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Kittleson, Mark Douglas

HYDRALAZINE PHARMACODYNAMICS STUDIED IN A MODEL OF LEFT VENTRICULAR FAILURE IN THE DOG

The Ohio State University

Ph.D. 1982

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HYDRALAZINE PHARMACODYNAMICS STUDIED IN A MODEL
OF LEFT VENTRICULAR FAILURE IN THE DOG

DISSERTATION

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

By
Mark Douglas Kittleson, B.S., D.V.M., M.S.

** ** **

The Ohio State University
1982

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TO MY WIFE, JUDY, DAUGHTER, ASHLIE, AND MY PARENTS,

NORMAN AND LAVONNE
ACKNOWLEDGMENTS

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HYDRALAZINE PHARMACODYNAMICS STUDIED IN A MODEL
OF LEFT VENTRICULAR FAILURE IN THE DOG

By

Mark Douglas Kittleson, B.S., D.V.M., M.S.

The Ohio State University, 1982
Professor Robert L. Hamlin, Advisor

The pharmacodynamics of hydralazine, an arteriolar dilator, were studied in dogs with experimentally induced heart failure. The dogs were studied five days after heart failure was induced by injecting microspheres into the left circumflex coronary artery. All dogs had a stroke volume index < 25 ml/beat/m² and a left ventricular filling pressure ≥ 16 mmHg. Approximately 1 mg/kg of hydralazine was given orally each hour until the total systemic resistance index decreased below 1700 dynes sec cm⁻⁵ m². The drug effect was followed hemodynamically until it dissipated.

Hydralazine increased the cardiac index from 3.06 ± 0.47 (± SD) to 6.81 ± 0.87 L/min/m² (P < 0.001), stroke volume index from 20.9 ± 1.6 to 36.8 ± 9.3 ml/beat/m² (P < 0.01) and heart rate from 146.2 ± 17.2 to 187.8 ± 42.8 beats/minute (P < 0.05). It decreased mean arterial pressure from 111.5 ± 20.4 to 83.8 ± 4.7 mmHg (P < 0.01) and total systemic resistance index from 2903 ± 149 to 992 ± 83 dynes sec cm⁻⁵ m² (P < 0.001). It did not affect left ventricular filling
pressure or contractile force. Peak drug effect occurred at 3-5 hours after drug administration and duration of effect was 11-13 hours. Recurrence of ventricular arrhythmias occurred in two dogs and one dog died during a recurrence.

Hydralazine improves cardiac performance in the dog with left ventricular failure.
INTRODUCTION

Vasodilator therapy for the treatment of chronic left-sided congestive heart failure is a recent concept. It has been shown to be effective in man for treating many types of left-sided failures. The concept has been discussed in veterinary medicine and some information has been disseminated about its attributes and possible uses, but no controlled studies have been performed in veterinary medicine to prove efficacy or to delineate the clinical pharmacology of any vasodilating agents.

This study was designed to delineate the pharmacodynamics of an arteriolar dilator (hydralazine) in myocardial failure in the dog so that it could be used clinically in veterinary medicine. In order to evaluate vasodilators the major obstacle to overcome was the production of a left ventricular myocardial failure model that was chronic and stable. To study a drug used for treating heart failure in a normal animal creates too many discrepancies between drug actions, bioavailability and pharmacodynamics when comparing the normal dog and the dog with heart failure.

There are numerous heart failure models in existence. Unfortunately, most of them do not produce myocardial failure. Instead they create severe pressure or volume overloads that "overwhelm" the pump. In other words, they exceed the capacity of the ventricle to either
eject its contents or to accept the venous return. They are generally
produced by creating a valvular lesion or a large shunt. Two examples
are severe aortic stenosis and severe mitral regurgitation. The aorta
can be banded to a point that stroke volume decreases and left ven-
tricular end-diastolic pressure rises, which produces the basic
symptoms of heart failure (i.e., reduced forward flow, elevated
ventricular filling pressures), yet the myocardium does not fail unless
the lesion is allowed to remain for long periods of time. Chordae
tendinae can also be severed to produce severe acute mitral regurgi-
tation. Once again the symptoms of backward and forward failure are
produced, but the myocardium functions normally. If models such as
these are utilized to study vasodilators, in particular arteriolar
dilators, problems arise which are unique to each model. In aortic
stenosis the left ventricular afterload is fairly well fixed by the
lesion. Since the goal of arteriolar dilator therapy is to reduce
impedence to flow, it appears unreasonable to use this type of pressure
overload model for this type of study. It appears more reasonable to
use a model that utilizes mitral regurgitation or some type of left
to right shunt to study an arteriolar dilator because arteriolar
dilators reduce the regurgitant fraction or the degree of shunting.
However, if a study is carried out using a model such as this, it in
reality becomes a study to determine the effects of vasodilators on
mitral regurgitation or left to right flow.

The ideal study, then, would involve determining the effect of
an arteriolar dilator on the performance of a failing left ventricular
myocardium. Therefore, a model was sought in which the ventricular
myocardium was partially destroyed.
Adriamycin, a known cardiotoxin in man and rabbit, has been studied in the dog previously. It has shown that mild heart failure is produced but that electrophysiologic changes dominate. Since it is difficult to examine hemodynamic variables when arrhythmias are present, this model was rejected.

Cobalt, another cardiotoxin, has been utilized in a number of dogs in our lab. The substance appears to affect too many other organ systems to make it a humane material for inducing myocardial failure.

Coronary injections of microspheres have been utilized in dogs previously to produce acute left ventricular failure and in calves to produce chronic left ventricular failure. In a pilot study in a Beagle hound, microspheres were injected into the left circumflex coronary artery. This produced a large non-contractile portion of the left ventricular free wall, pulmonary edema and a lowered venous Po2.

Hydralazine was the vasodilator chosen to be studied because it is the arteriolar dilator of choice in man, it is available in an oral form and it is documented to increase stroke volume and not increase heart rate in man.

The study had four purposes: 1) to identify a means of producing a myocardial failure model; 2) to prove that hydralazine produces beneficial hemodynamic responses in the dog; 3) to define the pharmacodynamics of the drug in the dog with myocardial failure; and 4) to identify clinical means of monitoring the hemodynamic effects.
LITERATURE REVIEW

Vasodilator Therapy

In addition to his observations on the relationship between myocardial fiber stretch and force generation, Starling also noted that, in the heart-lung preparation, with constant inflow, outflow remained fairly constant, independent of the peripheral resistance. He utilized the term afterload to describe the phenomena associated with ventricular emptying. Therefore, he noted that cardiac output was insensitive to overload.²

This finding was refuted in later research when studies were performed in the intact animal. When control and compensatory mechanisms were abolished, it was noted that afterload was a determinant of the output of the ventricle. However, when compensatory mechanisms were intact, stroke volume remained the same over wide ranges of impedance.³ This is an extremely important differentiation. In the normal animal, stroke volume at rest remains the same over wide ranges of impedance. When the control or reserve mechanisms are no longer functional, stroke volume is highly dependent on impedance. The only situation that is seen clinically in which the reserve mechanisms can no longer compensate for changes in afterload is heart failure. Therefore, in heart failure, stroke volume is extremely dependent on afterload.⁴ Subsequently, it is unreasonable to study the action of a drug that alters afterload in a normal animal if the
changes that it can induce in an animal with heart failure are to be defined.

Afterload is systolic myocardial wall stress. It is the force that opposes myocardial fiber shortening. For illustrative purposes, Laplace's formula for determining the wall stress of a thin walled sphere can be used. More complex formulas are needed for actual calculations of the wall stress of a thick walled chamber. When adapted to the left ventricle, Laplace's formula is:

\[
\text{wall stress} = \frac{\text{systolic pressure} \times \text{radius}}{\text{wall thickness}}
\]

By using this formula, wall stress or afterload can be broken down into several components. Systolic intraventricular pressure is determined by aortic input impedance, stroke volume and rate of ventricular ejection. Impedence is the instantaneous relation between aortic flow and pressure. Its components include large artery compliance, peripheral vascular resistance and blood inertiance. The formula for resistance is

\[
R = \frac{8 \mu l}{r^4}
\]

where

- \( R \) = resistance
- \( \mu \) = viscosity
- \( l \) = length
- \( r \) = radius

The formula for ineriance is

\[
L = \frac{p l}{r^2}
\]

where

- \( L \) = ineriance
- \( p \) = density
and the other symbols are the same as before. Ventricular ejection rate is determined by contractility. Ventricular radius is determined by ventricular volume.

Arteriolar radius is determined by systemic arteriolar tone. Arteriolar radius is the most important factor (i.e., it is raised to the fourth power) in determining peripheral resistance and the most important factor in inertia (i.e., it is raised to the second power). Subsequently, it is the major determinant of impedance. It is also the factor that lends itself most readily to pharmacologic manipulation.

In heart failure, systemic vascular resistance and inertia are increased by increases in arteriolar smooth muscle tone. The increased tone results from neural, humoral and structural changes in the arteriolar bed. This occurs in response to the cardiac output decrease so that systemic blood pressure remains constant. Aortic compliance is also decreased in heart failure, which adds to the increase in aortic input impedance.

Ventricular volume increases also increase wall stress in heart failure. They combine with impedance changes to increase afterload. Compensatory hypertrophy occurs to offset this increased load. The amount of hypertrophy a ventricle can generate in response to this load determines the ability of that ventricle to compensate and is a major factor in determining resultant systolic ventricular function.

Afterload can be reduced in heart failure with vasodilation and by reducing left ventricular volume. As can be seen in Figure 1, when peripheral vascular resistance is reduced, stroke volume increases in heart failure patient. In either case, when the force against which
Figure 1. Relationship between stroke volume and peripheral vascular resistance in the normal and failing heart.
Stroke Volume

Peripheral Vascular Resistance

Figure 1
a weakened myocardium must push is lessened, fiber shortening and stroke volume increase. In addition, the rate of ejection increases. 7

Pressure-volume loops can be used to depict the effects of preload, afterload and contractility changes on ventricular function. 8 The ability of the myocardium to develop force and to shorten forms the conceptual framework for understanding the interplay among the three determinants of stroke volume. Figure 2 depicts the length-tension relationship of a single muscle bundle. The bottom curved line represents the preload or resting tension placed on the muscle and is analogous to the diastolic pressure-volume relationship of the ventricle. The isovolumic pressure line represents the total force that can be developed at each preload at a certain contractile state. The slope of the line defines that contractile state.

Figure 3 depicts the same relationship for an intact ventricle as a pressure-volume loop. For a given contractile state, the end-systolic pressure-volume point always ends on the isovolumic pressure line independent of preload and afterload. Loop B represents ventricular function with a loop generated at a certain preload. Loop A is generated from a greater preload. If no change in afterload or contractility occurs, stroke volume increases because of the increase in end-diastolic volume.

Figure 4 shows the effect of changing contractility on systolic ventricular function. A contractility increase results in the isovolumic pressure line moving up and to the left. If preload and afterload are unchanged, the end-systolic volume decreases and stroke volume increases.

Figure 5 illustrates how afterload affects stroke volume. Once again, contractility and preload changes do not take place, as in heart failure. Curve B could represent a myocardial failure patient with a
Figure 2. Tension or pressure developed from a given preload for a given contractile state.
Figure 2
Figure 3. Two pressure-volume loops. Loop B is generated from a given preload, afterload and contractile state. Loop A represents increasing preload only resulting in a larger stroke volume.
Figure 3
Figure 4. Two pressure-volume loops representing the increase in stroke volume that results from increasing contractility while keeping preload and afterload constant.
Figure 4
Figure 5. Two pressure volume loops in which Loop A represents high afterload and a small stroke volume and Loop B represents a decrease in afterload with a resultant increase in stroke volume.
Figure 5
high afterload and a small stroke volume. When afterload is decreased in curve A, end-systolic volume decreases and stroke volume increases.

Heart failure is characterized by a high impedance to left ventricular outflow. When cardiac output falls, a number of compensatory mechanisms come into play to maintain systemic arterial pressure at a normal level. Teleologically pressure receptors dominate over flow receptors (juxtaglomerular apparatus). Most of the regional circulations do not need the high pressure that exists within the systemic circuit to maintain adequate flow through them. Their innate resistance is not high enough to preclude flow at low pressures. Three regional circulations require high pressure drive to maintain adequate flow. The first is the heart. Because of the high systolic resistance created by muscular contraction around the arterioles and capillaries, very little flow occurs during systole. Most of the flow occurs during diastole but still requires pressure > 60 mmHg to maintain adequate flow. The major organ that requires high pressure drive is the brain. There is little vascular control by neurohumoral agents on the cerebral circulation. The major controls of vasomotor tone are the blood gases. Subsequently, the circulation to this area is quite dependent on systemic blood pressure. In accordance, the major baroreceptors are present in the carotid arteries. This control is obviously more important in an upright being such as man but is still important in quadrupeds where lowering and raising of the head occurs many times per day. The brain circulation still only needs perfusion pressures > 60 mmHg for adequate flow. As such, the normal blood pressure (mean = 100-110 mmHg) represents a large reserve. The renal circulation also requires pressures > 60 mmHg to maintain flow through its long, intricate capillary beds.
When cardiac output falls, the baroreceptors detect a fall in pressure. The sympathetic nervous system releases more norepinephrine, which increases heart rate, cardiac contractility, and constricts systemic arterioles. Vagal tone also decreases. Renin release is stimulated, which ultimately results in the formation of angiotensin II. This hormone is a potent vasoconstrictor of both arterioles and veins. Angiotensin also facilitates the release of more norepinephrine. In addition, it promotes aldosterone release from the adrenal cortex. This results in sodium and water retention. The net result of all these factors is a rise in systemic blood pressure. If the heart is unable to respond to the inotropic stimuli, peripheral vascular resistance increases and stroke volume falls. When the initial rise in peripheral vascular resistance decreases the stroke volume further, resistance must rise further until resistance and left ventricular outflow achieve an equilibrium that results in a normal systemic blood pressure. The net result on cardiac function is a decrease in stroke volume, below the level it would be at if peripheral vascular resistance was normal in heart failure.\(^{12}\)

In addition to the increased resistive forces, compliance is decreased in heart failure patients due to increased sympathetic tone and to increased \(\text{Na}^+\) and \(\text{H}_2\text{O}\) content of the walls of the large arteries. In addition, the reduction in flow velocity of the blood through the microcirculation results in an increased viscosity.\(^{13}\) All of these contribute to the increased impedance.

The end result is that the cerebral and coronary circulations are protected from possibly lethal hypotension but the failing left ventricle is subjected to an inordinately high load which in itself may be lethal. Fortunately, the impedance of the systemic circulation is not set at
the minimum that can be tolerated but at some point above minimum. The fact that it is allows the opportunity to modify the system and to decrease impedance through vasodilation without any serious detrimental effects.

In contrast to the effects of vasodilators on the ejection characteristics of the left ventricle, some of the vasodilators also affect the inflow characteristics. They do this by dilating systemic veins. This allows more blood to pool within the venous capacitance system. In left ventricular failure there is a redistribution of blood volume. There is a larger volume of blood and a larger percentage of blood volume in the pulmonary circuit. Dilating systemic veins allows the blood to redistribute back to the periphery, decreases pulmonary blood volume and reduces pulmonary congestion and edema. In right-sided congestive failure, dilating systemic veins decreases the pressure in the systemic venous circuit, which reduces the congestive signs.

In 1956, Judson et al. first described the possibility of utilizing a vasodilator to increase cardiac output. Interestingly, the first compound studied for its beneficial effects on heart failure was hydralazine. The subject apparently met with very little interest because it did not reappear in the literature again until 1971 when phentolamine, an alpha blocking agent, was utilized for the same purpose.

Afterload reduction was utilized prior to 1971 to improve cardiac performance. It was accomplished by mechanical rather than by pharmacologic means, however. The arterial counterpulsation device was described in 1961 and utilized clinically long before vasodilator therapy.
The hemodynamic effect of all vasodilators is qualitatively the same, but they differ quantitatively in their effects on the circulatory system. Therefore, a brief review of the more common vasodilators and studies on their effects follows.

**Nitroprusside**

Sodium nitroprusside was first utilized in clinical medicine in 1929. It was not utilized for congestive heart failure but for systemic hypertension. Nitroprusside has been utilized and studied more recently in situations involving acute congestive heart failure. Since it has an extremely short half-life, it can only be utilized intravenously, so it is indicated only in acute situations. Because of the possibility of cyanide toxicosis with prolonged therapy, it is limited to short term use.

Cohn et al. studied the effects of nitroprusside in eleven acute myocardial infarction patients. They noted that the left ventricular filling pressure decreased and stroke volume increased in eight of their patients.

Chatterjee et al. studied twenty-seven patients with acute myocardial infarction and divided them into three groups. Group I was free of clinical signs and had left ventricular filling pressures less than 15 mmHg. Group II had filling pressures greater than 15 mmHg and a stroke work index greater than 20 g·m/m² and Group III had filling pressures greater than 15 mmHg and stroke work indices less than 20 g·m/m². The patients in the last group were generally hypotensive and several were in cardiogenic shock. The hemodynamic responses consisted of a slight to moderate decrease in mean arterial pressure, a decrease in left ventricular filling pressure, and a decrease in
systemic and pulmonary vascular resistance. Cardiac index did not increase in Group I patients, increased 15% in Group II patients, and increased 23% in Group III patients.

Chatterjee et al.\textsuperscript{20} studied the effects of nitroprusside in a large group of myocardial infarction patients with moderate to severe heart failure. Cardiac index was $1.7 \pm 0.1$ (SEM) liter/minute/m$^2$ for the group. Stroke work index was $14 \pm 1$ g·m/m$^2$. Cardiac index increased in 42 of 43 patients to an average value of $2.2 \pm 0.1$ liter/minute/m$^2$. This was a 29% increase. Left ventricular filling pressure decreased 35%.

These data document that nitroprusside decreases systemic vascular resistance and decreases peripheral venous tone. They also document that it improves cardiac output by a greater percentage in patients with severe failure than it does in patients with moderate failure. It has little effect on cardiac output in patients without myocardial failure.

\textbf{Phentolamine}

Phentolamine is an alpha-adrenergic blocking agent. It also directly dilates vascular smooth muscle. It reduces peripheral vascular resistance and increases peripheral venous capacitance.

Walinsky et al.,\textsuperscript{21} Gould et al.,\textsuperscript{22} and Perret et al.\textsuperscript{23} have demonstrated beneficial hemodynamic responses in patients with acute myocardial infarction. The responses were very similar to those seen for nitroprusside except for one significant difference: in about 80% of the patients studied, tachycardia developed. It was shown by Dairman et al.\textsuperscript{24} that phentolamine increases synthesis and release of cardiac norepinephrine, which may explain the tachycardia.
Phentolamine has been studied in dogs with surgically created ventricular septal defects by Synhorst et al. They demonstrated that they could reduce systemic resistance 42% with either phentolamine or phenoxybenzamine and, by doing so, reduce the magnitude of the shunt by 32%. They also noted heart rate increases. Their dosage for phentolamine was 1 mg/kg.

**Nitrates**

Nitroglycerin is the primary example of this group. It has been studied in acute myocardial infarction patients both in sublingual, intravenous and topical forms. The consensus of the studies by Williams et al., Flaherty et al., and Armstrong et al. is that nitroglycerin reduces left ventricular filling pressure by increasing venous capacitance while having very little effect on systemic vascular resistance. They suggest that if the initial left ventricular filling pressure is less than 15 mmHg, reducing the filling pressure further with nitroglycerin causes a decrease in stroke volume. When the filling pressure is 15 mmHg or greater, stroke volume remains essentially unchanged. This agrees with the theory of reducing filling pressure in a patient with a depressed Frank-Starling curve. That is, the patient's ventricle is functioning on the flat portion of the curve so changing filling pressure has negligible effects on stroke volume (Figure 6).

Lancelin et al. verified the results found in the previous studies. Their patients consisted of nine cases with myocardial infarction, two with ischemic heart disease and one with congestive cardiomyopathy. They used topical nitroglycerin and noted a marked reduction in left ventricular filling pressure (21.8 ± 16.9 to
Figure 6. Frank-Starling curves generated from a normal patient and a patient with severe myocardial failure.
Figure 6
12.75 ± 8.6) and no change in cardiac index (2.7 ± 1 to 2.8 ± 0.5). The duration of effect was six hours and was maximal at two hours.

Another nitrate that has been used extensively in human medicine for reducing the signs of venous congestion is isosorbide dinitrate. Franciosa and Cohn10 have performed the most recent study. They utilized a placebo and a treatment group who were assigned randomly in a double blind fashion. The placebo group experienced no significant hemodynamic response. The group on isosorbide dinitrate experienced a significant decrease in pulmonary wedge pressure and systemic vascular resistance. This effect persisted when the drug was given for three months, suggesting that no tolerance to the drug developed.

Prazosin

Prazosin is a relatively new drug released on the market in 1976.31 It exerts its vasodilator effects by blocking vascular α-adrenergic receptors.32 It is a "balanced" vasodilator in that it relaxes smooth muscle of both arterioles and veins.

Miller et al.33 studied the effects of prazosin in ten patients with severe ischemic cardiomyopathy. It lowered mean systemic arterial pressure from 95.3 ± 5.3 to 76.2 ± 3.8 mmHg, lowered left ventricular filling pressure from 30.2 ± 2.9 to 17.7 ± 1.4 mmHg and elevated cardiac index from 2.07 ± 0.12 to 2.94 ± 0.10 liters/minute/m². This effect lasted for six hours. An index of myocardial oxygen consumption (systemic diastolic blood pressure x heart rate) was reduced from 3293 ± 191 to 2793 ± 188 mmHg sec per minute. Systemic vascular resistance declined from 2074 ± 183 dynes sec cm⁻⁵ to 1156 ± 83 dynes sec cm⁻⁵. Forearm venous tone was lowered by prazosin from 58.9 ± 13.8 to 18.5 ± 3.9 ml/mmHg.
This same group\textsuperscript{34} reported prolonged beneficial effects of prazosin in nine patients with refractory heart failure due to coronary artery disease. After two weeks on the drug they reported that the left ventricular end-diastolic diameter decreased from $5.7 \pm 0.4$ to $5.4 \pm 0.4$ cm ($P < .001$) and that the end-systolic diameter decreased from $4.2 \pm 0.4$ to $3.9 \pm 0.4$ cm ($P < 0.001$). In addition, the shortening fraction increased from $27.6 \pm 6.5$ to $30.2 \pm 4.5\%$ ($P < 0.005$).

Packer et al.\textsuperscript{35} compared the effects of prazosin and nitroprusside in nine refractory heart failure patients. Each patient was given each drug separately so as to produce a similar decrease in left ventricular filling pressure. Both drugs produced similar decreases in mean right atrial pressure, mean pulmonary arterial pressure and systemic and pulmonary vascular resistance. Similar changes were also noted in stroke volume index ($+11.7$ ml/beat/m$^2$ with nitroprusside vs. $+12.5$ with prazosin), but prazosin reduced heart rate more than did nitroprusside. They suggested that prazosin could have a negative chronotropic effect, separate from its peripheral vascular effects.

Subsequent to this paper, Packer et al.\textsuperscript{36} found that tolerance developed to prazosin by the third dose. They found they could partially reverse this by increasing the dosage. In addition, two other studies\textsuperscript{37,38} found similar evidence. They compared the hemodynamic responses after the first and fifth doses and found the effects markedly attenuated after the fifth dose.

Aranow\textsuperscript{39} refuted this by demonstrating significant clinical and echocardiographic improvement after six weeks of prazosin therapy. Collucci et al.\textsuperscript{40} attempted to resolve the controversy by performing a randomized, double blind study of prazosin vs. placebo in twenty-two
patients. Their study is the best to date. It evaluated clinical, echographic and radionuclide data. The mean New York Heart Association (NYHA) class decreased from 3.7 ± 0.2 to 2.3 ± 0.2 (P < 0.01). The mean velocity of circumferential fiber shortening increased from 0.69 ± 0.07 to 0.80 ± 0.09 circumferences/second (P < 0.06) and the ejection fraction increased from 24.8 ± 2.2 to 32.1 ± 2.9% (P < 0.001). The placebo group showed no significant changes. They withheld therapy in six patients for forty-eight hours and documented that their hemodynamic parameters went back to control values and then readministered the drug and documented that cardiac function improved again. They also noted that plasma renin activity increased in the prazosin-treated group and that they required increased diuretic dosages.

One paper has appeared in the veterinary literature on the use of prazosin in dogs. The assessment of the cases was purely clinical—all four dogs had signs of right sided congestive heart failure due to dirofilariasis and tricuspid regurgitation. They were refractory to digitalis and furosemide. Three of the dogs were less than 11 kg and received 0.5 mg of prazosin BID. One dog weighed 30 kg and received 1.0 mg of prazosin BID. All dogs experienced marked clinical improvement. They became more alert, active and started to eat. The amount of ascites decreased and it disappeared completely in three dogs.

**Hydralazine**

Koch-Weser reviewed the pharmacology of hydralazine in 1976. Hydralazine (1-hydrazinophthalozine) has been used to treat hypertension for twenty-five years. However, when utilized alone, increases in cardiac output have oftentimes negated its effects in the hypertensive patient. Therefore, until beta-blocking therapy was introduced to
negate the cardiac output changes, hydralazine was not used extensively.

Hydralazine is a direct relaxer of arteriolar smooth muscle. The cellular mechanism is thought to be due to hydralazine's ability to reduce ferric (Fe^{+++}) to ferrous (Fe^{++}) ion. Ferric ion is needed for lipoxygenase activity and ultimately an increase in PGI\textsubscript{2} synthesis. Vascular beds do not respond uniformly to the drug. Coronary, cerebral, splanchnic and renal circulations dilate more than skin and muscle do. Hydralazine affects venous capacitance vessels almost negligibly and it has no appreciable effects on non-vascular smooth muscle.

Hydralazine increases renin levels and so increases sodium and water retention and edema formation. This is not due to increased renal blood flow or glomerular filtration rate, both of which are generally increased or unchanged during hydralazine therapy. The sodium and water retention can be controlled by diuretic administration. Propranolol will effectively reduce the increased renin secretion.

In man hydralazine is rapidly and almost completely absorbed after oral administration. Peak serum concentrations are attained in one or two hours following administration. During the initial couple of hours serum concentrations correspond to the vasodilatory effect. However, the half-time of the antihypertensive effect is much longer than the plasma elimination half-life. This can be explained by the fact that hydralazine has a special affinity for the walls of muscular arteries. Radioautographic studies have shown that hydralazine binds tightly to these sites. Therefore, the plasma half-life is two to four hours while the duration of clinical effect is about twelve hours. About 85\% of hydralazine is albumin bound.
Hydralazine is metabolized in the liver by acetylation in man. There is a considerable "first pass effect", so serum concentrations are considerably lower after oral ingestion than after intravenous injection. Since the major pathway is acetylation, it is of great importance in human patients to determine whether they will be fast or slow acetylators.

High serum concentrations have been found in man when renal failure is present. Renal excretion is generally not important, so it is most likely that hydralazine metabolism proceeds more slowly in uremia.

The major metabolite of hydralazine is a hydralazine pyruvic-acid hydrazone. In rabbits, renal clearance is the major route for its excretion, accounting for 80 to 90% of the total body clearance. It is actively secreted by the renal tubules. This metabolite has been shown to be inactive physiologically, in concentrations up to fifty times therapeutically. There are eleven total hydralazine metabolites excreted in the urine. The other major one is phthalazinone. Some of the metabolites apparently are able to reduce arterial blood pressure in rats and rabbits. This also may help explain the discrepancy between plasma half-life and drug half-time.

Lack of specific assay methods has limited the study of hydralazine pharmacokinetics. However, the important aspects of hydralazine kinetics have been clarified semiquantitatively in man. $^{14}C$-labelled hydralazine studies have indicated nearly complete intestinal absorption following oral administration. First pass enterohepatic removal of the drug markedly reduces the bioavailability of the drug. Approximately 78% is removed by the liver in rapid acetylators and 62% in
slow acetylators. Plasma half-life is independent of acetylator phenotype, which suggests other major routes of metabolism. Food intake enhances the bioavailability of hydralazine by changing the site of drug absorption so that less hydralazine is exposed to a small region of the small intestine where there is an acetyl transferase.

No studies on pharmacokinetics or pharmacodynamics have been done in the dog.

Besides its well known vasodilatory properties, hydralazine also can increase myocardial contractile force and heart rate. Klatari et al. investigated this in dogs by suturing Walton-Brody strain gauges to the left ventricular epicardium. They noted a 27% increase in contractile force and a 7% increase in heart rate after giving 20 mg of hydralazine intravenously to 18 to 22 kg anesthetized dogs. They compared this to nitroprusside's effects by decreasing the systemic blood pressure to the same level as that attained with the hydralazine. Nitroprusside only increased contractile force 10% and heart rate 2%. The differences between the two drugs were statistically significant. In addition, they directly injected hydralazine and nitroprusside into a coronary artery and measured contractile force in the area pertused. Hydralazine consistently increased contractile force, while nitroprusside, even in large doses, exerted no effect. Hydralazine's effect was blocked by propranolol, which suggests a direct beta adrenergic mechanism for the heart rate and contractile force increases.

Gershwin et al. also studied this phenomenon in isolated guinea pig atria. They found that hydralazine was a direct releaser of histamine. They noted that the increase in contractile force and heart rate could be blocked by propranolol and the antihistamines...
diphenhydramine and tripelennamine. They concluded that hydralazine directly stimulated histamine release, which in turn stimulated release of catecholamines, which produced the contractile force and heart rate increases.

Leier et al.\textsuperscript{52} are the only investigators to examine this effect in clinical patients with congestive heart failure. They utilized fourteen patients with severe heart failure due to either ischemic or idiopathic congestive cardiomyopathy and gave each patient either 75 or 100 mg of hydralazine. They used the pre-ejection period and the isovolumic developed pressure/duration of isovolumic contraction (\(\Delta P/\Delta T\)) as indices of contractile force. Hydralazine produced small significant increases in the \(\Delta P/\Delta T\) at both the 75 and 100 mg doses and significantly decreased the pre-ejection period at both doses. This suggested that hydralazine did increase contractile force in the failing left ventricle of man.

Engel et al.\textsuperscript{53} reported the effects of hydralazine on automaticity in patients with sick sinus syndrome. They utilized nine hypertensive patients with sinus bradycardia and evidence of sinoatrial dysfunction on electrophysiologic testing. They gave 0.15 mg/kg of hydralazine intravenously. This dose was too low to produce any change in blood pressure. Heart rate increased in all patients from a mean of 61.9 \(\pm\) 41 to 68.6 \(\pm\) 4.9 beats/min (\(P < 0.001\)). Sinus node recovery time shortened in all patients, changing from 3,207 \(\pm\) 1,098 to 2,064 \(\pm\) 573 m sec (\(P < 0.05\)). When corrected for the accelerated heart rate, eight of the nine patients improved. Sinus nodal recovery time minus cycle length went from 2,164 \(\pm\) 1,089 to 1,159 \(\pm\) 552 m sec (\(P < 0.06\)). Junctional escape beats continued to occur in these patients and junctional recovery time decreased from 2,525 \(\pm\) 692 to
Therefore, hydralazine's side effects may be useful in patients with diseased sinus node tissue and/or atrial tissue.

Hydralazine's effects on heart rate have been studied in the dog by Spokas et al. In six chronically instrumented dogs, 0.5 mg/kg of hydralazine given intravenously increased heart rate 50% (P < 0.01). This heart rate increase had no apparent relationship with the magnitude of blood pressure decrease. Heart rate changes and cardiac output changes were significantly correlated (r = 0.897, P < 0.001).

Spokas et al. also studied the effects of hydralazine on five regional circulations in the dog: the superior mesenteric, left renal, left common carotid, left femoral, and left circumflex coronary arteries. They recorded flows continuously with electromagnetic flowmeters in anesthetized dogs. Again, 0.5 mg/kg of hydralazine was given intravenously. Mean arterial blood pressure decreased 17% (P < 0.01). Cardiac output increased significantly. Heart rate only increased 6% (P < 0.05) in the anesthetized preparation. The effect lasted two hours. They also utilized 0.05-01 mg/kg and 1.0 mg/kg doses and noted that the heart rate, pressure, cardiac output and peripheral resistance effects appeared to be dose-related. Resistance in each regional circulation decreased significantly and flow through each increased. This was apparent in all except the renal artery within one to two minutes after injection and maximal within ten minutes. Renal blood flow did not attain maximum until forty-five minutes. The increase in femoral flow was transient, lasting only fifteen to twenty minutes. They found no change in inotropy or chronotropy after injecting hydralazine into the vertebral or the coronary arteries. In addition, they infused indomethacin or
diclofenac sodium into some of the dogs to inhibit prostaglandin synthesis. This resulted in antagonism of the renovesodilation. They concluded that the renal vascular bed differs from the others and its hydralazine induced vasodilation is due to a prostaglandin mechanism.

The other side effect of hydralazine in man is a lupus erythematosus-like syndrome. It is a dose-related phenomenon and usually is not seen at levels less than 3 mg/kg. Other untoward side effects include headache, dizziness, flushing, nasal congestion, and anginal attacks.

**Hydralazine Use in Congestive Heart Failure**

No studies have been performed on the use of hydralazine in congestive heart failure in veterinary medicine.

Chatterjee et al. evaluated hydralazine therapy in nine patients with chronic refractory heart failure. Four patients had idiopathic congestive cardiomyopathy, two had ischemic cardiomyopathy and four had myocardial failure secondary to valvular lesions. Nine of the patients were classified in NYHA Class IV and one in Class III. All were digitalized and were taking furosemide, 160 to 840 mg daily. Five of the patients had evidence of mitral regurgitation. They gave 25 mg of hydralazine orally to each patient after taking baseline data and then repeated them in two to three hours. If there was no response another 25 mg dose was given and this was repeated until a significant increase in cardiac output was obtained. They did not define what a significant increase was. Two of the patients responded to a total dose of 50 mg of hydralazine, while eight responded to 75 mg. There was no significant change in heart rate (all were digitalized), pulmonary
capillary wedge pressure, or mean right atrial pressure. Mean arterial pressure and pulmonary artery pressure decreased slightly. There was a significant reduction in both systemic and pulmonary vascular resistance. There was a marked increase in cardiac output and stroke volume. These changes were evident at two to three hours and at six to eight hours but the maximum increase in cardiac output occurred at twenty-four hours. Nine of the ten patients continued to use hydralazine and eight remained improved at three to seven months after starting the drug. Seven were in Class II and one was in Class III. Two patients experienced weight gain. Salt restriction prevented further weight gain in these patients.

Fitchett et al. 57 compared the effects of intravenous and long-term oral hydralazine in sixteen patients. Fourteen of their subjects had congestive cardiomyopathy and two had hypertensive heart failure. All had an ejection fraction less than 35%. Mitral regurgitation was present in four. Ten of the sixteen were in NYHA Class III or IV. All of the patients were on digoxin and diuretics, which were continued. For the intravenous study, hydralazine, 20 mg, was given over ten minutes. Studies were repeated ten, fifteen and twenty minutes after the completion of the injection. For the oral study, nine patients received 75 mg hydralazine QID and four received 50 mg QID. They were studied again four to six weeks later. The doses were determined by the tolerance each patient had to the drug with regard to the appearance of headache.

The maximal effect of the drug occurred between ten and fifteen minutes after intravenous administration. Mean arterial blood pressure decreased from $91 \pm 3$ to $76 \pm 4$ mmHg ($P < 0.001$). Heart rate did not change ($90 \pm 5$ to $89 \pm 4$ beats/min). Cardiac index increased 64%
(\(2.2 \pm 0.2\) to \(3.3 \pm 0.3\) liters/min per m\(^2\), \(P < 0.001\)) and forearm blood flow 59\% (\(2.7 \pm 0.5\) to \(4.3 \pm 0.9\) ml/min per 100 ml, \(P < 0.05\)). Systemic vascular resistance decreased 49\% (1,861 \pm 170 to 957 \pm 112 dynes sec cm\(^{-5}\), \(P < 0.01\)).

Seven of thirteen patients completed the oral study. As a group they had poorer hemodynamic variables than the other patients. At four to six weeks their cardiac index increased 79\% (1.9 \pm 0.2 to 3.4 \pm 0.3 l/min per m\(^2\), \(P < 0.001\)), stroke volume index 71\% (21 \pm 3 to 36 \pm 4 ml/m\(^2\), \(P < 0.001\)) and forearm blood flow 41\% (2.9 \pm 0.7 to 4.9 \pm 0.5 ml/min per 100 ml, \(P < 0.05\)). Systemic vascular resistance decreased 51\% (2,150 \pm 308 to 1,066 \pm 194 dynes sec cm\(^{-5}\), \(P < 0.005\)). Mean arterial blood pressure dropped from 96 \pm 6 to 84 \pm 7 mmHg (\(P < 0.001\)). Heart rate did not change significantly (all patients were still digitalized). Pulmonary arterial diastolic pressure decreased 25\% (32 \pm 5 to 24 \pm 4 mmHg, \(P < 0.05\)).

Hydralazine was then discontinued in all seven of these patients. Hemodynamic measurements were repeated forty-eight to seventy-two hours later. Mean arterial pressures and pulmonary arterial diastolic pressures increased to values not significantly different from control, but cardiac index remained higher than control.

Two studies have looked at the improved exercise capability that patients have after hydralazine administration. Hindman et al.\(^{58}\) looked at twelve patients in NYHA Class III or IV heart failure due to ischemic heart disease. Each patient was studied before and forty-eight hours after taking either 50 or 75 mg of oral hydralazine every six hours. Parameters monitored included oxygen consumption, cardiac output, arteriovenous oxygen difference, pulmonary capillary wedge pressure, systemic vascular resistance, left ventricular end-diastolic
volume, and ejection fraction. All but end-diastolic volume and ejection fraction improved after hydralazine at rest and during two workloads (150 and 300 Kilopond-meters/minute) on a bicycle ergometer.

Franciosa et al. used patients with a lesser degree of failure and combined hydralazine with isosorbide dinitrate for their study on exercise capacity. They studied twenty-two patients with Class II or III heart failure during exercise before and ninety minutes after a random double blind administration of hydralazine or placebo. Hydralazine was administered at a dosage of 100 mg and isosorbide dinitrate at a dosage of 40 mg. They noted no benefit, as evidenced by exercise duration, maximal oxygen consumption, maximal cardiac index and systemic vascular resistance at peak exercise. At submaximal exercise (300 Kilopond-meters/min), cardiac index and systemic vascular resistance did improve significantly ($P < 0.05$) in the hydralazine group.

From these two studies it appears as if hydralazine improves submaximal exercise but does not improve maximal exercise capacity.

A similar study has been performed by Greenberg et al. on patients with severe aortic insufficiency. Their workload started at 100-200 Kilopond-meters and increased every four minutes until maximum exercise performance was reached. Measurements were repeated at maximal exercise. Regurgitant fraction in this group averaged 63%. At maximum exercise hydralazine reduced pulmonary capillary wedge pressure (21 to 12 mmHg, $P < 0.05$) and increased cardiac index 31% ($P < 0.05$). There was no significant increase in stroke volume. Therefore, it appears that even maximal exercise can be improved by hydralazine in this subset of heart failure patients.
In addition, Greenberg et al. studied patients with severe mitral regurgitation (N=16). Hydralazine improved resting cardiac index (2.5 ± 0.1 to 3.7 ± 0.2 liters/min per m², P < 0.001), resting stroke volume index (30 ± 2 to 44 ± 2 cc/beat per m²), pulmonary artery wedge pressure (18 ± 2 to 15 ± 2 mmHg, P < 0.025), "V" wave amplitude (34 ± 4 to 22 ± 3 mmHg, P < 0.005) and systemic vascular resistance (1,385 ± 88 to 964 ± 76 dynes sec cm⁻⁵, P < 0.001). During maximal exercise hydralazine improved systemic vascular resistance (1,111 ± 118 to 735 ± 72 dynes sec cm⁻⁵, P < 0.005), cardiac index (3.7 ± 0.2 to 4.9 ± 0.3 liters/min per m², P < 0.001), stroke volume index (36 ± 3 to 45 ± 3 cc/beat per m², P < 0.005), pulmonary artery wedge pressure (27 ± 3 to 21 ± 2 mmHg, P < 0.001), and "V" wave amplitude (48 ± 6 to 38 ± 6 mmHg, P < 0.025). They concluded that hydralazine improved resting and exercise cardiac performance in patients with mitral regurgitation.

Rubin et al. set out to determine why hydralazine increased cardiac output but did not increase exercise capacity. They studied thirteen patients with severe heart failure due to either ischemic heart disease or congestive cardiomyopathy. They found essentially the same thing as Francios and Hindman. In addition, they documented that peak blood lactate levels and the rate of lactate disappearance during recovery from exercise did not change. They concluded that even though hydralazine increased cardiac output, it did not improve nutritional flow to exercising muscles.

An interesting study was performed by Cogan et al. to elucidate the effect of hydralazine on renal hemodynamics and function in congestive heart failure patients. All of their patients were NYHA Class III or IV. All medications were discontinued twenty-four to
forty-eight hours prior to the study. They gave 5 mg hydralazine intravenously every ten to twenty minutes for a total dose of 10-60 mg (mean - 34 mg). They found that after the acute administration of hydralazine, total renal resistance decreased and renal blood flow increased. The percentage of the total cardiac output that the kidneys received did not change; that is, it remained depressed at a level of 13%. GFR did not change so filtration fraction decreased toward normal values. This resulted in increased excretion of cations. These changes, of course, represent short term changes without the long term adjustments in renin secretions, etc., that occur.

Packer et al. determined the effect that hydralazine had on forty patients. All of them were NYHA Functional Class IV despite therapeutic maintenance dosages of digoxin and furosemide. Their patients required single doses of hydralazine from 75 to 100 mg orally to obtain an effective response. Four required 600 to 1000 mg and one required 20 mg intravenously. Once an adequate dosage was identified, it was administered every eight to twelve hours and sustained effect confirmed for twenty-four to forty-eight hours before discontinuing invasive monitoring. Patients were evaluated three days before, fourteen to twenty-one days after and six months after receiving hydralazine. After gathering their data they divided the patients into two groups. Group I had a left ventricular end-diastolic diameter on echocardiogram ≥ 60 mm and Group II had an end-diastolic diameter < 60 mm (normal 38-56 mm). They noted that the patients in Group I responded better to hydralazine than those in Group II. Group I had a greater increase in cardiac index (+1.12 vs.+0.71 liters/min per m², P < 0.01) and a greater increase in stroke volume index (+12.1 vs. 4.9 cc/beat per m², P < 0.001) when compared to Group II. They also
had a lesser decrease in mean arterial pressure (-9.0 vs. -15.9 mmHg, \( P < 0.01 \)). In addition, Group I did not have a significant increase in heart rate while Group II did. Left ventricular filling pressure decreased significantly in Group I but not in Group II. Twenty-four patients comprised Group I, while sixteen patients were included in Group II. They explained the difference between the two groups as follows. Patients with large dilated ventricles have large increases in systolic wall tension. By reducing systemic vascular resistance, increases in circumferential fiber shortening are allowed and stroke volume increases. Patients with normal chamber size and wall thickness do not have the preexisting afterload increase, so that decreasing it results in no clinical improvement. Alternatively, they said, the explanation could be due to the differences in magnitude of mitral regurgitant flow between the two groups. Those patients with large dilated left ventricles often have mitral regurgitation due to annular dilatation and papillary muscle dysfunction and/or angulation changes. Since decreasing resistance to forward flow results in decreased regurgitant flow, this could explain the difference very well.

In addition to their major findings, they noted two adverse effects of hydralazine on their patients. Three had to stop the study because of severe nausea and vomiting and three had to discontinue use because of persistent hypotension. Fifteen of the patients in Group I experienced clinical benefit, while only two out of thirteen patients in Group II improved.

Packer et al. studied forty-five consecutive patients with Class IV heart failure. They divided them into twenty-six patients that responded to 100 mg of hydralazine or less (Group A) and nineteen patients that required more than 100 mg (Group B). Fourteen of the
subjects in Group B required 150 to 300 mg of hydralazine; three required 600 to 800 mg; two responded only to intravenous administration of the drug (20 mg). Control cardiac indices, mean arterial pressures, heart rates and pulmonary vascular resistances were similar between groups. Each group responded significantly to the drug. Only two variables were different between the groups. Patients in Group B had higher control values for right atrial pressure (14.0 ± 1.5 vs. 9.2 ± 1.3 mmHg, P < 0.025) and left ventricular filling pressure (25.5 ± 1.2 vs. 21.7 ± 1.0 mmHg, P < 0.05). The changes in these variables were similar after hydralazine therapy. Therefore, it appears that dosage requirements for hydralazine are variable and that this variability may have something to do with the severity of the "backward" failure.

Manthey et al. went one step further in elucidating the mechanism for the variable dosage requirements. They measured plasma renin activity and plasma levels of norepinephrine and vasopressin in seventeen patients with congestive heart failure before and after giving 50 mg of hydralazine and 40 mg of isosorbide dinitrate orally. In all patients the plasma renin increased (4.0 ± 1.3 to 6.5 ± 1.8 ng/ml/h, P < 0.001) and vasopressin increased (6.9 ± 1.8 to 21.0 ± 6.6 pg/ml, P < 0.001). Plasma norepinephrine did not show such a unidirectional response. Those patients that had less than a 10% drop in systemic vascular resistance after therapy (N=7) experienced an increase in norepinephrine levels (352 ± 92 to 435 ± 93 pg/ml, P < 0.05). The patients that responded with a greater than 10% decrease in resistance tended to decrease (521 ± 130 to 436 ± 144 pg/ml, P < 0.1 NS). A positive correlation was found between the change in vascular resistance and the change in norepinephrine levels (r=0.57, P < 0.01).
Apparently the patients that started with higher levels of norepinephrine responded better to hydralazine also, although this was not noted in the abstract. Were their ventricles more dilated than those that did not respond? What were their filling pressures? Obviously a more definitive study must be done incorporating all the possible factors.

Myocardial Failure Models

Models of volume overloaded (e.g., mitral regurgitation, aorto-caval shunt), pressure overloaded (e.g., aortic banding, pulmonic banding) and compliance (e.g., cardiac tamponade) failure will not be discussed.

Myocardial failure is due to myocardial destruction or dysfunction. At the cellular level it is due to primary or secondary sarcoplasmic reticulum abnormalities or to cellular necrosis.67

Global myocardial failure has been produced by various myocardial toxins, myocardial depressants and myocardial injuries. Myocardial depressants (e.g., barbiturates, halothane, propranolol) are used for acute myocardial failure studies and will not be discussed. Myocardial toxins include cobalt, Adriamycin, and ethanol. A good model of ethanol cardiomyopathy has not been delineated.68 Adriamycin produces myocardial failure in several species, including the dog, but in the dog it oftentimes produces serious arrhythmias before or concomitantly with the failure.69 If the model is to be used for hemodynamic studies, the arrhythmias must be medically controlled. This makes the model less than ideal for vasodilator study. Cobalt has been used to produce cardiomyopathy in the dog. In one study it produced hemodynamic evidence of mild myocardial failure (i.e., LVEDP 9-15 mmHg,
normal systolic function). In another it produced pathologic evidence of congestion but no further data were gathered. In both studies microscopic evidence of myocytolysis and cell degeneration was seen. The mild signs of heart failure, the lack of a specific endpoint and the time required for heart failure induction make this model less than ideal. Cobalt also induces skeletal muscle damage, produces anorexia, and induces vomiting. These changes are severe enough to make the model inhumane.

Regional myocardial failure is induced by producing an infarct or infarcts. It is generally used to model acute coronary occlusion of man.

Acute ischemic myocardial failure has been produced by progressive coronary artery ligation, embolization of the coronary bed by mercury, coronary thrombosis induced by passing current through an intracoronary electrode, and by embolizing the coronary vascular bed with plastic microspheres, either globally or regionally. Cardiogenic shock with associated high mortality was commonly seen with these preparations.

Models of chronic myocardial failure are conspicuously lacking. Munro was the first to produce chronic myocardial failure by global microembolization with 152-608 micron plastic microspheres. He injected microspheres (10 mg/kg) into the coronary circulation of dogs by occluding the proximal aorta with a balloon and injecting the spheres proximal to the occlusion. The dogs were studied for 8-10 months by assessing exercise tolerance. Duration of exercise was reduced in all dogs although clinical evidence of failure at rest was not reported. At postmortem examination, multiple infarcts were found. They were estimated to encompass 20% of the myocardium.
The other studies have been done on calves. Weber et al.\textsuperscript{91} infused 6-14 micron plastic microspheres into the left main coronary artery over 4-6 hours. Two doses were used, 4 and 5 mg-spheres/kg body weight. They found no alterations from baseline hemodynamic recordings during the infusion. On day 1 the LV end-diastolic pressure rose to 18 mmHg in both groups and it rose further to 21 mmHg on day 3. This elevation persisted for up to 28 days. The group that received 5 mg/kg had significantly lowered stroke volume, cardiac output, peak systolic pressure and maximal rate of pressure rise. Both groups had altered ventricular function curves which were generated by angiotensin infusion.

LaFarge et al.\textsuperscript{92} produced severe (LVEDP $> 40$ mmHg) in calves that had left ventricular assist devices implanted. They found that the best way to produce chronic irreversible failure was microsphere infusion. They infused 10-20 ml of a 3\% solution of 6-14 micron plastic microspheres. The calves were studied 4-64 days after infusion. They had continuous evidence of left ventricular failure when their assist devices were turned off.

Stone et al.\textsuperscript{93} performed an acute study in dogs to determine the quantity of microspheres needed to produce failure and the quantity of microspheres present in the myocardium following injection. They used radioactive microspheres (Ir\textsuperscript{192}) with an average diameter of 285 microns (range 100-360). Injections were made proximal to a proximal aorta occlusion so that the total coronary bed was embolized. They gave incremental injections of 6-10 mg every 20 minutes to 17-25 kg dogs. They obtained left ventricular function curves after each injection by rapid bleeding and rapid infusion of blood coupled with end-diastolic pressure and cardiac output measurements. They found a
linear drop in cardiac function after each injection until a critical point was reached. When this critical point was attained, cardiac function deteriorated rapidly with no additional microsphere injections. Average amount of microspheres given at this critical point was 38 mg (1.5-2.2 mg/kg). They also found that a large number of microspheres wash through the myocardium. Four of their animals died immediately following the first injection. In these animals they found 60% of the injected microspheres, indicating that 40% either failed to enter the coronary circulation or washed through in the first one to two minutes. In the animals surviving the entire experiment, they found only 21% (range 10-32%) of the microspheres remaining in the myocardium. Therefore, a large number of microspheres, even of this large size, wash through the coronary vascular bed or are removed via lymphatics.

Many papers have described the clinical and theoretical disadvantages of an infarcted ventricle, but a recent paper has reviewed the theoretical aspects and formulated a model of infarction. A discussion of the mathematics is beyond the scope of this review, but the model encompasses systolic function computed from end-systolic pressure-volume relationships and diastolic function computed from diastolic pressure-volume changes. Changes in systolic and diastolic function were computed for infarcts encompassing 14.6, 25 and 41.3% of the left ventricular wall in the immediate post-infarction phase, several hours, one week and months following infarction. In addition, the model was utilized to predict function in adjacent viable myocardium. Since the model utilized for the present study has an infarct approximately 40% of the left ventricle, only that size will be discussed.
The systolic and diastolic changes seen with an evolving infarct are complex. Diastolic function immediately after infarction is essentially normal. As the infarcted cells die and are replaced by fibrous tissue, diastolic function deteriorates. Diastolic pressure-volume relationships shift upwards and to the left so that a greater pressure is needed to attain the same volume (decreased compliance). Systolic function, on the other hand, is worst immediately after infarction. The end-systolic pressure-volume relationship shifts down and to the right. The systolic pressure-volume curve also becomes flatter. As the infarct evolves from acute to chronic, systolic function improves, shifting the curve up and to the left. Net ventricular function (stroke volume = end-diastolic volume - end-systolic volume) becomes a complex interaction between systolic and diastolic function. However, if end-diastolic pressure is set at 24 mmHg (the assumed maximum for Frank-Starling reserve), computations can be made of net results. Stroke volume hours after a 41% infarction will be 65% of normal, one week later will be 77% and months later will be 69%. As can be seen, maximum attainable function should occur one week after infarction in the subacute stage. This is where our model was studied.

The acutely infarcted ventricle should respond better to wall stress reduction than should a chronically infarcted ventricle, because the isovolumic pressure line (emax) is flatter. The other stages are progressively in between. Arteriolar dilator therapy should work less well at one week than one day after infarction but better than months after infarction for this reason. Systolic stress is increased in the myocardium adjacent to the infarct. Because the infarct is distensible immediately after infarction, it imposes more stress on adjacent myocardium than does a chronic infarct. Calculations of adjacent wall
stress for a 41% infarct for immediate, acute, subacute and chronic situations are 4.0, 3.7, 3.1 and 2.0 times normal, respectively. Reductions in wall stress would be expected to enhance function better in greatly stressed regions, so this also explains why arteriolar dilator therapy should favor ventricles with fresh infarcts.

Thermal Dilution Cardiac Output

In 1954, Fesler introduced the concept of measuring cardiac output by thermal dilution. Sanmarco et al. confirmed that the thermal dilution technique of recording cardiac output is valid in dogs. They used five anesthetized dogs weighing from 14 to 24 kg. Simultaneous cardiac outputs were determined by thermal dilution and with an electromagnetic flow probe on the ascending aorta. They used 5 cc of room temperature saline for their indicator. The thermistor was in the main pulmonary artery and the saline injection was made into the anterior vena cava. They generated 120 sets of simultaneous determinations of cardiac output. They varied cardiac output in each dog by infusions of Dextran or isoproterenol. The correlation coefficient was 0.973 and the standard error of estimate was 0.45 liter/minute. To determine the reproducibility of the method, they made two successive determinations within one minute and compared them. They did 67 comparisons and found an overall value for two standard deviations of the difference equal to 344 ml/minute, or 6% of the cardiac output. This compares favorably with data reported for the dye dilution method. The standard deviation of the difference between successive estimates for thermal dilution was 3 to 3.5%, while for dye dilution it is 8 to 11%.
Merrick et al. confirmed this work in ten dogs weighing 16.6 to 24.9 kg. They also compared the thermodilution technique to data obtained from an electromagnetic flow probe. They compared the method during normothermia and hypothermia. Their correlation coefficient was 0.96 and their standard error of estimate was 0.44 liters/minute at normothermia. Their standard deviation of the difference between successive estimates was 5% of the mean cardiac output. The data were similar for hypothermia.

Venous Oxygen Tension

The venous oxygen tension is an excellent indicator of the adequacy of peripheral oxygen delivery. Oxygen delivery is dependent on cardiac output, oxygen saturation of hemoglobin and hemoglobin concentration. These three factors combine to meet the tissue's oxygen demands or oxygen consumption. Once oxygen has been transported to the systemic capillary, it enters the cell by passive diffusion. Since diffusion is dependent on a pressure gradient, partial pressure of oxygen is the major factor determining the amount of oxygen transported into the cell. Since the mitochondrial Po2 is 1-2 mmHg, it is the capillary Po2 that determines the rate and distance over which diffusion takes place. The Po2 is high at the arterial end of the capillary but falls as blood travels to the venous end. The cells near the venous end are dependent on the venous Po2 and suffer hypoxia first when O2 transport is inadequate. When the venous Po2 falls below 30 mmHg, tissue oxygen delivery is inadequate and compensatory factors attempt to increase it. When it falls below 20 mmHg, cellular oxygen delivery is grossly inadequate so that anaerobic mechanisms must be utilized for metabolism. As a result, lactic acid is produced. This
is true for most organs; however, the brain and myocardium function normally with venous $P_{O_2}$'s of 25-30 mmHg.

If cardiac output, oxygen saturation or hemoglobin values decrease, tissue oxygen delivery can become impaired. However, compensatory changes take place to assure adequate oxygen delivery when oxygen saturation or hemoglobin becomes inadequate. With acute hypoxemia, cardiac output increases to compensate. With chronic hypoxemia, cardiac output increases and red cell production increases. The net result is that it takes severe hypoxemia to produce inadequate tissue oxygen delivery. I have documented clinically that arterial oxygen tension can decrease to levels of 40-50 mmHg without decreasing the venous $P_{O_2}$ below 30 mmHg. Anemia is also compensated for by an increase in cardiac output.

When cardiac output falls, there are no compensatory mechanisms to aid oxygen delivery. Therefore, if hypoxemia and anemia are not present, venous oxygen tension should correlate with cardiac index. If hypoxemia is present, as in a patient with pulmonary edema, it must be relatively severe to have a combined effect on tissue oxygen delivery.

Goldman et al. studied thirty-one patients admitted to a coronary care unit because of acute myocardial infarction. They were divided into three groups, with Group II having subsets. Group I included eleven patients with no evidence of heart failure. Group II had fifteen patients who had evidence of failure at some point during their hospital stay. Failure was defined as the presence of a gallop rhythm, pulmonary edema and an elevated central venous pressure. Group II was broken down into Group IIA, which consisted of members of this group when not in failure, and Group IIB, when they were in failure. Group
III included four patients with congestive heart failure and cardiogenic shock. Venous oxygen saturations were determined in each of these patients at multiple times. The venous sample was taken from the superior vena cava. In Group I, sixty-one determinations were made. The venous oxygen saturations were 71 ± 7% (venous $P_{O_2} = 39$ mmHg at pH = 7.4). Only four determinations were below 60%, and each time the determinations before and after were greater than 60%. One hundred fourteen determinations were made in Group II, thirty-two when there was no evidence of failure and eighty-two when there was. Only five values in Group IIA were less than 60%, and the mean value was 66 ± 8% (venous $P_{O_2} = 36$ mmHg at pH = 7.4). In Group IIB the mean value was 56 ± 10% (venous $P_{O_2} = 31$ mmHg at pH = 7.4). Twenty-five of the eighty-two determinations were greater than 60%. However, ten of these were obtained within twenty-four hours preceding the disappearance of all clinical signs of failure. Twenty-five determinations were made on the four patients in Group III. No value was greater than 60%. The mean value was 43 ± 1% (SEM) (venous $P_{O_2} = 26$ mmHg at pH = 7.4). In patients who did not receive oxygen, the oxygen saturation averaged 40% (venous $P_{O_2} = 24$ mmHg at pH = 7.4). All four patients had a value less than 45% at some time. Differences in venous oxygen saturation between each group were all significant. They also correlated arteriovenous oxygen differences and venous oxygen saturation in two Group I, four Group IIB and three Group III patients. From their graph I calculated a correlation coefficient of -0.805. None of their patients were anemic and all were in a resting state.
Mean Electromechanical $\Delta P/\Delta t$

Diamond et al.\textsuperscript{100} developed a means of non-invasively evaluating $dP/dt$ in 1972. They theorized that if they divided the arterial diastolic minus the left ventricular diastolic pressure by the pre-ejection period they would have an index of contractile force. They studied 50 patients with acute myocardial infarction. They obtained systolic time intervals using an electrocardiogram, phonocardiogram and carotid pulse waveforms. Left ventricular filling pressure was measured either as the pulmonary arterial end-diastolic or pulmonary capillary wedge pressure. In eighteen patients, cardiac catheterization was performed at bedside to obtain left ventricular $dP/dt$. The correlation coefficient between $\Delta P/\Delta t$ and $dP/dt$ was 0.96 ($P < 0.001$) over a wide range of values. There was a fair correlation between LVET/PEP and $\Delta P/\Delta t$ or $dP/dt$. $\Delta P/\Delta t$ was also a good prognostic indicator. A $\Delta P/\Delta t$ of 500 separated survivors from non-survivors with a minimal overlap of only 7% of the total range. PEP, LVET, LVET/PEP, blood pressure and left ventricular filling pressure all did a poor job of determining prognosis. $\Delta P/\Delta t$ also paralleled the degree of clinical cardiac impairment with little overlap, whereas LVET/PEP had a marked overlap. They concluded that $\Delta P/\Delta t$ could be used serially to determine response to therapy and could be used by the clinician to determine a prognosis so that more aggressive therapeutic measures could be taken.

Leier et al.\textsuperscript{52} used a similar index when they studied hydralazine's effect on inotropy. They utilized the isovolumic contraction time instead of the pre-ejection period for $\Delta t$. To determine the isovolumic contraction time, they utilized an apexcardiogram to determine the onset of left ventricular contraction. Subtracting the period from the
onset of the Q wave of the electrocardiogram to the onset of the upstroke of the apexcardiogram from the pre-ejection period yielded the isovolumic contraction time.

Echocardiography

Echocardiography in dogs is a new field. The first published study utilizing echocardiography in awake dogs was published by Mashiro et al.\textsuperscript{101} in 1976. In it they established normal values for left ventricular end-diastolic diameter, left-ventricular end-systolic diameter, left ventricular free wall thickness and septal thickness in sixteen dogs weighing 11 to 24 kg. The equation for predicting left ventricular end-diastolic diameter was \( y = 0.099x + 1.99 \) cm, where \( y \) = diastolic diameter and \( x \) = body weight (kg). The regression line for systolic diameter was \( y = .076x + 1.24 \) cm (correlation coefficient = 0.755).

The correlation coefficient between body weight and left ventricular free wall thickness was 0.570 with a regression line equation of \( y = 0.157x + 3.49 \) mm. Septal thickness and body weight had a correlation coefficient of 0.73 and the equation was \( y = 0.24x + 2.13 \) mm. They also reported that they were able to obtain echocardiograms from the right chest well in 100% of the dogs when they placed the transducer over the apex beat. They published normal echoes showing the motions of the left ventricular free wall and septum and, in addition, they verified the various chambers they were seeing by injecting dextran into the chambers and watching them on the echocardiogram fill with echoes.

Subsequently, Pipers et al.\textsuperscript{102} established normal values for the pre-ejection period, left ventricular ejection time and their ratio from the echocardiogram in awake dogs. The systolic time indices were:
pre-ejection period index (msec) = 70-0.02 HR and left ventricular
ejection time index (msec) = 222-0.55 HR.

Dennis et al.\textsuperscript{103} established normal values for closing slopes of
the mitral valve. The E-F slope was 94.0 ± 5.7 mm/sec (SEM) with a
range of 59.5 to 142.8 mm/sec. The A-C slope was 320.2 ± 21.0 mm/sec
(SEM), range = 238.7 to 585.1 mm/sec. They noted that the E-F slope
decreased in two dogs with mitral valve fibrosis.

Left ventricular wall motion is reduced in patients with anterior
wall infarction and patients with coronary artery disease in man.\textsuperscript{104}
MATERIALS

All experiments were performed on German Shorthair Pointer dogs weighing 20-24 kg. No attempt was made to control sex distribution. All dogs were normal on physical exam. The cardiovascular system of each dog was assessed to be normal by physical exam and by evaluating the hemodynamic parameters obtained during the control state.

Anesthesia, when it was utilized, was induced with intravenous thiopental and maintained with halothane, 1%, mixed in 99% oxygen. When thoracotomies were performed, the animals were intubated with a cuffed endotracheal tube and ventilated by a positive pressure ventilator (Harvard Apparatus Company, Millis, MA).

Blood gases were analyzed on a radiometer blood gas analyzer (Radiometer-Copenhagen, Model BMS3 MK2, Copenhagen, Denmark). Blood pressures that were obtained through fluid-filled catheters were monitored with standard pressure transducers (Stratham Laboratory, Model P23 dB, Hato Rey, Puerto Rico). Direct blood pressures were obtained with miniaturized pressure transducers (Konigsberg Instruments, Inc., Model No. P6, Pasadena, CA). Dye dilution cardiac output determinations were performed with a cuvette densitometer (Gilford Instruments, Inc., Model #103-IR, Oberlin, OH). All of these plus an electrocardiogram were recorded on a light writing multichannel oscillograph (Electronics for Medicine, Model DR8, Pleasantville, NY).
Indirect blood pressures were obtained by placing a cuff over the mid metatarsal region and recording pressure by an automated sphygmomanometric technique (Applied Medical Research, Dinamap Research Model 1245, Tampa, FL). Echocardiograms were recorded with a 5.0 MHz transducer on an echocardiograph (Picker Corp., Model #595221, Northford, CT). Triple-lumen balloon-tipped thermodilution catheters (Electro-Catheter Corp., Rahway, NJ) were utilized to obtain pulmonary capillary wedge pressures, mixed venous oxygen tensions and cardiac output. Thermodilution cardiac output was determined with a cardiac output computer (Columbus Instruments International Corp., Columbus, OH).

Hydralazine (Apresoline, CIBA, Summit, NJ) was utilized as 25 mg tablets. Dobutamine (Dobutrex, Eli Lilly Co., Indianapolis, IN) was utilized as an intravenous infusion. Quinidine sulfate (Quinalube, Eli Lilly Co., Indianapolis, IN) was an injectable compound with a concentration of 80 mg/ml. Lidocaine (20 mg/ml) (Veratex Corp., Troy, MI) was administered as an intravenous infusion.

Calibration Procedures

The fluid-filled pressure transducers were calibrated with a mercury manometer. The miniaturized implantable pressure transducers were calibrated by placing them in a sealed glass chamber and generating a pressure within that chamber. The chamber pressure was simultaneously monitored with a mercury manometer and the transducer output recorded on the multichannel recorder to generate a calibration constant (mV/mm deflection). A standard 1 volt signal was then placed into the DC input prior to each recording so that a constant for
determining the number of mm in a mV could be determined. The calibration constants were as follows:

\[
\begin{align*}
\#183 &= \frac{8.4 \text{ mV}}{\text{mmHg}}, & \#184 &= \frac{8.5 \text{ mV}}{\text{mmHg}}, & \#185 &= \frac{8.4 \text{ mV}}{\text{mmHg}}, & \#186 &= \frac{8.5 \text{ mV}}{\text{mmHg}}.
\end{align*}
\]

The amplifier that was utilized had a frequency response flat to 100 Hz. The amplifier included a device for generating a reference voltage with regard to barometric pressure. Its position remained stationary so that the entire pressure tracing moved up or down with barometric pressure in reference to this voltage. This voltage represented a pressure that was determined by generating a known zero pressure in the vascular space by occluding the artery proximal to the transducer or by stopping cardiac motion with acetyl choline and referencing the pressure obtained to the voltage and the barometric pressure. The offsets obtained were as follows: transducer \#183 = \[(\text{B.P.} - 723) + P\text{ chamber}\]; \#184 = [\text{B.P.} - 726] + P\text{ chamber}]; \#185 = \[(\text{B.P.} - 752) + P\text{ chamber}\]; \#186 = [(\text{B.P.} - 724) + P\text{ chamber}].

The Swan-Ganz thermodilution catheters were calibrated at the factory to have a sensitivity of 250 Ohms/\text{°C}. They were recalibrated by placing the thermistor in a water bath, changing the temperature and recording the change in resistance. Sensitivity ranged, in the three catheters used, from 222 to 236 Ohms/\text{°C}. The resistance was set at 7000 Ohms at 36.6°C.

The cuvette densitometry apparatus was calibrated after each set of determinations by passing a known concentration of green dye in blood through the densitometer and recording the deflection produced. A calibration constant was then determined.
METHODS

Pilot Studies

Heart failure induction pilot studies were carried out on a Beagle Hound, 8 Foxhounds and 3 large mixed breed dogs. The Beagle Hound was anesthetized and received incremental injections (50,000 spheres/injection) of 70 μ nonradioactive microspheres into the proximal left circumflex coronary artery until the left ventricular free wall was completely akinetic. The Foxhounds were injected with 10-15 μ microspheres, 1,500,000 per injection, into the proximal left circumflex coronary artery until the free wall was akinetic and were monitored echographically. Several were reinfarcted when free wall contractile motion returned. The 3 mixed breed dogs received injections of 80 μ microspheres. They were chronically instrumented with a left atrial and an aortic cannula and with miniaturized pressure transducers in the left ventricle. They received microsphere injections (75,000/time) 5-8 days following thoracotomy. The injections were continued until the left ventricular free wall was akinetic and the left ventricular filling pressure was >20 mmHg.

Experimental Design

The experiments were designed so that each dog served as its own control. Hemodynamic parameters were measured at repeated intervals over time. Experimental maneuvers, where possible, were kept constant.
Instrumentation

The first three dogs were chronically instrumental for recording left ventricular and aortic pressures and dye dilution cardiac outputs. After anesthesia a left lateral thoracotomy was performed. The pericardium was incised and the left ventricular apex lifted out of the chest. A pursestring suture was placed around the apex and a stab incision made through the apex into the left ventricular cavity. A sterile Konigsberg miniaturized pressure transducer was placed in the left ventricular cavity with its lead wire exiting through the apex. The pursestring suture was tightened down around the lead wire to maintain hemostasis. The proximal descending aorta was isolated just distal to the left subclavian artery. A Statinsky clamp was placed so that a portion of the aortic wall was isolated from the flow of blood. A longitudinal incision was made into this wall, slightly shorter in length than the diameter of the pressure transducer. The pressure transducer was placed in the aorta and the incision sutured closed. Hemostasis was maintained by applying digital pressure until blood coagulation occurred. The lead wires were brought out of the chest through a stab incision between the ribs, one rib space anterior to the thoracotomy site. They were tunnelled through the subcutaneous tissue to a spot under the dorsal skin of the neck. A stab incision was made in the neck and the leads brought out and sutured to the skin. A pursestring suture was placed in the left atrial appendage and silastic tubing passed into the left atrium through a stab incision. The pursestring was tightened and a preplaced piece of dacron, cemented to the tubing, was sutured to the left atrial wall. The tubing was brought out along with the lead wires and filled with heparin. The thoracotomy site was closed routinely. The left carotid artery was
exposed and another silastic tube was placed in it so that the tip was lying in the aorta. It was filled with heparin and tunneled subcutaneously to another site on the dorsal neck. Each silastic tube was closed off with a metal stylet that fit snugly in the lumen. The silastic tubes were flushed daily with heparin. The dogs were allowed to recover for four to seven days before the studies were performed.

The next seven dogs were chronically instrumented with Swan-Ganz balloon-tipped thermodilution catheters. Following anesthesia the right jugular vein was exposed and the fluid-filled catheter advanced so that the tip was lying in the distal main pulmonary artery. Position of the proximal injection port in the distal anterior vena cava was verified by injecting contrast media and observing its passage with image intensification fluoroscopy. The catheter was tied in place and the incision closed. The catheter was bandaged to the neck. Both ports were flushed daily with heparinized saline and filled with heparin.

Procedure

On the control day each dog was brought into the laboratory and allowed to acclimate to his surroundings. Baseline hemodynamic parameters were recorded following this acclimation period. The variables recorded were as follows: body weight (kg), systolic, diastolic and mean systemic blood pressure (mmHg), left ventricular filling pressure (mmHg), cardiac output (liters/minute), heart rate (beats/minute), venous oxygen tension (mmHg), pre-ejection period (milliseconds), left ventricular ejection time (milliseconds), end-diastolic diameter (cm) and peak-systolic diameter (cm).
The systemic blood pressure was measured from the aortic pressure transducer in those dogs instrumented with miniaturized pressure transducers. It was recorded non-invasively by the automated sphygmomanometric technique otherwise. Six recordings were taken and averaged for the value. Left ventricular filling pressure was measured as the left ventricular end-diastolic pressure in the dogs with miniaturized pressure transducers in their left ventricles and as the pulmonary capillary wedge pressure or pulmonary artery diastolic pressure in the dogs with Swan-Ganz catheters. Cardiac output determinations were performed in the dogs with silastic tubing by injecting 2.5 mg of green dye rapidly through the left atrial cannula. Simultaneously blood was drawn out of the carotid cannula, through a cuvette densitometer and a curve inscribed and recorded from a DC input on the multi-channel recorder. Green dye cardiac outputs were recorded in triplicate and averaged for each determination. In order to calculate the cardiac output from the curves, the forward triangle method was used, in which:

\[
\text{CO} = \frac{I \times 60 \times K'}{\text{PC}} \times \text{BT}
\]

where:

- \( \text{CO} \) = cardiac output (liters/minute)
- \( I \) = amount of the indicator injected (mg)
- \( 60 = 60 \text{ sec/min} \)
- \( K' = \) empirical constant = 0.37
- \( \text{PC} = \) peak concentration (mg/l)
- \( \text{BT} = \) buildup time (seconds)

For the thermodilution cardiac outputs, the resistance and sensitivity of the thermistor were entered on the cardiac output computer. An injection of 2.5 cc of room temperature saline was made through the proximal port, lying in the anterior vena cava. The cardiac output
computer received the temperature change curve from the thermistor and calculated the cardiac output from the formula:

\[
CO = \frac{V_i P_i C_i (T_b - T_i) \times 0.82 \times 60}{P_b C_b \times \int_0^{\infty} \Delta T_b(t) dt \times K}
\]

where:

- \(V_i\) = volume of injectate (ml)
- \(P_i\) = specific gravity of injectate
- \(P_b\) = specific gravity of blood
- \(C_b\) = specific heat of blood
- \(C_i\) = specific heat of injectate
- \(T_b\) = initial temperature of blood (°C)
- \(T_i\) = initial temperature of injectate (°C)
- 0.82 = empirical correction factor for indicator loss between end and tip of the catheter
- 60 = 60 seconds/minute
- \(K\) = calibration factor for the curve (°C/mm deflection)
- \(\int_0^{\infty} \Delta T_b(t) dt\) = area under the deflections-time curve registered following injection of the thermal indicator (°C sec)

The Columbus Instrument Computer assumed the exponential decay of the deflection-time curve to begin at 83.4% of the peak value. It added the integrated area up to that point to the area beneath the exponential portion of the curve. This area \(A\) was calculated from the formula:

\[
A_2 = \frac{0.834 C_p}{K}
\]

where:

- \(C_p\) = peak concentration
- \(K = \frac{2.13}{t}\) where \(t = t_2 - t_1\) (seconds)

The net result was read out digitally. Six consecutive values were
taken and averaged to get the value for cardiac output. The venous oxygen tensions were taken from the jugular vein in the dogs that did not have Swan-Ganz catheters implanted. They were taken from the pulmonary artery in those that did. The pre-ejection period was taken from a simultaneous recording of an electrocardiogram and an echocardiogram. It was measured from the onset of the QRS complex to the opening of the aortic valve in each dog. The left ventricular ejection time was measured from the opening to the closing of the aortic valve. Left ventricular end-diastolic diameter was obtained from an echocardiogram taken immediately below the mitral valve. The measurement was taken simultaneous with the "R" wave peak. Left ventricular peak systolic diameter was taken from the same spot in the left ventricle, when the septal wall reached its nadir.

The following variables were calculated from the above data by their respective formulas:

\[
\text{body surface area (m}^2\text{)} = 0.112 \times \left[\text{body weight (kg)}\right]^{2/3}; \quad (4)
\]

\[
\text{mean pressure (mmHg)} = \frac{\text{systolic pressure} + \left(\text{diastolic pressure} \times 2\right)}{3}; \quad (5)
\]

for the invasive determinations;

\[
\text{cardiac index (liters/minute per m}^2\text{)} = \frac{\text{cardiac output}}{\text{body surface area}}; \quad (6)
\]

\[
\text{stroke volume (ml/beat)} = \frac{\text{cardiac output}}{\text{heart rate}}; \quad (7)
\]

\[
\text{stroke index (ml/beat per m}^2\text{)} = \frac{\text{stroke volume}}{\text{body surface area}}; \quad (8)
\]

\[
\text{total systemic resistance (dynes sec cm}^{-5}\text{)} = \frac{\text{mean arterial pressure}}{\text{cardiac output}} \times 80; \quad (9)
\]
total systemic resistance index (dynes sec cm$^{-5}$ m$^{-2}$) 

\[= \text{total systemic resistance} \times \text{BSA}; \quad (10)\]

\[\text{diastolic systemic blood pressure} \quad \Delta P/\Delta T \text{ (mmHg/sec)} = \frac{\text{left ventricular filling pressure}}{\text{pre-ejection period}}. \quad (11)\]

and

\[\Delta D = \frac{\text{left ventricular peak systolic diameter}}{\text{left ventricular end-diastolic diameter}}. \quad (12)\]

Following the control recording, the dog was anesthetized and a Judkins right coronary artery catheter was introduced via the right common carotid artery. The tip of the catheter was placed in the proximal portion of the left circumflex coronary artery. The position was verified by injecting contrast medium into the artery. This injection was made prior to each injection of microspheres in order to insure the proper placement of the catheter. A control recording of the left ventricular filling pressure was taken along with an echocardiogram. Injections of 80 ± 20 µ latex carbonized non-radioactive microspheres (3-M Company, Minneapolis, MN) commenced into the left circumflex coronary artery. The spheres were suspended in 10% Dextran with no Tween-80. The concentration of the spheres was 150,000/ml. Injections of 75,000/time were made. The spheres tended to settle out in the container so they were agitated in an ultrasonic cleaner (Cole-Parmer, Chicago, IL) prior to each injection. The spheres also adhered to the plastic syringe and catheter so repeated flushings were made with normal saline following each injection. Five to twenty minutes were allowed between each microsphere injection.
The first three dogs received repeated injections of microspheres until the left ventricular free wall was completely akinetic on the echocardiogram and the left ventricular filling pressure exceeded 20 mmHg. The last seven dogs received injections until the wall had 10% or less increase in wall thickness from diastole to systole and the left ventricular filling pressure exceeded 16 mmHg.

Within one hour following the infarction, the same hemodynamic variables as before were recorded or computed. Electrocardiograms and blood pressure determinations were monitored constantly for six to twenty-four hours after the infarction procedure. If the mean blood pressure dropped below 80 mmHg, dobutamine (5-20 μg/kg/min) was infused for inotropic support. When the ventricular arrhythmias commenced, they were controlled with intravenous lidocaine (1-2/#boluses, followed by 30-80 mg/kg/min infusions) and/or intramuscular quinidine (6-10 mg/# every four to six hours). When the dogs were conscious enough to swallow, they were administered oral procainamide (500 mg QID).

The dogs that survived the first twenty-four hours had their hemodynamic variables recorded and computed again the day after the infarction procedure. Because several of the first dogs died after being stressed by handling on days 2 and 3 post-infarction, no records were obtained subsequently on those days. Electrocardiograms were repeated on post-infarction day 4 or 5. If the ventricular arrhythmias had abated, data were obtained again. If the dogs were in heart failure, they were started on the hydralazine study. They were judged to be in heart failure if their stroke volume index was less than or equal to 25 ml/beat per m² and their left ventricular filling pressure was greater than or equal to 16 mmHg.
The data collected on post-infarction day 4 or 5 were used as the control data for the hydralazine portion of the study. Once they were obtained, 25 mg of hydralazine per os was administered to each dog. One hour later all of the hemodynamic parameters were again collected. If the total systemic resistance index had not decreased to a level less than 1700 dynes sec cm$^{-5}$ m$^{-2}$, another 25 mg dose was administered and records taken again in one hour. This protocol was continued until the appropriate response was present. Once this response was evident, the hemodynamic variables were collected every two hours until the total systemic resistance rose again to a level greater than 2000 dynes sec cm$^{-5}$ m$^{-2}$.

Following the study each dog was euthanatized with an overdose of pentobarbital intravenously. The thorax was opened and any catheters or transducers were retrieved. The heart was removed, washed, and photographed. It was sectioned, breadloaf fashion, and photographed again. The photographs were projected on a grid. The area of infarcted and total tissue was measured at each level sectioned. The percent tissue infarcted was calculated. The tissue was submitted for histopathologic analysis.

Statistical Analysis

The data presented in the text, figures and tables of this dissertation were analyzed by analysis of variance for repeated measurements involving split plots. The experimental design allowed each dog to serve as its own control. The sources of variation were time and dogs. The sums of squares ($SS_T$, $SS_D$, $SS_E$ and $SS_Y$) were generated by a computer program written for a programmable calculator (Texas Instruments Model #59, Dallas, TX). For the pre- and post-heart failure induction
data, n equaled 5. For the hydralazine study, n equaled 4. Levels at which the data are significant are presented with the data. Differences between specific points were clarified with t-tests for paired data.
RESULTS

Heart Failure Induction

All ten dogs survived the instrumentation procedure and lived long enough to be infarcted. Five of the ten dogs survived the induction of heart failure. One of the three (33%) dogs that had a thoracotomy and was infarcted to a left ventricular filling pressure of 20 mmHg survived the infarction. One of these died during the coronary artery catheterization when the catheter migrated distally into the artery and created an acute occlusion of the artery. The other one died forty-two hours after being infarcted when it struggled during the recording procedure and developed ventricular fibrillation. Four of the seven (57%) that were instrumented with Swan-Ganz catheters and infarcted to a left ventricular filling pressure of 16 mmHg survived. One of these was inadvertently given a bolus of 150,000 microspheres and died an acute arrhythmic death. The dog that received the largest total quantity of microspheres (975,000) died from acute left ventricular failure and refractory arrhythmias nine hours after the infarction procedure. The other dog died from severe ventricular arrhythmias and an overdosage of quinidine which was being utilized to control the arrhythmias.

The total number of microspheres injected into each dog ranged from 0 to 1,107,954/m² and the mean was $542,686 ± 316,145$ (± SD). The total number of microspheres injected into dogs that survived ranged
from 481,928/m² to 887,097/m² and the mean was 636,729 ± 128,744/m².
The total number injected into dogs that died ranged from 0 to 1,107,954/m² and the mean was 448,644 ± 421,794/m². There was no significant difference between those dogs that survived and those that did not.

All of the dogs that survived long enough developed ventricular arrhythmias within one to two hours post-infarction. Initially there was progressive S-T segment elevation in lead aV₉. Following that, nonparoxysmal (heart rate < 180 beats/minute) ventricular tachycardia developed. In five dogs paroxysmal ventricular tachcardia developed. The dogs that developed paroxysmal ventricular tachcardia were treated aggressively with intravenous lidocaine and/or intramuscular quinidine sulfate (6-8 mg/# every six hours). Three survived, one was refractory to antiarrhythmic therapy and one was refractory and died of quinidine overdosage.

In three dogs only nonparoxysmal ventricular tachcardia developed. Two survived and one died eighteen hours after infarction when stressed. They were treated less aggressively with only intramuscular quinidine (4-6 mg/# every six hours).

Three dogs required dobutamine infusion post-infarction. Two survived and the other died from cardiogenic shock and refractory ventricular arrhythmias.

Figure 7 is a graph of the average mean systemic blood pressure before, one hour after, one day after and four or five days after infarction for the five surviving dogs. Mean pressure decreased significantly (P < 0.05) after heart failure induction. It was not significantly different than before heart failure induction on day 4 or 5.
Figure 7. Mean arterial pressure before and after heart failure induction. Values (mmHg) are shown as mean ± SD. Asterisk indicates significant (P < 0.05) change from control value.
Mean Arterial Blood Pressure

![Graph showing mean arterial blood pressure over time.](image)

- Control
- 1 hour
- 1 day
- 4-5 days

Figure 7
Figure 8 is a graph of the mean total systemic resistance index ± 1 standard deviation at the same time intervals. All of the values after the induction of heart failure are different (P < 0.01) from the value prior to heart failure induction.

The graph in Figure 9 shows the change in stroke volume index after heart failure induction. All of the values after induction of heart failure are significantly (P < 0.01) different from before. They do not differ from each other.

Figure 10 shows the change in cardiac index. Again, all of the values after heart failure induction are significantly (P < 0.01) less than before. They are not significantly different from each other.

Figure 11 exhibits the change in venous oxygen tension following heart failure induction. No values for venous Po₂ were taken immediately after heart failure induction, since the dogs had been anesthetized and on 100% oxygen during the procedure. The values for one day after and for four or five days after are significantly (P < 0.01) less than before heart failure induction.

Figure 12 shows a graph of the heart rates over time. Heart rate did not change significantly over time (P < 0.05).

Figure 13 is a graph of the change in left ventricular filling pressure. It changed significantly (P < 0.01) after heart failure induction. It did not change once heart failure was present.

The graph in Figure 14 shows what happened to ∆P/∆T after heart failure induction. It decreased significantly (P < 0.01) after heart failure induction and did not change after that.
Figure 8. Total systemic resistance index before and after heart failure induction. Values (dynes sec cm$^{-5}$m$^2$) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Total Systemic Resistance Index

Figure 8
Figure 9. Stroke volume index before and after heart failure induction. Values (ml/m²) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Stroke Volume Index

Figure 9
Figure 10. Cardiac index before and after heart failure induction. Values (l/min/m²) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Cardiac Index

Figure 10
Figure 11. Venous oxygen tension before and after heart failure induction. Values (mmHg) are shown as mean ± SD. Asterisks indicate significant ($P < 0.01$) change from control value.
Figure 12. Heart rate before and after heart failure induction. Values (beats/min) are shown as mean ± SD. Asterisks indicate significant (P < 0.05) change from control value.
Heart Rate

Figure 12
Figure 13. Left ventricular filling pressure before and after heart failure induction. Values (mmHg) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Left Ventricular Filling Pressure

Figure 13
Figure 14. The ΔP/ΔT before and after heart failure induction. Values (mmHg/sec) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Figure 14

ΔP/ΔT

mm Hg/sec

control  1 hr  1 day  4-5 days

Figure 14
Figure 15 exhibits the change in shortening fraction. It also decreased significantly (P < 0.01) and remained depressed after heart failure induction.

Hydralazine Study

Two dogs required a total hydralazine dose of 75 mg and three required 50 mg to obtain an adequate (total systemic resistance index < 1700 dynes sec cm⁻⁵ m⁻²) response. All dogs achieved an adequate response. One dog died of ventricular fibrillation three hours after receiving its last dose of hydralazine. Therefore, all of the data in the hydralazine study are based on four dogs. Of the dogs that survived, one required 3.68 mg/kg, one 2.5 mg/kg, one 2.45 mg/kg and one 2.08 mg/kg of hydralazine. Mean dosage was 2.68 ± 0.69 mg/kg.

Two dogs experienced recurrences of their arrhythmias. The one dog died from ventricular fibrillation after his arrhythmias had been noted at the one-hour recording. The other dog's arrhythmia consisted of multifocal premature ventricular contractions that occurred at a rate of 10 to 16/minute. They were not treated and the records were analyzed during sinus rhythm. The arrhythmia abated again after the hydralazine effect had dissipated.

Figure 16 shows the time course of the drug effect on mean blood pressure. The pressure decreased significantly (P < 0.05) following hydralazine administration and stayed depressed for 11 to 13 hours.

The total systemic resistance index, shown in Figure 17, had the same time course, but its changes were greater and were more significant (P < 0.001).
Figure 15. Shortening fraction before and after heart failure induction. Values (%) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Shortening Fraction

![Graph showing shortening fraction over time](image)

Figure 15
Figure 16. Mean arterial blood pressure after oral hydralazine administration to dogs with heart failure. Values (mmHg) are shown as mean ± SD. Asterisks indicate significant ($P < 0.05$) change from control value.
Mean Arterial Blood Pressure

Figure 16
Figure 17. Total systemic resistance index after oral hydralazine administration to dogs with heart failure. Values (dynes sec cm$^{-5m^2}$) are shown as mean ± SD. Asterisks indicate significant (P < 0.001) change from control value.
Total Systemic Resistance Index

Figure 17
In Figure 18 it can be seen that the stroke volume index increased significantly \( (P < 0.01) \) for the same time period, and Figure 19 shows the same response for the cardiac index. Figure 20 indicates that the changes in venous oxygen tension presented the same pattern as the cardiac index. The level of significance is \( P < 0.05 \).

Heart rate (Figure 21) increased significantly \( (P < 0.05) \) during the time that hydralazine was effective.

Left ventricular filling pressure (Figure 22), \( \Delta P/\Delta T \) (Figure 23) and shortening fraction (Figure 24) did not change significantly after hydralazine administration.

Three of the dogs returned to a total systemic resistance index value greater than 1700 dynes sec cm\(^{-5}\) m\(^2\) eleven hours after the last dose of hydralazine. One dog required thirteen hours for the drug effect to dissipate.

Peak drug effect occurred at three to five hours after the last dosage administration.

**Complications**

One dog experienced mild signs of cerebral hypoxia when it assumed an upright position (orthostatic hypotension). This dog would place its front feet in the lap of a seated person in order to get petted. He could stay in this position for approximately 30 seconds before becoming unstable and mildly disoriented. He would jump back down when this occurred and would recover in 20-30 seconds.

One dog died from ventricular arrhythmias. One dog had a recurrence of his ventricular arrhythmias but suffered no consequences.
Figure 18. Stroke volume index after oral hydralazine administration to dogs with heart failure. Values (ml/m²) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Stroke Volume Index

Figure 18
Figure 19. Cardiac index after oral hydralazine administration to dogs with heart failure. Values (l/min/m²) are shown as mean ± SD. Asterisks indicate significant (P < 0.01) change from control value.
Cardiac Index

Figure 19
Figure 20. Venous oxygen tension after oral hydralazine administration to dogs with heart failure. Values (mmHg) are shown as mean ± SD. Asterisks indicate significant (P < 0.05) change from control value.
Venous Oxygen Tension

Figure 20
Figure 21. Heart rate after oral hydralazine administration to dogs with heart failure. Values (beats/min) are shown as mean ± SD. Asterisks indicate significant (P < 0.05) change from control value.
Heart Rate

beats/min

control 1 hr 3 hrs 5 hrs 7 hrs 9 hrs 11-13 hrs

Figure 21
Figure 22. Left ventricular filling pressure after oral hydralazine administration to dogs with heart failure. Values (mmHg) are shown as mean ± SD. No significant changes were noted.
Left Ventricular Filling Pressure

Figure 22
Figure 23. The \( \Delta P/\Delta T \) after oral hydralazine administration to dogs with heart failure. Values (mmHg/sec) are shown as mean ± SD. No significant changes were noted.
Figure 23
Figure 24. Shortening fraction after oral hydralazine administration to dogs with heart failure. Values (%) are shown as mean ± SD. No significant changes were noted.
Shortening Fraction

Figure 24
Venous Oxygen Tension as a Means of Predicting Cardiac Index

Venous oxygen tension was collected each time cardiac index was calculated. Linear regression analysis was done on all of these data, first for all dogs together and then for each separate dog.

Venous oxygen tension vs. cardiac index for every data point collected is shown in Figure 25. The formula for the regression line is \( F(x) = 29.7489 + (2.04317 \times X) \) and the correlation coefficient is 0.633. The correlation is significant at \( P < 0.001 \). However, as seen in Figure 25, the 95% confidence limits are large, being \( \pm 11.2 \) mmHg.

The correlations for the individual dogs that survived heart failure induction are shown in Figures 26 through 30. Correlations were stronger for each of these, being 0.774, 0.808, 0.740, 0.776 and 0.803. All were highly significant \( (P < 0.001) \).

Pathology

A representative picture of the hearts photographed before sectioning is seen in Plate I. The gross pathology showed an extensive infarct encompassing the posterolateral left ventricular free wall from apex to base. A small portion of the posterior right ventricular free wall was involved. The left atrium was infarcted in two of the five dogs but not extensively in either case. The infarct appeared mottled when viewing the epicardium. White areas of fibrosis were interposed with more normal appearing myocardium.

When the heart was sectioned breadloaf fashion the extent of the infarct could be more readily appreciated. In Plate II the sections progress upward in a clockwise fashion from apex to base. The
Figure 25. Linear regression plotting cardiac index vs. venous oxygen tension for all dogs (n=10). Dashed lines represent 95% confidence intervals. $r=0.633 \ (P < 0.001)$. 
Cardiac Index (L/min/m²)

Venous Oxygen Tension (mm Hg)
Figure 26. Linear regression plotting cardiac index vs. venous oxygen tension for dog #453. $r=0.774$ ($P < 0.001$).
Figure 26

Cardiac Index (L/min/m^2)

Venous Oxygen Tension (mm Hg)

25 30 35 40 45 50 55 60

1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0

* * *
Figure 27. Linear regression plotting cardiac index vs. venous oxygen tension for dog #452. $r=0.808 \ (P < 0.001)$. 
Venous Oxygen Tension (mm Hg)

Cardiac Index (L/min/m²)

Figure 27
Figure 28. Linear regression plotting cardiac index vs. venous oxygen tension for dog #448. $r=0.740$ (P < 0.001).
Figure 28

Cardiac Index (L/min/m²)

Venous Oxygen Tension (mm Hg)
Figure 29. Linear regression plotting cardiac index vs. venous oxygen tension for dog #451. $r=0.776$ ($P < 0.001$).
Figure 29

Venous Oxygen Tension (mm Hg)

Cardiac Index (L/min/m²)
Figure 30. Linear regression plotting cardiac index vs. venous oxygen tension for dog #445. $r=0.803$ ($P < 0.001$).
Plate I. Gross specimen showing the appearance of the posterolateral left ventricular infarct in dog #453.
Plate II. Cross sections of the heart from dog #453 delineating the extent of the infarct.
extensive posterolateral distribution of the infarct can be seen. It encompassed 39.3-43.5% of the myocardium (41.4 ± 1.9%).

The slides from dogs 445 and 448 were misplaced. Histopathology of the other three dogs was characterized by massive transmural fibrosis interspersed with normal myocardium in the infarcted region. Fibrosis in the regions affected most severely constituted 50-60% of the myocardium. The fibrosis centered around blood vessels and some of these vessels contained microspheres. Some regions contained areas of necrosis and active inflammation. The remaining islets of normal myocardium did not appear to be hypertrophied. The distribution of fibrosis followed the gross distribution of the infarct very closely. There were some areas within regions that were not infarcted that contained small numbers of beads and milder fibrosis. These generally bordered on the regions that were infarcted.

Pilot Studies

The Beagle Hound survived for 17 days with a stable akinetic left ventricular free wall and stable, moderate pulmonary edema and died from a spontaneous tension pneumothorax following radiography on day 17. The Foxhounds originally had akinetic free walls but contractile motion returned from day 7 through day 15. Biochemically and histologically they had less severe disease than dogs given 80 μ microspheres. CPK values obtained the day after infarction for several of these dogs were approximately 1000 U. Comparatively, CPK values taken on several dogs receiving 80 μ microspheres were approximately 10,000 U. Several Foxhounds were subsequently reinfarcted with 10 μ microspheres and CPK values attained comparable levels of around 10,000 U. All of the mixed breed dogs instrumented and infarcted with 80 μ microspheres died within 48 hours of infarction.
DISCUSSION

Heart Failure Induction

This portion of the study demonstrated that myocardial failure can be produced in the dog by incrementally injecting 80 μ microspheres into the left circumflex coronary artery. It showed that it is a readily reproducible model that is hemodynamically stable at the fifth day following the microsphere injections. In this initial study the mortality was 50%, but this figure improved throughout the study. This occurred because less invasive hemodynamic monitoring was utilized, a lesser end-point was used and technique improved as the study progressed.

It was important at the onset of this study to produce a model of myocardial failure. As stated earlier, a model of myocardial failure was a prerequisite, since congestive heart failure caused by surgically-induced valvular lesions creates disease that is either difficult to correct with vasodilator therapy (e.g., aortic stenosis) or is too variable (e.g., mitral insufficiency). Another prerequisite was a model of left-sided failure. Since the drug to be studied was a systemic arteriolar dilator, the most logical chamber to study would be the left ventricle. Hydralazine may have some activity on pulmonary resistance vessels, but resistance is difficult to evaluate in pulmonary vessels because of recruitment of other vessels when flow
increases. Therefore, another type of study would have to be designed
to study the effects of hydralazine on pulmonary vascular resistance.

The model that was devised has many advantages. No thoracotomy
was required for the induction of failure; therefore, the added stress
of major surgery was not added to that of infarction, so recovery was
rapid and mortality was lessened. In addition, the model was repro­
ducible. A finite endpoint was identified and achieved in each dog.
This resulted in a model that had very small deviations in left ven­
tricular outflow parameters. Stroke volume index \( \pm 2 \) standard devia­
tions five days after heart failure induction was 21.1 \( \pm 2.8 \) cc/beat
per \( m^2 \) and peripheral vascular resistance index \( \pm 2 \) standard deviations
was 2928 \( \pm 280 \) dynes sec cm\(^{-5} \) m\(^2 \). Both parameters provide evidence of
a very compact population. The inflow parameter was not as finite
(left ventricular filling pressure \( \pm 2 \) standard deviations = 20.4
\pm 16 mmHg), but this was due to one dog with a high value (34 mmHg)
greatly influencing a small population. The other four dogs had
filling pressures ranging only from 16 to 21 mmHg.

The model was also stable over the period of study. The hemo­
dynamic variables all returned to values not significantly different
from control when the drug effect dissipated. In addition, the model
took very little time to stabilize as opposed to models that involve
cardio-toxins (i.e., adriamycin, cobalt).

A possible disadvantage of the model is that it does not produce
global failure. It produces a regional infarct in which there is a
large mass of normal myocardium and a large mass of abnormal myocardium
side by side in series. This makes the model an excellent one of
ischemic cardiomyopathy. However, it makes it a poor model of con­
gestive cardiomyopathy. This is a major factor if one wants to study
a positive inotrope. There is too much normal myocardium to respond to the drug. In congestive cardiomyopathy there is a heterogeneous population of myocardial cells within the ventricle. Some have died and been replaced by fibrous connective tissue, while some are relatively normal and most are in varying stages of failure. The way in which each population of cells responds to a positive inotrope may be different. This model does not generate a population of cells in varying states of failure. However, if one is studying the effects of a drug on a ventricle but the drug does not directly affect the myocardium (i.e., a vasodilator, a diuretic), then it makes no difference as to the type of myocardial failure that is present. In a model of a failing ventricle, one needs a certain population of cells that are no longer functioning or one needs a larger population of cells that are functioning poorly or a combination of the two populations to have a ventricle that is failing. It makes no difference when giving a vasodilator what type of myocardial failure is present. There is still going to be an abnormal amount of tension placed on the remaining functioning cells. By definition, if there is failure present, the functioning cells cannot shorten adequately against the tension on them even with compensatory changes (i.e., increased sympathetic drive, increased preload). They cannot shorten far enough and fast enough to produce normal pump function. A vasodilator is going to improve function in any type of myocardial failure by decreasing myocardial wall stress and allowing further fiber shortening.

The major problem encountered in defining this model was identifying an endpoint where the dog would survive but still be in stable heart failure. Initially, microspheres were injected into the left
circumflex coronary artery until there was no longer contractile motion of the left ventricular free wall visible on the echocardiogram. This coincided with a left ventricular filling pressure of 20-24 mmHg. One of the three dogs infarcted in this manner survived. Therefore, it was decided to make the filling pressure the major criterion for the endpoint and to only take the filling pressure to 16-20 mmHg. This coincided with the left ventricular free wall having only about 10% of it contractile motion. When this endpoint was utilized, four out of seven dogs survived. Obviously, comparison of these two groups is not feasible because of the small numbers. However, the lesser endpoint does produce clinically detectable heart failure that is reproducible, stable and therefore satisfactory.

Hydralazine Study

This portion of the study demonstrated that dogs with myocardial failure respond to the administration of hydralazine similarly to man. Hydralazine produced a significant beneficial hemodynamic response that decreased peripheral vascular resistance and increased stroke volume.

Hydralazine produced an increase in stroke volume with no change in left ventricular filling pressure, which indicates enhanced left ventricular performance. It did not do this by increasing contractile force, since there was no change in the $\Delta P/\Delta t$. Therefore, if contractile force did not increase, stroke volume did increase and peripheral vascular resistance fell, the improved performance had to be due to a fall in afterload. Since hydralazine is a known arteriolar dilator, it can be assumed that a decrease in systemic resistance had to be part of the afterload reduction. Hydralazine could also have increased
compliance of the arterial bed and it could have reduced left ventricular size. However, the left ventricular internal diameter did not change significantly after hydralazine administration, so reduction in chamber size is ruled out. Compliance changes are difficult to monitor in the intact animal, so changes here cannot be ruled out. However, aortic compliance changes only produce small changes in left ventricular unloading, so it is impossible that this factor could completely explain the improved ventricular performance. Beneficial changes in inertiance also occurred because of the reduction in peripheral vascular resistance.

Reduction of mitral regurgitation is another factor that could explain the improved stroke volume. Mitral regurgitation could have been produced in this model. The posterior papillary muscle was involved in the infarction and must have functioned abnormally. Chamber dilatation could have contributed to the generation of mitral regurgitation also. However, the chamber dilatation was small, no murmurs were heard in any of the dogs and no evidence of giant "C-V" waves was found on the pulmonary capillary wedge pressure tracings. Therefore, the possibility of mitral regurgitation being a significant factor is small.

The improved cardiac performance was not explained by an increase in preload. In this study left ventricular filling pressure did not change after the administration of hydralazine. Hydralazine does not relax venous smooth muscle, so changes in venous capacitance would not be expected. The changes noted in this study were acute. Hydralazine is known to increase plasma renin levels; therefore, increases in sodium and water retention could increase preload in these patients over time.
In the present study each dog was initially given 25 mg of hydralazine and this dosage repeated every hour until an adequate decrease in total systemic resistance was identified. The initial dose given was approximately 1 mg/kg. This method of administration was safe. One dog died after hydralazine administration but not from hypotension. Since the dosage of hydralazine is so variable in man and since dogs are not classified into fast or slow acetylators, it is recommended that a similar protocol as the one adhered to in the study be used in clinical heart failure patients. Therefore, even though a dosage was established for this study, it is not recommended to give an average dose. The drug must be given so that it is tailored to meet the patient's needs. This means that the dosage must start at a low level and be gradually increased while hemodynamic effects are monitored.

Every dog cannot be monitored with a Swan-Ganz balloon-tipped thermodilution catheter in a practice situation. However, two relatively non-invasive and simple methods of monitoring the response to a vasodilator were identified in this study. Systemic blood pressure can be monitored non-invasively by a number of ways in the dog. The automated sphygmomanometric method used in this study has proven to be an accurate means of doing this. In this study mean arterial blood pressure consistently decreased during the time that hydralazine was decreasing peripheral vascular resistance. It decreased approximately 15-30 mmHg. Therefore, mean systemic blood pressure can be used to monitor the effectiveness of a given hydralazine dosage.

As evidenced by the regression analysis, venous oxygen tensions cannot be used to predict absolute values of cardiac index, as the confidence intervals are too large. However, the high correlation
between the two in individual dogs proves that the venous oxygen tension can be used effectively to follow trends. As such, the venous oxygen tension is a good means of documenting the beneficial or deleterious effects of drugs on cardiac output. Since it is the best indicator of the adequacy of peripheral tissue oxygenation, it is probably the best parameter to monitor during therapy to determine hemodynamic benefit. A major reason for selecting a patient for vasodilator therapy is inadequate peripheral flow, as evidenced by a low venous oxygen tension. Poor flow can be documented by a number of means (e.g., thermodilution cardiac output), but inadequacy of that flow can only be documented by measuring venous oxygen tension. Therefore, the major goal in a patient with low output heart failure should be to increase venous oxygen tension into the normal range.

The major question to be answered in the future is whether or not vasodilator therapy will increase longevity. Preliminary studies in man suggest that patients with myocardial failure do not live longer on vasodilators. Since afterload reduction reduces wall tension, a major determinant of myocardial oxygen consumption, it may also reduce the rate of myocardial decay in patients with myocardial failure secondary to volume overloading. This, along with the fact that arteriolar dilators reduce mitral regurgitation, may result in longer lifespans for mitral regurgitation patients with heart failure.

Hydralazine significantly increased heart rate in this study. It is known to increase heart rate in humans with hypertension. It has not been noted to increase heart rate in studies involving hydralazine usage in heart failure patients. It has generally been conjectured but never proven that the increased blood flow produced by hydralazine resulted in a decrease in sympathetic discharge and plasma
catecholamines, which offset the increased chronotropic effect of hydralazine. It generally has not been pointed out that the patients that were studied were on digitalis glycosides, potent negative chronotropic agents. In this study plasma catecholamines were not measured. However, digitalis was not administered and heart rate did increase. Digitalis may need to be continued to be given to patients on hydralazine to control heart rate increases. It is possible that if lower doses of hydralazine are utilized lesser heart rate changes will be noted. However, this is unlikely since heart rate did increase with the 25 mg dose in this population of dogs and since very small doses have produced positive chronotropic changes in earlier reports.  

This study also proved that the duration of hydralazine's arteriolar dilating effect lasts 11 to 13 hours in the dog with left-sided myocardial failure. Therefore, dosing every twelve hours is recommended. The biokinetics of the drug may change in dogs with right-sided congestive heart failure due to hepatic congestion and/or rises in mesenteric venous pressures. The biokinetics could also change after the first dose of hydralazine due to increased hepatic blood flow and more rapid hepatic metabolism. However, these changes would most likely affect the pharmacokinetics of the drug. Since it is known that the most important factor determining the duration of effect for this drug is the drug binding on the arteriolar smooth muscle, a lesser effect can be contemplated for those factors affecting serum half-life. On the other hand, these factors may definitely change the effective dosage of hydralazine, especially by affecting bioavailability.

Two dogs experienced recurrences of their ventricular arrhythmias after hydralazine administration. One of the dogs had only a mild
recurrence, while the other one died. This can be explained by hydralazine's effect on automaticity. It might be expected in a dog that has recent myocardial injury that an agent that can increase norepinephrine levels could provoke a recurrence of the arrhythmia. It could be argued that increasing blood flow to the myocardium with a vasodilator would be beneficial for ischemic induced arrhythmias. However, it is unlikely that blood flow would increase to an area supplied by an arteriole occluded by a microsphere. In fact, the opposite could occur—the so-called coronary steal syndrome. In the clinical patient with a ventricular arrhythmia not due to ischemia or infarction, it is difficult to judge the net effect that hydralazine could have on an arrhythmia. Therefore, it is recommended that hydralazine be given cautiously when ventricular arrhythmias are present.

One dog developed postural hypotension. None of the other dogs were placed in an upright position to test for the presence or absence of postural hypotension. It presumably occurred in this one dog because of reduced cerebral flow secondary to the decrease in systemic blood pressure. This complication is rarely seen in human patients. It would not appear to be a major complicating factor in treating canine heart failure patients, since only on rare occasions do dogs assume an upright stance.

This portion of the experiment was designed so that each dog served as his own control. The ideal experimental design would have included a control group given a placebo at the same times as the study group. However, the drug study encompassed a short period of time (13-16 hours) and all values returned to control at the endpoint, so the probability of the changes noted in this portion of the
experiment occurring due to spontaneous changes in the model during this time is very small.

Venous Oxygen Tension as a Predictor of Cardiac Index

All correlations were highly significant, but the confidence intervals for the data of all 5 dogs together were very large, showing that a finite value for cardiac index cannot be predicted from a venous oxygen value. One dog's sample (#453) was taken from the jugular vein, while the others' came from the pulmonary artery. Although it is unlikely, this dog's values could have altered the results. Dog #453's formula for the regression line and dog #445's formula were almost identical.

The regression lines for individual dogs were all highly significant. The mean correlation coefficient for the 5 dogs was 0.78. A diagnostic test should usually attain a correlation coefficient of 0.85 with some "gold standard" in order to be considered a reliable indicator. Venous oxygen tension approaches this value in this small number of dogs. However, it only does this when dogs are considered individually, so it should only be considered a marginally reliable indicator of trends in cardiac index changes.

However, if one looks at this from another viewpoint, any venous PO$_2$ changes are highly significant. Venous oxygen tensions should be considered the "gold standard" for adequacy of peripheral tissue oxygen delivery and it is the most important parameter to monitor in patients with peripheral tissue oxygen delivery derangement. Measuring cardiac index only confirms that the derangement is cardiac in origin. This confirmation can also be made by ruling out changes in hemoglobin concentration and hemoglobin saturation. This study, then, only confirms what is already known—peripheral tissue oxygen delivery is
directly dependent on cardiac index and compensatory mechanisms for
decreases in cardiac index do not exist.
LIST OF REFERENCES


