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Hemodynamics During Pregnancy: A Model for Cardiac Enlargement

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Cardiac output increases by 30-50% during mammalian pregnancy. This increase is reflected by elevation in both heart rate and stroke volume. The primary mechanism of increased stroke volume appears to be cardiac enlargement, rather than increased preload, afterload, or contractility. Animal studies have shown that enlargement of the heart occurs prior to an increase in uterine blood flow during pregnancy and this type of enlargement can be mimicked by sex steroid administration.

Systemic vascular resistance greatly decreases during pregnancy and with sex steroid administration. It has been postulated that systemic vascular resistance may be a signal for heart size changes. This study attempted to chronically decrease systemic vascular resistance by administration of an arterial vasodilator (hydralazine) over a three week period to guinea pigs. At the time of study hemodynamics were measured which included, heart rate, arterial pressure, right atrial pressure and cardiac output. In vitro left ventricular pressure volume relationships were also evaluated, as was total plasma volume.

Systemic vascular resistance after 21 days was slightly, though not statistically significantly, decreased (0.319 ± 0.071 vs. 0.360 ± 0.088 Wood Units, p = n.s.). This reflected a slight drop in mean arterial pressure (62 ± 8.6 vs. 64 ± 5.1 mm Hg, p = n.s.), as well as a slight increase in cardiac output (241 ± 34 vs. 230 ± 29 ml/min, p = n.s.). There was no detectable change in left ventricular chamber size as assessed by left ventricular pressure volume relationships.

The difficulties of chronic pharmacologic systemic vasodilation of the normal circulation are discussed with reference to the variety of compensatory mechanisms that are brought into play.

HEMODYNAMICS DURING PREGNANCY: A MODEL FOR CARDIAC ENLARGEMENT

by

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REVIEW OF THE LITERATURE

During pregnancy cardiac output increases by 30-50% in all mammals studied to date, including humans (1-6). The time course of this increase has been a topic of investigation in the past, but most authorities report peak values by the second trimester (1,2). The determinants of cardiac output, stroke volume and heart rate, both increase during pregnancy (1,2). However, mechanisms responsible for these changes have been inadequately explained. Recent studies from our laboratory in the Pygmy goat suggest that the heart rate increase may be both mediated autonomically as well as mediated through a change in intrinsic sinus node automaticity (4). The increase in stroke volume is also not agreed upon. The potential mechanisms by which stroke volume could be increased are preload, afterload, and contractility.

Many studies have shown a 40-50% increase in blood volume during pregnancy (2,7,8,9). This would seem to suggest that increased preload (sarcomere length at the end of diastole) may be important to increased cardiac output. However, infusion of whole blood or dextran in amounts sufficient to double left ventricular filling pressure have shown only small changes in left ventricular dimensions, stroke volume, and cardiac output (10,11). This evidence suggests that an increase in preload from increased blood volume contributes little to increased stroke volume during pregnancy. Moreover, studies in women (12) and pregnant guinea pigs (13) have failed to show increased filling pressures.

Left ventricular function has been assessed by noninvasive measurements of contractility such as systolic time intervals and echocardiographic ejection phase indices. Results from systolic time interval studies have not been consistent. In one study Rubler et al. reported that the isometric contraction period was shorter during the third trimester of pregnancy than postpartum and concluded that left ventricular contractility was greater during pregnancy (14). Burg et al. also measured systolic time intervals and reported a prolonged pre-ejection period and a shortened left ventricular ejection time, suggesting impaired left ventricular performance (15). A recent serial echocardiographic study has shown that left ventricular performance is not changed during pregnancy (16). In addition, data suggest that calculations by systolic time intervals are influenced by maternal position (15,16). However, since these methods are sensitive to changes in preload and afterload, conclusions about ventricular function during pregnancy need qualification (17).

Changes in afterload are also difficult to evaluate. Afterload is probably best approximated by wall stress of the ventricle. The parameters of left ventricular wall stress are left ventricular chamber size and wall thickness (La Place), and systemic vascular resistance (18). Other factors also include rate of ventricular emptying and aortic impedance (18). During pregnancy the left ventricular chamber size to wall thickness ratio increases which would tend to increase afterload. However, systemic vascular resistance and aortic impedance are reduced as is left ventricular ejection time (16), factors all tending to reduce afterload.

A fourth determinant of stroke volume, ventricular enlargement, was shown as early as 1825 to occur in pregnancy (19). With a larger heart, none of the traditional determinants of stroke volume need play a role. Experiments of near term guinea pig pregnancy have shown that the left ventricle is remodeled so that its volume is larger at any given filling pressure (13). Enlargement of the heart would have the advantage of increasing stroke volume without changing filling pressure and would not change the short term operating mechanisms for stroke volume so that preload, contractility, and afterload could still change in accordance to cardiovascular demands.

Morphologic changes of the heart are not unique to pregnancy. Increased heart size and mass are observed in response to vigorous physical activity. In an echocardiographic study of 56 trained athletes, Morganroth et al. compared left ventricular end diastolic pressure (LVEDP) to wall thickness ratios in both isotonic and isometric exercise groups to control groups (20). Morganroth and his colleagues also calculated heart mass. Results showed that the isotonic exercise group increased LVEDP and heart mass but not wall thickness compared to controls. Athletes involved in isometric exercise increased wall thickness and mass but left ventricular end diastolic volume (LVEDV) did not change significantly. In a study of chronic volume overload caused by arteriovenous (A-V) fistula on dogs, Ross showed a thicker, more massive heart developed although contractility did not change. When the fistula was removed, hearts returned to normal states (21). The implications of these results are two fold. The heart responds chronically to increased cardiovascular

demands by morphologic changes. Also the morphologic changes are demand specific.

The mechanisms for cardiac enlargement during pregnancy have not been adequately explained. One of the first hypotheses for enlargement during pregnancy was presented by Burwell in 1938 (22). He proposed that the placenta acts as an A-V fistula. Blood flow through the placenta is parallel to maternal circulation; thus, blood pressure is lowered and other circulatory changes may be a result of this. Some hemodynamic changes seen in pregnancy, such as increased heart rate and cardiac output, and decreased A-V oxygen difference, are also characteristics of an A-V fistula. Although this concept was widely accepted for many years, there are problems with this interpretation. The cardiac enlargement produced by experimental A-V fistula is dissimilar to that seen in pregnancy as filling pressures are markedly elevated (21,23). Furthermore, Hart et al. have shown that blood volume, cardiac output, stroke volume and heart size are all increased during the first trimester of guinea pig pregnancy, well before a change in uterine blood flow takes place (13). The increase in left ventricular chamber size was associated with an increase in the ratio of left ventricular chamber radius to wall thickness, a morphologic change previously described as being associated with pregnancy (16). Table I compares the cardiac enlargement associated with pregnancy to other known conditions associated with cardiac enlargement. As can be seen, the cardiac enlargement associated with pregnancy appears to be a unique physiologic adaptation.

TABLE I. TABLE OF CHANGES

	Stroke-Vol.	LVEDP	LVED Diam.	LV Wall Thickness	Radius-Wall Thickness
Pregnancy	↑	---	↑	---	↑
Expt. AV Fistula	↑	↑	↑	?	?
Isotonic Training	↑	---	↑	↑	---
Isometric Training	---	---	---	↑↑	↓↓

Hormones have long been known to be powerful mediators of control mechanisms. Estrogen and progesterone levels are elevated in pregnancy. The corpus luteum and the placenta both contribute to this increase. In 1955, Brehm suggested that cardiac output may be regulated by peripheral resistance and that maternal hormones were a fundamental cause of cardiac variation. Exogenous estrogen administration was studied by Parer and Ueland in ewes (24). They showed that cardiac output and heart rate were elevated and mean arterial pressure and peripheral resistance decreased. These changes were similar to those seen in pregnant ewes (25). Other studies of women taking oral contraceptives have also demonstrated increased cardiac output, stroke volume, blood volume and blood pressure (26,27). In one study, progesterone and estrogen were administered separately (28). Cardiovascular changes similar to those in pregnancy were seen only in those patients given estrogen. Studies in our laboratory on guinea pigs chronically receiving progesterone and/or estrogen confirm these observations. Estrogen treated animals had

significant increases in cardiac output, stroke volume, blood volume and left ventricular chamber size compared to controls, essentially mimicking the hemodynamic changes seen in pregnancy. Several studies of hormone receptors have shown that the heart and major arteries have estrogen and androgen receptors, suggesting that the central cardiovascular system may be a target organ for these hormones (29,30,31,32).

A fall in systemic vascular resistance appears to be common to most, if not all, instances where cardiac enlargement occurs (pregnancy, estrogen administration, A-V fistula). To test the hypothesis that systemic vascular resistance has a primary role in determining left ventricular chamber size, hydralazine (an arterial dilator) was administered chronically to guinea pigs.

METHODS

Choice of Experimental Animal

Male guinea pigs were chosen as the experimental model for this study. Substantial literature exists using guinea pigs as models for cardiovascular physiologic investigation (3,13,33,34,35,36,37). Males were used to avoid any estrus related hormone variability. The guinea pig is relatively small and easy to handle, but large enough for thorough hemodynamic investigation. In addition, the Heart Research Laboratory has had extensive experience with this animal (13,38,39). The above reasons made the guinea pig an attractive model for the study of maternal cardiovascular physiology.

Choice of Pharmacologic Drug

Hydralazine was chosen as the drug to reduce vascular resistance primarily because of its mechanism of action: relaxation of arterial smooth muscle, particularly at the arterioles (40). It has no direct effects on the autonomic nervous system (40) nor any known direct effects on the cardiac muscle. Chronic administration of hydralazine has been used in rodents with the appropriate fall in systemic vascular resistance (41). Finally, the extensive use of hydralazine in treatment of hypertension and congestive heart failure clinically adds interest to experimental results (42,43).

Determination of Drug Dose

Dose testing was performed using two separate protocols. The first group was dosed subcutaneously by implantation of hydralazine

tablets (hydralazine with cholesterol, lactose, and methylcellulose). These animals were first anesthetized with ketamine/xylazine (see Instrumentation). An incision in the neck was made and the carotid artery was isolated and cannulated with a polyvinyl catheter (see Instrumentation). The catheter was tunneled to the ventral part of the neck, filled with heparin (500 units/ml) and capped. This catheter allowed blood pressure, and heart rate measurements to be made. Baseline weights, blood pressure, and heart rates were taken and compared with post-implantation measurements every other day. Measurements were continued until blood pressures returned to baseline.

The second protocol differed only in the form of hydralazine administration. These animals were dosed orally via their drinking water. Powdered hydralazine hydrochloride (apresoline: 1-hydrazinophthalazine) was used. Anesthesia, surgery, dose levels and daily measurements were conducted exactly as in Protocol 1.

Both protocols reduced arterial blood pressure by about the same amount and for the same duration (see Results). The oral dosing method was chosen for this study for two main reasons: it was less traumatic for the animals, and it was much more convenient to administer.

Animal Preparation

Thirty male guinea pigs between the weights of 700 and 1000 grams were matched according to weight and strain (Duncan-Hartley or Topeka) and placed into two groups: treated and control. The animals were purchased from and housed in the Oregon Health Sciences

University Department of Animal Care. The housing included continuous access to food and water, a 12-hour light cycle, and a constant room temperature of 21 degrees centigrade. The treated group was given hydralazine in their drinking water daily for three weeks. The beginning dose was 5 mg/kg/day. At the beginning of weeks 2 and 3 the dose was increased by an additional 5 mg/kg/day. During the three weeks, animal water consumption was randomly measured to verify that dosing was consistent (evaporation was accounted for). At the end of three weeks animals were instrumented and studied.

Instrumentation

On the appropriate day, animals were given an intramuscular injection of ketamine (25 mg/kg) and xylazine (0.15 mg/kg) to provide a surgical level of anesthesia (44). Ketamine acts as a dissociative anesthetic and xylazine as a non-narcotic sedative and muscle relaxant. The combination of these two drugs is often used to provide anesthesia during invasive instrumentation. Cardiovascular effects of this combination have been investigated in the guinea pig (44). Adequate anesthesia is provided for approximately 90 minutes and by 3 hours post injection hemodynamics have returned to baseline. This time period provides ample time to instrument the animals and allow them to recover so that the studies can be performed in one day without altering hemodynamic measurements. Surgery was performed under clean but not sterile conditions. A transverse ventral incision was made in the neck. The jugular vein and carotid artery were isolated and cleaned of fat and connective tissue. A thermodilution probe (Edwards Lab 1.5F) was inserted into the carotid artery and

advanced retrograde 4 cm into the ascending aorta. A second incision was made in the right groin and the superficial saphenous artery was isolated. A polyvinyl catheter (0.9 mm O.D., 0.5 mm I.D.) was inserted and advanced 6 cm retrograde into the abdominal aorta. Placement of catheters was verified by pressure monitoring. Catheters were then tunneled subcutaneously to the dorsal part of the neck, filled with heparin solution (150 units/ml), capped and secured until the time of study. Animals were placed in a large recovery cage and allowed free access to food and water.

Study

Animals were allowed to recover for 6 to 7 hours post anesthesia injection. At this time animals were placed in a study cage which permitted little movement. The animals were left in the darkened, quiet room for a 30-minute acclimation period.

Resting values for systolic, diastolic, and mean blood pressures, as well as respiratory and heart rates were measured simultaneously using Statham P-23 Gb pressure transducers zeroed to mid-chest and displayed on a Gilson 5/6 stripchart recorder. A typical pressure recording is shown in Figure 1.

Cardiac output was determined using the thermodilution method. Thermodilution cardiac outputs were performed as follows: 0.4 milliliters of room temperature saline were injected as a bolus into the right atrial catheter. Temperature change was registered by the thermistor probe, and cardiac output was calculated with a dedicated thermodilution cardiac output computer (Edwards Laboratories Model 9520A) using the formula:

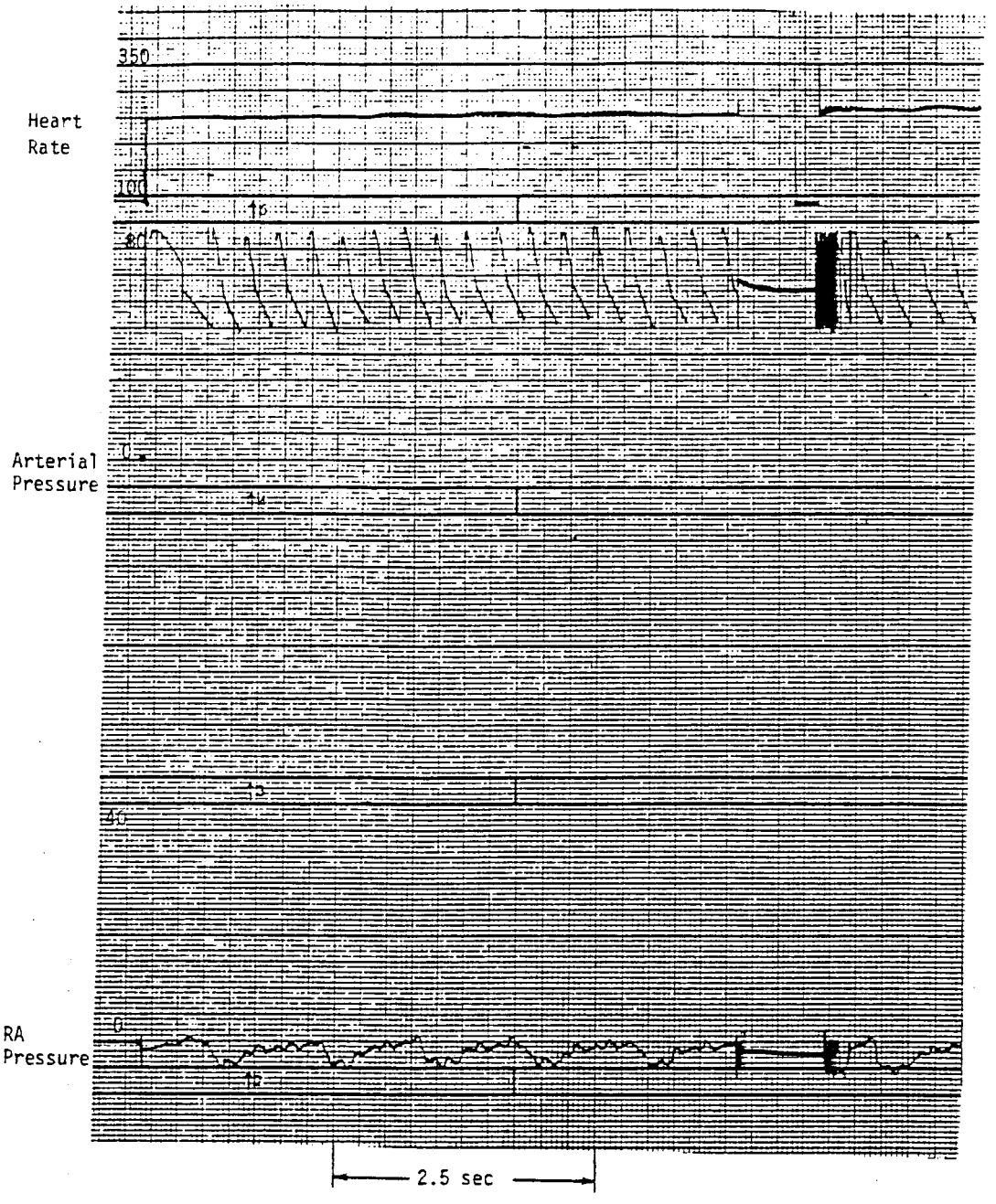

Heart Rate
350
100
80
Arterial Pressure
0
40
RA Pressure
0
2.5 sec

FIGURE 1

$$CO = \{\rho Co\ (injectate)\ \ (60)\ \ Ct\ VI\ \ (Tb-TI)\}\ /$$

$$\{\rho Co\ (blood)\ \ \int_0^{\tau}\ Tb\ (t)\ dt + c\}$$

where CO = cardiac output, ρCo = density x specific heat of the injectate or blood, VI = injectate volume, Ct = dead space correction factor, Tb = blood temperature, TI = injectate temperature, τ = 30% of peak value of descending limb of thermodilution curve, $\int_0^{\tau} Tb\ (t)\ dt$ = area under the thermodilution curve to τ , and c = remaining area under the thermodilution curve (45). Based upon the volume of the injectate, the dead space and calculated heat loss using the right atrial catheter, a computation constant (1.08 Ct (60) VI) of 0.20 was utilized. A typical thermodilution curve is shown in Figure 2. Validation of this method of cardiac output determination in guinea pigs has been performed in our laboratory by comparing thermodilution cardiac output to aortic flow as measured by calibrated electromagnetic flow probe. The results are shown in Figure 3. The correlation between aortic flow and thermodilution was 0.88 ($p < 0.05$).

The hematocrit was also determined using packed cell volumes of samples centrifuged for 5 minutes in standard capillary tubes. Blood volume was determined by dye dilution (34). Briefly, 0.40 ml of an Evans blue dye (T-1824) standard solution was infused into the right atrial catheter, followed by 2 ml of saline to ensure complete delivery. After 5 minutes, a 4 ml sample of blood was removed from the arterial catheter. The sample was centrifuged and the plasma

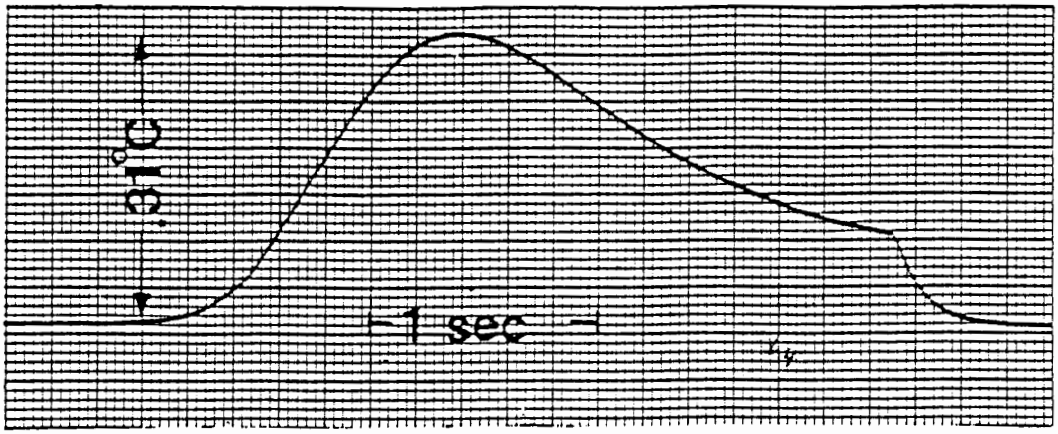


FIGURE 2

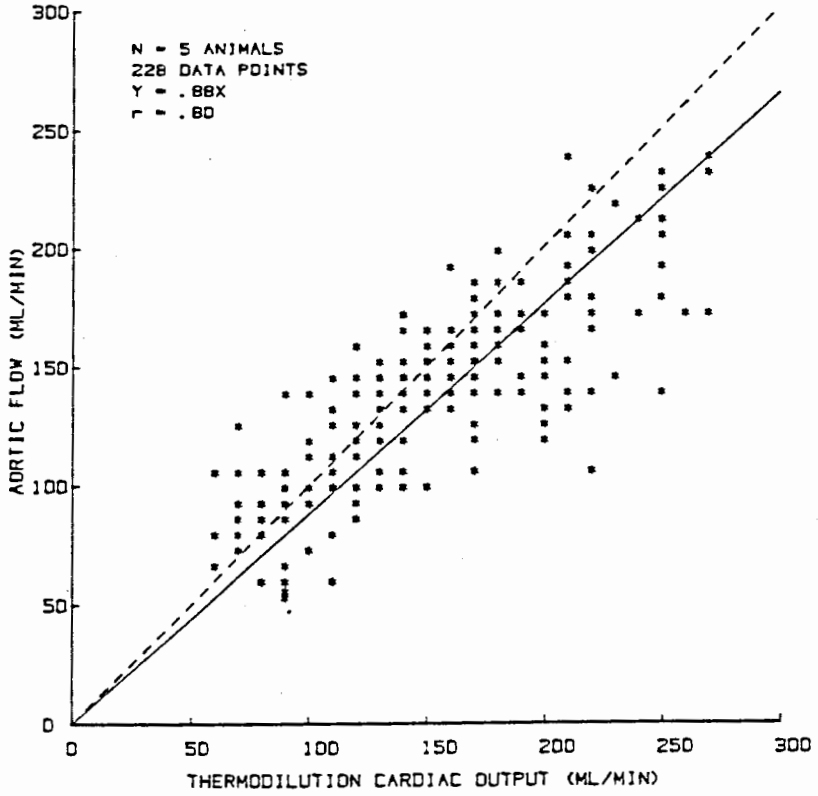
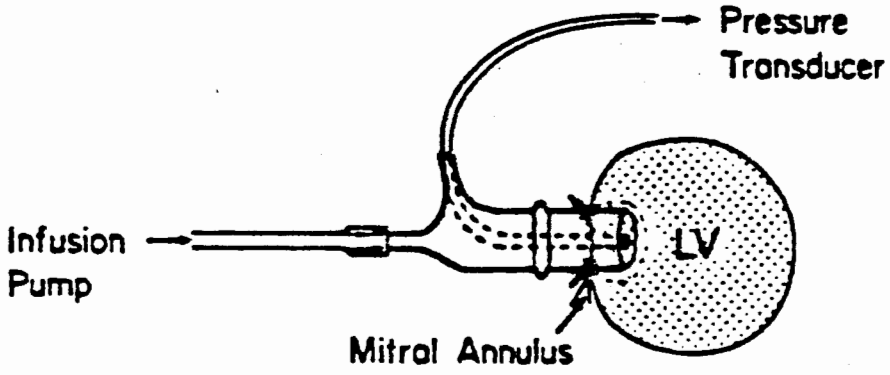


FIGURE 3

removed. Dye concentration was measured with a spectrophotometer (Coleman Junior II model 6/20) at a wavelength of 620 nm. The spectrophotometer was zeroed with a blank plasma reference (taken before dye infusion) from the same animal. Plasma volume was calculated from a known standard curve.

Following in vivo studies, in vitro left ventricular pressure-volume data were generated as follows. Animals were anesthetized with 20 mg Bio-tal® and then lethally injected with 1 ml of saturated potassium chloride intravenously which resulted in diastolic cardiac arrest. The chest was then opened and the heart was removed. The right ventricle and atrium were dissected away. A small incision was made in the left atrial appendage and a double lumen grooved plug was inserted to the level of the mitral annulus (Figure 4). A silk suture was tied tightly around the atrial ventricular groove. With the left ventricle isolated and secured the plug was connected to a 10 ml syringe on a Harvard infusion/withdrawal pump and to a Statham p23 Gb pressure transducer zeroed at mid-ventricular level. The system was

Figure 4. Apparatus used to isolate left ventricle during pressure-volume measurements.



filled with saline and all air bubbles flushed out. The left ventricle with plug inserted was suspended in a saline-filled dish. Intraventricular pressure was measured continuously from zero pressure and volume during constant infusion for 5 to 10 seconds at a calibrated rate. The pressure was allowed to reach only 30 mm Hg to avoid stretching. A typical pressure-volume curve is shown in Figure 5. After three successful curves had been recorded, the left ventricle was removed from the plug, cut open, blotted and weighed.

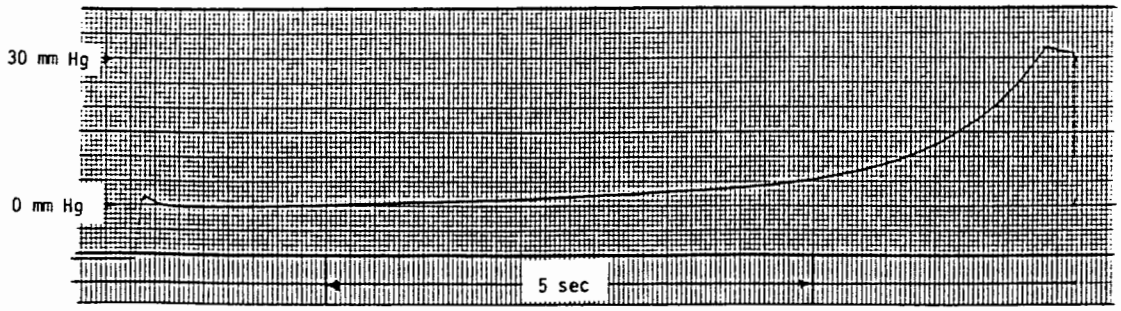


FIGURE 5

Utilizing the calibrated infusion rate, pressure time recordings were converted to pressure-volume values. Values were taken at 0.05 ml increments and from 2 to 24 mm Hg, and were compared between groups. All pressure-volume studies were completed within 15 minutes of KCl injection. We have noted rigor (a leftward shift in the pressure-volume curve) in the guinea pig in no less than 40 minutes.

Statistics

Student's t test for non-paired data was used for this investigation. Significance was considered present if $p < 0.05$.

RESULTS

Dose Determination Study

Figure 6 shows arterial pressures over time for the animals dosed subcutaneously and orally with hydralazine. Arterial pressures initially were 15% below control and returned to control values by day 14.

Chronic Dosing Study

Fifteen animals were randomized to each study group. Table II shows body and left ventricular weights, total plasma volume, and hematocrits. All animals gained weight during the study as would be expected of healthy, growing animals. Study groups were well matched as seen by similar mean body weights.

TABLE II

	Control	Treated
Weight (kg)	0.899 ± 0.805	0.903 ± 0.806
LV weight (g)	1.355 ± 0.166	1.328 ± 0.153
Plasma volume (ml)	40.7 ± 5.0	43.4 ± 5.5
Hematocrit	39.5 ± 2.9	39.4 ± 2.8

Values are mean ± S.D.; n = 15

Table III displays the hemodynamic data for both groups. Systolic and diastolic pressures were slightly lower in the treated animals but the differences were not significant. Right atrial pressure was not different between groups.

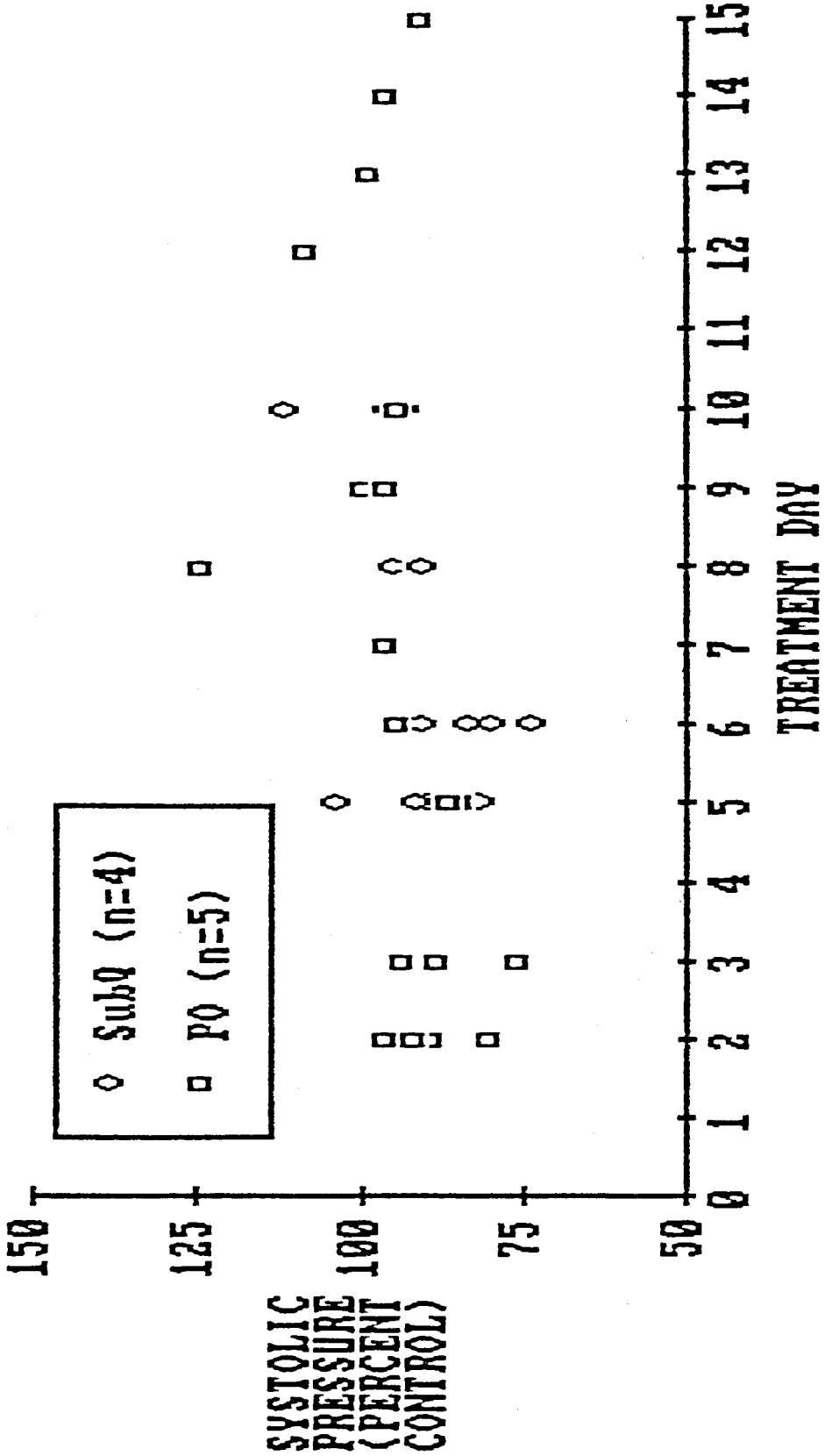

PRELIMINARY DOSING STUDIES
SubQ (n=4)
PO (n=5)
SYSTOLIC PRESSURE (PERCENT CONTROL)
150
125
100
75
50
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
TREATMENT DAY

FIGURE 6

TABLE III

	Control	Treated
Heart rate (beats/min)	246 ± 33	249 ± 27
Systolic pressure (mm Hg)	83 ± 8	79 ± 10
Diastolic pressure (mm Hg)	51 ± 4	51 ± 7
Mean pressure (mm Hg)	64 ± 5	62 ± 9
Right atrial pressure (mm Hg)	0.05 ± 0.70	0.93 ± 1.40
Cardiac index (ml/min/kg)	230 ± 28	241 ± 35
Stroke volume index (ml/kg)	0.93 ± 0.13	0.97 ± 0.15
Systemic vascular resistance	0.360 ± 0.088	0.319 ± 0.071
LV volume at various pressures:		
2 mm Hg	0.513 ± 0.131	0.559 ± 0.127
4 mm Hg	0.769 ± 0.138	0.796 ± 0.105
6 mm Hg	0.915 ± 0.141	0.930 ± 0.093
8 mm Hg	0.998 ± 0.147	1.019 ± 0.095
10 mm Hg	1.058 ± 0.149	1.075 ± 0.099
12 mm Hg	1.020 ± 0.301	1.121 ± 0.105
14 mm Hg	1.142 ± 0.156	1.157 ± 0.108

Values are mean ± S.D.; n = 15

Cardiac output was normalized to body weight so that different sized animals could be more accurately compared. Cardiac "index" (cardiac output/body weight) was slightly higher in the treated group and systemic vascular resistance lower, but the differences were not significant. Stroke volumes were the same for both groups.

Plasma volume was slightly elevated in the treated group but not statistically different. Hematocrit was the same for both groups.

Left ventricular weights were the same for both groups. Left ventricular size at any given pressure was slightly larger for the treated group (Figure 7), but again, not significant.

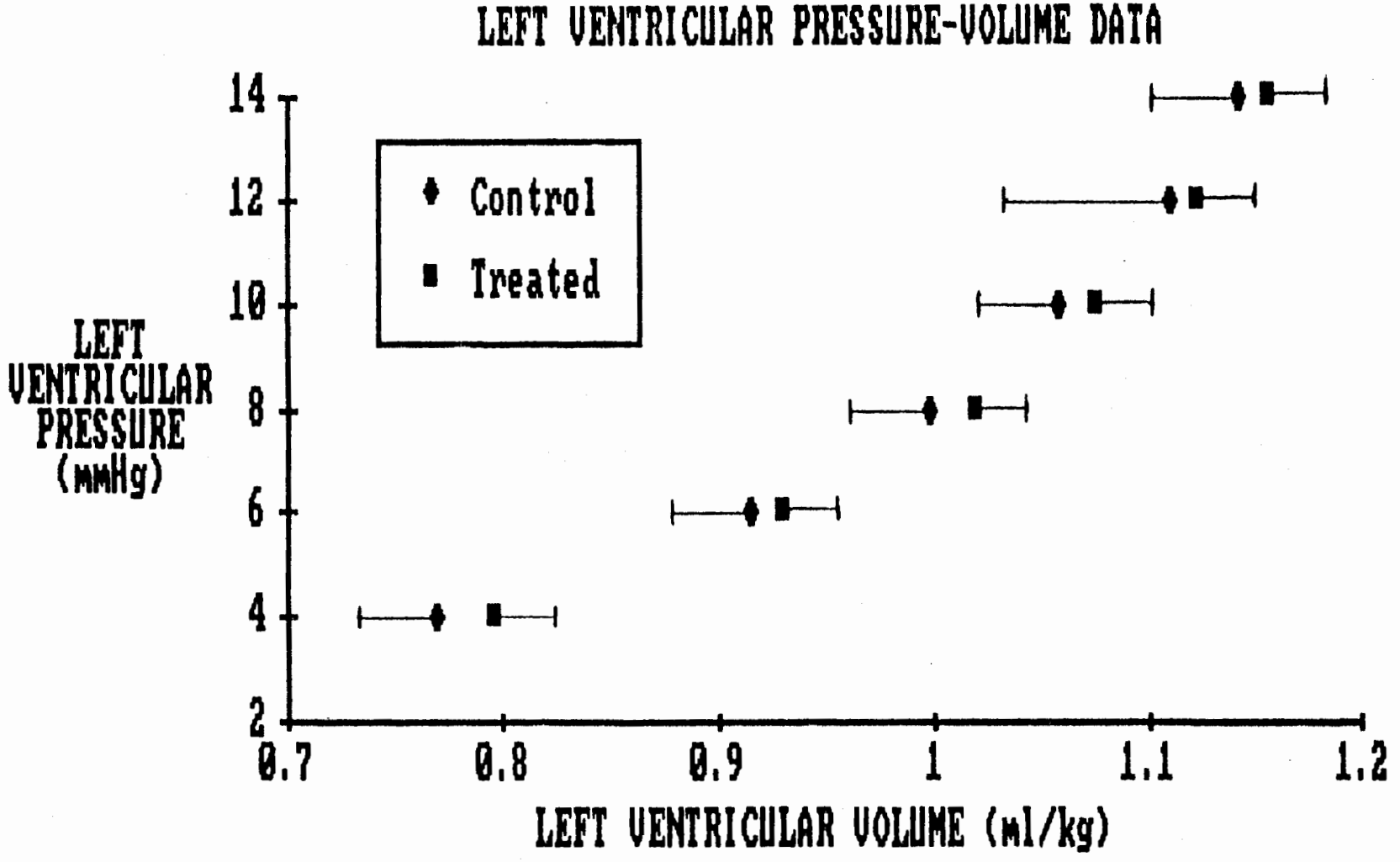


FIGURE 7

(Values are mean ± S.E.; n = 15)

DISCUSSION

This study demonstrates the difficulties associated in attempting to change hemodynamic homeostasis chronically. Despite large doses of hydralazine given orally, systemic vascular resistance was only mildly affected at three weeks. Along with the small decrease in systemic vascular resistance, a small decrease in blood pressure was observed, as well as a slight rise in cardiac index and stroke volume index. Also, left ventricular chamber size tended to be larger at any given filling pressure for the hydralazine treated animals. Although no changes listed above were statistically significant, the direction of the changes is similar to that seen in pregnancy or sex steroid administration (12,13).

Hydralazine was administered orally. The decision to use hydralazine was based on several criteria: 1) hydralazine is easy to administer when dissolved in water; 2) hydralazine is easily absorbed; 3) hydralazine has a bioavailability of 30-50% which can be increased if given simultaneously with solid food; 4) the area of action appears to be only on smooth muscle with no direct cardiac effects or effects on regulatory systems (40). Other potential vasodilators include captopril, prazosin, phentolamine, and nitroprusside. These drugs were not used because of their potential effects on cardiac muscle directly, on complex interaction with renal function, and/or the autonomic nervous system. Additionally, side effects associated with these drugs may have complicated the investigation.

Subacute hemodynamic measurements were used for this study rather than chronic measurements. This helped to insure that animals were free from infection at the time of study and also insured a high percentage of catheter patency. Furthermore, this laboratory has demonstrated that subacute hemodynamics following ketamine/xylazine anesthesia accurately reflects chronic hemodynamics in the guinea pig (44).

In vitro passive pressure volume curves were used to evaluate left ventricular chamber size. It has been recognized that the in vitro pressure-volume relationship is only one of several factors that determines pressure-volume relations in vivo (46). Other factors include restraint caused by simultaneous right ventricular pressure (47), the percardium (46), and coronary artery pressure (48). Despite these additional influences, the left ventricular pressure-volume relationship is a primary determinant of left ventricular chamber size in vivo.

The thermodilution method of determining cardiac output was utilized in this study. We felt justified in using this method as it has been validated directly in our laboratory by simultaneous comparison with aortic flow in the guinea pig. Other potential options for determining cardiac output in small animals include the Fick method and the microsphere indicator dilution technique. The Fick method would require pulmonary artery catheterization and the additional restraint of the animal in a sealed chamber while attempting to measure resting hemodynamics. The use of microspheres requires handling of radioactive isotopes which are costly and require

special disposal. In addition, multiple cardiac output determinations within a single animal require multiple labels. Thermodilution allows for repeated measurements in a single animal easily and reproducibly.

Hydralazine was used to increase the diameter of the resistance vessels (49,50,51). A larger vessel provides less resistance and permits more flow:

$$Q = \frac{\Delta P \pi R^4}{8 \eta \ell}$$

where ΔP = the change in pressure along a vessel, R = the radius of the vessel, η = the viscosity of the fluid, and ℓ = the length of the vessel. Systemic vascular resistance is calculated using a hemodynamic adaptation of Ohm's law from the formula: R = map-rap/CO, where map is mean arterial pressure, rap is right atrial pressure, and CO is cardiac output. Units are in Pru's (peripheral resistance units) or Wood units. A change in systemic vascular resistance would be indirectly shown by an increase in cardiac output and/or a decrease in mean arterial pressure. During preliminary dosing studies it was possible to monitor blood pressure for up to two weeks. The fact that blood pressure was generally decreased indicated that systemic vascular resistance was probably being decreased also (there was no reason to expect that cardiac output would have decreased).

The difficulties of maintaining a decreased systemic vascular resistance for three weeks may have been a result of hemodynamic compensation. The effects of vasodilation, in particular decreased blood pressure, can be countered by many physiologic mechanisms. The two major categories of blood pressure control mechanisms are short and long term regulation.

One of the primary short-term blood pressure control mechanisms is the baroceptors. Baroreceptor (pressor) reflexes, which sense a drop in pressure, decrease inhibitory impulses to the vasoconstriction center and stop excitation of the vagal center. Chemoreceptors responding to increased carbon dioxide molecules and hydrogen ions, and to decreased oxygen availability (due to decreased flow) excite nerve fibers leading to the vasomotor center. The final response is the same as that of the baroreceptors. Diminished blood flow due to acute vasodilation may also cause an ischemia in the brain eliciting a direct excitation of the vasomotor center. This causes a strong sympathetic response resulting in systemic vasoconstriction. Although this ischemia mechanism is usually augmented only in severe pressure loss situations, it is very powerful.

In addition to rapidly acting nervous mechanisms for blood pressure control, there are several hormonal mechanisms that also provide acute or subacute compensation. Sympathetic stimulation resulting from the above mechanisms causes release of epinephrine and norepinephrine from the adrenal medulla into the circulation. The increased adenergic activity stimulates beta receptors to increase heart rate and contractility. Alpha receptors are stimulated to produce vasoconstriction in the arteries and veins.

Reduced arterial pressure stimulates the release of renin by the juxtaglomerular cells of the kidneys, thus producing angiotensin I and II. Angiotensin II is a powerful vasoconstrictor and acts acutely on the arterioles and venuoles. In addition to the nervous and hormonal mechanisms, two other physical mechanisms of the circulation help to

directly alter blood pressure. These mechanisms are the capillary fluid shift and the vascular stress relaxation mechanisms.

Many of these mechanisms may have contributed to compensation against the effects of hydralazine in this study. Short term mechanisms in general, however, lose their ability to control blood pressure after a few hours to a few days. This is because the nervous pressure receptors lose their responsiveness and adapt. During the dose study the treated animals had lower blood pressures for up to two weeks. This would seem to indicate that the hydralazine given was effective enough to decrease blood pressure in spite of short term compensatory mechanisms.

A drop in arterial pressure greatly decreases the rate at which the kidneys excrete water and salt. This is the result of the renal-body fluid mechanism. This long term mechanism is complex and not completely understood. Briefly, it controls blood pressure primarily via blood volume. A decrease in pressure causes the kidneys to decrease the output of water and salt. In addition to this pressure (diuresis and natriuresis), the low pressure causes increased secretion of renin by the kidneys, increased aldosterone secretion by the adrenal cortices, and increased sympathetic signals to the kidneys. All these in turn decrease the renal output of water and salt by various submechanisms.

In this study plasma volume was only increased by 2 ml and was not statistically significant in the treated animals. However, it has been shown that a two percent increase in blood volume can increase the mean circulatory filling pressure by five percent (52). An

increase in cardiac output of five percent can increase systemic vascular resistance 25-50%. These figures suggest that a two percent increase in blood volume may increase arterial pressure 30-57%. A small increase in blood volume may therefore have been enough to cause blood pressure to stay near normal in the hydralazine treated animals.

Of the many mechanisms that work to regulate blood pressure directly and systemic vascular resistance indirectly, only one was the focus of this study: that of local vasomotion. It is possible that compensatory mechanisms such as the renal fluid-body and renin-angiotensin mechanisms were engaged to such a degree that treated animal hemodynamics remained in normal ranges. One way to further address this problem would be to manipulate more than one hemodynamic control mechanism at a time. For example, a future study could vasodilate locally as in this study and at the same time inhibit angiotensin with a drug such as captopril. Then a portion of both the long and short term control systems would be affected.

This study was unable to provide conclusive evidence that systemic vascular resistance is a signal for heart size. The primary difficulties experienced seemed to stem from an inability to maintain a decreased systemic vascular resistance. The hypothesized results appeared in the form of trends all in the expected directions (increased cardiac output, left ventricular chamber size, and stroke volume), but were not statistically significant. In order to study the effects of systemic vascular resistance on heart size, future studies may have to direct efforts of controlling more than one hemodynamic control mechanism. This could be accomplished with multiple drugs administered simultaneously.

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