PERIPHERAL VASCULAR MANIFESTATIONS OF MYOCARDIAL ISCHEMIA IN THE ANESTHETIZED DOG

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ABSTRACT

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By

David Edward Dobbins

Collateral-free, innervated, naturally perfused canine forelimbs were used to study the peripheral vascular manifestations of myocardial infarction. An attempt was made to gain insight into changes in blood volume and forelimb blood flow, which affect cardiac function and organ function respectively. From this knowledge, conclusions can be made as to whether hemodynamic changes in the periphery contribute significantly to death during cardiogenic shock. One week after implanting a catheter into a branch of the left circumflex coronary artery, 0.2 ml. of metallic mercury was injected into this vessel to produce a selective embolization of the left ventricle. In a second group of animals, a large side branch of the left circumflex artery was ligated upon catheter implantation. This insured the presence of previous necrotic heart damage at the time of embolization. All hemodynamic parameters were followed for a period of four hours. Embolization of the left ventricle, even in animals with previous necrotic heart damage, produced only small changes in all parameters studied.

The parameters measured included mean aortic pressure, forelimb weight, forelimb skin and skeletal muscle blood flows, vascular pressures in large and small precapillary and postcapillary vessels and total and segmental (large artery, small vessel, large vein) vascular resistances. These changes were not greatly different from those seen in non-embolized control animals. However, Lead II electrocardiographic recordings showed elevation of the S-T segment immediately following embolization, indicating the presence of severe myocardial ischemia. At autopsy, mercury was found widely distributed throughout the posterior-lateral wall of the left ventricle and, in the second group of animals, anterior infarction was present as well. These data indicate that selective embolization of the left ventricle with mercury does not produce cardiogenic shock in the anesthetized dog. Furthermore, these data clearly indicate that severe left ventricular heart damage need not result in marked changes in mean aortic pressure or forelimb skin and skeletal muscle blood flows, vascular pressures or segmental vascular resistances.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

Myocardial infarction has emerged as one of the leading causes of death in this country. One of the grave consequences of myocardial infarction is the development of cardiogenic shock. While this syndrome may be exhibited in only 15% of the patients suffering a myocardial infarction, it has a mortality rate of 75-80%.

One reason for the high mortality rate attendant with this circulatory derangement, is the lack of definitive pathophysiological data on this syndrome upon which effective treatment could be based. This is especially true with respect to the peripheral vasculature. A study was therefore initiated to determine some of the peripheral vascular effects of myocardial infarction as complicated by cardiogenic shock. It is important to know if peripheral vascular factors contribute significantly to death from this shock state. Measurements of forelimb blood flows, pressures, vascular resistances and weight were made in order to infer changes in blood volume and tissue blood flow. Changes in blood volume, via transvascular fluid fluxes and/or intravascular pooling, affect cardiac function

by affecting venous return and consequently cardiac filling and stroke volume. Changes in blood flow have a direct affect on organ function.

Due to the difficulty of obtaining definitive serial data in a clinical setting, many attempts have been made to produce an animal model which closely resembles the syndrome of cardiogenic shock as seen in man. In this study, we employed a modification of such a model, the mercury embolization technique developed by Lluch and his coworkers. In the unanesthetized dog, this technique results in a transmural infarct in the posterior-lateral wall of the left ventricle and a shock-like state resembling that as seen in man (53).

The forelimb was chosen as the test organ in this study for several reasons, First, it consists mainly of skin and skeletal muscle. Since these two tissues comprise the bulk of the soft tissue body mass, derangements in these two vascular beds could bear importantly on the response of the body as a whole. Secondly, the preparation used produces sufficent separation between skin and muscle to allow analysis of changes in these two parallel vascular beds. Finally, through the use of a gravimetric technique, the preparation allows the study of transvascular fluid fluxes which are not well understood in cardiogenic shock.

LITERATURE REVIEW

CARDIAC PHYSIOLOGY

The heart is a unique organ in that its flow to metabolism ratio is so low. While the heart accounts for approximately 12% of the total body oxygen consumption, it receives only 5% of the cardiac output. Relative to its oxygen consumption, this makes the heart the most underperfused organ in the body. Because of the heart's high oxygen consumption in relation to its low oxygen delivery, the heart has a low tissue fluid oxygen tension (77,78). A small fall in the tissue fluid oxygen tension therefore results in prompt dilation of the coronary vascular bed. The mechanism of this dilation of the coronary bed is uncertain. Some investigators believe the low oxygen tension itself causes the dilation (16,66) while others believe that the oxygen decrease results in the buildup of vasodilator metabolites (6,7,36,38). Amoung the metabolites suggested as causing this dilation are Mg^+, K^+, H^+ and adenosine and the adenine nucleotides. Concomitant with the coronary vasodilation in response to a decrease in the tissue fluid oxygen tension in the heart, is a decrease in the contractile strength of the heart. This tends to readjust coronary blood flow to

the metabolic rate of the heart. This readjustment of the flow to metabolism ratio tends to restore the tissue fluid oxygen tension in the heart. The regulation of tissue fluid oxygen tension is important in both the normal regulation of coronary blood flow and in various pathological states which alter coronary flow such as atherosclerosis and thrombis.

A fall in tissue fluid oxygen tension can result either from an increase in oxygen consumption via increases in heart rate, strength of contraction, decreased coronary efficency etc. or by a decrease in oxygen delivery via a decrease in coronary flow, arterial oxygen tension or carrying capacity of the blood.

It is clear however, that oxygen is not the sole local determinant of myocardial strength. It has been shown that an increase in coronary flow rate, even with anoxic blood, improves myocardial contractile force over that seen during perfusion with anoxic blood at a low flow rate (17).

The coronary circulation is atypical in that not all of the blood follows the classical artery-arteriole-capillary-venule-vein pathway (3). The coronary circulation contains sinusoids (75) which interconnect with the coronary arteries and the left ventricular lumen. Studies have shown that under normal conditions, 5% of the left coronary artery flow drains through these sinusoids and into the left ventricle. The

coronary circulation also contains Thebesian channels which provide drainage of arterial blood into both the left and right ventricular lumens. Flow through these channels under normal conditions has been shown to be about 2% of the left coronary artery flow passing into the left atrium and ventricle and 13% of the left coronary artery flow draining into the right atrium and ventricle (59).

Observations made on injected canine hearts (11) reveals that the large coronary arteries are essentially true end arteries, i.e. there are few artery to artery anastomoses which would provide blood to a given capillary field from several arterial sources. This fact has importance in cases of coronary occlusion, for when a coronary artery becomes blocked, the capillary field it supplies is no longer adequately perfused (6). The coronary arteries give rise to arterioles which divide by dichotomous branching until the final division results in two daughter capillaries which often course off in opposite directions. It appears that a specific area of a cardiac muscle fascicules is supplied by several arterioles whose capillaries intermesh (11). On the venous side, venules receive capillaries from several arterioles and each venule drains a single muscle fascicule. The venules in turn join to form the cardiac veins which in turn pass their blood into the coronary sinus (10).

MYOCARDIAL INFARCTION

Severe local hypoxia of the heart, due to an excessive narrowing or occlusion of a coronary artery, results in several alterations in the physiological properties of the affected muscle. These effects include; a diminished force of contraction in the hypoxic area, an impairment of the area's ability to conduct a wave of electrical depolarization and an increase in the irritability of the affected tissue which often leads to spontaneous depolarizations (26). If the hypoxic period persists long enough, cell death ensues and an infarct results. The number of reported cases of myocardial infarction is on the rise in this country and myocardial infarction has emerged as a major health problem. Acute myocardial infarction in the clinic is frequently found in association with coronary atherosclerosis. Coronary thrombosis may lead to myocardial infarction as can coronary embolism, although the latter is rare due to the capacity of the lungs to filter emboli. Indeed, myocardial infarction can occur in the absence of coronary occlusion (35).

The prognoses for patients suffering a myocardial infarction varies widely for myocardial infarction is not a homogeneous syndrome. The clinical symptoms and signs displayed by patients with a myocardial infarction depend on the amount of necrotic heart muscle, the area of the heart infarcted (i.e. atrial muscle,

ventricular muscle or specialized conduction tissues) and preexisting conditions in the patient prior to the infarct (47). Clinicians report that cardiac output is often significantly reduced in patients following myocardial infarction (25,67) but may be normal or even elevated in some cases(51). Likewise, total peripheral resistance may be slightly or moderately elevated following myocardial infarction but may also be normal. Mean systemic arterial pressure is usually near normal after infarction but may be slightly depressed. Heart rate is usually moderately elevated (19), stroke volume isusually reduced, central venous pressure may be elevated and circulation time is usually reduced (25,40,51). Central blood volume is usually normal and therefore, the decreased cardiac output results from a decreased ability of the heart to pump blood rather than from hypovolemia. Not only do patients often respond poorly to transfusion following a myocardial infarction but some investigators find that removal of small volumes of blood helps to relieve substernal pain without deliterious circulatory effects (25).

Little clinical data are available on peripheral blood flow following myocardial infarction, but Lee (51) has reported a 50% decrease in forearm blood flow as measured by plethysmography. Hutton et al (46) reported that normotensive patients had a normal renal blood flow following myocardial infarction but that patients who

were hypotensive following myocardial infarction had reduced renal blood flows.

The picture of experimental myocardial infarction in the dog is similar to the clinical picture. Again the changes in various circulatory parameters depends on the insult applied to the heart. Cardiac output is usually decreased and total peripheral resistance is usually elevated (54,56). Arterial pressure may be normal (50,54) or decreased significantly (56). Heart rate is often elevated and central venous pressure may also be higher than normal (50,54,56).

CARDIOGENIC SHOCK

The term cardiogenic shock is applied to the hypotensive state which sometimes follows acute myocardial infarction (14). The symptoms and signs most commonly seen in the clinic are chest pain, hypotension, pale moist skin, cold extremities, collapsed veins, depressed sensorium and oliguria or anuria (37). Cardiac output is often seriously reduced in these patients but is not so in all cases (14,22). Likewise, total peripheral resistance may or may not be elevated (34,70,73). The outlook for patients suffering from this syndrome is uniformly poor, with a mortality rate of 75-80% (24). Indeed, cardiogenic shock has emerged as one of the leading causes of death from acute myocardial infarction amoung hospitalized patients in this country (9). One reason that the outlook for patients in cardiogenic

shock remains poor, is the lack of definitive data on the pathophysiology of this condition. For obvious reasons, adequate serial data is very difficult to obtain in a clinical setting. Consequently, many attempts have been made to develop an experimental model in animals which closely resembles the syndrome as seen in man.

It is believed that the basic defect in cardiogenic shock is a reduction in the tissue fluid oxygen tension below which the coronary vascular bed can compensate for by dilation (37). This results in a fall in tissue fluid oxygen tension below the threshold level necessary for mitochondrial oxidative phosphorylation. ATP synthesis is then shifted to the cytoplasm where it is accomplished anaerobically with a concomitant great decrease in ATP production. This deficency in high energy phosphate production results in a hypodynamic area in the ventricle, decreased contractile strength of the left ventricle, decreased cardiac output and subsequent hypotension (37). Concomitant with the decreased cardiac output, is underperfusion of the periphery and the heart leading subsequently to death.

EXPERIMENTAL MODELS

Most experimental models of cardiogenic shock have been developed in the dog. The dog does not simulate many of the preexisting conditions that occur in man, such as atherosclerosis, diabetes mellitus or hypertension,

but these models have nevertheless provided useful information and therefore will be described.

Four major models of cardiogenic shock are used, some more frequently than others.

One model involves the selective ligation of the coronary arteries until sufficent hypotension is obtained to satisfy the criteria established for cardiogenic shock. This procedure (45,64) causes reduction of cardiac blood flow with resultant decreases in the contractile strength of the left ventricle and left ventricular stroke output. This procedure has at least two inherent disadvantages. First, ventricular fibrilation often occurs before a shock-like state is obtained. A second drawback to this procedure is that a thoracotomy is necessary (52,76). It has been demonstrated that a thoracotomy in itself alters cardiac output, possibly subsequent to a decreased venous return and increased pulmonary vascular resistance (33). Thus, changes in the cardiovascular system resulting from the coronary ligation would tend to be augmented by the changes caused by thoracotomy. This experimental model is not currently in widespread use.

In another experimental model, hexachlorotetrafluorobutane is used as the necrotizing agent (5,12,49). This agent leads to decreases in left ventricular dp/dt, total peripheral resistance and cardiac output. This model has the disadvantage of producing a high

degree of ventricular fibrilation, about 50%. It also produces hemorrhage due to rupture of vessels of arteriolar size. Hemorrhage is uncommon with natural myocardial infarction. Finally, although fluoronated hydrocarbons are usually thought to be biologically inactive, some experiments have shown that they do produce toxic effects. Thus, the hemodynamic changes arising from the cardiac necrosis may be augmented by direct effects of the infarcting agent on the heart or peripheral vasculature (13). This experimental model is not currently in widespread use.

A third experimental model of cardiogenic shock involves the embolization of the coronary arteries with multiple microspheres (8,34,69,73). Although glass microspheres have been used, plastic spheres of styrene-di-vinyl copolymer benzene in the range of 250-350 microns are used more often. The microspheres are usually injected into the aorta at the level of the coronary ostia. Immediately following embolization, cardiac output falls to about 50% of it's control value and remains depressed. Systemic pressure is likewise reduced by 40-50% and remains at hypotensive levels. Changes in Lead II electrocardiograms are similar to those seen with natural infarction, (elevation of the S-T segment, inverted T-waves and later deeper Q-waves) and postmortem examination of the heart reveals multiple infarctions of the left ventricle. The total

peripheral resistance may or may not increase following embolization. The lack of an increase in total peripheral resistance, observed by some investigators, even in the presence of severe hypotension, has been the subject of widespread investigation. It has been proposed that this results from initial inhibition of the normal baroreceptor response of reflex vasoconstriction due to increases in the activity of cardiac vagal afferents whose receptors lie in the ventricle (49,71,73). It is thought that the increased input on the vasomotor center from the heart tends to balance out the decreased activity from the baroreceptors in response to hypotension. Whether these receptors respond to paradoxical stretch of the ventricular myocardium in the area of the infarct during systole (15, 48,71) or whether these receptors are chemosensitive to some substance liberated from the ischemic myocardium (18), is yet to be established. The value of such a response is unclear, but this lack of vasoconstriction soon gives way to the normal baroreceptor response of vasoconstriction. The effect of a lack of vasoconstriction on the ultimate fate of the patient has not been established. It has been shown that the hemodynamic state of an animal at the time of the infarction and up to three hours after the infarction has a pronounced effect on the size of the infarct (60). Thus, this response may have profound effects on the

course of the syndrome.

The advantages of this experimental model are several. First, it does not require a thoracotomy and the microspheres themselves are inert, having no toxic effects. Another advantage of this procedure is that with doses of microspheres of 2-4 mg/kg and averaging 325 microns in diameter, ventricular fibrilation is minimal and yet acute hypotension accurs.

One of the drawbacks to the use of multiple microspheres to infarct the heart is the possibility of the microspheres escaping the coronary arteries and infarcting other organs. Thus, damage to other organs may give rise to cardiovascular changes which would augment those changes resulting from the infarction of the heart. The percentage of microspheres recoverable from the heart ranges from about 95% of that injected (3) to 60% of that injected in a single dose (69), and may fall as low as 10% of the total injected when multiple injections are used (69). A second disadvantage of this procedure is that it doesn't simulate natural infarction, i.e. the whole heart is subjected to multiple small infarcts whereas in the natural state, one large transmural infarct is usually found. This experimental model has gained widespread use.

The most recent experimental model developed to study myocardial infarction with shock, is the selective embolization of the left circumflex coronary artery

with 0.2 ml. of metallic mercury (20,53,57,58). This procedure was originally designed to study various circulatory parameters in the unanesthetized state. Immediately following embolization with mercury, cardiac output falls by 50% and remains depressed and systemic pressure falls to 70-75% of its control value (27). Also seen are anuria or oligouria, delayed tachycardia, depressed sensorium and ECG Lead II changes indicative of acute myocardial infarction. This syndrome very closely resembles that as seen in man. Post mortem examination of the heart shows infarction of the posterior-lateral wall of the left ventricle, the posterior papillary muscle, the posterior wall of the right ventricle and the posterior one half to one third of the intraventricular septum. Post mortem removal of the heart and digestion with KOH results in approximately a 90% recovery of the mercury from the heart. The 10% which is not recoverable from the heart is apparently retained in the coronary arterial tree, for x-rays of the vital organs, including kidney, liver, brain, gut, muscle etc. shows no traces of mercury (53). This is one of the advantages of the mercury embolization technique over the microsphere technique where some embolization of the kidneys usually occurs. One of the disadvantages of the mercury embolization technique is the time course of the resultant hypotension. Immediately after embolization, the systemic

pressure falls by about 25-30% but remains at this level until just before death. Thus this procedure produces a milder hypotension than does the microsphere technique. This experimental model is gaining widespread use.

PERIPHERAL VASCULAR MANIFESTATIONS

Little data is available on the serial peripheral adjustments during cardiogenic shock. This includes information on resistance changes in precapillary and postcapillary vessels, and differential adjustments of the vascular resistance and blood flows of the different organs of the body. Hanly et al (41,43) in experiments with intermittant coronary occlusion, reported that at constant flow there were consistent increases in vascular resistance of gracili and consistent decreases of resistance in paw, a bed consisting mainly of skin. In the hindleg perfused at constant flow (a bed consisting of both skeletal muscle and skin) these investigators found a decrease in resistance but this decrease was less than that found in skin alone. Gorfinkel et al (30,31) in studying renal hemodynamics following mercury embolization of the heart, reported a decrease in renal blood flow and a 30% decrease in renal resistance. Hanley et al (76) in studying renal hemodynamics following intermittant coronary occlusion also reported a decrease in renal resistance. This data agrees with clinical data

reported by Hutton et al (46) who found decreased renal flow in patients who were hypotensive following myocardial infarction. In a companion study on hemorrhagic shock by Gorfinkel et al, they reported a 500% increase in renal resistance with cardiac output and systemic pressure changes comparable with those in cardiogenic shock. They therefore concluded that these two forms of shock have different pathophysiological pathways and concomitant neuorohumeral adjustments. Thus, further investigation on the peripheral manifestations of cardiogenic shock is necessary to corroborate these findings and to elucidate the responses of other organs of the body. Also, there is little known about transvascular fluid fluxes in cardiogenic shock. Some investigators report a 10% decrease in total blood volume in both man and animals (53). These measurements are made using dye dilution techniques. Unfortunately, this technique does not allow deliniation of reduced blood volume due to transvascular fluid fluxes as opposed to a decrease in the effective circulating blood volume due to intravascular pooling. Intravascular pooling is known to occur in other forms of shock such as endotoxin shock (44,74).

According to Pappenheimer (62) transcapillary fluid flux is dependent on the capillary to tissue osmotic pressure gradient and the capillary to tissue hydrostatic pressure gradient. The net osmotic force

tends to retain fluid within the capillary while the net hydrostatic force tends to move fluid out of the capillary. In order to maintain a normal blood volume, the capillary hydrostatic pressure gradient must very nearly equal the colloid osmotic pressure gradient. Therefore, for fluid efflux to occur, the hydrostatic pressure gradient must excede the osmotic pressure gradient. This can occur through changes in any of the four parameters governing these gradients (capillary hydrostatic pressure, tissue hydrostatic pressure, capillary colloid osmotic pressure and tissue colloid osmotic pressure). It is generally accepted that both the tissue osmotic pressure and hydrostatic pressure are near zero under normal circumstances. Therefore, the most important determinants of fluid flux are the capillary hydrostatic pressure and the capillary colloid osmotic pressure. The determinants of the capillary hydrostatic pressure, Pc, are systemic pressure, precapillary resistance, postcapillary resistance and right atrial pressure. The major determinant of the osmotic pressure gradient is the permeability of the microvasculature to proteins. Thus if the 10% blood volume reduction in cardiogenic shock is an accurate measurement, Pc must rise above capillary osmotic pressure, COP, in the face of marked hypotension, or the COP must decrease below Pc due to an increase in the capillary permeability to proteins. Whether or not these changes occur in cardiogenic shock is yet to

be established. The deliterious effects of such changes are obvious. A decreased blood volume would lead to a decreased cardiac output through decreased venous return, a situation which could only serve to accentuate the gravity of the syndrome. Knowledge of the differential responses of the peripheral circulation in cardiogenic shock is vital to the management of this syndrome because peripheral manifestations may ultimately supercede central manifestations and be the direct cause of death.

PURPOSE OF STUDY

Although the heart has been extensively studied in cardiogenic shock, there is virtually no data concerning the peripheral vascular manifestations of this condition. What little data are available is frequently conflicting. This information is need because peripheral vascular changes indirectly influence cardiac function. It is important to know if peripheral vascular factors contribute significantly to death from cardiogenic shock. Further investigations are to be conducted in the renal and splanchnic beds to shed light on the response of these organs as the contribute to the whole animal response. By laying such a background, it was hoped that an effective program of therapy of this circulatory derrangement could be launched. Indeed, before productive theraputical research can be initiated, the problem dealt with must be better understood.

METHODS

PRE-EXPERIMENTAL SURGICAL PREPARATION

Adult mongrel dogs of either sex, ranging in weight from 12-30 kilograms were utilized in this study. All animals were anesthetized with sodium pentobarbital (30 mg/kg) injected intravenously, The animals were intubated with a cuffed endotracheal tube and placed on positive pressure ventilation (Harvard Aparatus Company) with room air. The thoracic area on the left side of the animals was shaved and cleansed with an antibacterial soap (pHisoHex). The operative field was then sprayed with 0.001% merthiolate. The skin and muscle layers were incised with a scalpel at the level of the 5th intercostal space. The pericardium was incised, leaving the phrenic nerve intact, and the left artium was retracted to to expose the course of the left circumflex coronary artery. A small side branch of the circumflex artery was isolated and a small bore (PE 50) polyethylene catheter, filled with a 1% heparin solution, was inserted into the vessel and advanced in a retrograde direction to the level of the left circumflex coronary artery. The catheter was then firmly sewn to the pericardium and one rib. Before closing the incision,

100,000 units of penicillin G and 125 mg. of dihydrostreptomycin base were injected into the thoracic cavity to prevent infection. The pericardium, skeletal muscle and skin were then sewn together using small diameter surgical silk (sizes 0 and 000). A latex drain was inserted into the skin incision to allow for any drainage from the wound. The distal end of the cardiac catheter was coiled and allowed to remain under the skin. These animals were the returned to their cages and allowed to recover for a seven day period. All animals were given food and water ad lib during the recovery period. On the day of the operation and on three succeeding days, all animals received 600,000 units of penicillin G and 750 mg. of dihydrostreptomycin base (I.M.).

In some of the animals, in addition to the above procedure, a large side branch of the left circumflex coronary artery was also ligated. This ligation was performed in order to insure the presence of previous necrotic heart muscle at the time of the experiment.

EXPERIMENTAL PREPARATION

On the day of the experiment, all animals were prepared in the following manner. The animals were anesthetized with sodium pentobarbital (30 mg/kg, IV) and were allowed to breathe spontaneously through a cuffed endotracheal tube. The skin of the right forelimb was circumferentially sectioned 3-5 centimeters

above the elbow. The right brachial artery, the forelimb nerves (median, ulnar, radial and musculocutaneous), the brachial vein and the cephalic vein were isolated. The muscle and remaining connective tissue of the forelimb were sectioned by electrocautery. The humerus was sectioned and the ends of the bone were packed with bone wax to prevent bleeding. Therefore, blood entered the limb only through the right brachial artery and exited only through the brachial and cephalic veins. The forelimb nerves were coated with an inert silicone spray to prevent drying. All animals were then well heparinized to prevent clotting (10,000 USP units).

Forelimb intravascular pressures were measured with small bore polyethylene catheters (PE 10-60) inserted into the following vessels; 1) a skin small artery (the third superficial volar metacarpal artery) on the undersurface of the paw; 2) a muscle small artery in the supply to a flexor muscle in the upper portion of the forelimb; 3) a skin small vein (the second superficial dorsal metacarpal vein) on the upper surface of the paw; 4) a muscle small vein from one of the deep vessels draining a flexor muscle in the middle portion of the forelimb; 5) skin large vein (the cephalic vein via the median cubital vein); 6) muscle large vein (the brachial vein via the median cubital vein). Small artery cannulae were inserted in a down

stream direction while small vein cannulae were inserted in an upstream direction (Figure 1). With the cannulae so inserted, the vessel acts as an extension of the cannula and reflects pressure in collatreals distal to the cannula tip. The pressure so measured is a true lateral pressure as long as the vessel is patent and without valves (28,29). This was checked by the ability to freely flush and withdraw through the cannula.

The brachial and cephalic veins were cannulated with a short section of polyethylene tubing (PE 320) 3-5 centimeters downstream from the sites of measurement of large vein pressures. Outflow from both veins was directed into a reservoir maintained at a constant volume with a variable-speed pump (Holter Company) which continually returned blood to the animal via a cannulated jugular vein (PE 320). Blood flows were determined by timed collections of the two venous outflows. In this preparation the median cubital vein represents the major anastomotic channel between the brachial and cephalic veins (55). Since this vessel was ligated in all experiments, the brachial venous outflow was predominately from muscle and the cephalic venous outflow was predominately from skin. Although this preparation does not accomplish complete functional isolation of skin and muscle blood flows, the degree of separation is sufficent to permit comparison of resistance changes in these two parallel vascular beds

(1,2,63).

When all cannulae were in place, the limb was suspended on a wire mesh platform attached to a sensitive I-beam strain gauge balance which could be calibrated by adding known weights to the platform (55). Addition of 2 grams to the platform usually resulted in a pen deflection of 10-15 mm.

A standard Lead II electrocardiogram was monitored on all animals to determine changes in the electrophysiology of the heart and to determine cardiac frequency.

EXPERIMANTAL MANEUVERS

The skin on the left thoracic area of the dog was incised and the distal end of the cardiac catheter was exteriorized. Following the establsihment of control variables, a bolus of 0.2 ml. of metallic mercury was injected into the cardiac catheter of all animals in the two experimental groups. The mercury was immediately flushed through the catheter with 2.0 ml. of normal saline. Another group of animals, which served as controls, were not injected. All variables were measured 2, 5, 10 and 15 minutes after injection of the mercury and every fifteen minutes thereafter until the end of the four hour experimental period. All animals received supplemental doses of pentobarbiatl upon exhibiting a corneal reflex. Upon completion of the four hour period, all animals were sacrificed and

their hearts excised and examined for the distribution of mercury and the amount, if any, of previous heart damage.

DERIVATION OF EXPERIMENTAL RESULTS

Total and segmental (large artery, small vessel, large vein) vascular resistances in muscle and skin were calculated by dividing the pressure gradients (mm Hg) by appropriate blood flows (ml/min/100 grams forelimb weight). In addition, resistance in total forelimb and in each of the combined skin and muscle segments was calculated as follows:

$$\text{Total forelimb resistance} = \frac{Rt_s \cdot Rt_m}{Rt_s + Rt_m}$$

$$\text{Total forelimb large-artery resistance} = \frac{Ra_s \cdot Ra_m}{Ra_s + Ra_m}$$

$$\text{Total forelimb small-vessel resistance} = \frac{R(sv)_s \cdot R(sv)_m}{R(sv)_s + R(sv)_m}$$

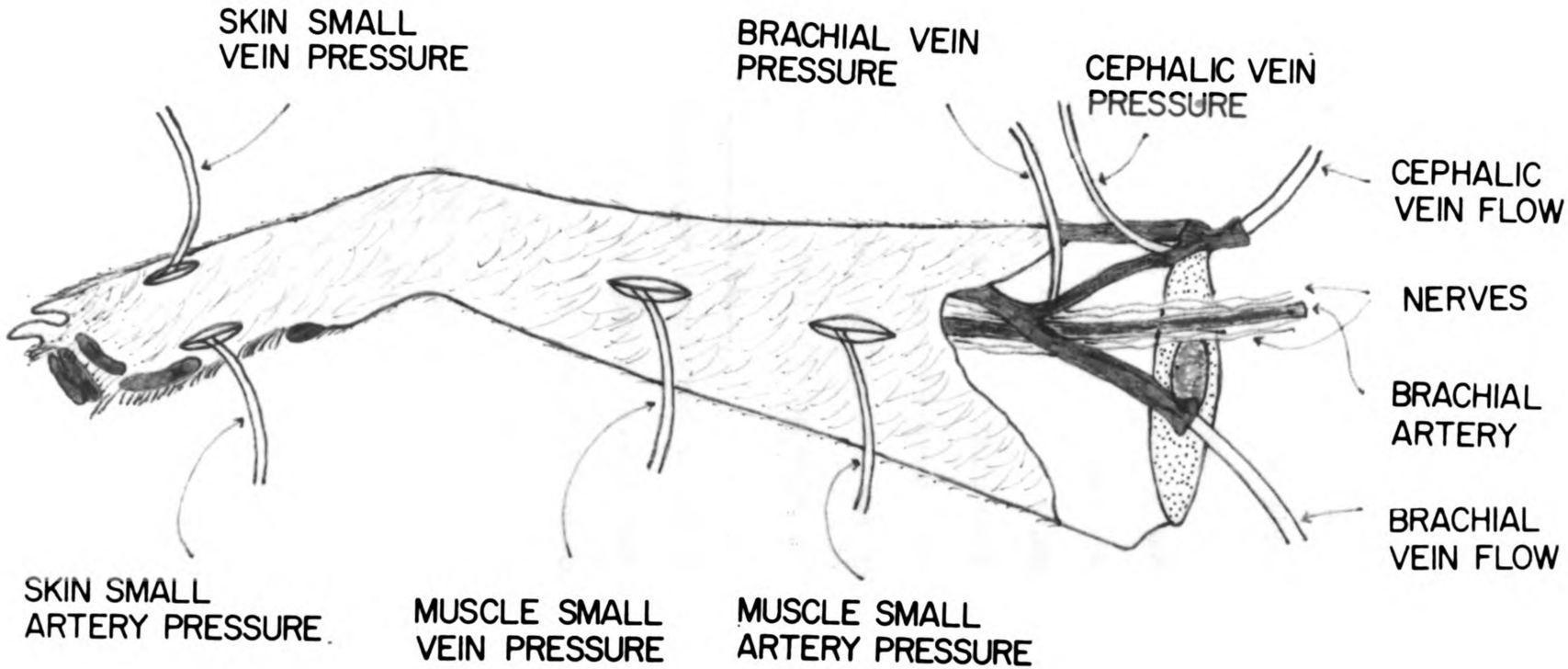
$$\text{Total forelimb large-vein resistance} = \frac{Rv_s \cdot Rv_m}{Rv_s + Rv_m}$$

Where R = resistance in milimeters of Hg per mililiter of blood flow per minute per 100 grams forelimb weight, t = total, s = skin, m = muscle, a = large artery, sv = small vessel and v = large vein.

In this preparation, transvascular fluid fluxes and vascular volume changes are inferred from changes in forelimb weight and segmental vascular resistances. The measurement of arterial pressure and venous pressures and the calculation of vascular resistances were used

to elucidate the mechanism of observed changes in forelimb weight. Statistical analysis of the experimental data was accomplished with the application of the Student's t test (paired replica) (21).

Figure 1. Forelimb preparation showing the location and placement of catheters for the measurement of pressures and flows.


SKIN SMALL
VEIN PRESSURE
BRACHIAL VEIN
PRESSURE
CEPHALIC VEIN
PRESSURE
CEPHALIC
VEIN FLOW
NERVES
BRACHIAL
ARTERY
BRACHIAL
VEIN FLOW
SKIN SMALL
ARTERY PRESSURE
MUSCLE SMALL
VEIN PRESSURE
MUSCLE SMALL
ARTERY PRESSURE

RESULTS

Data presented herein were obtained from 21 mongrel dogs. These animals were divided into three groups as follows; control animals (n=7), mercury embolized animals (n=9) and mercury embolized animals with previous necrotic heart damage (n=5). All data are presented as the mean value ± standard error. Statistical evaluation of the data was accomplished using the Student's t test (paired replica). A statistically significant difference at the $p \leq 0.05$ level was considered as a true difference within the groups.

Forelimb weight - Table 1

Forelimb weight increased slightly with time in all animals. This weight increase was statistically significant in both experimental groups ($p \leq 0.05$) but was not statistically significant in control animals.

Mean aortic pressure - Table 1

Mean aortic pressure was unchanged relative to the control period values from minute 10 to minute 240 in all groups studied. From minute 0 to minute 10 however, mean aortic pressure decreased slightly but significantly ($p \leq 0.05$) in both experimental groups. In non-embolized control animals, mean aortic pressure was unchanged relative to the control period from minute 0 to minute 10.

Heart rate - Table 1

Heart rate decreased with time in all three groups of animals. The decrease in heart rate showed periods of statistical significance ($p \leq 0.05$) in both the control animals and animals with previous heart damage but not in animals embolized without previous heart damage. From minutes 2-15, heart rate was significantly increased relative to the control period in animals with previous heart damage.

Forelimb vascular pressures - Tables 2,3 and 4

Small artery, small vein and large vein pressures in both skin and skeletal muscle were either unchanged relative to the control period or slightly but significantly ($p \leq 0.05$) decreased relative to the control period in all groups of animals studied. These changes were greatest in the small arteries.

Forelimb blood flows - Tables - 1,2 and 3

Skin blood flows were essentially unchanged relative to the control period in all animals studied. Skeletal muscle blood flows displayed greater fluctuations, being either unchanged or significantly ($p \leq 0.05$) decreased in all animals studied. Total forelimb blood flow was minimally affected, periodically being slightly but significantly ($p \leq 0.05$) decreased relative to the control period.

Forelimb total and segmental resistances - Tables 4,5 and 6

Total forelimb vascular resistance was essentially unchanged relative to the control period in all groups

studied. Total skin resistance was unchanged relative to the control preiod in all animals whereas total skeletal muscle resistance increased slightly but significantly ($p \leq 0.05$) in the experimental animals but was unchanged relative to the control period in control animals. Large vein resistances, in both skin and skeletal muscle, were unchanged relative to the control period in all animals. Large artery and small vessel resistances were unchanged in skin and either unchanged or slightly but significantly ($p \leq 0.05$) increased in skeletal muscle in all animals.

Lead II electrocardiograms - Figure 2

Standard Lead II electrocardiograms displayed gross elevation of the S-T segment, indicative of severe myocardial ischemai, immediately following embolization in the experimental animals. This segment remained elevated throughout the four hour observation period. A deepened Q-wave was displayed in Lead II of the animals with previous heart damage, prior to embolization. No changes were evident in the Lead II electrocardiograms of non-embolized control animals.

Post-mortem examination of the heart

Post-mortem examination of the hearts of experimental animals revealed a wide distribution of mercury throughout the posterior-lateral wall of the left ventricle. Mercury was also found at times in the left atrium and the papillary muscles. In animals with previous heart damage, varying amounts of necrosis was

observed. The amount of necrosis ranged from large transmural infarcts to smaller, more patchy areas of necrosis. This necrosis was located on the anterior-lateral wall of the left ventricle.

Figure 2 Electrocardiographic Lead II tracings in control animals, mercury embolized animals (group 1) and mercury embolized animals with previous heart damage (group 2). Chart speed = 20 mm/second.

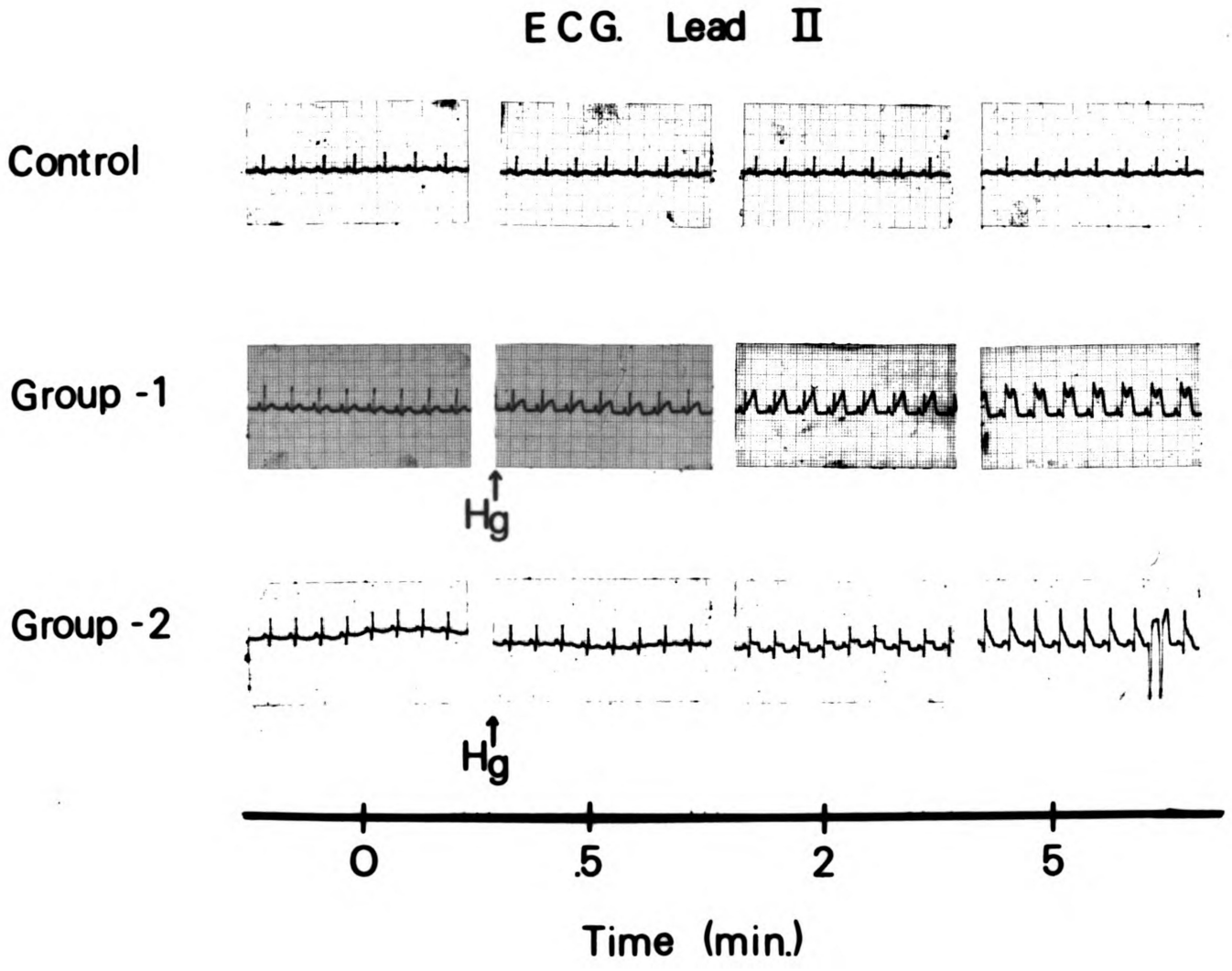

E C G. Lead II
Control
Group -1
Hg
Group -2
Hg
0
.5
2
5
Time (min.)

Table 1 Mean values and standard errors for accumulated weight (Wt.), arterial pressure (AP), heart rate (Hr.) and total forelimb blood flow per 100 grams of forelimb weight (Ft/100 G) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 1

	Δ Wt.			AP		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.00	0.00	0.00	130 ±2.9	116 ±3.7	110 ±6.7
0	+0.33 ±0.1	+0.86 ±0.6	+0.40 ±0.4	131 ±2.8	115 ±4.3	108 ±8.0
2	-0.01 ±0.4	+0.79 ±0.7	+0.84 ±0.4	131 ±3.4	104* ±3.2	102* ±7.2
5	-0.20 ±0.5	+1.28 ±0.8	+0.96* ±0.5	130 ±3.7	109* ±4.3	109 ±7.4
10	-0.20 ±0.5	+1.90 ±0.8	+1.60* ±0.7	128 ±5.6	116 ±5.6	113 ±9.5
15	-0.24 ±0.6	+2.55* ±0.9	+2.64* ±0.7	128 ±4.7	115 ±4.7	116 ±7.5
30	+0.06 ±0.7	+4.05* ±1.1	+4.44* ±1.2	128 ±4.2	114 ±5.0	115 ±7.4
60	+1.00 ±0.8	+5.60* ±1.1	+7.36* ±1.6	124 ±5.5	106* ±4.0	116 ±5.2
120	+2.93 ±1.6	+7.43* ±1.8	+12.28* ±1.3	130 ±5.5	105 ±2.2	114 ±6.1
180	+6.09 ±2.5	+8.65* ±2.4	+16.08* ±1.4	135 ±5.5	106 ±3.9	116 ±5.8
240	+5.15 ±3.1	+7.19* ±2.9	+17.76* ±1.6	127 ±6.9	103 ±3.6	112 ±4.0

TABLE 1 cont.

	Hr.			Ft/100 G		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	150 ±7	150 ±5	124 ±8	24.2 ±1.4	16.4 ±1.6	25.7 ±2.6
0	147 ±8	145 ±4	126 ±9	24.8 ±1.7	16.1 ±1.5	25.0 ±2.8
2	147 ±8	148 ±5	138* ±10	24.9 ±1.7	13.4* ±1.3	22.1* ±2.6
5	144 ±8	151 ±5	142* ±9	23.9 ±1.7	14.6 ±1.0	22.7 ±3.0
10	146 ±7	156 ±6	134 ±6	22.5* ±1.8	14.8* ±1.2	23.6 ±3.3
15	147 ±9	159 ±8	136* ±7	22.1* ±1.8	14.7* ±1.2	23.3 ±3.5
30	136* ±7	158 ±8	134 ±5	23.1 ±1.8	14.3 ±1.5	24.3 ±3.8
60	136* ±9	159 ±13	132 ±9	23.5 ±2.2	12.2* ±1.0	22.9 ±3.3
120	130* ±10	141 ±7	128 ±12	21.7 ±2.5	11.9* ±1.3	22.6 ±3.8
180	124* ±9	131 ±8	118* ±7	22.9 ±3.3	12.9 ±2.3	22.2 ±4.5
240	130 ±10	138 ±9	108* ±10	19.6* ±1.7	10.3 ±2.2	20.5 ±3.5

Table 2 Mean values and standard errors for skin small vein pressure (Pssv), skin large vein pressure (Plsv), skin small artery pressure (Pssa) and skin blood flow per minute per 100 grams of forelimb weight (Fs/100 G) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 2

	Pssv			Plsv		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	14 ±1.9	9 ±0.9	14 ±0.7	5 ±1.3	4 ±0.8	8 ±1.6
0	14 ±1.7	8 ±1.1	14 ±0.9	5 ±1.2	4 ±0.8	8 ±1.5
2	14 ±1.7	8 ±1.3	12* ±0.8	5 ±1.1	3 ±0.7	7* ±1.4
5	13 ±1.7	8 ±1.1	12* ±1.1	5 ±1.1	4 ±0.8	7 ±1.3
10	13 ±1.7	8 ±1.0	13 ±1.2	5 ±0.9	4 ±1.0	8 ±1.6
15	13* ±1.6	8 ±0.9	13 ±1.1	5 ±0.9	4 ±0.9	8 ±1.4
30	13 ±1.6	8 ±1.1	14 ±0.9	5 ±0.9	4 ±1.0	8 ±1.3
60	14 ±1.4	7 ±1.0	14 ±1.2	5 ±1.0	3 ±1.0	9 ±1.4
120	15 ±1.9	7 ±1.0	11 ±1.2	5 ±1.2	4 ±1.1	6 ±1.2
180	16 ±2.5	9 ±1.7	13 ±2.0	6 ±1.7	4 ±1.3	6 ±0.7
240	17* ±2.7	7 ±1.1	13 ±0.9	5 ±2.2	3 ±1.2	6 ±0.4

TABLE 2 cont.

	Pssa			Fs/100 G		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	108 ±2.0	98 ±5.3	83 ±8.3	11.9 ±1.3	9.0 ±1.4	13.6 ±3.1
0	109 ±2.9	98 ±5.3	82 ±8.7	12.3 ±1.5	9.2 ±1.3	12.9 ±3.2
2	109 ±3.1	90* ±5.4	81 ±8.0	12.7 ±1.5	7.7* ±1.1	11.8 ±2.9
5	109 ±3.9	92 ±6.1	84 ±9.4	12.6 ±1.7	8.7 ±1.1	12.1 ±3.0
10	106 ±5.0	99 ±6.7	89 ±11.0	12.3 ±1.8	8.7 ±1.1	12.1 ±3.0
15	106 ±4.9	96 ±5.7	87* ±8.6	12.4 ±1.7	8.9 ±1.2	11.9 ±3.0
30	104 ±3.6	95 ±6.9	89 ±8.4	13.0 ±1.9	8.9 ±1.2	12.8 ±3.1
60	97* ±5.3	84* ±5.6	87 ±6.6	13.3 ±1.9	7.2* ±1.0	12.3 ±3.2
120	98 ±6.3	84* ±3.3	84 ±6.8	11.9 ±1.6	7.2* ±1.0	12.6 ±3.6
180	97* ±6.0	79* ±4.9	85 ±5.7	12.1 ±2.2	7.9 ±1.5	12.7 ±4.3
240	80* ±6.9	72* ±5.4	79 ±5.8	9.5 ±1.0	6.6 ±1.7	11.3 ±3.8

Table 3 Mean values and standard errors for muscle small vein pressure (Psmv), muscle large vein pressure (Plmv), muscle small artery pressure (Psma) and muscle blood flow per minute per 100 grams of forelimb weight (Fm/100 G) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 3

	Psmv			Plmv		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	15 ±1.1	10 ±1.2	10 ±1.5	8 ±1.1	5 ±0.7	7 ±0.8
0	14 ±1.2	9 ±1.0	10 ±1.7	8 ±1.1	5 ±0.6	7 ±0.9
2	14 ±0.9	8* ±0.9	9 ±1.9	7* ±1.1	4 ±0.4	6 ±1.2
5	13 ±1.0	8* ±0.7	9 ±2.0	7* ±1.0	5 ±0.5	7 ±1.2
10	13 ±0.7	8* ±0.7	9 ±2.0	7 ±1.1	4 ±0.5	7 ±1.3
15	12* ±0.6	8* ±0.8	10 ±2.1	6* ±0.9	4 ±0.5	7 ±1.3
30	11* ±0.8	8 ±0.8	9 ±1.4	6 ±1.1	5 ±0.5	7 ±1.0
60	11* ±0.6	7 ±0.8	9 ±1.2	6 ±1.0	5 ±0.4	7 ±0.8
120	11* ±1.4	7 ±0.8	9 ±1.0	7 ±1.2	5 ±0.4	6 ±0.8
180	11* ±1.2	7 ±0.8	8 ±1.1	7 ±1.1	5 ±0.5	5 ±0.7
240	12 ±1.4	5* ±0.4	7 ±0.7	7 ±1.5	4 ±0.4	5 ±0.6

TABLE 3 cont.

	Psma			Fm/100 G		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	108 ±2.8	100 ±4.4	88 ±3.9	12.3 ±1.2	7.4 ±1.1	12.1 ±1.2
0	111 ±3.1	100 ±4.9	88 ±5.0	12.5 ±1.2	6.9 ±1.0	12.1 ±1.2
2	110 ±2.8	93 ±4.2	88 ±4.4	12.2 ±1.2	5.7* ±0.8	10.3* ±1.0
5	110 ±3.1	96 ±4.9	92* ±6.0	11.2 ±1.0	5.9* ±0.8	10.5 ±1.1
10	108 ±4.3	100 ±6.4	95 ±6.8	10.2* ±1.0	5.9* ±0.8	11.4 ±1.3
15	109 ±3.6	98 ±6.4	93* ±4.3	9.8* ±0.9	5.9* ±0.8	11.4 ±1.4
30	109 ±3.9	99 ±5.6	95 ±5.8	10.1* ±1.0	6.0 ±1.3	11.4 ±1.3
60	103* ±4.4	91* ±4.8	97 ±4.9	10.2* ±1.0	5.0* ±1.1	10.6 ±1.2
120	107 ±4.9	87* ±2.6	92 ±6.0	9.8* ±1.4	4.8* ±1.2	10.0 ±0.9
180	110 ±5.7	86* ±4.2	96 ±3.7	10.9 ±1.8	5.0 ±1.2	9.5 ±0.8
240	96 ±7.2	69* ±9.7	92 ±3.5	10.0 ±1.8	3.7* ±0.9	9.2* ±0.7

Table 4 Mean values and standard errors for skin large artery resistance (Rsa), skin small vessel resistance (Rs(s-v)), skin large vein resistance (Rsv) and total skin resistance (Rst) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 5

	Rsa			Rs(s-v)		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	2.0 ±0.2	2.7 ±0.9	2.2 ±0.3	8.6 ±1.2	11.9 ±1.8	7.5 ±3.2
0	2.1 ±0.4	2.4 ±0.6	2.4 ±0.5	8.4 ±1.0	11.4 ±1.8	8.0 ±3.3
2	1.9 ±0.3	2.3 ±0.8	2.1 ±0.4	8.2 ±1.1	12.6 ±2.2	9.0 ±3.8
5	1.9 ±0.3	2.6 ±0.8	2.1 ±0.1	8.5 ±1.1	11.2 ±1.8	9.7 ±4.4
10	2.1 ±0.3	2.5 ±0.6	2.2 ±0.4	8.4 ±1.2	11.9 ±2.0	10.5 ±4.9
15	2.1 ±0.4	2.8* ±0.7	3.0* ±0.7	8.5 ±1.1	11.4 ±1.9	10.5 ±5.0
30	2.1 ±0.4	2.8 ±0.8	2.6 ±0.6	8.0 ±1.2	12.0 ±2.0	10.2 ±4.8
60	2.4 ±0.6	3.9* ±1.1	2.9 ±0.7	7.0 ±0.9	12.4 ±2.1	9.9 ±4.1
120	3.0* ±0.6	3.8 ±0.9	3.0 ±0.5	7.6 ±0.8	13.1 ±2.6	10.7 ±5.2
180	3.6* ±0.6	4.6 ±1.1	3.4 ±1.0	7.5 ±1.0	12.4 ±3.3	11.4 ±5.1
240	5.3* ±0.8	6.7 ±1.9	4.5 ±1.7	6.9 ±0.8	16.9 ±4.7	11.1 ±4.2

TABLE 4 cont.

	Rsv			Rst		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.98 ±0.5	0.62 ±0.1	0.58 ±0.2	11.6 ±1.7	15.3 ±2.5	10.3 ±3.6
0	0.90 ±0.4	0.57 ±0.1	0.56 ±0.2	11.4 ±1.7	14.3 ±2.1	11.0 ±4.0
2	0.88 ±0.4	0.69* ±0.1	0.56 ±0.2	11.0 ±1.6	15.6 ±2.4	11.7 ±4.4
5	0.90 ±0.5	0.62 ±0.1	0.64 ±0.3	11.3 ±1.8	14.4 ±2.2	12.4 ±4.8
10	0.91 ±0.5	0.55 ±0.1	0.57 ±0.2	11.4 ±1.7	15.0 ±2.4	13.2 ±5.5
15	0.86 ±0.4	0.51 ±0.1	0.65 ±0.3	11.4 ±1.7	14.8 ±2.3	14.1 ±5.8
30	0.89 ±0.5	0.54 ±0.1	0.59 ±0.2	11.0 ±1.9	15.3 ±2.3	13.4 ±5.5
60	0.85 ±0.4	0.73 ±0.2	0.68 ±0.3	10.2 ±1.7	17.7 ±2.9	13.5 ±5.1
120	1.04 ±0.4	0.70 ±0.2	0.63 ±0.3	11.6 ±1.3	17.6 ±3.5	14.3 ±5.8
180	1.21 ±0.5	0.83 ±0.2	0.70 ±0.3	12.3 ±1.6	17.8 ±4.5	15.5 ±6.3
240	1.51 ±0.6	1.04 ±0.5	0.99 ±0.4	13.7 ±1.7	24.7 ±6.8	16.6 ±6.2

Table 5 Mean values and standard errors for muscle large artery resistance (Rma), muscle small vessel resistance (Rm(s-v)), muscle large vein resistance (Rmv) and muscle total resistance (Rmt) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 5

	Rma			Rm(s-v)		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	1.9 ±0.4	2.5 ±0.4	1.8 ±0.2	8.3 ±1.2	14.5 ±2.1	6.7 ±0.9
0	1.7 ±0.2	2.7 ±0.4	1.7 ±0.2	8.5 ±1.2	15.7 ±2.5	6.7 ±0.9
2	1.8 ±0.2	2.0 ±0.6	1.3 ±0.3	8.6 ±1.2	17.6* ±2.4	8.0* ±1.0
5	1.9 ±0.3	2.4 ±0.4	1.6 ±0.2	9.2 ±1.2	17.3 ±2.5	8.2* ±1.0
10	2.0 ±0.3	3.2 ±0.6	1.6 ±0.2	10.4* ±1.7	18.4* ±2.8	7.9 ±1.1
15	2.0 ±0.3	3.1 ±0.4	1.9 ±0.3	10.8* ±1.6	18.2 ±2.8	7.9 ±1.3
30	1.9 ±0.3	3.1 ±0.6	1.8 ±0.3	10.7* ±1.8	19.9* ±3.1	8.1 ±1.3
60	2.0 ±0.4	4.0 ±0.8	1.7 ±0.2	9.9 ±1.7	22.0 ±3.8	8.9* ±1.5
120	2.8 ±0.8	5.2* ±1.0	2.4 ±0.6	12.3 ±3.1	23.2 ±3.5	8.6 ±1.2
180	2.9 ±0.9	6.0* ±1.1	2.1* ±0.3	12.6 ±3.6	24.8 ±5.0	9.5* ±0.9
240	4.4 ±1.4	13.1* ±4.2	2.3 ±0.5	10.5 ±2.0	28.0 ±8.6	9.6* ±1.2

TABLE 5 cont.

	Rmv			Rmt		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.60 ±0.1	0.68 ±0.2	0.19 ±0.1	10.8 ±1.4	17.7 ±2.4	8.7 ±0.9
0	0.58 ±0.1	0.73 ±0.2	0.23 ±0.1	10.7 ±1.4	19.1 ±2.8	8.6 ±0.9
2	0.58 ±0.1	0.61 ±0.1	0.26 ±0.1	10.9 ±1.4	20.2 ±2.5	9.6* ±1.1
5	0.61* ±0.1	0.65 ±0.1	0.25 ±0.1	11.7* ±1.5	20.4 ±2.7	10.0* ±1.0
10	0.67 ±0.2	0.65 ±0.1	0.17 ±0.1	13.1 ±1.9	22.2* ±3.4	9.7 ±1.1
15	0.65 ±0.2	0.66 ±0.1	0.24 ±0.1	13.5* ±1.8	22.0 ±3.0	10.1 ±1.3
30	0.53 ±0.1	0.49 ±0.1	0.19 ±0.1	13.1* ±1.8	23.5 ±3.6	10.0 ±1.5
60	0.52 ±0.1	0.39 ±0.1	0.28 ±0.1	12.5 ±1.7	26.4 ±4.4	10.9* ±1.6
120	0.52 ±0.1	0.40* ±0.1	0.30 ±0.1	15.7* ±3.6	28.8* ±4.4	11.3* ±1.5
180	0.41 ±0.1	0.43* ±0.1	0.30 ±0.1	15.9 ±4.2	31.3* ±5.8	12.0* ±1.2
240	0.53 ±0.1	0.60 ±0.2	0.22 ±0.1	15.4 ±3.6	41.7* ±8.6	12.1* ±1.5

Table 6 Mean values and standard errors for total large artery resistance (Rta), total small vessel resistance (Rt(s-v)), total large vein resistance (Rtv) and total forelimb resistance (Rt) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 6

	Rta			Rt(s-v)		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.9 ±0.1	1.0 ±0.1	1.0 ±0.1	4.0 ±0.3	5.9 ±0.6	2.9 ±0.5
0	0.9 ±0.1	1.0 ±0.1	1.0 ±0.1	4.0 ±0.3	6.0 ±0.7	3.0 ±0.6
2	0.8 ±0.1	0.9 ±0.2	0.8 ±0.2	4.0 ±0.3	6.8 ±0.9	3.5* ±0.6
5	0.8 ±0.1	1.0 ±0.1	0.9 ±0.1	4.0 ±0.3	6.2 ±0.6	3.7* ±0.8
10	0.9 ±0.1	1.2 ±0.1	0.9 ±0.1	4.3 ±0.5	6.5* ±0.7	3.8 ±0.9
15	0.9 ±0.1	1.3 ±0.2	1.1 ±0.2	4.5 ±0.5	6.3 ±0.7	3.8 ±0.9
30	0.9 ±0.1	1.2 ±0.1	1.0 ±0.2	4.2 ±0.4	6.9 ±0.8	3.8 ±1.0
60	1.0 ±0.1	1.6* ±0.2	1.0 ±0.1	3.9 ±0.5	7.2 ±7.2	4.0 ±1.0
120	1.3 ±0.2	1.7* ±0.2	1.3 ±1.3	4.5 ±0.7	7.5 ±1.1	3.8 ±0.9
180	1.4* ±0.2	2.2* ±0.3	1.3* ±0.2	4.4 ±0.8	7.9 ±1.9	4.2 ±1.1
240	1.9* ±0.3	3.2* ±0.6	1.4* ±0.2	3.8 ±0.5	9.5 ±3.0	4.1 ±0.9

Table 6 Mean values and standard errors for total large artery resistance (Rta), total small vessel resistance (Rt(s-v)), total large vein resistance (Rtv) and total forelimb resistance (Rt) in control animals (C, n=7), mercury embolized animals (Gp 1, n=9) and mercury embolized animals with previous heart damage (Gp 2, n=5). * = $p \leq 0.05$.

TABLE 6

	Rta			Rt(s-v)		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.9 ±0.1	1.0 ±0.1	1.0 ±0.1	4.0 ±0.3	5.9 ±0.6	2.9 ±0.5
0	0.9 ±0.1	1.0 ±0.1	1.0 ±0.1	4.0 ±0.3	6.0 ±0.7	3.0 ±0.6
2	0.8 ±0.1	0.9 ±0.2	0.8 ±0.2	4.0 ±0.3	6.8 ±0.9	3.5* ±0.6
5	0.8 ±0.1	1.0 ±0.1	0.9 ±0.1	4.0 ±0.3	6.2 ±0.6	3.7* ±0.8
10	0.9 ±0.1	1.2 ±0.1	0.9 ±0.1	4.3 ±0.5	6.5* ±0.7	3.8 ±0.9
15	0.9 ±0.1	1.3 ±0.2	1.1 ±0.2	4.5 ±0.5	6.3 ±0.7	3.8 ±0.9
30	0.9 ±0.1	1.2 ±0.1	1.0 ±0.2	4.2 ±0.4	6.9 ±0.8	3.8 ±1.0
60	1.0 ±0.1	1.6* ±0.2	1.0 ±0.1	3.9 ±0.5	7.2 ±7.2	4.0 ±1.0
120	1.3 ±0.2	1.7* ±0.2	1.3 ±1.3	4.5 ±0.7	7.5 ±1.1	3.8 ±0.9
180	1.4* ±0.2	2.2* ±0.3	1.3* ±0.2	4.4 ±0.8	7.9 ±1.9	4.2 ±1.1
240	1.9* ±0.3	3.2* ±0.6	1.4* ±0.2	3.8 ±0.5	9.5 ±3.0	4.1 ±0.9

TABLE 6 cont.

	Rtv			Rt		
Time	C	Gp 1	Gp 2	C	Gp 1	Gp 2
-5	0.22 ±0.03	0.25 ±0.01	0.11 ±0.02	5.2 ±0.3	7.3 ±0.7	4.2 ±0.5
0	0.20 ±0.03	0.24 ±0.02	0.13 ±0.01	5.2 ±5.2	7.4 ±7.4	4.3 ±4.3
2	0.21 ±0.03	0.26 ±0.03	0.13 ±0.01	5.1 ±0.3	8.1 ±0.8	4.6* ±0.8
5	0.21 ±0.03	0.24 ±0.02	0.13 ±0.01	5.3 ±0.3	7.5 ±0.6	4.8* ±0.7
10	0.21 ±0.03	0.24 ±0.02	0.10 ±0.01	5.6 ±0.5	8.0* ±0.8	5.0 ±1.0
15	0.22 ±0.03	0.27 ±0.01	0.15 ±0.01	5.7 ±0.5	7.9 ±0.7	5.2 ±1.0
30	0.21 ±0.03	0.22 ±0.02	0.12 ±0.01	5.4 ±0.4	8.3 ±0.9	5.1 ±1.2
60	0.22 ±0.02	0.17 ±0.03	0.14 ±0.01	5.3 ±0.5	9.5 ±1.2	5.3 ±1.0
120	0.23 ±0.04	0.16 ±0.04	0.19 ±0.04	6.2 ±0.8	9.5 ±1.3	5.5 ±1.1
180	0.21 ±0.03	0.23 ±0.04	0.18* ±0.02	6.3 ±0.9	10.7 ±2.4	5.9 ±1.2
240	0.26* ±0.04	0.35 ±0.10	0.15 ±0.02	6.4 ±0.7	14.3 ±3.6	5.9 ±1.0

DISCUSSION

These data clearly indicate that severe left ventricular heart damage need not result in significant changes in forelimb blood flows, pressures or segmental vascular resistances.

Indirect evidence of left ventricular heart damage in this study was obtained from standard Lead II electrocardiograms. Marked elevation of the S-T segment immediately after embolization and a later deepening of the Q-wave was observed in the experimental animals. These electrocardiographic changes are recognized as important, reliable, diagnostic indices of myocardial infarction (72). Visual observation, made at the time of autopsy, served to confirm the evidence supplied by the electrocardiograms. The post-mortem findings revealed a wide distribution of mercury throughout the left ventricle where it was observed filling several epicardial branches of the left circumflex coronary artery. Autopsy findings also revealed the amount of previous necrotic heart damage in group 2 experimental animals. This damage ranged from large transmural infarcts to smaller, more patchy areas of necrosis.

In this study, selective embolization of the left ventricle, even in the presence of previous heart damage, produced only slight changes in forelimb weight, mean aortic pressure, forelimb pressures and forelimb vascular resistances. These changes were not greatly different from those seen in non-embolized control animals.

The absence of the development of prolonged systemic hypotension in this experimental model is indeed interesting. There is some data in the literature to suggest that cardiogenic shock should not result from this procedure. Page et al (61) in a clinical study of human hearts, attempted to correlate the mass of ventricular myocardium lost by a patient with the development of cardiogenic shock. In measuring both recent and old infarcts in relation to total ventricular mass, they found that patients who had died in cardiogenic shock had lost 40% or more of their left ventricular myocardium. Conversely, patients who had died after myocardial infarction in the absence of cardiogenic shock had lost 35% or less of their left ventricular myocardium. Visual observations of hearts following embolization with 0.2 ml of mercury suggested that less than 40% of the left ventricular myocardium was lost in the experimental animals in this study. Regan et al (65) in studying experimental coronary occlusion,

concluded that obstruction of a major branch of the left common coronary artery, in a previously normal ventricle, is seldom associated with the development of shock, either clinically or experimentally. The data obtained in our study would tend to support this conclusion. Finally, Guyton et al (34) in their computer model of the circulatory system has found that a 66% decrease in the pumping ability of the heart resulted in only a 10% decrease insystemic pressure.

However, there is other data in the literature to suggest that cardiogenic shock should develop in this model. The mercury embolization technique was developed by Lluch et al in unanesthetized dogs (53). In their study, a 16% decrease in mean aortic pressure was reported four hours after embolization with mercury. Unfortunately, they failed to report any values for control animals after a four hour period. Marked hypotension was not found by these investigators until approximately 16 hours after embolization when mean aortic pressure had declined to 70% of the control value. Edelman et al (20) in studying pulmonary performance after mercury embolization of the heart in unanesthetized dogs, reported a 22% decrease in mean aortic pressure four hours after embolization. Unfortunately, they also failed to report hemodynamic values in control

animals after four hours. It is not suggested that the changes in mean aortic pressure in these two studies are necessarily artifacts of the preparations. It is suggested that the 11% decrease in mean aortic pressure found in our study might not be significantly different from results obtained in these two previous studies for which no control values were reported.

Glenn et al (27) in studying the production of MDF in the anesthetized, open chest, dog following mercury embolization of the heart, found a 23% decrease in mean aortic pressure after four hours. In a series of control animals, no significant change was found in mean aortic pressure after four hours. Unfortunately, because this technique involved open chest, anesthetized dogs, it differed both from the procedure of Lluch and Edelman and from the procedure utilized in our study.

More consistent results are apparently found in cardiac output measurements following mercury embolization of the heart. Cardiac output is usually reported to fall by 40% or more and remain below control values until death (20,27,31,53). Although no measurement of cardiac output was made in our study, the fact that mean aortic pressure was not reduced and resistance in the forelimb was only slightly elevated, suggests that cardiac output was

perhaps not seriously reduced in this preparation.

It must be pointed out that the technique used in this study differed significantly from the original technique of Lluch (53). All dogs in our study were anesthetized whereas those in the original study were unanesthetized. It is difficult, indeed, to ascertain the effects of anesthesia on the response following mercury embolization. However, considering the cardiodepressant effects of pentobarbital, coupled with the reduced gain of the compensatory reflexes, one would expect to see the anesthetized animal fare worse than the unanesthetized animal, not better. Another significant difference between the Lluch technique and that employed herein, is that the former technique makes the entire circumflex artery liable to embolization while the latter technique does not subject the most anterior portions of this vessel to embolization. Thus, it may be argued that the portion of the left ventricle supplied by the most anterior branches of the left circumflex is more vital to the maintenance of cardiac output than the more posterior portions of the ventricle. However, there is data in the literature to suggest that all portions of the left ventricle are equally vital to the maintanence of cardiac output (61).

Data on blood volume during myocardial infarction are exceedingly sparse and conflicting. Some

investigators have reported a decrease in blood volume in both man and animals following myocardial infarction complicated with cardiogenic shock (53). In this study, transvascular fluid fluxes and/or intravascular pooling, are inferred from changes in forelimb weight and segmental vascular resistances. An increase in forelimb weight, while resistances in the small vessel and large vein segments (capacitance vessels) are constant or rising, must be attributed to transvascular fluid filtration. That is, mean vessel caliber is either constant or decreasing, hence, intravascular blood volume must be either constant or decreasing. A constant intravascular blood volume would have no effect on forelimb weight whereas a decrease in intravascular blood volume would decrease organ weight. An increase in forelimb weight, concomitant with a constant or decreasing intravascular blood volume must therefore be attributed to transvascular fluid filtration. Transvascular fluid filtration ensues when the capillary to tissue hydrostatic pressure gradient exceeds the capillary to tissue osmotic pressure gradient. Changes in the capillary to tissue hydrostatic pressure gradient can occur through changes in systemic pressure, precapillary resistance, postcapillary resistance or venous pressure, which are the indirect determinants of Pc, the capillary hydrostatic pressure. Likewise,

changes in the volume and/or compliance of the interstitial space, the determinants of tissue hydrostatic pressure, can affect the hydrostatic pressure gradient. Changes in the capillary to tissue osmotic pressure gradient may occur through changes in the capillary osmotic pressure, COP, or the tissue osmotic pressure. Changes in the protein concentration of the blood affect COP. Changes in the tissue protein concentration, via changes in the capillary permeability to proteins or the rate of fluid removal by the lymphatics, affect the tissue osmotic pressure.

In both groups of embolized animals in this study, forelimb weight increased significantly relative to the control period, by the end of the four hours. No significant change in forelimb weight was seen in the non-embolized control animals. Due to the fact that forelimb weight was increasing concomitant with a decreased or constant intravascular blood volume (i.e. resistances either decreased or were constant) the weight gain observed in these animals must be attributed to transvascular fluid filtration. The minimal changes observed in small vein pressures, which represent a minimum for Pc, coupled with the insignificant or slightly increased small vessel and large artery resistances suggests that an increased Pc is not responsible for the

transvascular fluid filtration. Perhaps a change in the capillary permeability to proteins may occur following myocardial infarction. These findings, especially the larger weight gain in the animals with previous heart damage, will require further investigation in order to clarify their significance.

It is evident that the technique employed in this study is not associated with the development of cardiogenic shock. Well over fifty dogs were utilized in an attempt to find a dose of mercury which would produce prolonged hypotension. Various doses of mercury were injected in many different ways. The total volume of mercury injected ranged from 0.1 ml to 10.0 ml. Nowhere in this dose range was a hypotensive dose found. These data also fail to support the conclusion by Lluch et al (53) that a dose of 0.3 ml of mercury results in ventricular fibrilation in virtually all animals.

Furthermore, if cardiogenic shock is to be defined as displaying marked systemic hypotension, the prolonged time course for the development of hypotension in the Lluch technique makes this technique of highly questionable value in the anesthetized dog.

Finally, recent evidence has indicated that this technique may be far less reproducible than originally reported. Early papers suggested that 90% of dogs

embolized with 0.2 ml of mercury could be expected to develop cardiogenic shock (20). However, in a recent paper, Gorfinkel et al (31) reported a far lower percentage of embolized animals developing cardiogenic shock.

SUMMARY

Severe myocardial ischemia was produced by selective embolization of the left circumflex coronary artery of anesthetized dogs with 0.2 ml of metallic mercury. Various circulatory parameters were measured in control animals, mercury embolized animals and mercury embolized animals with previous necrotic heart damage. All parameters were followed for a four hour observation period. Standard Lead II electrocardiographic recordings showed marked elevation os the S-T segment, indicative of severe myocardial ischemia, immediately following embolization. No changes were observed in the Lead II electrocardiograms of non-embolized control animals. Embolization resulted in a transient, mild hypotension with mean aortic pressure returning to control values by minute 10. No transient hypotension was observed in the non-embolized control animals. Changes in forelimb weight, large and small precapillary and postcapillary vessel pressures, skin and skeletal muscle blood flows and total and segmental (large artery, small vessel, large vein) vascular resistances in experimental animals did not differ importantly

from changes in the non-embolized control animals. Post-mortem examination of the hearts of experimental animals revealed a wide distribution of mercury throughout the posterior-lateral wall of the left ventricle. In animals with previous heart damage, varying amounts of necrosis were present from large transmural infarcts to smaller, patchy areas of necrosis.

These data, therefore, clearly indicate that progressive degrees of left ventricular heart damage need not produce marked alterations in the forelimb vasculature. Furthermore, these data indicate that the selective embolization of the posterior-lateral circumflex coronary artery of anesthetized dogs, even in the presence of previous necrotic heart damage, does not lead to the development of cardiogenic shock within a four hour observation period. Therefore, it is suggested that the mercury embolization technique for the production of experimental cardiogenic shock is of highly questionable value in the anesthetized dog.

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