels. A reduction (i.e., depolarization) in membrane potential results in opening of the voltage-operated channels, and the receptor-operated channels are affected by agonists such as catecholamines. Although there are other (i.e., mitochondrial, sarcolemmal, Na\textsuperscript{+}-Ca\textsuperscript{2+} exchange) affectors of Ca\textsuperscript{2+} kinetics, it is thought that at therapeutic concentrations, diltiazem affects principally the movement of Ca\textsuperscript{2+} from extracellular to intracellular space. We do not know which of the above determinants of Ca\textsuperscript{2+} kinetics may be responsible for differences between humans and dog.

A dose of diltiazem of 0.938 mg/kg caused RAP and LVEDP to increase to values greater than obtained during SR, and a dose of 1.938 mg/kg caused CO and Pa\textsubscript{o} to
decrease to values below those obtained during SR. Mean systemic arterial pressure differed between the group serving as vehicle-controls and the group receiving diltiazem at baseline and during the AF. Although the means differed significantly (p= 0.04), the absolute difference was less than 20 mmHg. We have no explanation for this difference because dogs were randomized to receive either vehicle or diltiazem. Similarly, CO differed at the onset of AF between dogs that received drug and those that served as controls. This difference, although statistically significant, was small (0.4 l/min) and probably was due to the small (0.1 l/min) increase in dogs that received the drug and a small decrease (0.05 l/min) in dogs that served as controls.

At a dose of 0.438 mg/kg, VR decreased to a value similar to that obtained during SR. During AF, dP/dt max remained higher than during SR. We assumed that physiological function during SR was optimal for survival. Therefore, we interpreted values that did not differ from those obtained during SR as being compatible with optimal function. With AF, the ventricles do not receive the usually small volume of blood (termed the atrial “kick”) during end-diastole. Without that contribution to preload, the force of ventricular contraction and stroke volume should be decreased according to the Frank-Starling mechanism. For this reason, VR in AF may have to be increased to compensate for reduced stroke volume. On the other hand, with cardiomegaly the natural (i.e., resonant) frequency of the heart would be reduced. In general, the closer to the natural frequency that a machine (in this case the left ventricle) works, the more efficiently it works. For example, the 7.5kg horse heart normally beats 30 times per minute whereas the 0.25 kg dog heart normally beats 90 times per minute. Therefore, with cardiomegaly, the heart may have to contract more slowly than without
cardiomegaly, because the resonant frequency of a massive heart is lower than for a normal heart. Another benefit of cardiodeceleration is lengthening of the time for both coronary blood flow and ventricular filling. With naturally-occurring heart disease, reduced ventricular compliance is common. Therefore, cardiodeceleration should improve impaired ventricular filling by prolonging filling time (i.e., diastole). This study was conducted on dogs without cardiomegaly, and we have no evidence that what might be optimal for our dogs would be optimal for dogs with cardiomegaly due to natural disease.

Cardiodeceleration caused by diltiazem may result in additional benefits to the cardiovascular system other than improving coronary blood flow and ventricular filling. Ventricular performance (including heart rate) is "tuned" to systemic arterial impedance (estimated roughly by the ratio of pulsatile pressure to stroke volume) in a manner that optimizes (i.e., makes more efficient) transfer of energy from the ventricle into the systemic arterial tree. At physiological VR, the left ventricle expends approximately 90% of its energy to overcome vascular resistance and 10% to overcome impedance. At higher VR, the amount of energy expended to overcome impedance may double or even triple. Thus, reducing heart rate could improve cardiac energetics by improving ventriculo-vascular coupling. However, we did not measure parameters of ventriculo-vascular coupling in this study.

Our index of left ventricular efficiency is fraught with many assumptions and approximations. Efficiency for the left ventricle, defined as work out \( (P_a \times CO) \) divided by energy in (myocardial oxygen consumption), should be the product of CO times mean ejection pressure, divided by the product of HR, afterload, and contractility. Mean
systemic arterial pressure rather than mean arterial pressure during ejection was used. Afterload was not measured and contractility was estimated by preload-dependent dP/dt_{\text{max}}. As mentioned previously, however, LVEDP (a minor determinant of preload) changed only slightly and not at all up to and including a dose of diltiazem of 0.438 mg/kg. However, LVEDP must be interpreted with regard to myocardial stiffness. If diltiazem rendered the myocardium less stiff, then a constant LVEDP still may have increased preload and dP/dt_{\text{max}}.

We described the effects of diltiazem on RPP in AF, because RPP is reported commonly in clinical medicine. It is of importance because it is comprised of 2 of the 3 major determinants of myocardial oxygen consumption and it is measured quite easily. As with our efficiency index, RPP reached a value during AF not different from that during the period of SR. This RPP was achieved at a dose of 0.938 mg/kg, which also was the dose at which the efficiency index returned to a value not different from that obtained during the SR. Nevertheless, we believe that our estimate of efficiency supports our view that a dose of diltiazem of between 0.438 and 0.938 mg/kg is optimal for a heart of normal mass.

dP/dt_{\text{max}} decreased in a dose-dependent manner, but it never reached values lower than those obtained during SR. The decrement in dP/dt_{\text{max}} may be a consequence of the decrease in HR (a Bowditch effect) produced by diltiazem. Although dP/dt_{\text{max}} decreases with a decrease in VR in the normal heart, it is thought not to decrease with decreasing VR when the heart is failing. Thus, we do not believe that, at the doses used in this study, diltiazem exerts negative inotropy other than that due to cardiodeceleration. Studies on humans with heart failure indicate that diltiazem seldom exerts significant
In a study of the effects of diltiazem in dogs with biventricular failure due to rapid pacing, diltiazem decreased myocardial contractility estimated by a reduction in dP/dt_max. This study, however, used 0.8 mg/kg of diltiazem, a dose much higher than we believe necessary to slow the ventricular rate. In our study, we observed reductions in dP/dt_max but never below control values even at a dose of 1.93 mg/kg. In another study, diltiazem did not decrease dP/dt_max in normal dogs. In dogs with volume-overload heart failure produced by aortic-caval shunt, however, a bolus injection of 200 μg/kg followed by a continuous infusion of 40 μg/kg/min resulted in a 20% decrease in dP/dt_max after 10 minutes. This decrease was modest but still may be clinically significant. Thus, caution should be exercised when using diltiazem in dogs with supraventricular tachycardia and mild to no ventricular compromise.

Both vagus nerves were sectioned so that a rapid ventricular response could occur in the presence of AF. This maneuver should not have altered the decrease VR due to diltiazem, because (unlike digitalis) diltiazem does not exert its negative dromotropism via a vagal mechanism. Whereas digitalis loses its negative dromotropism during exertion or excitement, diltiazem does not. Furthermore, sectioning both vagus nerves may mimic more closely the response of a dog in AF with heart failure, because vagal tone is known to be low in heart failure.

In human beings, diltiazem is the drug of choice for reducing VR in AF. This choice is a result of the negative dromotropism of diltiazem. Diltiazem exerts its negative dromotropic effect rapidly, its dose-response properties allow prediction of precisely how much ventricular slowing is expected, it has few adverse effects, and
(unlike digitalis), diltiazem continues to slow HR even during exercise or excitement.\textsuperscript{7,43,44}

This study was conducted on beagle dogs anesthetized with alpha chloralose and put into AF. The typical clinical patient with AF is a large breed dog (i.e., Great Dane, Irish Wolfhound, Doberman Pinscher),\textsuperscript{26,45,46} unanesthetized, with heart disease, and in long-standing, naturally-occurring AF. Therefore, data from this study must be interpreted cautiously in clinical patients. If effects of diltiazem on dogs with AF and heart failure mimic those observed in this study, diltiazem would be an effective and safe compound for the management of ventricular rate in dogs with AF.
References:


CHAPTER 3

CARDIOVASCULAR EFFECTS OF ORAL DILTIAZEM ON THE DOGS WITH INDUCED ATRIAL FIBRILLATION

Introduction:

Atrial fibrillation (AF) with a rapid ventricular response (VR) is an arrhythmia of hemodynamic and prognostic importance in canine medicine. It occurs most frequently in dogs with left atrial enlargement caused most commonly by mitral regurgitation or dilated cardiomyopathy. Since it is often impossible to convert these patients into sinus rhythms (SR), the principal goal of medical management of these patients is to slow the VR with agents (i.e., digitalis, beta blockers, calcium channel blockers) that slow AV conduction. Of these compounds, calcium channel blockers are by far the most efficacious, and diltiazem has emerged as the compound used most commonly and effectively. Although in a previous study we proposed an optimal dose when given iv,^ the present study was designed to determine an optimal dose when given orally.

To our knowledge, no detailed prospective study has been carried out to determine an optimal dose of oral diltiazem in respect to major determinants of cardiac oxygen consumption and efficiency.
Materials and Methods:

ANIMALS: Twelve, young-mature, healthy beagles of either sex were anesthetized with thiopental (12 mg/kg iv) and alpha chloralose (100 mg/kg iv), and anesthesia was maintained with alpha chloralose (30 mg/kg/hour iv). Dogs were intubated and ventilated with a tidal volume of 12.5 ml/kg (room air) and at a frequency of 12 to 15 breaths per minute to sustain PaCO₂ between 35 to 45 mmHg. Dogs were placed on heating pads to sustain body temperature. A solid state, catheter-tip micromanometer was placed into the left ventricle, and fluid-filled catheters were placed in the thoracic portion of the descending aorta, in the right atrium, and in the pulmonary trunk. Pressures were recorded from the left ventricle, aorta, and right atrium, and cardiac output (CO) was measured by thermodilution after injecting 5 ml of room temperature saline into the right atrium and sampling the temperature of blood in the pulmonary trunk. A bipolar pacing catheter was placed in the high right atrium for pacing (50 Hz, 2 V, 2 ms pulses) into AF. Myocardial oxygen consumption (MVO₂) was estimated by the product of heart rate (HR) and mean systemic arterial pressure (Pₐo), termed the rate-pressure-product (RPP).

\[
\text{MVO}_2 \equiv HR \times P_{a_o}
\]

As an estimate of left ventricular efficiency (E), we calculated useful work (i.e., CO \times Pₐo) and divided that product by an estimate of myocardial oxygen demand (i.e., HR \times Pₐo \times \text{dP/dtmax})

\[
E \equiv \frac{(CO \times P_{a_o})}{(HR \times P_{a_o} \times \text{dP/dtmax})}
\]

This equation simplifies to:

\[
E \equiv \frac{CO}{HR \times \text{dP/dtmax}}
\]
PROTOCOL: Control measurements of all physiological parameters were made from all dogs. The vagus nerves were cut so that high ventricular responses could occur without significant block in the atrioventricular (AV) node, and physiological measurements were repeated. All dogs then were paced into sustained AF as described above. A nasogastric tube was placed into the stomach to administer diltiazem diluted with 10ml of saline. One third of the dogs received saline in volumes comparable with the volume of diltiazem, another third received doses of diltiazem of 2.5 mg/kg, and another third received 5.0 mg/kg of diltiazem. Data were collected during SR and AF, and 0.5, 1, 2, and 3 hours after production of AF. Just before each physiological measurement, arterial blood samples were drawn for analysis of plasma concentration of diltiazem. These samples were analyzed in the Analytical Toxicology Laboratory, College of Veterinary Medicine, The Ohio State University (Dr. Richard Sams) using high pressure liquid chromatography. The lower limit of quantitation was 10 ng/ml.

STATISTICS: Means and standard deviations of all parameters measured or calculated at all recording periods were compared by a 2-way ANOVA with repeated measure design. When indicated by a significant F-statistic, specific means were compared by Turkey post hoc test. We determined when values did not differ either from those during either SR or immediately after onset of AF using Dunnett’s t-test. A p value < 0.05 was considered statistically significant. Graphs were made plotting values SR, immediately after production of AF but before therapy, and at 0.5, 1, 2, and 3 hours after the dogs received either 2.5 or 5.0 mg/kg of diltiazem or placebo. In addition, plots were made of percent in each parameter compared to the values during SR and AF.
Results:

When dogs were put into AF, VR (Figure 3.1.A) increased in all groups from 120 to 270 bpm, an increase of approximately 220% greater than during SR. In the controls, there was no change in VR over the time. For dogs receiving 2.5 or 5.0 mg/kg VR decreased, but the decrease was significant only at the 5.0 mg/kg dose during the 1st, 2nd, and 3rd hours post-dosing (Figure 3.1.A). During the 2nd and 3rd hour, the VR did not differ from that during SR. Figures 3.1.B and 3.1.C, show plots of the percent that VR is of that during SR (3.1.B) or AF (3.1.C). It is clear that there were dose-response relationships in both instances, however statistical comparisons were conducted only on absolute values. Plasma concentrations of diltiazem versus time after administration are shown (Figure 3.2) for both doses. It can be observed that plasma concentrations were higher with the 5.0 mg/kg dose than with the 2.5 mg/kg dose. Insignificant differences in concentrations existed between the 1 and 3 hour samples of each dose, and only the 5.0 mg/kg dose developed plasma concentrations considered within the therapeutic range (i.e., 50-200 ng/ml). At 3 hrs when the plasma diltiazem concentration became maximum (Figure 3.2). Figure 3.3 shows the relationship with regression equation between plasma concentration (abscissa) and VR (ordinate). The reduction in VR is related to the plasma concentration with r^2 of 0.865.

Figure 3.4 and 3.5 show plots of RPP and efficiency expressed as absolute values (A), and percents that each value is of the value during SR (B) and AF (C). It can be observed that RPP increased between SR and AF, remains unchanged for dogs receiving vehicle or 2.5 mg/kg diltiazem, but decreases during hours 1, 2, and 3 post-dosing. It is shown in figure 3.4.C that the 2.5 mg/kg dose had a slight, but statistically
insignificant, reduction in RPP when comparing RPP to that measured during AF. It is shown that efficiency decreased precipitously between SR and AF, remained different from that during SR for all time and for both doses except that at 3 hours post-dosing, it returned to a value not different from that during SR for the 5.0 mg/kg dose.

Figure 3.6 shows plots of the ratio of the number of left ventricular pressure pulses greater than 60 mmHg to the number of QRS complexes. It can be observed that the ratio decreased precipitously between SR and AF, remained depressed for dogs receiving vehicle, and returned to values not different from that during SR during all post-dosing recordings.

Table 3.1 demonstrates that there are no significant differences in any other hemodynamic parameters in response to either dose of diltiazem. Although not achieving statistical significance, $dP/dt_{\text{max}}$ and right atrial pressure (RAP), tended to increase between SR and AF. Cardiac output tended to decrease for all group--albeit insignificantly--throughout the duration of this study.
Figure 3.1: Plots of mean and standard deviation of ventricular response (VR) in beats/minute on the ordinate when dogs were in sinus rhythm (SR), in atrial fibrillation (AF) but untreated, and in AF but after receiving vehicle, 2.5 mg/kg or 5.0 mg/kg diltiazem for 0.5, 1, 2, and 3 hours. Means followed by an “a” indicate that they did not differ from those during SR within a group. Means followed by a “b” indicate that they did differ from values obtained from the vehicle group at the same time. Means followed by a “c” show that they did differ from means of the groups receiving 2.5 mg/kg at the same time. A shows absolute values for parameters, B shows percent difference from that during SR, and C shows percent difference from that during AF. Statistical comparison was not made for the percentage differences, but they are included as another method of demonstrating responses. Notice the increase in VR between SR and AF, the constancy of VR during AF with only vehicle, and the decrease in VR with both doses of diltiazem, but the greater and statistically significant decrease with the 5.0 mg/kg dose.
Figure 3.2: Plots of plasma concentration of diltiazem (ng/ml on ordinate) versus time (hours) after dosing of 2.5 or 5.0 mg/kg. Blood concentrations followed by the same letters did not differ from each other. Drug levels differed between groups, but did not differ within groups from 1 hour after dosing to the end of surveillance.
Figure 3.3: Relationship between VR (ordinate) in BPM and plasma concentration (abscissa) of diltiazem (mg/kg). The equation of regression and the coefficient of determination are shown.
Figure 3.4: Plots of mean and standard deviation of rate-pressure product (RPP) in BPM mmHg on the ordinate when dogs were in sinus rhythm (SR), in atrial fibrillation (AF) but untreated, and in AF but after receiving vehicle, 2.5 mg/kg or 5.0 mg/kg diltiazem for 0.5, 1, 2, and 3 hours. Means followed by an "a" indicate that they did not differ from those during SR within a group. Means followed by a "b" indicate that they did differ from values obtained from the vehicle group at the same time. Means followed by a "c" show that they did differ from means of the groups receiving 2.5 mg/kg at the same time. A shows absolute values for parameters, B shows percent difference from that during SR, and C shows percent difference from that during AF. Statistical comparison was not made for the percentage differences, but they are included as another method of demonstrating responses. Notice the increase in RPP between SR and AF, the constancy of VR during AF with only vehicle, and the decrease in RPP with both doses of diltiazem, but the greater and statistically significant decrease with the 5.0 mg/kg dose.
Figure 3.5: Plots of mean and standard deviation of efficiency in ml/sec/bpm/mmHg on ordinate when dogs were in sinus rhythm (SR), in atrial fibrillation (AF) but untreated, and in AF but after receiving vehicle, 2.5 mg/kg or 5.0 mg/kg diltiazem for 0.5, 1, 2, and 3 hours. Means followed by an “a” indicate that they did not differ from those during SR within a group. Means followed by a “b” indicate that they did differ from values obtained from the vehicle group at the same time. Means followed by a “c” show that they did differ from means of the groups receiving 2.5 mg/kg at the same time. A shows absolute values for parameters, B shows percent difference from that during SR, and C shows percent difference from that during AF. Notice the decrease in efficiency between SR and AF, the constancy of efficiency during AF with vehicle and 2.5 mg/kg dose, and the increase in efficiency with the 5.0 mg/kg dose.
Figure 3.6: Plots of mean and standard deviation of the ratio of number of left ventricular pressure pulses greater than 60 mmHg to the number of QRS complexes on ordinate when dogs were in sinus rhythm (SR), in atrial fibrillation (AF) but untreated, and in AF but after receiving vehicle, 2.5 mg/kg or 5.0 mg/kg diltiazem for 0.5, 1, 2, and 3 hours. Means followed by an “a” indicate that they did not differ from those during SR within a group. Means followed by a “b” indicate that they did differ from values obtained from the vehicle group at the same time. Means followed by a “c” show that they did differ from means of the groups receiving 2.5 mg/kg at the same time. Notice the decrease this ratio between SR and AF, the constancy of this ratio during AF with only vehicle, and the increase in this ratio with both doses of diltiazem.
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Table 3.1: Mean and standard deviation of hemodynamic parameters recorded when dogs were in sinus rhythm (SR), in atrial fibrillation (AF), and in AF after treatment with vehicle, 2.5 mg/kg or 5.0 mg/kg of diltiazem, for 0.5, 1, 2, and 3 hours. Values followed by the letter “a” differed from that during SR.
**Discussion:**

Our results demonstrated that a dose 5.0 mg/kg of diltiazem, given orally by nasogastric tube, reduced VR in dogs with AF to levels that did not differ from those during SR at 2 and 3 hours post-dosing. Although a dose of 2.5 mg/kg decreased VR, the decrease still did not result in VR obtained during SR. When VR slowed, there were slight, but statistically and clinically insignificant changes in parameters of mechanical function (i.e., mean systemic arterial pressure, ventricular filling pressures, cardiac output, dP/dt\text{max}). We cannot exclude the possibility that these changes could have been related to the change in heart rate, but were a direct effect of diltiazem on myocardial or vascular smooth muscle mechanics. Diltiazem is known to relax vascular smooth muscle and therefore decrease systemic vascular resistance\(^6\); and this effect might also decrease preload and dP/dt\text{max} (a Frank-Starling effect\(^1\)). No doubt, however, the decrease in VR decreased dP/dt\text{max} in accordance with the Bowditch effect\(^1\).2

Our results also demonstrated that the 5.0 mg/kg dose of diltiazem returned all indices of ventricular efficiency (i.e., rate-pressure product, rate-pressure product divided by cardiac output, ratio of numbers of left ventricular pressure pulses greater than 60 mmHg to the number of QRS complexes) to values not different from those during SR at 3 hours post-dosing. Thus a dose of 5.0 mg/kg given orally normalized cardiac function at 2 and 3 hours post-dosing.

The plasma concentration of diltiazem at 5 mg/kg at 2 to 3 hours post-dosing was 70 ng/ml, a value in the range between 50 ng/ml and 200 ng/ml considered useful in dogs.\(^1\) These values are low compared with the report which gave 3.0 mg/kg of diltiazem for consecutive days and achieved plasma concentrations after 5 days of 224 ng/ml.\(^1\) It
is difficult to reconcile our results with those of chronic oral dosing. With repeated oral dosing, it is possible that hepatic enzymes could become saturated, thus decreasing the "first-pass" effect, and making diltiazem more bioavailable or possibility even toxic after repeated dosing.\textsuperscript{14} We would have preferred conducting these experiments on awake dogs with long-standing, naturally-occurring AF. However, ethical considerations and unavailability of subjects interdicted our preference. Consequently we conducted the study on normal dogs with AF produced experimentally, and restrained with alpha chloralose, an anesthetic regimen known to affect autonomic control less than any other regimen.\textsuperscript{15} We do not know if this anesthesia impacted on our results.

The vagosympathetic trunks were cut so that the VR would be accelerated, without AV block, during the AF. We produced AF, acutely, by pacing the right atrium as in previous studies,\textsuperscript{5} and studies were conducted after the dogs had been in AF for 15 minutes. We do not know whether dogs with chronic, naturally-occurring AF would respond as the dogs in this study, but there is abundant data to support electrophysiological remodeling of the atria that depends upon the duration of AF,\textsuperscript{16,17} and that enlarged atria are more prone to develop AF and no doubt respond differently to drugs.\textsuperscript{18}

Diltiazem powder diluted in 10 ml of physiological saline was administered through a nasogastric tube directly into the stomach. This method no doubt decreased the time to peak plasma concentration, since no time was required for dissolution of a tablet. The doses of 2.5 mg/kg and 5.0 mg/kg were used because they represent a dose
recommended in the literature\(^1\) (i.e., 0.5 to 2.5 mg/kg) and a dose twice that (i.e., 5.0 mg/kg). We sought a plasma concentration greater than 50 ng/ml, which is recommended as being therapeutic for dog,\(^1\) and achieved that end using the 5.0 mg/kg dose.

Plasma concentrations of diltiazem reach a near plateau by the 1\(^{st}\) hour post-dosing, and did not change significantly at the 3\(^{rd}\) hour post-dose. However, it appeared that concentrations increase—although insignificantly—between the 1 and 3 hour samples. Only dogs receiving 5.0 mg/kg developed plasma concentrations considered therapeutic (50 ug/ml to 200 ug/ml), however, it is clear that even the 2.5 mg/kg dose produced a reduction—albeit insignificant—in VR. The plasma half-life for diltiazem, given iv, is 2.5 and 4 hours,\(^{19,20}\) so if we state that we achieved peak concentrations at 3 hours, then we would not expect—but did not monitor for—a sustained reduction in VR for another 3 to 6 hours in this study. However, when diltiazem is administered multiple times a day in the patients with heart disease, the reduction in VR would be expected.\(^*\) We believe that possibly 3.75 mg/kg might produce a decrease in VR that is clinically significant and might have less possibility for producing systemic arterial hypotension particularly in ill patients, however, we did not observe any adverse responses to 5.0 mg/kg given to otherwise healthy dogs.

Figure 3.3 shows the relationship between the rate of VR and diltiazem plasma concentration based upon 4 samples for each of 6 dogs. It is clear and was expected that, with reasonable assurance ($r^2=0.865$), the VR can be predicted by the plasma

\(^*\) In 2 dogs with naturally-occurring AF and high VR, VR decreased for up to 8 hours after an oral dose of 5.0 mg/kg.
concentration. We do not know if a greater \( n \) would have changed the contour of this relationship.

The rate-pressure-product (RPP) is the product of mean systemic arterial pressure and heart rate. This product is used commonly in clinical studies to estimate myocardial oxygen consumption\(^7\)\(^8\). We recognize that using RPP alone neglects the effect of afterload and myocardial contractility. In this study, it was shown that RPP increased dramatically from SR to AF, resulting from the dramatic increase in VR with little to no change in systemic mean arterial pressure. Then, when VR decreased in response to diltiazem, RPP — and presumably myocardial oxygen consumption and possibly myocardial oxygen debt — decreased.

One factor in determining myocardial oxygen consumption, and efficiency, is the oxygen utilized in depolarization and repolarization represented by the QRS and ST-T of the ECG. Quite clearly, if a QRS and ST-T — implying opening and closing of ionic channels and ionic pump — occurred, but no useful contraction developed, then the energy used for generation of the QRS and ST-T was “wasted”, leading to inefficiency. Furthermore, we believe that a left ventricular peak systolic pressure of less than 60 mmHg would probably have resulted in no stroke volume thus, could not have resulted in useful work. Therefore, we took the ratio of the number left ventricular pressure pulses with systolic pressure greater than 60 mmHg to the number of QRS complexes as an estimate of relative efficiency. Using these arguments, our data showed that efficiency fell dramatically from SR to AF — as was shown in Figure 3.6 — but that efficiency returned towards normal (i.e., ratio of pressures greater than 60 mmHg to number of QRS complexes returned to 1.0) as VR slowed in response to diltiazem.
In conclusion, for healthy dogs with rapid VR due to AF produced by atrial pacing, a dose of 5.0 mg/kg of diltiazem (producing plasma concentrations of 70 ng/ml) given orally reduced VR and altered estimates of cardiac efficiency to levels not different from those during SR. This normalization occurred between 1 and 3 hours after oral administration. The results of this study must be extrapolated with caution to dogs with naturally-occurring AF of long standing.
References:


11. Starling EH. The Linacre lecture on the law of the heart. London: Longman, Green;1918;


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CHAPTER 4

THE EFFECT OF SUSTAINED RELEASE DILTIAZEM ON THE DOGS WITH NATURALLY-OCcurring ATRIAL FIBRILLATION

Introduction:

Diltiazem is one of the most commonly used drugs for the treatment of atrial fibrillation (AF) in dogs. In a previous study, the optimal dose of diltiazem given either orally or intravenously was established as that dose which decreased the ventricular response (VR) most but sustained both cardiac output and mean arterial pressure at near normal levels in dogs with acutely induced AF. It is important that the results of the previous study with iatrogenic AF be extrapolated cautiously to dogs with AF occurring because of heart disease. The present study was designed to determine the ability of a sustained release form of diltiazem (SRD) at slowing the VR in dogs with naturally-occurring AF. Also the functional refractory period of the AV node (given by the shortest inter-beat interval) and parasympathetic restraint (given as the longest inter-beat interval) were estimated. In the last few decades, many different types of sustained release formulations have been developed to improve efficacy of the drug and patient compliance.\textsuperscript{1,2} We are aware of no reports describing the ability of a SRD at slowing the VR in dogs with naturally-occurring AF, or in determining the effects of diltiazem on the functional refractory period of or parasympathetic tone to the AV node.
Materials and methods:

This study was conducted on dogs with AF. Two females with apparent “lone”AF were large breeds (128 and 135 pounds), one small female who presented to the clinic with severe heart failure caused by mitral insufficiency, 2 males were large dogs (between 70 and 80 pounds) that had been subjected to rapid ventricular pacing for 6 months and had been in AF for 3 months. We consider the AF in the latter two dogs to be naturally-occurring, because it occurred after the dogs had developed and had sustained severe cardiomegaly, reduced LV shortening fraction, exercise intolerance, and ascites. None of the dogs was receiving therapy that might have affected the cardiovascular system.

After electrocardiograms were obtained with the dogs at rest, 3 dogs (1 with lone AF and 2 with AF in the presence of heart failure) were given, orally, 8.0 mg/kg and 2 dogs (1 with lone AF and the other with mitral insufficiency) were given, orally, 4.0 mg/kg of sustained release diltiazem (SRD, Dilacor XR 240mg capsules*). Electrocardiograms and venous blood samples were obtained from all dogs 4 hours after the initial dose, and for the 2 dogs with AF (DOG 1, 2) and heart failure, at 0.5, 1, 2, 4, 6, 8, 12, 20, 24, and 36 hours post-dosing. The latter 2 dogs (DOG 1,2) were given the same dose daily for 4 consecutive days, and VR was measured before dosing, and at 4, 12 and 24 hours post-dosing. Average RR interval was determined by dividing 60,000 (ms/minute) by the number of QRS complexes that occurred in a 1 minute tracing, but both maximal and minimal RR intervals were calculated was well. It may be considered that maximal RR interval is a surrogate of the degree of concealed conduction, and that

* Rhone-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA
minimal RR interval reflects the functional refractory period of the AV node; although both are dependent upon other factors (i.e., the rate of atrial activity, the direct drug effects on and degree of concealment within the AV node). Plasma diltiazem concentrations were measured by high pressure liquid chromatography (Laboratory of Toxicology, College of Veterinary Medicine, OSU, Mayo Medical Laboratory, Rochester, Minnesota). The limit of quantitation is 10 ng/ml.
Results:

Figure 4.1 shows RR intervals and plasma concentrations of diltiazem for 2 of the dogs (DOG 1,2) that were studied for 36 hours post-dosing. Notice that the maximal RR interval increased more than the minimal increased in response to diltiazem, and that they reached peaks at 4 hours post-dosing, close to when plasma concentrations peaked. Functional refractory periods for the AV nodes for both dogs were 200ms before dosing, and one prolonged to 375 ms (87.5%) and the other to 500 ms (150%) 4 hours post-dosing. The maximal RR interval (an estimate of the concealed conduction) for both dogs, pre-dosing was 200 ms, and prolonged to 1500 ms (200%) 4 hours post-dosing. The approximate half-time for the return of RR interval to normal after dosing was 12 hours.

Figure 4.2 shows heart rates and plasma concentrations for the same 2 dogs (DOG 1,2) only after given the sustained release form of diltiazem daily for 4 days. Notice that the maximal increases in RR intervals always occurred approximately 4 hours post-dosing, and that they returned to baseline by 24 hours post-dosing. Notice also that, with the exception of the 3rd dose in one dog, plasma concentrations for each dog achieved peaks of similar concentrations for all 4 days at the 4 hours post-dose sampling.

Figure 4.3 shows the RR intervals pre-dosing and at 4 hours after dogs in AF received SRD. The RR intervals in 3 dogs receiving 8.0 mg/kg increased from a mean of 319 ms to a mean of 800 ms (an increase of 150%), while the dog receiving 4.0 mg/kg increased from 410 ms to 638 ms (an increase of 56%). There was little effect on DOG 5. Figure 4.4 shows plasma diltiazem concentrations 4 hours after dosing from DOG 1,2, and 5. Unfortunately, laboratory error precluded obtaining diltiazem concentrations from
DOG 5 had less than 10 ng/ml. Either this dog vomited his tablet, or possibly absorption was delayed so that a sample 4 hours post-dosing had no diltiazem. Plasma concentrations for DOGS 1 and 2 were 150 and 90 ng/ml, respectively.
Fig 4.1 Plots of RR interval and plasma concentration of diltiazem (ng/ml) versus time after administration of 8.0 mg/kg of sustained release diltiazem for DOGS 1 and 2.
Fig 4.2 Plots of RR interval and plasma diltiazem concentration (ng/ml) versus time after dosing. Dogs were given 8.0 mg/kg of sustained release diltiazem for 4 days. The measurements were obtained before (BL), and 4 and 24 hours after administration for 4 days.
Fig. 4.3 Plots of maximal, mean, and minimum RR intervals during baseline (BL) and 4 hours after administration of sustained release diltiazem to 4 dogs.
Fig 4.4 Plots of diltiazem plasma concentration 4 hours after administration of sustained release diltiazem to 3 dogs.
Discussion:

In two previous studies we investigated the effects of intravenous and oral diltiazem given to healthy beagle hounds with AF induced acutely. An optimal dose was described as that dose which slowed the VR to a level not different from that during sinus rhythm and which permitted sustenance of normal cardiac output and mean systemic arterial pressure. Because of the relatively short half-life of regular release diltiazem (4 to 6 hours following oral administration), it must be given at least 3 times a day, and client compliance is severely diminished. Furthermore, many animals are reluctant to take medicine three times a day.

With the development of oral sustained release (SR) formulations in the past decade, these problems are circumvented. Dilacor is one of the SR forms of diltiazem (D) developed to improve clinical efficacy (i.e., sustain blood concentrations for prolonged periods) of the drug and patient compliance because of decreased dosing frequency. The mechanism is called "Geomatrix Release Mechanism", which is designed to achieve constant release of diltiazem for 24 hours. The capsule contains three layers, a core containing the active diltiazem in hydrophilic and hydrophobic material which swells in an aqueous medium, and two inactive surface layers sandwiched around the core. Diltiazem is released initially from the core by hydration at a rate proportional to the core's swelling. The two inactive surface layers hydrate slowly to prevent drug release.

To detect the time of maximal effect (i.e., when maximal RR interval is achieved), the duration of the effect, and the degree of increase in mean RR, SRD was given once in the morning and monitored for 36 hours to two dogs. In both dogs, the
time of maximal effect was 4-6 hours post-administration and the duration of the effect was about 24 hours. Mean RR intervals increased from 300 to about 700 msec for both dogs. To study the repeatability of the effect, SRD was given in the morning for 4 days. In both dogs, the maximal prolongation of the RR interval occurred during the 4th hour after administration, and the RR intervals still remained slightly longer than during baseline for 24 hours for 4 days.

No adverse effects were seen even at the dose of 8.0 mg/kg in DOG 1 and 2. However, on one of the dogs with naturally-occurring AF (DOG 3), there was a severe reduction in VR with 8.0 mg/kg. Unfortunately, we were unable to measure the plasma concentration. It is possible that this dog may have been very sensitive to diltiazem. In veterinary cardiology, the dose of 1.5-6.0 mg/kg is recommended for the use of Dilacor in the dog. But there is no original reference for this dose range. Because there is no study of SRD conducted in dogs with AF, the dose used in this study was extrapolated from the dose used in cats with hypertrophic cardiomyopathy. The approximate half-time for the return of RR interval to normal after dosing was 12 hours.

Because of the limitation of the number of the dogs in this study, it is hard to identify a proper starting dose. In this study, two dogs had a response with 8.0 mg/kg comparable to what we considered optimal in the previous 2 studies. However, one dog had severe bradycardia response with same dose. One dog had an adequate response to 4.0 mg/kg of diltiazem, however, one dog had little response to this dose. Therefore, dosing must have to been established individually, starting at 4.0 mg/kg.

The VR resulting from supraventricular activity traversing the AV conducting system is extremely complex and still not fully understood. While it is clear that one
determinant of the VR is how rapidly the supraventricular focus discharges, another equally important and more dynamic determinant of VR is related to AV nodal propagation. This is determined by the site(s) of origin into the AV node from the atria, and by the absolute refractory periods and conduction velocities of the potential pathways. Thus the net VR depends upon the frequency and rhythmicity of the supraventricular input to, and the degree of concealment within, the AV node. This has been expressed as the frequency of engagement of the AV node and how successful the transmission was.6

Our study measured the effect of diltiazem on the longest and on the shortest RR interval in dogs with AF. The longest RR interval is thought to lengthen as more waves of depolarization entering the AV node from the atria become concealed in the AV node. Alternately, a reduction in the rate of AF (i.e., input to the AV node) might slow the VR, or if it results in less concealment, the VR may actually increase. Concealment refers to a wave entering and depolarizing the dorsal portion of the node, but not being propagated into the ventral portion. The only way, without studying electrograms from various regions of the AV node, of knowing that such concealment occurs, is that the following beat which is propagated through the AV node is propagated with relatively slow conduction—thus prolongation of the PQ interval. The slow conduction occurs because the propagated wave traverses the zone of the AV node which is in its relative refractory period due to the concealed wave. The degree of concealment depends upon how rapidly waves enter the concealing zone and upon the electrophysiological properties of that
zone. One major determinant of the likelihood of concealment is the parasympathetic tone which slows conduction,\(^7\) thus increasing the likelihood for a wave failing to be propagated.

In this study the longest RR interval was prolonged dramatically due to diltiazem. It is unlikely that this prolongation is due to slowing of the rate of fibrillation and decreasing the numbers of waves entering and traversing the AV node. It is further unlikely that slowing is due to a vagomimetic action, since this has not been attributed to diltiazem. Rather, it is most likely that the decreased VR arises from increased concealment within the AV node due to negative dromotropic properties of the calcium channel (L-type) blockade.

It is thought that the shortest RR interval reflects the functional refractory period of the AV node including all structures propagating from the AV node to the first portion of the ventricle depolarized.\(^8\) In fact, propagation from atria to ventricles occurs over at least two pathways, one conducting rapidly but with a relatively long absolute refractory period and one conducting slowly but with relatively short absolute refractory period. In our study, as in a study of vagal effects on VR in AF, diltiazem had little effect on the shortest RR interval. This suggests that the effect of diltiazem is not mediated via a change in the effective refractory period of AV node, but mainly by increasing degree of concealment or a directly negative dromotropic effect. It is plausible that diltiazem does not affect the pathway with the slowest conduction velocity and the shortest absolute refractory period. Our findings are partially consistent with the study of Theisen et al,\(^9\) in which five patients had proportional increases in the shortest and in the longest RR intervals, but five other patients (like the dogs in this study) had increases in only the
longest RR intervals. They postulated that the decrease in VR resulting from diltiazem was due to increased concealment caused primarily by an increase in AF rate (in the patients with prolongation in only the longest RR intervals), and secondarily by both an increased rate of fibrillation and prolonged effective refractory period (in the patients with increases in both the shortest and longest RR intervals). However, they made this statement about the increased rate of fibrillation despite having no electrophysiological evidence of such. Fujimoto et al\textsuperscript{10} found that both functional and effective refractory periods of the AV node were prolonged by diltiazem. Talajic's et al\textsuperscript{11} examined the effects of diltiazem on the VR during experimental AF in dogs, and attributed a decrease in VR to a rate-dependent increase in both functional refractoriness of and concealed conduction within the AV nodal. Diltiazem increased the effective refractory period of the AV node in a frequency-dependent manner without affecting the atrial effective refractory period, thereby increasing the potential zone of concealment within the AV node. Faster stimulation of the AV node seen in AF limits the recovery time available between impulses, leading to an accumulation of diltiazem binding and enhanced drug effect. In contradistinction, a slower rate of stimulation prolongs diastole, and allows more drug unbinding and less AV nodal depression. This results in increased efficacy for diltiazem at higher heart rates (use dependence), when it is needed the most. A possible explanation for why we did not see an increase in the shortest RR interval in response to diltiazem may be because of a relatively low rate of atrial input to the AV node.

There was no effect of diltiazem at the dose of 4.0 mg/kg in DOG 5, but no diltiazem was detected in the plasma at 4 hours after administration of this drug. From analysis of blood concentrations of diltiazem in previous studies conducted on dogs,
therapeutic concentrations of diltiazem were measured following a dose similar to the one used in this dog. It is difficult to explain why—despite the same close—no diltiazem was measured in plasma obtained 4 hours post-administration. Possibly the dog vomited the diltiazem. However, if it did in fact receive the diltiazem, it is possible that the capsule either did not dissolve or dissolved so slowly that blood concentrations of diltiazem were not measurable 4 hours post-dosing. Furthermore, this dog had mitral regurgitation, AF, and signs/symptoms of severe heart failure; therefore, we presume that sympathetic tone was too elevated to permit the negative chronotropy or dromotropy of diltiazem. Therefore, in this case, the dose of diltiazem should be increased or β blockers could have been added.

There are two opposite opinions about the effect of diltiazem in patients with heart disease. Studies with diseased human myocardial tissue conducted by Schwinger showed negative inotropic properties of diltiazem even though this effect was weak compared with other calcium channel blockers.12 Wong's study showed that diltiazem reduced the contractile function in right ventricular systolic hypertension induced by ligation of pulmonary arteries.13 Diltiazem also impaired cardiac function in the dogs with pacing induced heart failure.14 Generally, this negative inotropic effect is reversed by the baroreceptor-mediated increase of cardiac output and contractility in healthy subjects. However, there is still some concern that diltiazem might cause deterioration of the patients because the negative inotropy cannot be counterbalanced by the baroreceptor response in the heart failure patients. In addition, patients with heart failure are particularly susceptible to the cardiodepressant actions of calcium channel blockers because of a profound defect in the delivery of calcium to the contractile proteins.15
In contrast to this, many beneficial effects of diltiazem were reported in patients with heart failure. The cardiodepressant effect was minimized by the ability of diltiazem to improve coronary blood flow and decrease afterload. Furthermore, by preventing calcium overloading of the myocytes during or after ischemic events, myocardial injury and cardiac dysfunction might be minimized or prevented. Maurer studied the influence of calcium channel blockers in cardiomyopathy. He found reduced afterload and improved the ventricular function. This occurred with both nifedipine, principally a vasodilator, and with diltiazem, a less active vasodilator. Neither blocker alters myocardial contractility substantially. Kulick evaluated the therapeutic potential and safety of diltiazem in patients with severe chronic congestive heart failure. In this study, none of patients had symptomatic deterioration after administration of diltiazem; however, depression of stroke volume index or an increase in LV filling pressure was occasionally seen. Walsh also observed the beneficial hemodynamic effects of intravenous and oral diltiazem in severe congestive heart failure. Patients with heart failure are more likely to have hepatic congestion, thus the bioavailability of the drug may increase due to the reduced hepatic deacetylation, the major route for elimination of diltiazem. Long term use of calcium channel blockers producing hypotension in patients with heart failure may cause activation of endogenous neurohormonal systems. This occurs more often with nifedipine than with diltiazem. Also in patients with heart failure, the sympathetic nervous system overshadowed the parasympathetic nervous system. In the study of Nayebpuur et al, sympathetic influences were capable of decreasing the rate-dependent increase in the zone of concealment caused by diltiazem.
This may be the reason for absence of a response to diltiazem in the case 5. Remember, however, that the plasma concentration of diltiazem was below detection (< 10 ng/ml) in this patient.

In conclusion, the use of diltiazem in patients with severe chronic heart failure is not without risk. There is a possibility of adverse hemodynamic or electrophysiologic effects, such as negative inotropy, excessive vasodilatation, or excessive cardiodeceleration. Sustained release diltiazem is superior when compared to the standard diltiazem because of its duration of the action. Because of the limited number of the dogs in this study, more cases are needed to investigate pharmacodynamic effects of SRD in the dogs with AF.
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CONCLUSION

Ventricular response in dogs with pacing-induced atrial fibrillation can be reduced safely and effectively with both oral and iv diltiazem. This can be accomplished without decreasing either cardiac output or systemic arterial pressure to levels below those that occur during sinus rhythm. Use of a sustained release form of diltiazem given orally can achieve the same results as when the standard form of the drug is given. This makes delivery of the drug easier for the client and, of course, makes the pharmacological effect prolonged and "smoother". Ventricular responses, in 4 out of 5 dogs with AF due to naturally-occurring heart diseased, decreased appropriately with doses of sustained release diltiazem between 4.0 and 8.0 mg/kg; however because of the rather few dogs studied, trials on a greater number must be performed.
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