MYOCARDIAL BLOOD FLOW DURING CARDIOPULMONARY BYPASS USING THE ROLLER AND THE PULSATILE PUMPS

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SUMMARY

Ischemia of the inner layers of the myocardium during cardiopulmonary bypass (CPB) is a major cause of mortality during and following surgery for acquired heart disease (18, 36, 41, 58, 71). Myocardial hypertrophy and ventricular fibrillation are present in most clinical cases and have been shown experimentally to be important contributing factors. Other factors have recently received attention (1, 14). These include lesions of the heart in which oxygen consumption of the myocardium is increased, e.g., aortic stenosis, especially after prolonged CPB (18), ischemic arrest of the heart during CPB (15), unbalanced coronary artery perfusion (58), increased tissue pressure from surface to deeper areas of the myocardium (5, 6, 7, 8, 9), and decreased oxygen tension from epicardium to endocardium (30), with a concurrent decrease in blood flow to the deeper areas (1, 11, 37).

An increasing amount of evidence has shown that pulsatile perfusion during CPB is superior to non-pulsatile perfusion (53, 60, 69, 74, 76). We hypothesized that the deleterious effect of ventricular fibrillation might be counteracted by using a pulsatile pump to restore rhythmic perfusion to the coronary bed and to promote a more normal and physiologic blood flow distribution to the myocardium.

Fifteen pigs which had their aorta banded at a young age, to create left ventricular hypertrophy, were placed on normothermic CPB and perfused with either the pulsatile or the non-pulsatile pumps. Myocardial blood flow distribution was studied by radioactive microspheres. So long as the perfusion rate was maintained at 70 cc/Kg/min blood flow distribution across the myocardial wall was identical in the normal sinus rhythm (NSR) and in the ventricular fibrillating groups (VF) irrespective of the type of perfusion. At low perfusion rates, subendocardial ischemia developed in all groups and was more profound in the fibrillating groups. The deleterious effect of ventricular fibrillation was not counteracted by pulsatile perfusion, and subendocardial ischemia was not reversed with pulsatile flow during cardiopulmonary bypass (CPB).

RESUME

L'ischémie des couches profoundes du myocardie pendant le pontage cardiopulmonaire est une cause principale de mortalité pendant la période chirurgicale et post-chirurgicale dans les maladies cardiaques acquises. Les facteurs principaux contribuant à la mortalité sont l'hypertrophie du myocarde et la fibrillation ventriculaire. Dernièrement, d'autres facteurs ont été précisés comme facteurs contribuant aux lésions du myocarde qui exige une plus grande consommation d'oxygène. Ce sont sténose de l'aorte, surtout après perfusion extra-corporèlle, déséquilibre électrolytique de la perfusion coronarienne, augmentation des tensions tissulaire entre les couches superficielle et profonde du myocarde, et diminution de la tension d'oxygène progressive à travers l'épaisseur du myocarde. L'évidence récente indiquerait que la perfusion pulsatile serait supérieure à la perfusion continue. Il nous semblait que les faits nocifs de la fibrillation ventriculaire pouvaient être prévenues en employant une perfusion pulsatile pour rétablir une perfusion rhythmique à la circulation coronaire qui produirait une perfusion plus physiologique au myocarde. L'hypertrophie ventriculaire gauche était produit dans quinze cochons de lait en rétrécissant l'aorte. Ces cochons étaient perfusés par la perfusion normothermique en perfusion extra-corporelle en employant les perfusions pulsatiles et non-pulsatiles. La circulation myocardique fut étudiée par moyens des microsphères radioactives. Quelque-soit la technique de rhythme

et perfusion employée, aucune différence a été notée dans la répartition du sang dans les myocardes hypertrophiés. Cependant à debit réduit, l'ischémie subendocardique était plus marquée dans les cas de fibrillations ventriculaires. La perfusion pulsatile ne semblair pas empêcher les effets nocifs de la fibrillation ventriculaire.

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CHAPTER 1: HISTORICAL BACKGROUND

FORWORD

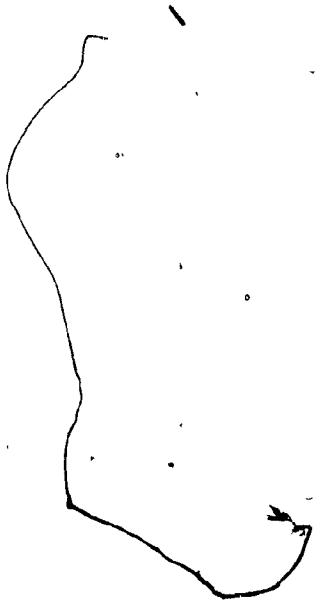
The modern era of cardiac surgery began just prior to World War II. There was little progression of this surgery during the War, but it accelerated thereafter especially with the development of extracorporeal circulation techniques. Cardiopulmonary bypass (CPB) made possible, in the early 1950s, a wide variety of operations on the heart and great vessels, and more recently has allowed surgeons to perform operations on the coronary arteries.

As one problem after another has been solved in the use of extracorporeal circulation, others have become apparent. Outstanding at the present time is the damage to blood elements (16), the denaturation of plasma proteins (48) and the interference with the microcirculation during CPB procedures, as will be described in this chapter.

The problem we are primarily interested in, is the alteration in the distribution of blood flow to the myocardium which occurs during CPB procedures on fibrillating hypertrophied hearts leading to subendocardial underperfusion and, in extreme cases, to subendocardial necrosis. Pathological observations at the Royal Victoria Hospital in Montreal, have shown that this lesion occurs exclusively in patients undergoing CPB procedures for acquired heart disease.

A historical background on the development of extracorporeal circulation will be presented. Later in this chapter, some pertinent

studies on the normal coronary artery physiology and the factors that contribute to the alteration in the normal physiologic distribution of blood flow will be reviewed. Finally, some studies comparing pulsatile and non-pulsatile extracorporeal perfusion are summarized, with particular attention on the physiologic changes on the cardiovascular system.



NOTES ON THE HISTORICAL DEVELOPMENT OF EXTRACORPOREAL CIRCULATION

The concept of an artificial perfusion with oxygenated blood was first suggested in 1813, by LeGallois (49). Von Frey and Gruber (74), in early 1885, constructed a pump device which consisted of a 10 cc syringe which had two one-way valves and was driven by an electric motor. This was a rather primitive type of extracorporeal apparatus, in which blood was oxygenated by flowing in a film over the inner surface of a rotating cylinder.

Carl Jacobi (42) in 1895, excised the lungs of animals, artificially ventilated them, and passed blood through them. S.S. Brukhonenko and S. Tchetchuline (13), in 1926, designed an extracorporeal system that used an excised animal's lung as the oxygenator and two mechanically actuated diaphragms as the blood pumps. Venous blood was pumped from the animal (dog) into the pulmonary circuit of the isolated lung and the oxygenated blood was then pumped back into the animal's arterial system. They were able to keep dogs alive sometimes for several hours after stopping their hearts.

The pioneer in the development of a heart lung machine was J.H. Gibbon, Jr. (28). This investigator became interested in extracorporeal circulation as he watched a woman die of a pulmonary embolus for which she had been operated upon. Gibbon's first oxygenator consisted of a vertical revolving cylinder. The centrifugal force produced by the

revolution of the cylinder maintained the blood film on the inner surface of the cylinder. The pump consisted of an air pump activating a finger-cot blood pump. The valves were made of solid rubber corks. Venous blood was pumped to the top of the oxygenator and filmed onto the inner surface of the oxygenator cylinder. As blood descended under the force of gravity, it absorbed oxygen and released carbon dioxide. The oxygenated blood was then returned to the animal's body through a metal cannula in the femoral artery. In full operation, the machine could oxygenate 500 ml of blood per minute.

Later Gibbon modified his machine with a DeBakey pump which was a modification of the roller pump. His work, however, was to be interrupted by World War II, after which he returned to Philadelphia as Professor of Surgery and continued his research. His first post-war machine consisted of a rotating vertical cylindrical oxygenator and modified DeBakey rotatory pumps. The blood pump was designed to prevent hemolysis and the oxygenator was designed to prevent air bubbles. He was then able to perform operations in small dogs with long-term survivors (26, 70). However, the oxygenator was too small to support total bypass in humans. A new oxygenator was designed consisting of parallel series of six flat stainless steel screens enclosed in a clean plastic case. In 1949, Gibbon began experimental bypass surgery in adult dogs and, at the same time, developed a suction device, learned how to prevent air embolism, and gradually increased the perfusion time (54).

Meanwhile other groups had become interested in heart-lung machines. In the latter 1940s, Clarence Dennis (45) in Minnesota, working with Karl. Karlson (45), developed an oxygenator consisting of multiple, slowly rotating screen disks. In April 1951, he explored a six-year old girl with end stage heart disease. She was found to have a very large atrial septal defect. The heart-lung machine functioned well but the patient did not survive.

Dodrill (20, 21, 22) in Detroit, developed a mechanical heart which did not contain a blood oxygenator and, on July 3, 1952, performed the first successful left ventricular bypass operation on a forty-one year old man with severe mitral insufficiency. A few months later, he performed the first successful right heart bypass on a sixteen year old boy with congenital pulmonic stenosis.

On May 6, 1953, Gibbon operated upon an eighteen year old girl with an atrial septal defect and did the first successful open-heart surgery under total cardiopulmonary bypass (27). Gibbon's cardiopulmonary bypass (CPB) device was well received but did not arouse immediate excitement among cardiac surgeons who were then most interested in the use of deep hypothermia.

It was C.W. Lillehei (17) who moved the CPB machine from the laboratory to clinical surgery. Lillehei initiated his work by developing a more suitable blood pump, a single commercially available Sigmamotor pump.

From 1953 to 1955, Lillehei, Cohen, Warden and Varco did extensive work on cross-circulation for intracardiac surgery and received the Lasker Award for medical research (51). Lillehei continued his work on the heart lung machine and developed the "reservoir" technique for operations in children.

In the early 1950s, Mustard (56, 57) in Toronto, used the heart-lung machine to operate on seven infants with transposition of the great vessels. None of the patients survived, primarily due to advanced, end-stage heart disease. They used a Cowan perfusion pump and a monkey or dog's lung as the oxygenator.

In 1955, Kirklin (44) modified the IBM-Gibbon machine and used it in thirty-eight operations with sixteen survivors. He demonstrated the usefulness of the machine to perform open-heart surgery.

A bubble oxygenator was developed by DeWall (50), working with Lillehei, and was first used in the summer of 1955. The simple, disposable plastic bag bubble oxygenator was also developed by DeWall (19). This oxygenator played a tremendous role in expanding open-heart surgery as seen today.

With the advent of better anesthesia, aseptic techniques, CPB procedures and better knowledge of cardiorespiratory physiology, cardiac surgery began a new era. Congenital heart defects were repaired, prosthetic valves were developed and replaced the diseased heart valves, and the diseased myocardium was surgically treated. More recently, coronary artery surgery and cardiac transplantation were performed.

NOTES ON THE PHYSIOLOGY OF THE CORONARY ARTERIES

Although knowledge of the coronary arteries dates to the sixteenth century when a fairly accurate anatomical description was given by Vesalius (67), knowledge of their function had to await the work of Harvey (35) in 1628, and that of Thebesius (72) in 1708. It was Thebesius who demonstrated by careful dissection the anastomotic channels between the coronary arteries.

Anrep et al. (3) in 1927, developed a method of measuring coronary blood flow using a platinum wire. After the coronary arteries had been cannulated, they were perfused with blood from a reservoir. Once the desired perfusion pressure was achieved they placed a heated platinum wire in the mouth of the reservoir. The temperature of the blood entering the coronary arteries was equilibrated with air flowing over the heated platinum wire. The range of cooling was calibrated and gave a measure of the phasic flow to the coronary arteries. They were able to demonstrate that flow to the myocardium was diminished in systole both in normal denervated hearts, as well as in heart-lung preparations.

Utilizing heart-lung preparation in dogs, Anrep et al. (4), in 1929, perfused with constant pressure the cannulated right and left coronary arteries, as well as the coronary sinus. They found that the outflow from the coronary sinus bore a direct relationship to the total coronary blood flow. Anrep et al. demonstrated that clamping one coronary

artery led to increased blood flow in the remaining artery. The data from these studies showed that 80 percent of the total coronary flow was via the left coronary artery, 50 percent by the circumflex, and 30 percent by the anterior descending artery. Approximately 20 percent of the total flow was carried by the right coronary artery.

Katz et al. (46) in 1938, using similar experiments subsequently confirmed these results. In addition they found that during ventricular fibrillation the left coronary artery carried 82 percent of the total coronary blood flow and the right coronary artery 18 percent.

In 1931, Anrep et al. (2), demonstrated phasic flow in the coronary arteries and pointed out that coronary artery blood flow occurred both in systole and in diastole. His team attributed the systolic flow to expansion of the large elastic coronary branches.

Wiggers et al. (78) in 1933, demonstrated that there was significant blood flow in the intramural vessels of the left ventricle during both systole and diastole, and that there was no arrest of blood flow during systole. They concluded that though the systolic events of the myocardium increased the resistance of the blood vessels, the resistance was not great enough to prevent the flow of blood.

Johnson et al. (43) in 1939, measured intramyocardial pressure using mercury manometers attached at either ends of the carotid artery inserted into the myocardium. Changes in pressure were transferred to an optical manometer and recorded. They found that during systole there

was a pressure gradient. This gradient decreased from the deeper to the more superficial layers of the myocardium. The intra-myocardial pressure in the deeper areas was greater than the aortic pressure. The intra-myocardial pressure in the superficial layers was equal to or less than the aortic pressure. Johnson et al. concluded that even though the endocardial vessels may be occluded during systole, there still may be a continuous flow of blood to the endocardial areas, when pressures are lower or equal to aortic pressures.

The modern era of phasic flow studies in the coronary arteries may be said to have started when constant pressure flowmeters were developed for application to the coronary arteries in situ. Much of what is known today about the coronary artery physiology we owe to Gregg and Green (32) in 1940. They described a method for continuous optical monitoring of the instantaneous inflow into a coronary artery by shunting blood from the aorta to the coronary artery via a short external circuit containing an orifice connected with a differential manometer. These investigators demonstrated that at the beginning of isometric contraction there was rapid retardation of coronary flow. As the aortic pressure rose during the ejection period, coronary inflow accelerated. A peak was reached during the middle of the rise of the aortic pressure and declined then at a constant rate of inflow during the latter part of systole. The rate of inflow at the end of diastole, just preceding isometric contraction, was taken as an index of intramural

blood flow during systole. Recording the rate of intramural blood flow and aortic pressure simultaneously, they calculated that the resistance to flow during the latter part of diastole increased from two to four fold during systole.

During the cardiac cycle, coronary artery perfusion occurs mostly during diastole. Systolic blood flow, as well as its relative distribution to the myocardium, was studied by Gregg et al. (33) in 1956. Using open-chest dog preparations to measure coronary blood flow during different times of the cardiac cycle, they showed that coronary flow invariably increased during induced ventricular asystole in both the left coronary artery (13 to 77 percent) and in the coronary sinus (17 to 76 percent). During ventricular fibrillation there was a similar increase in the coronary blood flow to the myocardium. This led them to conclude that contraction of the myocardium acted to impede coronary flow through the left ventricular wall.

Sabiston et al. (65), in 1957, studied the effects of organized myocardial contraction on coronary blood flow in 27 dogs by cannulating the coronary vessels and perfusing them at a constant pressure, which approximated that of the prevailing systemic pressure. Coronary flow was measured simultaneously in the left coronary artery and in the coronary sinus. Experiments were done in (1) normally beating hearts, (2) during ventricular asystole induced by vagal stimulation, and (3) during ventricular fibrillation. The average control inflow to the

left coronary artery in a beating heart was 93 ml/min and rose to 141 ml/min following asystole (59 percent increase). Coronary sinus flow was 80 ml/min in control animals and with asystole rose from 16 to 76 percent that of the control value. In the ventricular fibrillation hearts the left coronary artery flow rose from 119 to 140 ml/min, with a mean increase of 26 percent, and coronary sinus flow rose from 74 to 121 ml/min. As shown by previous researchers (33), these studies supported the idea that contraction of the myocardium impeded coronary blood flow.

Granata et al. (30) in 1965, put electromagnetic flowmeters around the coronary arteries in dogs and simultaneously stimulated the stellate ganglion. They showed that coronary blood flow was abruptly decreased just prior to systolic ejection. During the ejection phase with the rise in aortic pressure, the flow increased. With isometric relaxation flow again increased. The flow then gradually declined with the diastolic fall of the blood pressure. Without any change in the blood pressure, the heart rate increased within six seconds of sympathetic stimulation. Mean coronary flow increased from 36 to 58 ml/min. The systolic and diastolic flows increased in the coronary arteries per beat. End-diastolic resistance to the coronary flow decreased 1.8 P.R.U. from the control value of 2.8 P.R.U. under sympathetic stimulation. In systole, inflow changes were smaller and variable according to the strength o

of stimulation. These data suggest that arteriolar dilatation may play a role in augmenting coronary blood flow.

Downey et al. (24) in 1974, perfused the coronary arteries of dogs with pressures equal to systemic pressures during systole, and a near zero pressure during diastole. The goal was to determine the transmural distribution of coronary blood flow during systole. A solution of 20 microcuries of 86 Rb Chloride diluted in 0.1 ml of normal saline was injected into the coronary arteries during the systolic phase. Forward flow and thus the delivery of 86 Rb occurred only in systole. The relative distribution of blood flow across the ventricular wall was determined. Downey et al. determined that there was non-uniform perfusion of the myocardium during systole and the outer fourth received over twice the blood flow of the inner fourth. The perfusion ratio of inner/outer layers was 0.52.

Prinzmetal et al. (61) in 1947, studied the coronary artery anastomotic channels in human hearts using red blood cells tagged with P 32 in the form of Na2HP04. In a similar experiment they also perfused the coronary arteries with glass spheres measuring 10 to 400 micra, suspended in a radiopaque medium. Numerous anastomotic channels were found between the coronary arteries on autopsy. Using the glass spheres and a calibrated reticule in the eye piece of a microscope the diameter of the intercoronary anastomoses was determined as measuring from 70 to 180 micra. The presence of arterio-venous anastomoses of 70 to 170 micra in diameter in the myocardium was also demonstrated. The function of these arterio-venous anastomoses, they postulated, was as a source of

oxygenated blood in case of an arterial occlusion. The anastomotic channels between the coronary arteries and either ventricular cavity measured 70 to 220 micra in diameter.

In 1961, MacLean et al. (52) used glass radioactive microspheres labelled with Na 24 and measuring 20 micra in diameter to study the distribution of blood flow to the myocardium of dogs. They showed the presence of a uniform distribution of spheres across the myocardial wall of the normally beating heart. The arterio-venous shunts, which were all greater than 50 micra, accounted for two to four percent of the total flow across the heart.

Salisbury et al. (66) in 1963, used a 2 percent solution of sodium fluorescein to study regional blood flow to the myocardium during CPB in dogs and they studied the hemodynamic factors that could cause subendocardial ischemia. Thick, confluent areas of totally ischemic myocardium existed when there was concomitantly low coronary perfusion pressure (below 70 mm Hg) and an abnormally elevated left ventricular diastolic pressure (above 25 mm Hg). Their results supported the idea that any region of the heart muscle will be deprived of blood supply, even during ventricular diastole, if the intramyocardial pressure remains higher than local coronary pressure.

Kirk et al. (47) in 1964, described a method of estimating myocardial tissue pressure in open-chest dogs which was based upon blood flow through a branch of the coronary artery. Fluid flow through this

segment of vessel will cease when the external pressure on the segment exceeds the distending pressure. The intramyocardial pressure reached a peak during isovolumetric contraction. The second peak of greater magnitude occurred during the ejection period. By measuring the intramyocardial pressure at different levels they showed that the peak tissue pressure in the inner half of the myocardium was twice that of the epicardium.

Noir et al. (55) in 1967, studied the distribution of blood flow to the inner and outer layers of the left ventricle using 86 Rb Chloride in anesthetized, open-chest dogs. The isotope was infused into the cannulated left coronary artery. They were able to show that under normal resting conditions the myocardium was evenly perfused. When the left intraventricular pressure was raised, but the coronary perfusion was held at levels sufficient to provide normal coronary flow, the endocardial distribution of the isotope was equal or slightly greater than that of the epicardium. However, when the coronary perfusion was lowered, maintenance of normal left intraventricular pressure resulted in marked underperfusion of the endocardium. Vasoactive drugs, dipyridamole, norepinephrine, vasopressin and beta adrenergic blocking agents (propanolol) increased the flow distribution to the endocardium of both normotensive and hypertensive left ventricles. They concluded that systolic tissue pressure which increases from epicardium to endocardium does not cause significant underperfusion of the endocardium in either normotensive or hypertensive left ventricles as long as normal coronary perfusion pressure and flow are maintained.

Griggs (34) in 1968, used Iodoantipyrine-131 I, a freely diffusable substance, to study the distribution of blood flow to the myocardium under normal and adverse conditions of myocardial ischemia. In the open-chest dog preparation they constricted the tubing of a cannula supplying blood flow to the left coronary artery, injected the isotope, quickly sacrificed the animal, and counted the radioactivity in the different areas of the myocardium. Under normal conditions, as well as with mild constriction of the tubing, there was slightly higher concentration of the isotope in the inner layers of the myocardium. In contrast, under more severe hemodynamic conditions, i.e., almost complete constriction of the cannula tubing, there was a relative exclusion of the isotope from the inner layers as compared to the outer layers. The puzzling question of why there was more isotope in the endocardium under normal conditions, they pointed out, could be due to: (1) direct entrance of the isotope from the ventricular cavity; (2) higher myocardial blood flow in the inner layers due to overshoot in vasodilatation in the deeper resistance vessels in response to the pressure gradient between aorta and the coronary arteries; and (3) greater energy expenditure for mechanical work in the deeper areas of the myocardium. They also postulated the existence of a richer capillary supply in the deeper areas of the myocardium, which would be responsible for the greater and more rapid accumulation of the isotope in these areas. They concluded that the isotope distribution underwent a transition from one of active vasomotor control under normal conditions, to one of passive dependence on intra and extravascular pressure phenomenon within the myocardium under ischemic conditions.

In 1969 Domenech et al. (23) studied the distribution of total and regional blood flow to the myocardium of dogs, using radioactive carbonized microspheres labelled with six different isotopes and measuring 14 to 16 micra in diameter. They injected the spheres into the left atrium of the animal and at the same time collected samples of blood from the coronary sinus. They showed that the total coronary flow in seven conscious dogs averaged 95 to 150 ml/min/100 GM of myocardium. Flow to the left ventricular myocardium was 111 to 169 ml/min/100 GM. The radioactivity per gram of the left ventricular myocardium was 2.5 times that of the epicardial muscle using spheres of size 51 to 61 micra in diameter. The radioactivity was 1.4 using spheres 20 to 23 micra in diameter, and 1.3 using spheres 14 micra in diameter. After successive injections of spheres into the left atrium, no change was observed in aortic pressure or coronary flow, indicating that the microspheres had not altered the vascular resistance. Only 0.1 percent of the total radioactivity appeared in the collected blood from the coronary sinus, indicating that the spheres were almost completely filtered out by the capillary bed of the myocardium.

Becker et al. (11) in 1973, studied the distribution of blood flow to the myocardium of normal pigs before and during CPB, using radioactive microspheres 15 $\pm$ 5 micra in diameter. These investigators used very low unphysiological perfusion flow rates. Prior to CPB the normally beating heart had an epicardium/endocardium ratio of 0.69 to 0.76. During

venfricular fibrillation on CPB the ratio had raised to 17.6 ± 4.37. By allowing the heart to beat spontaneously during CPB the ratio reversed to 0.88 ± 0.09. When the fibrillating heart was perfused with pulsatile flow the ratio declined to 3.12 ± 1.55. The conclusion was that the subendocardium was markedly underperfused when the heart remained in ventricular fibrillation during CPB. Vasodilatation with dipyridamole or perfusion with a pulsatile pump improved the gradient but still favored the epicardial side. Normal distribution of blood flow across the myocardial wall was only observed when the normal heart was allowed to beat spontaneously.

Taber et al. (71), in 1967, published a paper on sixteen patients who had died following open-heart surgery. Fourteen of sixteen patients had aortic and mitral valve disease, with aortic stenosis in seven, and aortic insufficiency in two. There were three types of clinical courses manifested by these patients: (1) three died on the operating table after two hours of fruitless partial support of the circulation; (2) three patients showed poor myocardial contractility in the operating room but the low-cardiac-output state only occurred four hours later and death within twenty-four hours; and (3) ten patients who had no signs of myocardial dysfunction in the operating room but developed low-output-syndrome four hours post-operatively. Five out of ten patients died within twenty-four hours, three within forty-eight hours and one at seventy-two hours. One patient died of unrelated causes. At

autopsy in these patients, left ventricular hypertrophy was found in all hearts. Localized myocardial infarction, as seen in coronary artery disease, was absent. No intracardiac thrombi could be found. Arteriograms were performed, primarily to exclude patients with significant (50 percent) stenosis of the coronary arteries. At microscopy, there was uniformity of findings in all 16 cases, namely, the presence of diffusely distributed myocardial microinfarcts surrounded by healthy tissue. Contraction bands were the principle manifestation of necrosis in one patient who died in the operating room. These infarcts did not resemble those seen in arteriosclerotic heart disease. Impaired coronary perfusion, air emboli, and platelet aggregates were believed to be responsible for these microinfarcts.

Early in 1949, Horn et al. (16) did elaborate studies in the hearts of twenty-five patients who died of myocardial injury in the absence of coronary artery occlusion. A pecutiar distribution and form of myocardial injury, limited in great part to the subendocardium and papillary muscle of the left ventricle, was recognized. Isolated, disseminated, hemorrhagic, mottled yellowish-greenish discolored areas were noted. The sizes of these lesions varied from a discrete pinhead to wider and flame-shaped zones, some averaging 5 to 10 mm in diameter. In seven hearts, there were broad confluent areas of discoloration running parallel to the endocardium, and most of them were restricted to the inner third wall of the myocardium. In these hearts there was no evidence of involvement of the subepicardial areas of the myocardium. The investigators correlated the severity of these lesions with the following factors:

(1) impairment of the myocardium to compensate with an increase in coronary flow during adverse conditions; (2) increase in the resistance due to obstruction of the coronary arteries; (3) valvular lesions (aortic stenosis and insufficiency) leading to a decrease in the effective perfusion pressure of the coronary arteries and (4) hypertrophy of the myocardium which augmented the requirements for myocardial blood flow. They also noted that hypertrophy of the myocardium occurred in twenty-two out of twenty-five patients and that the most striking findings had occurred in the hypertrophied hearts. They speculated that there was a disparity between the enlarging heart and its blood supply and that the thickness of the hypertrophied muscle fibers militated against proper oxygen diffusion.

Najafi et al. (59) in 1969, reported autopsy findings in thirty-one patients dying in the early post-operative period following open-heart surgery, and who had suffered a common characteristic cardiac lesion. Twelve of these patients were Grade IV (New York Heart Association Classification), fifteen were in class III, and four patients were class II. Patients in class II were operated upon due to severe aortic stenosis causing syncope and angina. Twenty-four of these patients were in congestive heart failure. Radiological evidence of cardiomegaly was present in all patients and left ventricular hypertrophy in twenty-nine patients. As in the previous study (36), they divided their patients into three groups: (1) two patients who died on the operating room; (2) ten patients who initially had excellent cardiac output but developed ventricular dysfunction within twenty-four hours, and (3) nineteen patients whose

impaired myocardial contractility was noted in the operating room but who were able to be weaned off CPB. All but two died within seventy-two hours after surgery. The typical picture of all deaths was that of low-output-syndrome leading to cardiogenic shock. Gross pathology in these hearts showed left ventricular hypertrophy in twenty-nine patients. Hemorrhagic necrosis of the left ventricle was the most striking finding in these hearts. The typical lesion appeared as an area of intense hyperemia and hemorrhage in the inner third of the myocardium. In two thirds of the patients it extended from the apex to the base of the heart and was circumferential involving the left ventricular side of the septum. In five patients it was less extensive involving either the anterior or the posterior left ventricular wall or both. The coronary arteries were normal in mineteen patients, atherosclerotic but patent in six, and partially occluded in six patients. Only one patient had extensive coronary artery disease. Microscopic findings in these hearts had five common features: contraction bands (in 21), interstitial hemorrhage (in 26), necrosis (in 28), fibrosis (in 3), and calcification (in 6 patients). Without exception the lesion was confined to the left ventricle and was either circumferential or semi-circumferential. It was never transmural and always localized to the subendocardium. It never followed the distribution of the coronary arteries and occurred in the absence of coronary artery disease. They were impressed with the frequency in which the lesion had occurred in hearts that fibrillated during the procedure (28 out of 31 hearts). This was a complete and classic study

of the lesion - subendocardial necrosis of the myocardium.

Using retrospective studies, Huang et al. (41) in 1970, studied forty-seven hearts of patients dying during CPB procedures. Subendocardial necrosis occurred in twenty-one of twenty-seven patients who had died within the first week of CPB due to low-output-syndrome. In five cases dying between two weeks and three months the lesions showed varying degrees of healing and formation of band-scar in the inner third of the myocardium. In 20 out of 27 patients hemorrhagic necrosis was present in the inner half of the myocardium. They believed that interference with the microcirculation to the myocardium was the most important factor leading to this injury to the myocardium.

In an attempt to reproduce subendocardial ischemia and necrosis in experimental animals, Najafi et al. (58) in 1971, first put dogs and later calves on CPB, and challenged them with unphysiological conditions that sometimes are encountered in the operating room such as ischemic arrest and unbalanced perfusion of the left and right coronary arteries. In eighty experiments in dogs they could not reproduce the lesion, concluding that the animal was not suitable. In the calves they subjected them to total ischemia for two hours, and found that it caused no injury to the myocardium. Perfusion of the coronary arteries with pressure in excess of 100 mm Hg showed that the hearts of these animals were uniformly unremarkable, and post-perfusion cardiac performance was excellent. In another group the entire myocardium was unevenly perfused. Here a wide

spectrum of pathological changes were found which varied from negligible myocardial injury to massive left ventricular hemorrhagic necrosis. They concluded that minimal changes occurred in the subendocardium when there was: (a) uneven coronary perfusion, (b) the perfusion pressure on the left coronary artery exceeded that in the right, and (c) with partial myocardial oxygenation in which only the right coronary artery was deprived of circulation. Lack of perfusion of the circumflex system produced a lesion within the distribution of that vessel. The greatest injury to the subendocardium occurred when the anterior descending or the left coronary artery was deprived of circulation while the right coronary artery was perfused at pressures in excess of 140 mm Hg.

Buckberg et al. (14) in 1972, studied experimentally normal hearts and hearts in which different shunts had been created. There was a homogenous blood flow distribution to the myocardium and hearts with a diastolic pressure time index/tension time index (DPTI/TTI) above 0.7, and there was no histochemical evidence of ischemia. In animals with DPTI/TTI below 0.7, on the other hand, there was evidence of ischemia, which was more severe in the endocardial areas. These investigators also reviewed the autopsy findings in twenty consecutive patients dying during CPB. All patients had electrocardiographic evidence of myocardial hypertrophy and/or ischemia. Normothermia was used in four, hypothermia in sixteen, and ventricular fibrillation in eight patients. Both coronary arteries were perfused in five patients (at pressures of 100 mm Hg), and ischemic arrest was used in seven patients. There were several common

features in these hearts: (1) all had ventricular hypertrophy, (2) the surgical repair was intact, (3) and all coronary arteries were patent. Four hearts had large infarcts involving the septum and large areas of the left ventricle. Hemorrhagic necrosis was transmural in two of sixteen grossly normal hearts. Four hearts showed necrosis localized to the subendocardium on staining with hematoxylin and eosin. Uniformly, all these changes were more striking in the hypertrophied hearts. These investigators could not identify a common factor related to CPB alone to explain the ischemia.

An interesting lesion was described in 1972 by Cooley et al. (18). These investigators reported thirteen patients (out of 4,732 CPB procedures) who died in the operating room from an unusual type of myocardial failure: small, spastic hearts, rigidly contracted. CPB could not be discontinued in these patients. They coined the term "stone heart" to describe this condition. The clinical features of these patients were similar to the ones described by Najafi et al. (59) and Taber et al. (71). All of these patients had acquired heart disease necessitating open-heart surgery. Eleven were in congestive heart failure and eight had angina. Ten patients were class IV and the remainder were class III categories. Over half had electrocardiographic evidence of left ventricular hypertrophy and most of them had conduction defects prior to operation. Eight patients had left ventricular end-diastolic pressure greater than 20 mm Hg almost all of them had pulmonary hypertension. Eleven had significant aortic valvular disease, five had had aortic valve replacement, and four

had had both aortic and mitral valves replaced. Some common features were found at autopsy: universally there was severe left ventricular hypertrophy grossly and microscopically; interstitial fibrosis was present in twelve, coronary artery disease in eight, and recent evidence of ischemia or acute myocardial infarction only in four patients. The common gross anatomical feature was severe myocardial hypertrophy resulting in a small left ventricular cavity. Most of these cases were due to aortic stenosis resulting in chronic left ventricular failure and myocardial fibrosis. All attempts to reverse the condition during CPB failed. They pointed out that factors leading to the development of "stone heart" should be searched for to prevent this condition in high risk patients.

The effects of continuous ventricular fibrillation current on the myocardium was studied by Reis et al. (62, 63) in 1967 and 1968. They reported that the application of a continuous fibrillating current to the myocardium led to increased vascular resistance in the coronary bed, decreased oxygen utilization and impaired ventricular performance after defibrillation. These changes were not observed when the heart was allowed to fibrillate spontaneously.

The effects of ventricular fibrillation on myocardial perfusion were studied by Hottenrott et al. (37) in 1973. Experiments were done in 23 dogs in which 15 were normal and 8 had supravalvular aortic stenosis.

Blood flow was measured using radioactive microspheres. These investigators found that the spontaneously fibrillating normal hearts had raised left ventricular oxygen consumption and subendocardial flow, with a low vascular resistance. There were no changes in myocardial function following CPB and histochemical studies of the myocardium were normal in these hearts. When hypertrophied hearts were fibrillating spontaneously, on the other hand, oxygen consumption failed to rise, vascular resistance was increased and biochemical evidence of ischemia was present. Ventricular function was also depressed in these hearts following CPB. They concluded that the most physiologic form of preservation during CPB was to allow the heart to beat while empty. Spontaneous ventricular fibrillation may be safe in a normal heart but detrimental to hypertrophied hearts.

Hottenrott et al. (38) in 1974, tested the hypothesis that distension of the fibrillating left ventricle compressed the coronary arteries, impeded subendocardial flow and caused ischemia of the subendocardium. The intracavitary pressure of the left ventricle was raised to 25 mm Hg while perfusion pressure was maintained at 100 mm Hg. There was marked underperfusion of the myocardium during the period of distension. Myocardial oxygen consumption was increased, and, as a result of the raised intracavitary pressure, blood flow failed to increase to the deeper areas. The continuously induced electrical fibrillating hearts had severe subendocardial ischemia.

These studies led Hottenrott et al. (39) in 1974, to compare the effects of spontaneous and continuous electrical fibrillation on

coronary blood flow distribution, myocardial function and metabolism. There were three groups of dogs studied in normal sinus rhythm (NSR), spontaneous fibrillation, and continuously induced electrical fibrillation. Regional blood flow was determined using radioactive microspheres. Coronary blood flow was measured with a flowmeter placed around the coronary arteries. In the normal sinus rhythm groups (working hearts) the total myocardial oxygen consumption was 5.7 cc/100 Gm/min and the left ventricle consumed 8.7 cc/100 Gm/min. With CPB and zero heart work, total oxygen consumption fell to 3.2 versus 3.7 cc/100 Gm/min. With spontaneous fibrillation, the oxygen uptake of the total heart and of the left ventricle rose and was similar to the beating-working hearts. With continuously induced electrical fibrillation, oxygen uptake fell in both the total heart and the left ventricle. Coronary blood flow was 67 $\pm$ 11 cc/100 Gm/min when the heart was beating and working, and decreased to 42 cc/100 Gm/min with CPB (beating empty heart). The spontaneously fibrillating hearts had a total coronary flow of 104 cc/100 Gm/min. The continuously electrically induced fibrillating hearts had coronary flows of 93 cc/100 Gm/min. The distribution of blood flow to the myocardium was normal in both the beating-working and the beating-non-working empty hearts. However, the absolute flow to the subendocardium fell 50 percent when the external work was eliminated by CPB. Spontaneous fibrillation increased the absolute subendocardial flow, whereas electrically induced continuous fibrillation decreased the total left ventricular blood flow, causing

even greater redistribution of blood flow in predilection to the epicardial areas. The vascular resistance was lowest in the beating working and spontaneously fibrillating hearts. It was highest (137 percent) in the continuously induced fibrillating hearts. Beating-working, beating-empty, and spontaneously fibrillating hearts had the same coronary pH, lactate and potassium. Continuously electrically induced fibrillating hearts were acidotic, lactate was lowered and hydrogen ions were produced. Myocardial performance following CPB was normal in the beating hearts. Spontaneously fibrillating hearts showed minimal depression in left ventricular function. Severe depression was noted in the hearts in which the fibrillating stimulus was maintained throughout the procedure. These investigators concluded that total myocardial oxygen consumption falls during electrically maintained fibrillation due to a reduction in oxygen delivery to the left ventricle and due to a redistribution of coronary blood flow to the epicardial areas.

The mechanisms of ischemia during ventricular fibrillation was studied more recently by Hottenrott et al. (40) in 1974. They demonstrated that coronary driving pressure, and the vascular resistance are the main factors determining flow to the myocardium. In the absence of coronary artery disease, the driving pressure equals the aortic root pressure minus the coronary sinus pressure (zero in the vented heart). Resistance to flow, therefore, is primarily determined by the vascular tone in the coronary arteries, and by the compression of these vessels by the surrounding myocardium. The tissue pressure which opposes flow, is due to muscular

contraction of the myocardium. During diastole, the compression forces are reduced, and flow to the myocardium occurs. With ventricular fibrillation, the frequency of asynchronous contractions is high and flow is impeded. Spasm of the coronary arteries, induced by a fibrillating stimulus, may play a role. In the hypertrophied myocardium, these forces (compressive forces during systole by the surrounding myocardium, due to raised intracavitary pressure, and due to myocardial edema) may become excessive, especially in the presence of left ventricular hypertrophy.

Baird et al. (5) in 1971, working on dogs studied the effect of localized ischemia on peak systolic intramyocardial pressure. Ischemia to the myocardium was produced by tying off the coronary arteries at different levels. Localized ischemia caused a fall in the intramyocardial pressure in the area. The intramyocardial pressure of the non-ischemic myocardium of the left ventricle increased in relationship to the simultaneously measured peak systolic intraventricular pressure.

The effect of local epicardiectomy on intramyocardial pressure was studied by Baird et al. (6) in 1971. Local epicardial resections were performed in dogs with simultaneous measurement of the peak systolic intramyocardial pressure. There was a 27 percent decrease in the intramyocardial pressure on the outer half of the denuded myocardium, compared with a 17 percent decrease in the inner half. They concluded that the relation of myocardial systolic pressure was not constant, but rather varied with local manipulation.

Baird et al. (7) in 1970, used an indirect technique to measure intramyocardial tissue pressure. Dogs' hearts were exposed, and a segment of a collapsible blood vessel was passed through the myocardium at a given depth. This preparation was then perfused with saline at a controlled and slowly changing pressure. In the normally beating-working heart, there was a peak systolic intramyocardial pressure gradient which went from a low level pressure near the epicardium to a high level pressure near the endocardium. However, even in the deepest areas of the myocardium the peak systolic intramyocardial pressure did not exceed the intra-ventricular systolic pressure. They concluded that despite the compressing action of the myocardial tissue in systole, some coronary flow was provided to the inner layers of the myocardium.

Baird et al. (8) in 1972, measured the peak systolic intramyocardial pressure and myocardial oxygen consumption in dogs using different coronary perfusion pressures of 50, 100 and 150 mm Hg. These investigators found that even when the intra-ventricular pressure was zero, there still was a systolic intra-ventricular gradient from the epicardium to the endocardium. In the empty beating heart the systolic gradient frequently exceeded the coronary perfusion pressure. Myocardial performance was a function of the level of the coronary artery pressure and flow. An increase in the systolic intramyocardial pressure increased the oxygen consumption of the myocardium.

Baird et al. (9) in 1972, pointed out that even in the empty beating, non-working heart with a near zero intra-ventricular pressure there was an intramyocardial pressure gradient from a low value in the outer epicardial zones to a higher value in the inner endocardial areas. These same investigators (5, 7) and Kirk et al. (47) already had demonstrated the existence of this gradient in a normal working-beating heart. Baird et al. (9) were unable to say whether this pressure gradient was caused by the anatomical location of the myocardial fibers or by the functional (contractile) relationships of the fibers. Since this pressure gradient existed in a normal working heart as well as in an empty, non-working heart, this gradient cannot result from mural transmission of intra-ventricular pressure but must be the result of the inherent structure and function of the left ventricle.

Buckbert et al. (15) in 1971, created left ventricular hypertension by supravalvular constriction of the aorta in fifteen anesthetized dogs and measured phasic flow in the coronary arteries with a flowmeter. Regional blood flow was determined with the use of radioactive microspheres 8 to 10 micra in diameter. The myocardial oxygen requirement increased 161 percent with aortic constriction. Although total left ventricular flow increased 63 percent there was a striking reduction of flow to the inner areas. They concluded that the reduction in subendocardial blood flow occurred because the high ventricular diastolic pressure impeded blood flow. In addition, they observed that the systolic time was increased with a concurrent reduction in the diastolic time.

DESCRIPTIVE ANALYSIS OF PULSATILE VS NON-PULSATILE BLOOD FLOW

Cardiopulmonary bypass procedures are done on a large scale using non-pulsatile blood flow techniques. Although pulsatile perfusion is thought to be superior to non-pulsatile, technical problems have prevented widespread clinical use of the pulsatile technique. We wish to review the physiologic advantages of pulsatile versus non-pulsatile perfusion.

Gesell et al. (25) in 1913, perfused kidneys of dogs with pulsatile and non-pulsatile flows. They demonstrated that while renal flow was independent of the magnitude of the pulse pressure, chloride, urea and nitrogen content of the urine varied directly with the magnitude of the pulse pressure.

Goodyer et al. (29) in 1951, demonstrated in dogs that as long as a constant mean arterial pressure was maintained, the excretion of water and electrolytes as well as the renal clearance of inulin and para-aminohippurate did not vary with either type of perfusion technique.

Selkurt (68) in 1951, and Ritter (64) in 1952, perfused a dog's kidney in situ and demonstrated that changes in arterial pulse pressure alone had no effect on renal blood flow. The renal vessels showed prolonged and significant autonomous variations in resistance following abrupt changes in the arterial pressure which were not due to pulse pressure. These studies and others (25, 29, 64, 68), indicated that the pulse pressure has no apparent role in renal dynamics.

In 1953, Wesolowski (76) perfused the pulmonary circulation of dogs with pulsatile and non-pulsatile perfusion. They noted that the lesser circulation of the lung could be maintained adequately with either type of flow. However, in the systemic circulation, pulsatile perfusion allowed maintenance of normal arterial blood pressure even when blood replacement was less than the blood lost during surgery. Non-pulsatile perfusion caused a systemic hypotension which did not respond even to infusions of blood up to four times the operative loss. This systemic hypotension, however, responded to neosynephrine hydrochloride infusion.

Later, in 1955, Wesolowski et al. (77) compared the effects of pulsatile and non-pulsatile perfusion in dogs and showed that irrespective of the type of flow used, blood pressure, pump minute flow, and blood volume remained constant. Animals in both groups, had normal functioning cardiovascular, renal and central nervous systems reactivity during perfusion. Their experimental data indicated that the total peripheral vascular tone remained wholly unaltered during non-pulsatile perfusion of the systemic circulation. No perfused organs were damaged with the non-pulsatile perfusion technique.

Nakayama et al. (60) in 1963, compared the advantages of pulsatile versus non-pulsatile perfusion in dogs. In the animals perfused with pulsatile flow there was an excellent venous return, a relatively normal and physiologic distribution of blood flow, and better tolerance to high flow. They estimated that pulsatile flow prolonged the safe

perfusion time by 30 percent. In the same study, seven patients undergoing CPB were perfused with pulsatile perfusion. Significantly, none of these patients required gravity force for draining the venous return; and, too, no cardiotonic drugs needed to be used in the post-operative period. There were no cases of post-perfusion syndrome. Post-operative urine output was similar to that after any major surgery.

Mandelbaum et al. (53) in 1965, studied the vascular response in dogs to pulsatile and non-pulsatile flow. The mean systemic resistance during total CPB was elevated in all animals during non-pulsatile perfusion. The mean systemic resistance increased an average of 125 percent compared with that recorded with pulsatile perfusion. Bilaterally nephrectomized dogs also experienced marked elevation in the mean systemic pressure during non-pulsatile perfusion. Following the administration of atropine and phenoxybenzamine hydrochloride, and denervation of the baro-receptors, the systemic pressure in the non-pulsatile groups was 119 percent of that associated with pulsatile perfusion. There was an increase in the pulmonary vascular resistance (127 percent) in the non-pulsatile group as compared with the pulsatile group. In the in vitro studies using plastic tubings, pulsatile and non-pulsatile perfusion produced equal mean pressure changes.

Using myocardial oxygen consumption as the primary indicator, Shepard et al. (69) in 1969, studied the perfusion of the capillary circulation of the myocardium. Mean oxygen consumption in thirteen calves was 101 cc/min/m^2 in the non-pulsatile group, compared to 126 cc/min/m^2 for the pulsatile group. Mean values for venous blood oxygen saturations

were 58.6 ± 8.3 percent for the non-pulsatile, and 40.6 ± 8.2 for the pulsatile group. Peripheral resistance in the non-pulsatile group was eight times that of the pulsatile group. Catecholamine levels in both groups were similar. They hypothetized that the differences in oxygen consumption between the two groups could be due to (1) distortion of the tissues during pulsatile flow, which may act to change the boundary layers of interstitial fluid around cell membrane and thus enhance diffusion; (2) lymphatic and interstitial fluid flow during pulsatile flow may be enhanced; and (3) pulsatile energy may be required to ensure that the normal percentage of the total number of arterioles in a vascular bed are open at any one time.

Trinkle et al. (73) in 1970, studied fifty consecutive patients undergoing elective open-heart surgery and randomly perfused them with either the standard roller pump or the Helton-Pemco Pulsatile pump. They summarized their results indicating the advantages of pulsatile over non-pulsatile flow. There were fewer transfusions required during CPB with pulsatile flow, and the vascular resistance was lower. Additionally, there were higher arterial pH and pO_2, lower lactate/pyruvate ratios, higher venous pO_2, smaller amounts of hemolysis, less defibrination and a smaller decline in hematocrit during CPB with pulsatile flow.

Wakabayashi et al. (75) in 1972, investigated whether coronary flow rate or perfusion pressure should be monitored during ventricular fibrillation, and whether non-pulsatile or pulsatile flow was preferable during ventricular fibrillation. Flow-regulated coronary artery perfusion

was found to be unsafe in a fibrillating heart. This was found to be valid because the thebesian shunt is unpredictable during ventricular fibrillation and poor myocardial perfusion may occur. On the other hand, non-pulsatile perfusion of the coronary arteries resulted in a more variable thebesian flow than did pulsatile perfusion. Furthermore, pulsatile coronary artery perfusion provides a more stable coronary vascular resistance than does non-pulsatile flow. Myocardial oxygen consumption is more stable because of better tissue perfusion during pulsatile flow as compared with non-pulsatile coronary perfusion.

CHAPTER II: BASIC QUESTION

"DOES PULSATILE PERFUSION DURING CARDIOPULMONARY BYPASS HAVE A BENEFICIAL EFFECT IN PROMOTING A MORE PHYSIOLOGIC DISTRIBUTION OF BLOOD FLOW TO THE MYOCARDIUM?"

CHAPTER III: DESIGN AND METHODOLOGY

In order to perform the experiment it was necessary to produce left ventricular hypertrophy in pigs. Supravalvular aortic stenosis was surgically created in 30 young pigs which were allowed to survive to adulthood (Figures 1 and 2). Cardiopulmonary bypass was instituted 16 weeks later, at which time all of the animals were found to have a significant degree of myocardial hypertrophy (Figure 3). All experimental conditions were maintained constant and the only variables were the pump flow, the type of perfusion and the rhythm of the heart. Myocardial blood flow distribution was studied using the microsphere method.

A. METHODOLOGY

1. Creation of Left Ventricular Hypertrophy

The infant pig was induced with 1-2 cc Sodium Thiopental, 50 mg/cc (Pentothal Sodium, Abbott Laboratories) via an ear vein, intubated with a pediatric endotracheal tube (12) and connected to a volume respirator on 100% oxygen. Anesthesia was maintained with Sodium Thiopental 4 mg/cc, the animal being "titrated" as to the depth of the anesthesia. No gas anesthesia and/or paralysing agents were given. A 5 cm incision was made in the area of the third interspace, the pectoralis muscle was spread in the direction of the fibres and the chest was entered with minimum bleeding. The ribs were gently spread apart. The phrenic nerve overlying the pericardium was identified in order to avoid injury. By index finger palpation, the aorta was identified. The thymus overlying it

was mobilized by sharp dissection with scissors and the pericardium was entered directly over the aorta. Stay sutures were placed in the pericardial edges in order to obtain a good view of the aorta. Rather than incising the visceral pericardium overlying the ascending arch, we used the transverse sinus route to encircle both the aorta and the pulmonary artery, thereby avoiding serious bleeding and trauma to these major vessels. We then dissected a well defined plane between the pulmonary artery and the aorta and withdrew the silk suture encircling the pulmonary artery. The aorta alone was thus encircled. The circumference of the aorta was measured using the same silk suture. A dacron graft 1.5 cm wide, and one third less in length than the silk, was then secured in place around the aorta. The graft ends were then sutured to each other and no sutures were placed in the vessel wall.

A thrill could be felt over the ascending arch after the banding. The pressure gradient measured at this time was 8 to 15 mm Hg across the stenotic segment. The pericardium was closed with two interrupted sutures. A small chest tube was left in place and removed when the pig was breathing on its own and there was no air leak. The ribs were approximated with pericostal sutures. The pectoralis muscle was approximated and the skin was closed. Using an Ambu bag, the lungs were completely re-expanded and the trachea was suctioned with a pediatric feeding tube.

Chloramphenicol 12.5 mg/Kg/day was given intramuscularly for the first five days post-operatively and the animals were then allowed to survive to adulthood.

2. Cardiopulmonary Bypass in the Pig

a) Anesthesia

At 16 weeks of age the banded animals were induced and intubated as in the banding procedure above. Most of the hypertrophied pigs were in severe congestive heart failure and were very vulnerable to hypoxia. After gentle induction with Sodium Thiopental via an ear vein, the animal was immediately tied on its back while breathing on its own. The mouth was held open by an assistant and the animal was then intubated. Anesthesia during CPB was maintained with a Pentothal drip alone in dose of 4 gm/500 cc of normal saline. Morphine, 5 mg, injected into the pump, was used during CPB.

b) Arterial and Venous Cannulations

In pigs the subclavian artery is the best artery for infusion because the other arteries are small and fragile. Attempts in cannulating the ascending aortic arch are usually unrewarding as the vessel falls apart. Ligation and cannulation of the proximal innominate artery is undesirable as it leads to cerebral death as both carotid and subclavian arteries derive from this vessel.

The animal was properly anesthetized, prepped and draped and heparinized. A small transverse incision was then made in the right neck. The subclavian artery was isolated and encircled with umbilical tapes distally and proximally. A small arteriotomy was performed and a 10 mm Morris aortic arch cannula was inserted into the vessel and secured in place with heavy silk ties.

Due to the deep position of the major vessels in the chest (Fig. 4), a bilateral thoracotomy, muscle-splitting incision was made from both axillae towards the second or third costochondral junctions. The heart and lungs were adherent to the left chest wall due to the previous surgery. The left internal mammary artery was cannulated in order to measure arterial pressures. A lower third sternotomy was then performed.

Following the initial banding procedures in these animals the thymus becomes enlarged and minimum amount of it was dissected to avoid bleeding. The pericardium overlying the right atrial appendage was then opened. Two separate pursestrings of 3-0 silk were then placed anteriorly in the right atrial appendage for individual cannulation. With a pointed knife, a small stab wound was made in the center of the pursestring. Bleeding was controlled with finger pressure. A 10 mm Bardex tube with side holes was then inserted into the atrium and the pursestring snared. The same procedure was repeated for the second Bardex tube inserted into the right atrium.

c) Decompression of the Ventricles

In order to avoid distension of the ventricles, right and left vents were inserted prior to CPB. A pursestring of 3-0 silk was placed in the wall of the ventricle, a stab wound was made with a sharp knife, the cannula was inserted into the ventricular cavity and the pursestring was snared.

d) The Azygous System

Both azygous veins were tied off in order to measure coronary artery blood flow, as the right azygous vein drains into the superior vena cava and the hemiazygous into the right atrium.

e) Control of the Pulmonary Artery

In some pigs control of the pulmonary artery was difficult due to severe adhesions between the pulmonary artery, the left atrial appendage and the aorta. For this reason, a vascular clamp had to be used to cross-clamp that vessel as an alternative to encircling it with umbilical tape.

Figure 5 shows an overall view of the cardiopulmonary bypass procedure during one of our experiments.

f) Myocardial Temperature

The intramyocardial temperature, measured by a probe, was maintained at 37 degrees C throughout the experiments.

g) Blood Pressure Recordings

Either the internal mammary artery or the femoral artery was used to measure blood pressures during CPB. Pressures were recorded by a Sanborn recorder with the use of a Statham transducer.

h) Pump Prime

Lactated Ringer's solution (500 cc) with 500 cc of 6% Dextran 75 (Gentran 75 in 0.9% NaCl, Travenol Laboratories) was used for priming the pump. Sodium Bicarbonate (NaHCO3) 88 mEq and Potassium Chloride (KCl) 20 mEq were added to this solution. Prior to CPB the solution was warmed up to 37 degrees C.

i) Measurement of Coronary Blood Flow

Coronary blood flow was measured by snaring the superior and the inferior vena cava, tying off both the azygous veins and snaring the pulmonary artery (Fig. 6). The effluent of the right ventricular cavity was taken as the coronary blood flow, and was measured by collecting the sample in a calibrated cylinder for one minute. Multiple measurements were made at regular intervals and the average of these measurements was taken as the coronary blood flow for a given pump rate.

B. DETERMINATION OF BLOOD FLOW

1. Radioactive Microsperes

Carbonized tracer microspheres (3M Company, Nuclear Products, St. Paul, Minnesota) were used to measure the distribution of blood flow

in the myocardium. These spheres measured 15 ± 5 micra in diameter and were labelled with the following different gamma-emitting isotopes:

Iodine (I)^{125}

Cerium (Ce)^{141}

Strontium (Sr)^{85}

Niobium (Nb)^{95}

These microspheres had an absolute density of 1.3 gm/cc, in a suspension of 20% Dextran. 5% Tween - 80 (polyoxyethylene sorbitan mono-oleate) was added to prevent clumping of the spheres. The lowest average number of spheres injected was 44,000 for Nb^{95}, and the highest was 969,000 for I^{125}. Prior to injection, the syringe was shaken for 10 minutes to allow for complete mixing and was then weighed. A single injection into the arterial line was then carried out as close to the pump as possible. The syringe was then reweighed and the amount injected accurately determined.

a) Preparation of the Standard Solution

The amount of radioactive counts injected at each flow rate was accurately determined by comparing the amount of isotope injected with a standard solution. This standard solution was prepared from the same vial as the isotope injected. The standard was counted at the same time as the other samples of the heart and contained 0.1 microcuries of the isotope.

C. EXPERIMENTAL GROUPINGS

The animals were divided into three distinct groups of five hypertrophied pigs each:

Group I : Normal sinus rhythm (NSR) perfused with the roller pump.

Group II : Ventricular fibrillation (VF) perfused with the roller pump.

Group III : Ventricular fibrillation (VF) perfused with the pulsatile pump.

In each group, normothermic CPB was instituted and the highest flow obtained was maintained for 90 minutes. At that time, pump flow was decreased in increments so that there were four different pump flows of 70, 50, 40 and 20 cc/Kg/min. Each animal was maintained at a given flow for 20 minutes. At each flow level, a different solution of microsphere was injected. Ten minutes after injection, that flow was changed to a lower flow level. The total time on CPB was 180 minutes. The heart was weighed at the end of the experiment.

D. PREPARATION OF THE MYOCARDIUM FOR RADIOACTIVE COUNTING

The heart was cleared of fat and pericardium, the atria were removed, and the free wall of the left and right ventricles were weighed. The interventricular septum was weighed with the left ventricle (free wall weight = entire heart - septum). Four samples of the free wall of the left ventricle and interventricular septum were taken for wet-counting

determination. The heart was then fixed in buffered formaldehyde for 12 hours, which allowed for easier handling of the tissue. The free wall of the left ventricle was then divided into three layers of equal thickness (epicardium, midmyocardium and endocardium) and the interventricular septum was equally divided into two layers (right and left). Each individual layer was then minced, dried at 37 degrees C for 48 hours and then weighed, and inserted into test tubes for radioactive counting. Each tube represented part of one layer. There were six tubes for each layer. The average of their counts represented the counts/min/gram of dry myocardium.

E. CALCULATIONS

The distribution of blood flow to the free wall of the left ventricle and interventricular septum was determined by the following ratios:

1) $\frac{\text{counts/min/gram of dry epicardium}}{\text{counts/min/gram of dry endocardium}}$

2) $\frac{\text{counts/min/gram of dry right interventricular septum}}{\text{counts/min/gram of dry left interventricular septum}}$

Coronary artery resistance was determined by the ratio of aortic root pressure divided by the coronary artery flow. Total body resistance was calculated from the aortic root pressure divided by the pump flow.

The percentage of the coronary flow to each layer was calculated in the following way:

1) counts/min/gram of epi + mid + endo = total counts

2) $\frac{\text{counts epicardium}}{\text{total counts}}$ = Percentage of counts to the epicardium

3) $\frac{\text{counts mid-myocardium}}{\text{total counts}}$ = Percentage of counts to the mid-myocardium

4) $\frac{\text{counts endocardium}}{\text{total counts}}$ = Percentage of counts to the endocardium

Blood flow to each layer was then calculated by multiplying the percentage of counts in an individual layer by the total measured coronary flow. Therefore:

1) Total blood flow to the epicardium = percent of counts epicardium times the total coronary flow

2) Total blood flow to the mid-myocardium = percent of counts mid-myocardium times the total coronary flow

3) Total blood flow to the endocardium = Percent of counts endocardium times total coronary flow

CHAPTER IV: THE EXTRACORPOREAL SYSTEMS

An elaboration on the use of the pulsatile pump is presented because of the numerous technical problems involved in its operation.

During our experiments two different types of CPB pumps were used: the Sarns roller pump and the Bentley pulsatile pump. Only the Bentley pulsatile pump will be described.

1. THE OXYGENATOR

Bentley Temptrol pediatric "bubble" oxygenators were used. Oxygen flow ranged from four to six liters per minute.

2. THE ARTERIAL CANNULAE

A 10 mm Morris aortic arch cannula was used in most of the experiments. This size of cannula is necessary because of the large gradient of pressure created across the cannula with pulsatile flow.

3. THE BENTLEY PULSATILE PUMP

A portable unit was provided by the Bentley Laboratories (Fig. 7). The pump itself is powered by any inert compressed gas at a pressure of 50 to 125 lbs per square inch (psi). Electrical power for the pump's electronic control system is provided by four D-size batteries. The actual recording of the arterial blood pressure before and during CPB using the pulsatile pump is shown in Figures 8 and 9.

The disposable ventricle (Fig. 10) is made of a thin, tough, durable polyurethane with polycarbonate inlet fittings which contain moulded silicone rubber inlet and outlet valves. The ventricle is made relatively antithrombogenic by having uniform negative charges in its inner surface.

The valves are made so as to allow undirectional laminar blood flow. These valves have negligible opening and closing pressures and have a low pressure differential during flow.

The pump actuator and housing consist of an aluminum chamber containing a working diaphragm actuated by an air cylinder. Pumping action is achieved when the diaphragm squeezes the ventricle inside the pump chamber. Stroke volume of the cylinder can be varied from zero to 100 cc per stroke. Stroke rate may also be varied from 20 to 120 strokes per minute. The pulsatile ventricle is capable of functioning at an average perfusion rate of zero to 6 liters per minute. This pump is not a positive displacement device but its perfusion rate varies with demand. If the venous return decreases, the stroke volume will decrease and the perfusion rate will also decrease. If the arterial pressure increases, the time for systole will increase and the pulse rate and perfusion rate will decrease.

4. DETERMINATION OF BLOOD FLOW

In order to determine flow rate of the pump, a flowmeter was inserted in the arterial line between the pump and the cannula because the pump does not contain a flowmeter.

5. THE USE OF AUTOTRANSFUSION

Blood loss before CPB was negligible and blood lost prior and during CPB could be suctioned into the oxygenator by a second roller pump.

A blood filter (400 micron pore size*) was inserted between the pump and the oxygenator in the suction device. Maintenance of adequate flow rates in these animals was made possible by donor blood from another pig. Ringer's lactate was also used to replace blood loss. Hematocrits were never below 17 percent at the end of CPB, with a mean value of 19.3 ± 2.1 percent.

6. CONTROL OF HEART RHYTHM

All of the hearts remained in normal sinus rhythm (NSR) after institution of CPB and had to be fibrillated when desired. During CPB no heart in NSR went into ventricular fibrillation, however, the fibrillating hearts, especially the ones perfused with the pulsatile pump had to be fibrillated once or twice during the experiment, as they tended to revert to NSR. Fibrillation, when needed, was achieved with a single AC-shock pulse.

7. PROBLEMS WITH THE PULSATILE PUMP

a) Size of the arterial cannula

A 10 mm Morris aortic arch cannula had to be used for the pulsatile pump experiments. The arteries of adult pigs were small and cannulation of these vessels was difficult. In two cases, an 8 mm cannula had to be used in order to avoid cannulation of the innominate artery.

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* Bentley Laboratories

b) Pressures generated by the pump

The gradient of pressures across the arterial cannula at extremes were in the range of 440 mmHg, and varied between 60 and 500 mmHg. The pump generates a maximum pressure of 500 mmHg in the arterial line after which a safety device turns it off. Using an 8 mm cannula, the mean gradient across the cannula was 150 $\pm$ 40 mmHg. Pressures between the oxygenator and the pulsatile pump ranged from -20 mmHg during filling to +40 mmHg during closure of the ventricle valve. At the vena cava site with the pump about one meter below the pig's heart, the pressure was in the range of -10 mmHg. Sucking of air into the right ventricle at the vent site was at times a problem, creating minor air locks in the venous drainage line.

c) Aortic root pressures achieved with the pulsatile pump

Severe vasodilatation occurred in the animals perfused with the pulsatile pump. Pressure recording in the ascending aorta, without use of any vasoactive drugs, had highest values of 65 mmHg and lowest at 35 mmHg. At that site, a nice pressure tracing (see Fig. 9) was seen in all cases. However, if the pressure recording was taken in the femoral artery the pressure curve was similar to one in the roller pump. The effect of the pulsatile flow at the periphery appeared to have been damped.

d) Flows and pressures

In most of the cases, aortic pressure was low with maximum pulsatile pump flow. This was of major concern to us during the experiment. Without the use of vasoactive drugs, we were unable to raise the arterial pressure. The pulsatile pump, when tested with normal saline and using

no cannulae, puts out flows in the range of 6 l/min at maximum readings. However, when tested with blood and under the same conditions, flow above 5 liters could not be obtained, perhaps due to the viscosity of blood. Therefore, even though aortic root pressures were low, perfusion was in the range of 4.5 to 5 l/min and we could not raise that perfusion due to inability of the pump to cope with that volume load in face of the severe peripheral vasodilatation.

e) Ventricle (pump) problems

Miniscule bubbles accumulated in the ventricles during recirculation in the oxygenator-pump system prior to bypass. In spite of efforts to remove them, they persisted to the end of CPB. Perhaps when one uses new ventricles, this is not a problem but we feel that air embolus in the arterial line is a major problem.

Leaking of these ventricles was a second minor problem encountered in three consecutive cases of our experiments. When testing the ventricles prior to bypass, by circulating fluid with a partially occluded outflow of the pump, no leak was observed. However, soon after bypass, minor to severe leaks occurred necessitating, in one case, a temporary switch to the roller pump. When leakage occurs, no matter to what degree, it is a serious problem. The ventricle lies in contact with the air-driven piston and damage to the equipment may occur.

f) Pump flow determination

Unfortunately, the pulsatile pump does not have a flowmeter. Trying to calculate flow by stroke volume of the pump multiplied by the rate is inaccurate. For a given reading of piston compliance, the stroke volume is not constant as it varies with venous return. Again, for a given rate setting of the pump, one may find that the pump rate is actually 30% off that reading. This is explained by the fact that as one increases the rate, the pump is unable to keep up with the high compliance and therefore slows the rate.

g) Pump rate vs heart rate

The pump rate ranges between 20 to 120 pulses/min according to specifications. However, for high compliances, pump rate above 60-70 pulses /min lead to lower pump output. If one tried to further increase pulses to 100/min, the pump remained at 70 to 80/min, unless compliance was significantly decreased. Another problem is that, normally, pigs' heart rate is around 130/min, a rate we could never achieve with the pump device.

h) Emergency device

In case of power failure (electric or gaseous), one can work the pump by using a crank. However, this crank case is located on the back of the pump underneath the arterial outflow line. The motion of the crank is only 180 degrees so that one has to perform a back and forth movement. We think that this safety device ought to be located elsewhere in the pump, away from the arterial or venous lines, and it ought to have 360 degrees motion to work properly.

CHAPTER V : RESULTS

The following data demonstrates that the experimental model produced the required left ventricular hypertrophy in all groups.

1. HEART WEIGHT IN ALL GROUPS

Heart weights in the three experimental groups are shown in Table I and Graph A. The data demonstrate that myocardial hypertrophy was achieved to the same degree in these three groups of animals. Normal animals had a mean heart weight of 210.0 ± 3.9* grams, as compared to 457 ± 8.7 grams for NSR roller, 370.0 ± 10.2 grams for VF roller and 384.0 ± 9.1 grams for VF pulsatile. This difference was statistically significant by an analysis of variance.

2. DEGREE OF LEFT VENTRICULAR HYPERTROPHY

An important variable during the experiment was the degree of left ventricular hypertrophy.. This was determined by the ratio of left ventricle weight/body weight (Table II). The groups were homogenous as can be seen by the ratios of 6.58 ± 1.07** for NSR roller, 7.01 ± 0.80 for VF roller and 7.23 ± 1.20 for VF pulsatile. There was no significant difference in these three groups of animals (analysis of variance). When compared to control, normal animals, with a left ventricle/body weight ratio of 3.95 ± 0.98, that difference was significant.

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* Standard error of the mean

** Standard deviation

RESULTS OF STUDY OF MYOCARDIAL BLOOD FLOW

3. Distribution of blood flow to the free wall of the left ventricle

The distribution of blood flow to the free wall of the left ventricle was determined by the relative counts of the microspheres in each layer. Table III and Graph F show this distribution as the ratio of epicardial blood flow/endocardial blood flow.

At high flows of 70 cc/min/Kg there was no significant difference* between the three groups. However, as flows declined from 70 cc/min/Kg to 20 cc/min/Kg, the epicardium/endocardium ratios changed from 1.47 $\pm$ 0.12 to 4.22 $\pm$ 0.52 for NSR roller, 1.42 $\pm$ 0.07 to 7.18 $\pm$ 1.67 for VF roller, and 1.32 $\pm$ 0.09 to 11.49 $\pm$ 1.81 for VF pulsatile.

The amount of blood flow in cc/min to each layer of the myocardium is shown on Graph B. At high perfusion of 70 cc/min/Kg both the epicardium and the endocardium are well perfused, and received approximately the same amount of blood in all three groups. As the perfusion rate decreases the subendocardium of all three groups is relatively underperfused as compared to the epicardium. There was no difference in the amount of blood flowing to the endocardium of all three groups. The epicardium of the fibrillating hearts, however, received more blood flow as compared to the NSR hearts. Presumably this blood has been redirected from the endocardial areas to the epicardial areas of the fibrillating hearts, since endocardial blood flow was equal in all three groups.

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* Analysis of variance

4. Calculated blood flow to each individual layer of the myocardium

Tables IV, V and VI, and Graphs C, D and E, show the calculated distribution of blood flow to each individual layer of the myocardium at high and low flows. Table IV shows that at high flows of 70 cc/min/Kg, 37.4 percent of the total coronary flow went to the epicardium and 30.6 percent went to the endocardium of the NSR roller group. As pump flows dropped to 20 cc/min/Kg, however, 46.8 percent of the flow went to the epicardium as compared to 13.3 percent to the endocardium. Although this reflects a rather large epicardium/endocardium ratio, it is of interest to note that a greater percentage of the total flow actually went to the epicardium. In other words, the epicardium/endocardium ratio is high not only because of less endocardial flow but also because of a larger epicardial flow.

Table IV shows the calculated distribution of blood flow to the myocardium of the VF roller group. At high flow rates of 70 cc/min/Kg, 38.0 percent of the total coronary flow went to the epicardium and 21.4 percent to the endocardium. As the perfusion pressure dropped to 20 cc/min/Kg, 50.8 percent of the total flow perfused the epicardium and only 7.2 percent perfused the endocardium.

Table VI shows the calculated blood flow to the VF pulsatile group. At high flows of 70 cc/min/Kg 36.4 percent of the coronary flow perfused the epicardium and 24.4 percent perfused the endocardium. At

perfusion rate of 20 cc/min/Kg, 45.2 percent of the coronary flow went to the epicardium and only 1.7 percent perfused the endocardium. As in the VF roller pump group, blood was redistributed to the epicardium at low pump flows.

Graphs C and E demonstrate the distribution of myocardial blood flow at flow rates of 70 cc/min/Kg. As can be seen, there is no difference between the three groups. One should observe that the mid-myocardium of the VF groups is relatively overperfused as compared to the NSR group. However, the subendocardium of all three groups are markedly underperfused at low flow rates (Graph D and E), with a large proportion of the blood flow being redirected to the epicardium.

5. Distribution of blood flow to the interventricular septum

Similarly, the interventricular blood flow distribution was determined by the ratio of right interventricular septum/left interventricular septum blood flow (Table VII). The interventricular septum behaved in a similar manner as the free wall of the left ventricle. At high flows of 70 cc/min/Kg, the right and the left septa were equally perfused. As flows declined from 70 to 20 cc/min/Kg, however, the ratio of right interventricular septum/left interventricular septum also changed from 1.31 $\pm$ 0.18 to 2.61 $\pm$ 0.43 for NSR roller, 3.52 $\pm$ 1.31 to 20.73 $\pm$ 10.73 for VF roller, and 2.72 $\pm$ 1.51 to 15.11 $\pm$ 9.38 for VF pulsatile.

6. Aortic pressure vs pump flow

Table VIII and Graph G show the relationship of aortic root pressures and pump flows. Aortic pressures were high during maximum perfusion rates, and were low when the perfusion pressure decreased. The drop in blood pressure in the VF pulsatile group was much less than in the other two groups. At high pump flows of 70 cc/min/Kg aortic root pressures were 72.0 ± 10.6 for NSR roller, 66.60 ± 4.90 for VF roller, and 43.6 ± 4.80 for VF pulsatile. The pulsatile group had the lowest pressures although flows were adequately high, meaning that the animals were severely vasodilated.

7. Coronary artery flow

The relationship of coronary blood flow and pump flow rate is shown in Table IX and Graph H. At high flows of 70 cc/min/Kg, the fibrillating hearts had the highest coronary blood flows with mean values of 105.0 ± 7.0 for VF roller, and 102.0 ± 6.4 for VF pulsatile. In contrast, the NSR roller group had the lowest coronary perfusion rate with mean values of 80.2 ± 4.7. The same relationship was maintained at low pump flows.

8. Coronary artery resistance

At high flows coronary artery resistance was lowest for the VF roller group with mean values of 0.67* ± 0.08, as compared to 0.68 ± 0.08 for VF pulsatile, and 1.02 ± 0.25 for NSR roller (Table X). The same relationship was maintained at low flow rates.

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* PRU

9. Total body resistance

Because total body resistance played an important role in the experiment especially during pulsatile perfusion, determination of total peripheral resistance was carried out (Table XI). At high flows, the VF pulsatile group had the lowest total body resistance with mean values of 0.73 $\pm$ 0.08 PRU, as compared to 0.87 $\pm$ 0.21 PRU for VF roller and 1.18 $\pm$ 0.13 PRU for NSR roller. At low flows, however, VF roller had the lowest values at 0.86 $\pm$ 0.25 PRU, followed by the VF pulsatile at 1.25 $\pm$ 0.22 PRU and NSR roller at 1.47 $\pm$ 0.30 PRU.

CHAPTER VI : DISCUSSION

The object of this study was to determine whether pulsatile perfusion had any beneficial effect in promoting a normal distribution of blood flow across the myocardium during cardiopulmonary bypass.

The model chosen for study was the pig heart which had been hypertrophied by means of supravalvular aortic stenosis.

It has been previously noted that myocardial hypertrophy and ventricular fibrillation were important predisposing factors which resulted in ischemia to the subendocardium during CPB (14, 18, 36, 41, 59, 71). This ischemic process culminated in a well known clinical entity known as concentric hemorrhagic necrosis of the myocardium (59). Concentric hemorrhagic necrosis of the myocardium lead to inability of the heart to support the circulation at the end of CPB. Even if the patient survived with the aid of cardiotonic drugs, the resulting low-output-syndrome, which invariably occurred early post-operatively, often resulted in death. It was this early or late post-operative death which continued to pose a problem for the cardiac surgeon. Concentric hemorrhagic necrosis of the myocardium lay at the crux of this problem.

At the Royal Victoria Hospital concentric hemorrhagic necrosis had occurred exclusively in patients with left ventricular hypertrophy due to aortic stenosis who had undergone CPB procedures. However, there has been a decrease in the incidence of this lesion during recent years (1973 and 1974). It may well be that during CPB procedures, ischemia was now occurring less frequently. There unfortunately was no good data

to either disprove or substantiate these findings. Additionally, overall results may be better solely because of better selection of patients who were younger in age with a healthier myocardium. Recently, several factors have contributed to greater safety in bypass surgery, such as, the use of the intra-aortic balloon counter-pulsation devices in high risk patients, the use of cold saline to cool the heart, better anesthesia, and the prevention of post-operative hypertension. Finally, the maintenance of high pump flows and high perfusion pressures are deemed essential in CPB procedures (10). We now recognize that concentric hemorrhagic necrosis of the myocardium is primarily due to ischemia to the inner areas of the endocardium. By maintaining the perfusion pressure at high levels we may minimize this endocardial ischemia process.

Induced ventricular fibrillation has been used to produce a quiet operative field. Awareness of the deleterious effect of ventricular fibrillation on the redistribution of blood flow away from the endocardium has been born out in several animal and human studies (11, 37, 38, 39, 40, 62). The fibrillating current is immediately turned off once ventricular fibrillation is induced, as it has been shown to be very harmful by causing spasm of the coronary artery (40) and redistribution of blood flow away from the inner myocardium (39). Allowing the heart to beat spontaneously while empty (9, 39) appears to be the most desirable way to preserve the endocardium in high risk patients with hypertrophied hearts.

In recent years a renewal of interest in the myocardial tissue pressure (43) has come about in an attempt to better understand the hemodynamics of the coronary circulation during CPB procedures. The inherent intramyocardial tissue pressure of the normally beating heart has been studied (5, 7, 8, 9, 43, 47) and compared to the unphysiologic conditions encountered in the operating room. Some of the factors considered have been the following: local epicardiectomy (6), decrease in coronary artery perfusion (8), increased intracavitary pressure (1, 38) and ventricular fibrillation (11, 37, 39, 40). The role of myocardial cell edema (40) as a compressive force impeding blood flow has been recently brought to light and will certainly be a subject of much further discussion and research in the future. Myocardial blood flow in systole has been shown to occur (2, 7, 78) and appears to be primarily directed to the epicardial areas (24). Loss of this phasic flow may be important in causing ischemia to the endocardium, especially if there is compensatory vasodilatation or constriction of the different areas of the myocardium during systole and diastole. If the systolic auto-regulation is related to and depends upon diastolic auto-regulation, absence of either during ventricular fibrillation could cause abnormal regulation of the vascular tone and thus lead to abnormal distribution of blood flow.

Ventricular distension due to raised intraventricular cavitary pressure may occur during CPB and has been shown to be harmful to the endocardium (1, 7, 38). Awareness of this phenomenon lead to the de-compression of ventricle during cardiopulmonary bypass procedures.

Although most of the CPB procedures in North America are done using non-pulsatile perfusion techniques, pulsatile perfusion is simply more physiologic. Despite the proven safety, reliability and simplicity of non-pulsatile perfusion several investigators have used pulsatile perfusion in animals (25, 29, 53, 60, 68, 75, 76, 77) and humans (60, 73), and these investigators have pointed out the beneficial effects of pulsatile perfusion.

It appears from our experiments that the perfusion rate is the major determinant of myocardial blood flow distribution during CPB. This is in agreement with the work of Baird et al. (10). At high pump rates of 70 cc/min/Kg both the epicardium and the endocardium are well perfused, irrespective of rhythm and without regard to the type of extra-corporeal systems used. However, as the perfusion rates declined from 70 cc/min/Kg to 20 cc/min/Kg, the subendocardium is relatively under-perfused as compared to the epicardium. Although the endocardium in the NSR group is slightly better perfused at low pump rates, this difference is not statistically significant, as compared to the fibrillating hearts. The epicardium of all three groups is well perfused at all flow rates. As pump flow declines, blood is redirected towards the epicardium. This was clearly demonstrated in graph B, and tables IV, V and VI, showing the actual coronary blood flow to each layer. Graph E demonstrates that the percent of blood flow to the epicardium actually increased relative

to the endocardium, as pump flows declined. Therefore, the ratio epi/endo per se does not really tell us what is happening to the blood flow distribution nor does it define the actual differential amount of blood flow to each layer. Flows to the midmyocardium had a similar pattern, as the epicardium. However, one should note that the midmyocardium received a greater percentage of blood flow than the epicardium in the fibrillating hearts at high pump flow rates.

Although the pump flow rate was similar in all three groups, as determined by a flowmeter inserted into the arterial line, the aortic root pressure and, therefore, the perfusion pressure, was not similar in all three groups. As can be seen in graph G, the VF pulsatile group had the lowest aortic perfusion pressures. This was mostly due to the severe peripheral vasodilatation that occurred in all animals perfused with the pulsatile pump.

Blood flows to both the interventricular septum and the free wall of the left ventricle were similar. The left ventricular side of the septum was well perfused at high flows and ischemic with low flows. This could explain the anatomic distribution of the lesion seen in concentric hemorrhagic necrosis which characteristically involves the left side of the septum. The etiologic rationale for the left side of the interventricular septum behaving differently in terms of perfusion dynamics from its counterpart on the right side remains unexplained.

It is important to note that coronary artery blood flow is significantly higher in the fibrillating hearts. The graphs C and D demonstrating blood flow to the individual layers of the myocardium clearly show that most of the excess flow in the fibrillating groups went to the superficial layers. The endocardium remained relatively underperfused. We postulate that there is less resistance in these surface vessels as compared to the deeper areas, and therefore perfusion is enhanced in these more superficial vessels.

Accordingly, coronary vascular resistance had high values in the NSR groups and low values in the fibrillating hearts. VF roller and VF pulsatile groups had the same calculated vascular resistance. This data substantiates the work of others (30, 33, 47, 65) in which the heart action appeared to impede blood flow due to myocardial compression.

Other investigators (53, 73) have confirmed that pulsatile perfusion by whatever mechanism promoted more peripheral vasodilatation. That non-pulsatile perfusion appears to raise the vascular resistance has also been corroborated by the previous investigators (53, 73). It is of interest to speculate why peripheral perfusion appears to be markedly improved by pulsatile perfusion whereas pulsatile and non-pulsatile techniques gave similar coronary perfusion.

An important factor to be considered in our experiments is that the flows in all groups were comparable. The perfusion pressures, on

the other hand, were different in all three groups. This was due to the fact that the pulsatile group was severely vasodilated peripherally and the systemic pressure could not be raised due to technical difficulties. One can postulate that ideally this ought to be the situation if the data is valid. Most of the investigators at present agree that pressure is the important determinant of coronary flow (10) and flow distribution.

With the present pulsatile device which is far from being ideal for human use, we have found no advantage in abandoning the conventional roller pump. We believe that to maintain as high a flow as possible, irrespective of rhythm, is one of the most important factors in preventing ischemia. Although we agree that the hypertrophied fibrillating myocardium is better off if allowed to beat spontaneously while being operated upon, with high flows the subendocardium should be well perfused. As we learn more of the factors involved in myocardial blood flow dynamics during CPB, we will hopefully be able to prevent a lesion which, for the present time, poses a major threat to patients undergoing cardiopulmonary bypass procedure: ischemia with resulting concentric hemorrhagic necrosis of the myocardium.

CHAPTER VII : CONCLUSION

The effects of pulsatile and non-pulsatile perfusions in the distribution of blood flow to the myocardium during cardiopulmonary bypass was studied using radioactive microspheres. Pump flow rate appeared to be the most important determinant in promoting normal distribution of blood flow across the myocardial wall. At high perfusion flows the endocardium was well perfused irrespective of rhythm and type of perfusion. However, at borderline low flow rates subendocardial ischemia developed in all groups but was more pronounced in the fibrillating hearts. The deleterious effects of ventricular fibrillation on the myocardium were not counteracted by the use of a pulsatile pump.

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FIGURES AND ILLUSTRATIONS

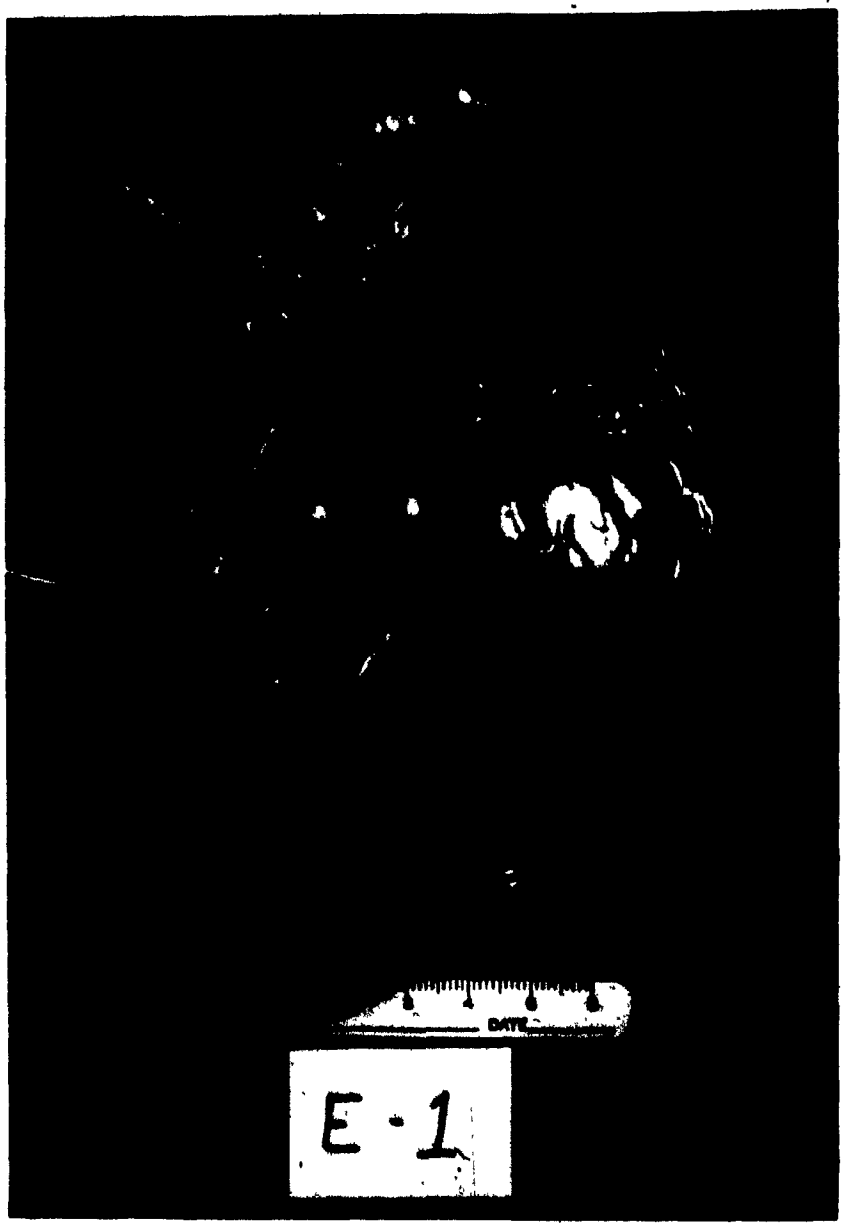


Figure 1. Heart showing site of banding.

Figure 2. Open aorta to show the stenosis

Figure 3. Heart in cross section showing LV hypertrophy

Figure 4. Picture showing the pig's anatomy

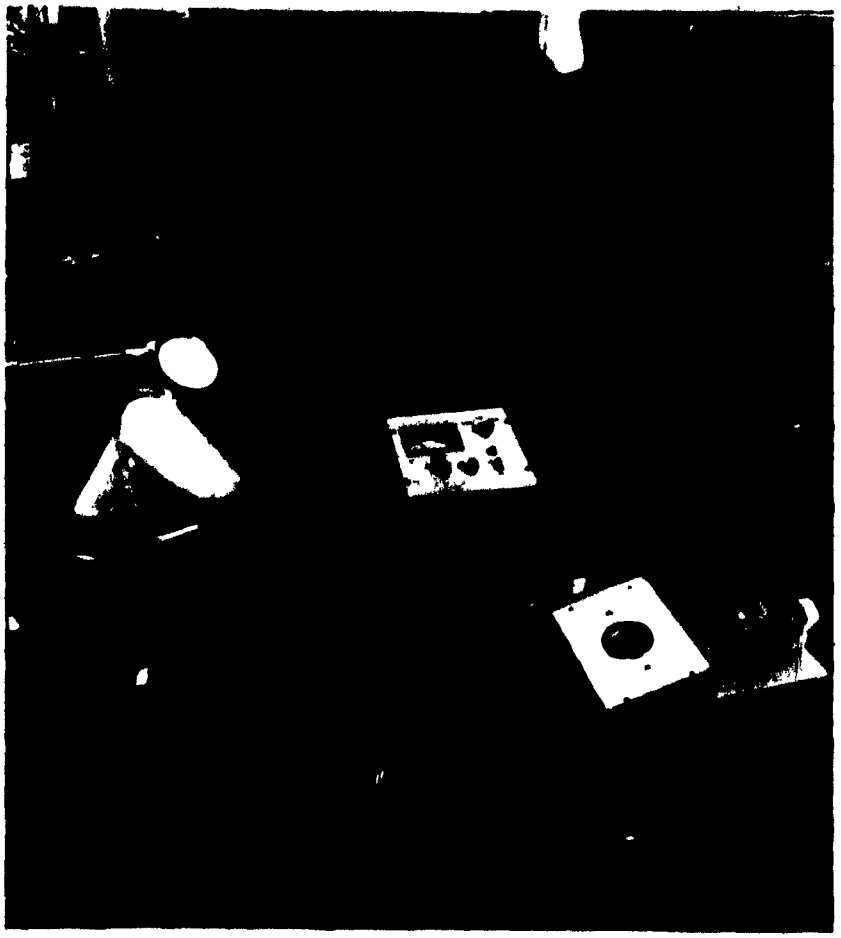


Figure 5. Overall view of CPB of pigs

Figure 5a. Overall view of CPB of pigs

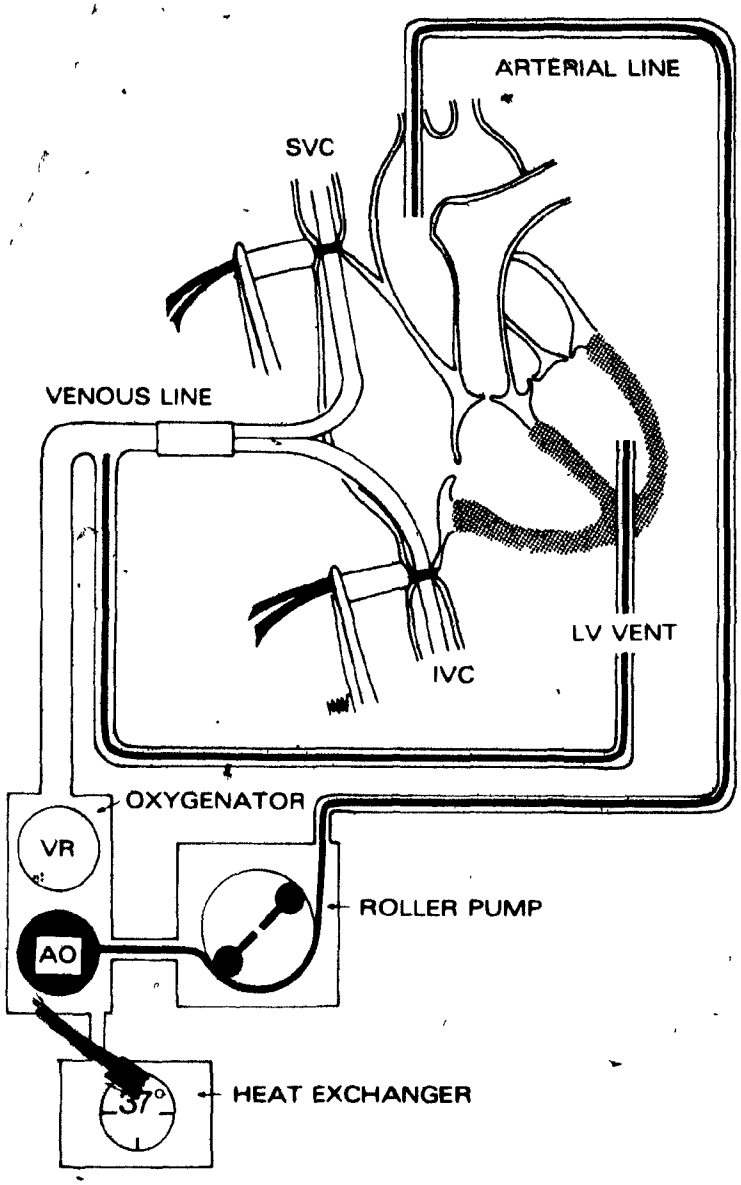


Figure 6. Diagram showing measurement of coronary flow

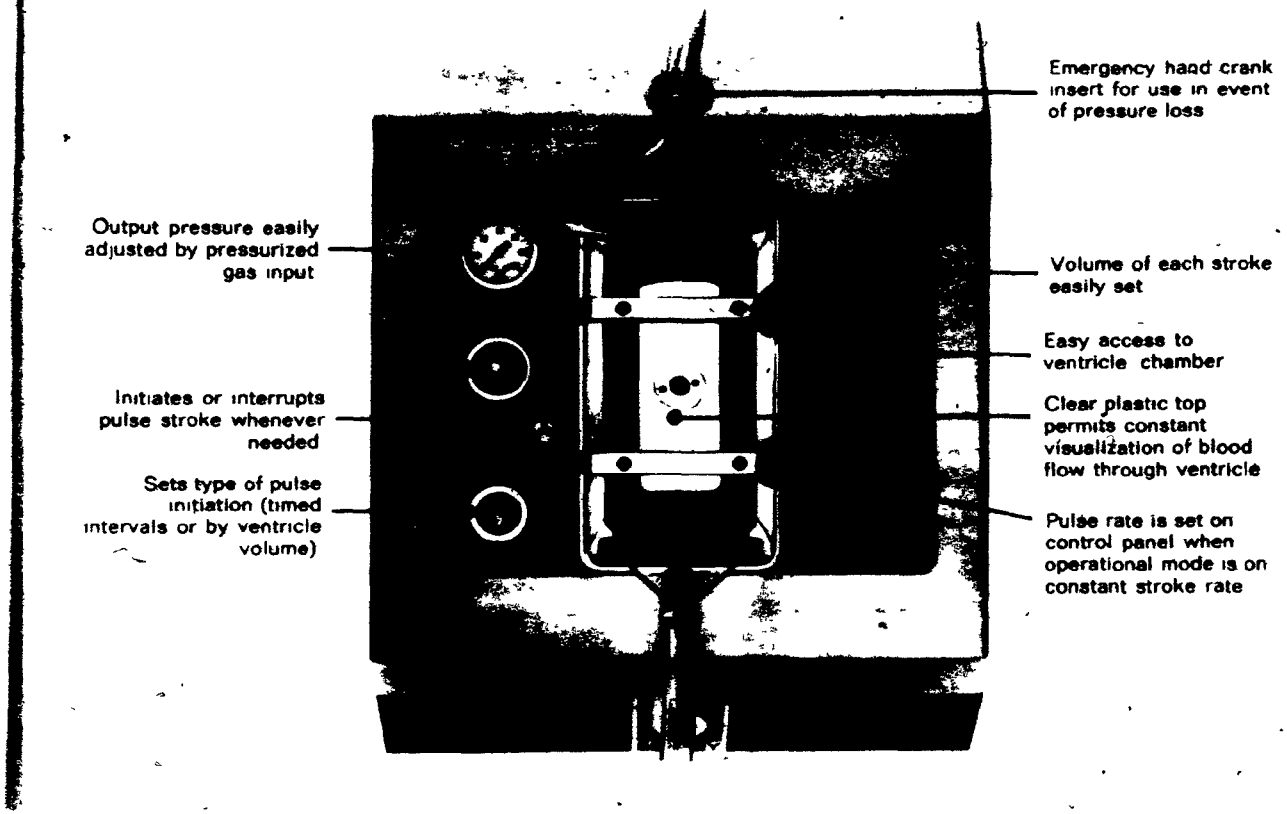


Figure 7. Bentley pulsatile pump

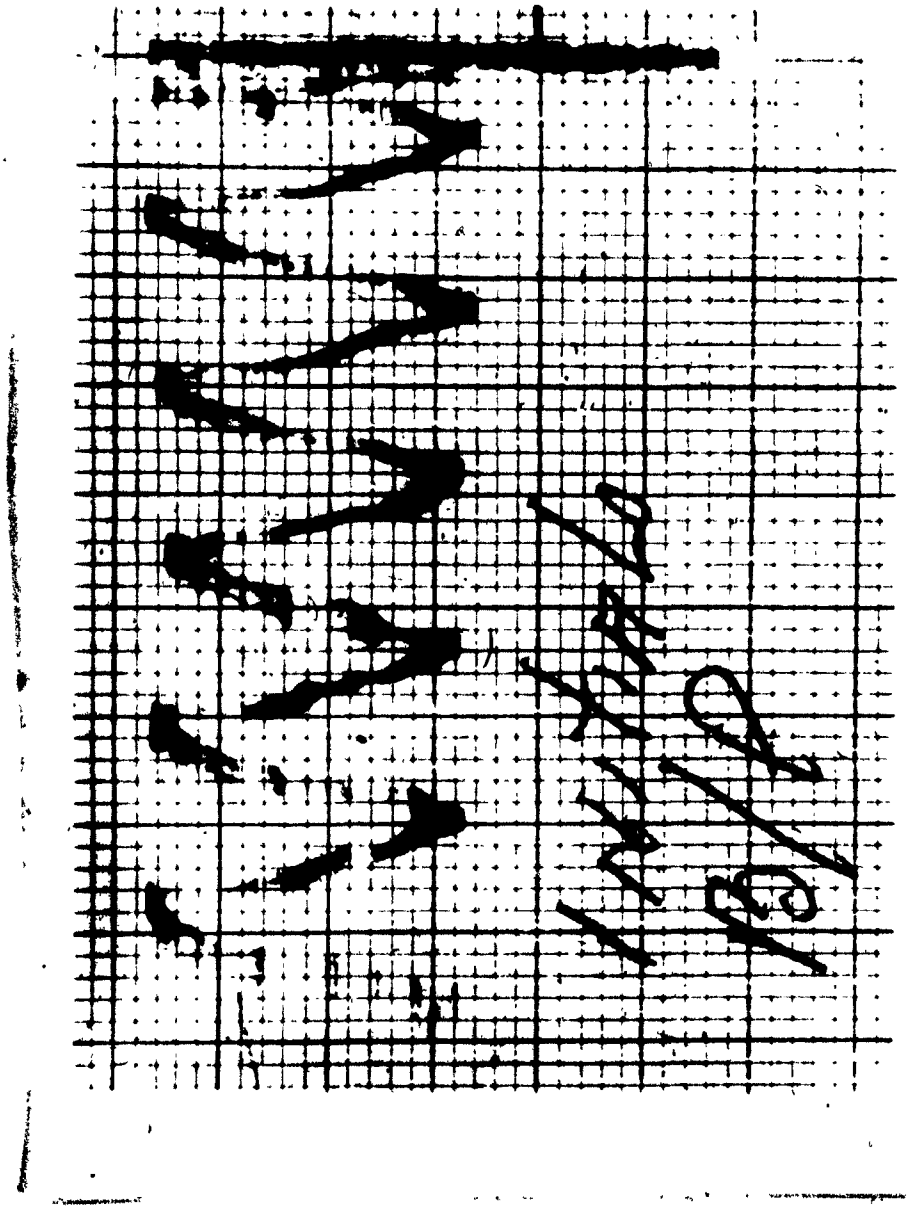


Figure 8. Blood pressure recording of a pig before CPB

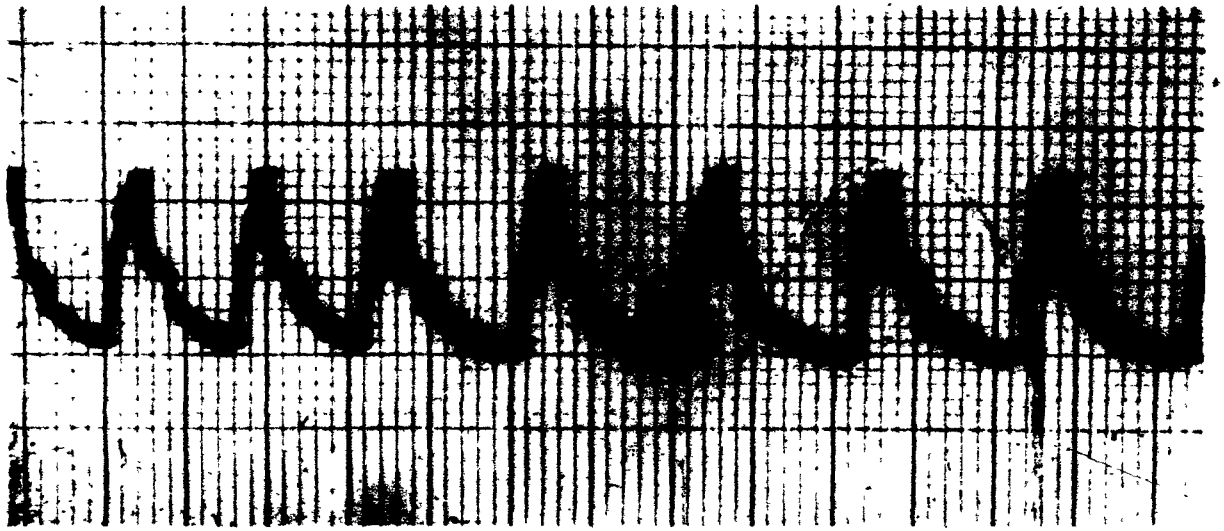


Figure 9. Blood pressure recording of a pig during pulsatile perfusion

Figure 10. Disposable ventricle

TABLE I

HEART WEIGHTS

		Weight (gm.)
Group I	NSR Roller	457.0 ± 8.7*
Group II	VF Roller	370.0 ± 10.2
Group III	VF Pulsatile	384.0 ± 9.1
Control (normal hearts)		210.0 ± 3.9

* Standard error of the mean

TABLE II

LEFT VENTRICULAR HYPERTROPHY

Left Ventricle Weight/Heart Weight

Group I	NSR Roller	6.58 ± 1.07*
Group II	VF Roller	7.01 ± 0.8
Group III	VF Pulsatile	7.23 ± 1.2
Control (normal animals)		3.95 ± 0.98

* Standard deviation

TABLE III

THE DISTRIBUTION OF BLOOD FLOW TO THE FREE WALL OF THE LEFT VENTRICLE

EPICARDIAL/ENDOCARDIAL RATIO

Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	1.47 ± 0.12*	2.14 ± 0.15	4.85 ± 0.88	4.22 ± 0.52
Group II	VF Roller	1.42 ± 0.07	3.71 ± 0.72	4.03 ± 0.51	7.18 ± 1.67
Group III	VF Pulsatile	1.32 ± 0.09	3.77 ± 0.53	8.55 ± 1.60	11.49 ± 1.81

* Standard error of the mean

TABLE IV

CALCULATED BLOOD FLOW IN THE NSR ROLLER GROUP

Pump Flow (cc/Kg/min)		70	50	40	20
Epicardium	Percent of total coronary flow (%)	37.4 ± 0.8*	43.6 ± 2.8	49.6 ± 4.0	46.8 ± 3.8
	Mean flow (cc/min)	30.0 ± 0.6	27.2 ± 1.9	23.0 ± 2.1	12.7 ± 1.9
Mid myocardium	Percent of total coronary flow (%)	39.0 ± 2.8	34.0 ± 3.01	37.5 ± 4.8	39.9 ± 3.9
	Mean flow (cc/min)	27.0 ± 2.0	21.0 ± 1.6	17.4 ± 2.3	10.0 ± 1.1
Endocardium	Percent of total coronary flow (%)	30.6 ± 4.8	21.8 ± 2.8	12.8 ± 2.1	13.3 ± 0.4
	Mean flow (cc/min)	24.0 ± 2.9	13.0 ± 1.7	5.9 ± 1.2	4.0 ± 0.2

* Standard error of the mean

TABLE V

CALCULATED BLOOD FLOW IN THE VF ROLLER GROUP

Pump Flow (cc/Kg/min)		70	50	40	20
Epicardium	Percent of total coronary flow (%)	38.0 ± 4.3*	45.6 ± 6.2	46.2 ± 7.3	50.8 ± 5.8
	Mean flow (cc/min)	39.0 ± 3.8	38.0 ± 5.7	31.0 ± 5.9	25.0 ± 3.9
Mid myocardium	Percent of total coronary flow (%)	40.6 ± 1.6	39.4 ± 1.8	39.8 ± 3.2	41.9 ± 2.8
	Mean flow (cc/min)	42.6 ± 1.3	33.0 ± 1.7	27.0 ± 2.6	20.0 ± 1.9
Endocardium	Percent of total coronary flow (%)	21.4 ± 4.2	14.0 ± 4.1	14.0 ± 4.5	7.2 ± 3.6
	Mean flow (cc/min)	22.4 ± 3.8	11.7 ± 3.9	6.7 ± 3.6	3.8 ± 2.8

* Standard error of the mean

TABLE VI

CALCULATED BLOOD FLOW IN THE VF PULSATILE GROUP

Pump Flow (cc/Kg/min)		70	50	40	20
Epicardium	Percent of total coronary flow (%)	36.4 ± 3.5*	47.6 ± 7.2	45.0 ± 7.2	45.2 ± 6.2
	Mean flow (cc/min)	37.0 ± 3.3	39.0 ± 6.1	24.0 ± 3.6	18.0 ± 3.1
Mid myocardium	Percent of total coronary flow (%)	38.6 ± 4.6	36.0 ± 5.3	48.0 ± 2.4	49.0 ± 2.7
	Mean flow (cc/min)	39.0 ± 2.9	29.0 ± 2.7	24.8 ± 2.1	19.0 ± 2.5
Endocardium	Percent of total coronary flow (%)	24.4 ± 4.0	15.8 ± 5.1	5.6 ± 5.4	4.4 ± 5.4
	Mean flow (cc/min)	25.0 ± 3.1	13.0 ± 4.7	2.9 ± 0.9	1.7 ± 0.3

* Standard error of the mean

TABLE VII

THE DISTRIBUTION OF MYOCARDIUM BLOOD FLOW TO THE INTERVENTRICULAR SEPTUM (IVS)

Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	1.31 ± 0.09*	2.08 ± 0.17	2.97 ± 0.37	2.61 ± 0.26
Group II	VF Roller	3.52 ± 0.50	11.06 ± 3.6	15.67 ± 4.73	20.73 ± 5.9
Group III	VF Pulsatile	2.72 ± 0.73	8.31 ± 2.83	13.30 ± 4.71	15.11 ± 4.64

* Standard error of the mean

TABLE VIII

MEAN AORTIC ROOT PRESSURES DURING CARDIOPULMONARY BYPASS

		AORTIC PRESSURES (MEAN)			
Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	72.0 ± 10.6*	61.4 ± 11.7	54.8 ± 7.8	38.2 ± 6.42
Group II	VF Roller	66.6 ± 4.9	43.2 ± 5.4	34.4 ± 4.82	28.0 ± 3.39
Group III	VF Pulsatile	43,6 ± 4.8	35.2 ± 5.8	39.0 ± 8.5	34.0 ± 7.2

* Standard deviation

TABLE IX

CORONARY ARTERY BLOOD FLOW

Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	80.0 ± 4.7*	62.4 ± 3.0	46.4 ± 2.1	27.4 ± 1.84
Group II	VF Roller	105.0 ± 7.0	84.0 ± 7.8	67.0 ± 7.3	52.0 ± 7.1
Group III	VF Pulsatile	102.0 ± 6.4	81.6 ± 6.2	51.8 ± 4.0	40.4 ± 5.4

* Standard error of the mean

TABLE X

CORONARY ARTERY RESISTANCE**

Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	1.02 ± 0.25*	0.97 ± 0.23	1.31 ± 0.22	1.47 ± 0.3
Group II	VF Roller	0.67 ± 0.08	0.60 ± 0.12	0.69 ± 0.20	0.73 ± 0.19
Group III	VF Pulsatile	0.68 ± 0.08	0.70 ± 0.06	0.77 ± 0.10	1.04 ± 0.24

* Standard error of the mean

** Peripheral resistance units

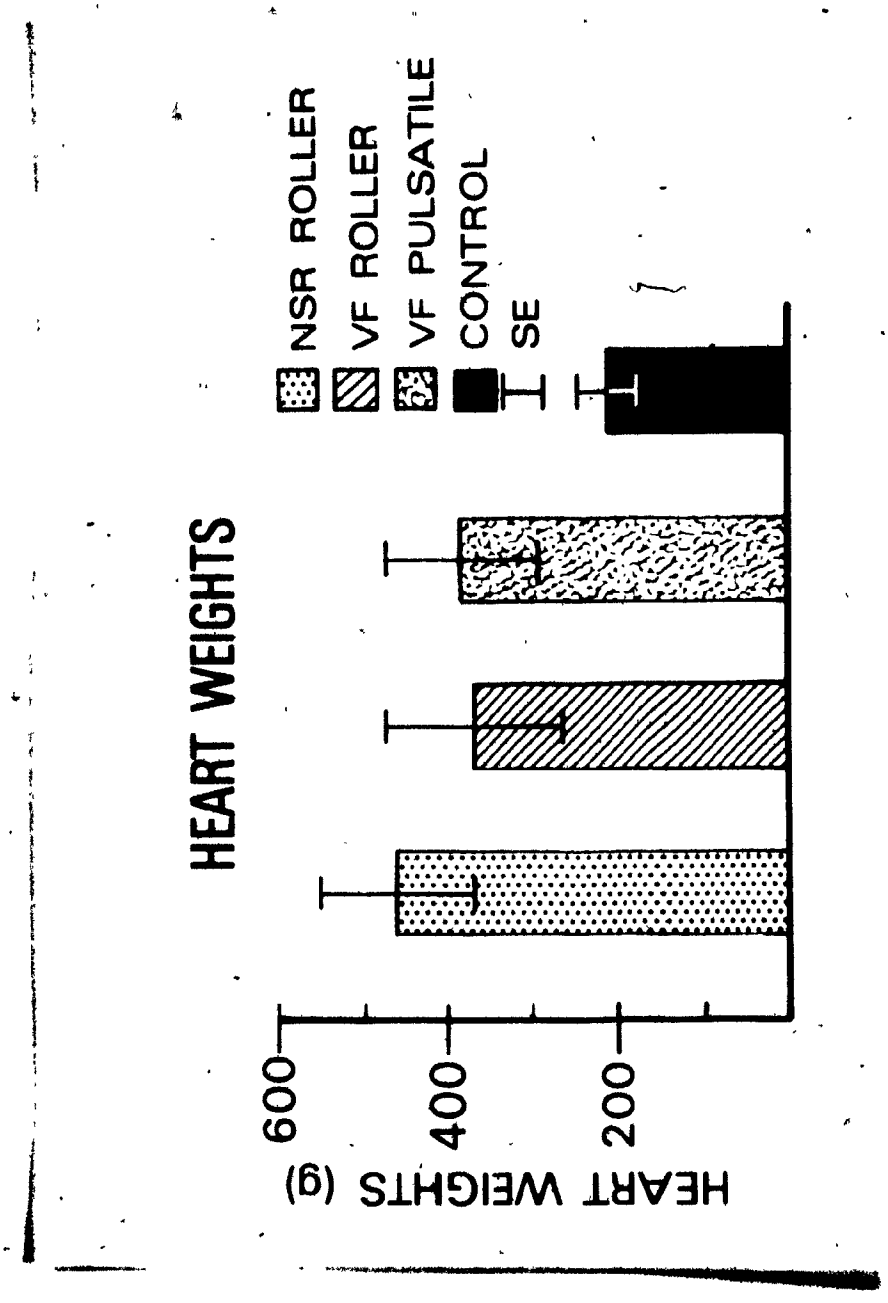
TABLE XI

BODY RESISTANCE**

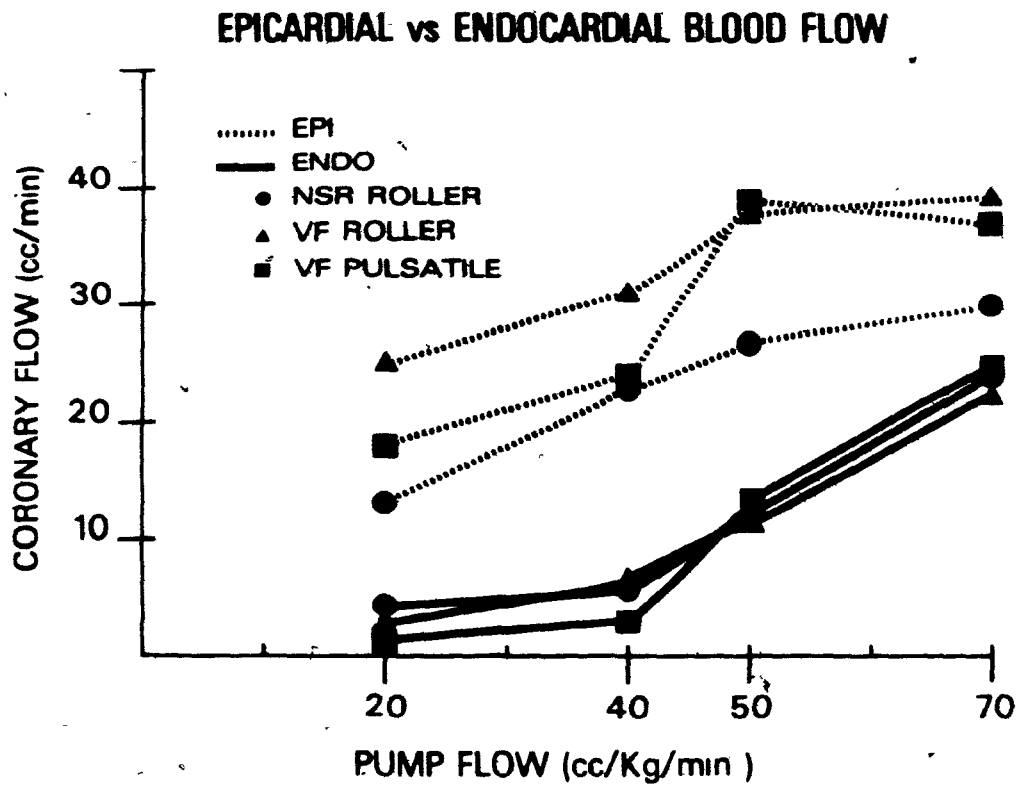
Pump Flow (cc/Kg/min)		70	50	40	20
Group I	NSR Roller	1.18 ± 0.13*	0.97 ± 0.23	1.13 ± 0.22	1.47 ± 0.3
Group II	VF Roller	0.87 ± 0.21	0.72 ± 0.19	0.74 ± 0.21	0.86 ± 0.25
Group III	VF Pulsatile	0.73 ± 0.08	0.72 ± 0.10	1.08 ± 0.20	1.25 ± 0.22

*Standard error of the mean

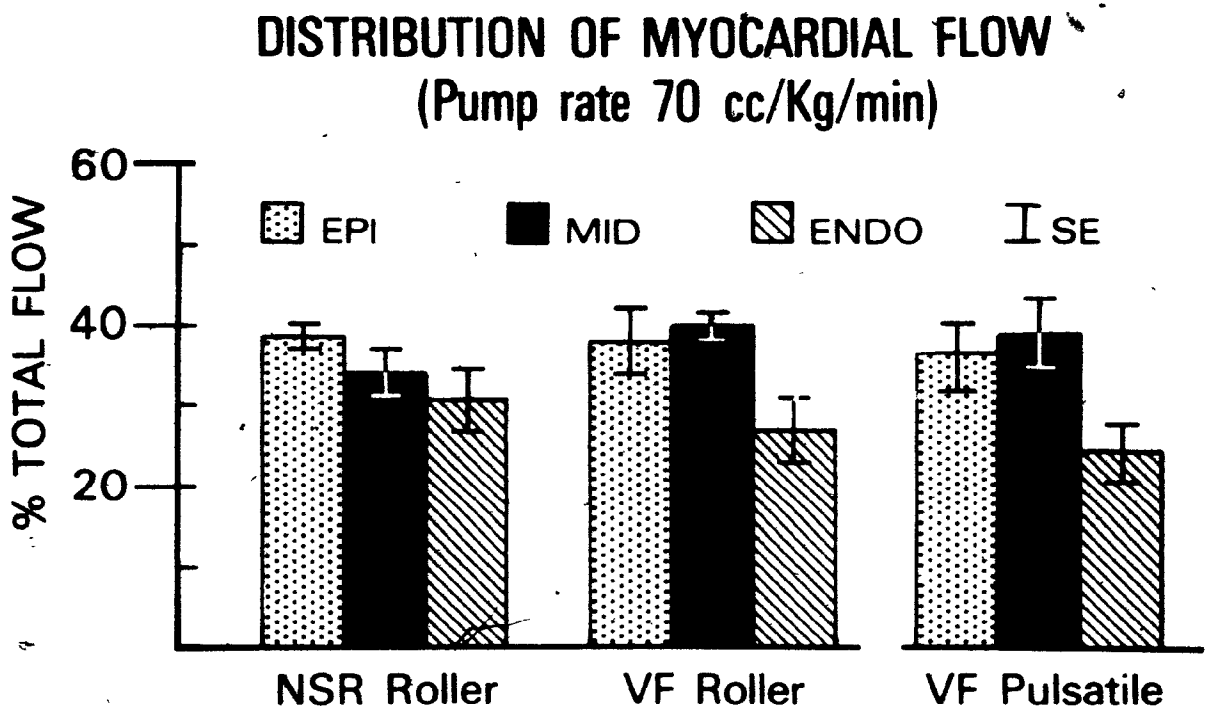
**Peripheral resistance units


HEART WEIGHTS
NSR ROLLER
VF ROLLER
VF PULSATILE
CONTROL
SE
HEART WEIGHTS (g)
600
400
200

GRAPH A

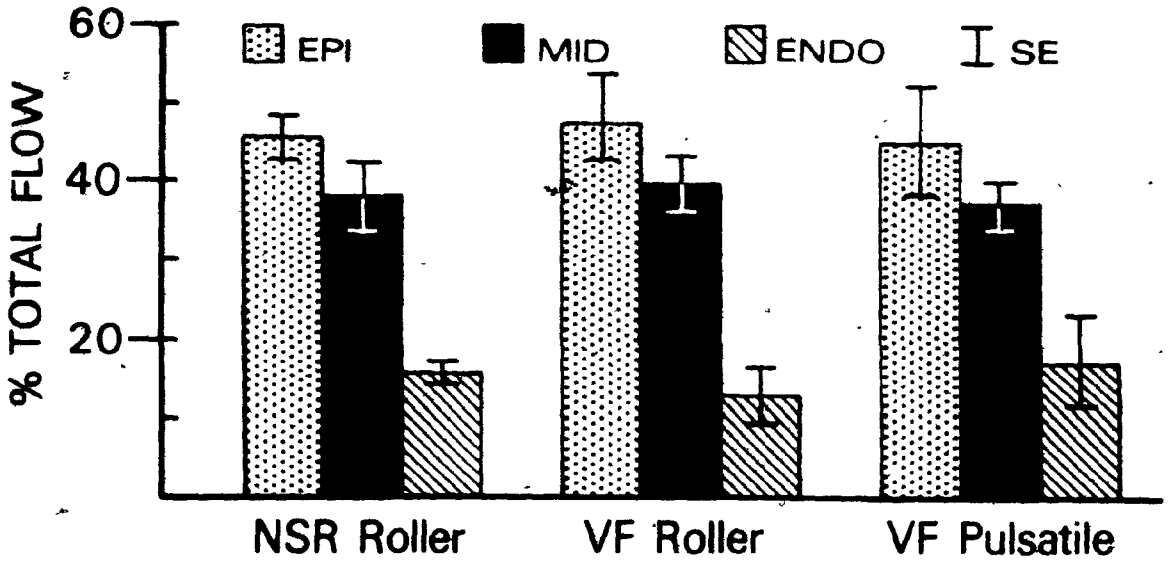

EPICARDIAL vs ENDOCARDIAL BLOOD FLOW
EPI
ENDO
NSR ROLLER
VF ROLLER
VF PULSATILE
CORONARY FLOW (cc/min)
40
30
20
10
20
40
50
70
PUMP FLOW (cc/Kg/min)

GRAPH B

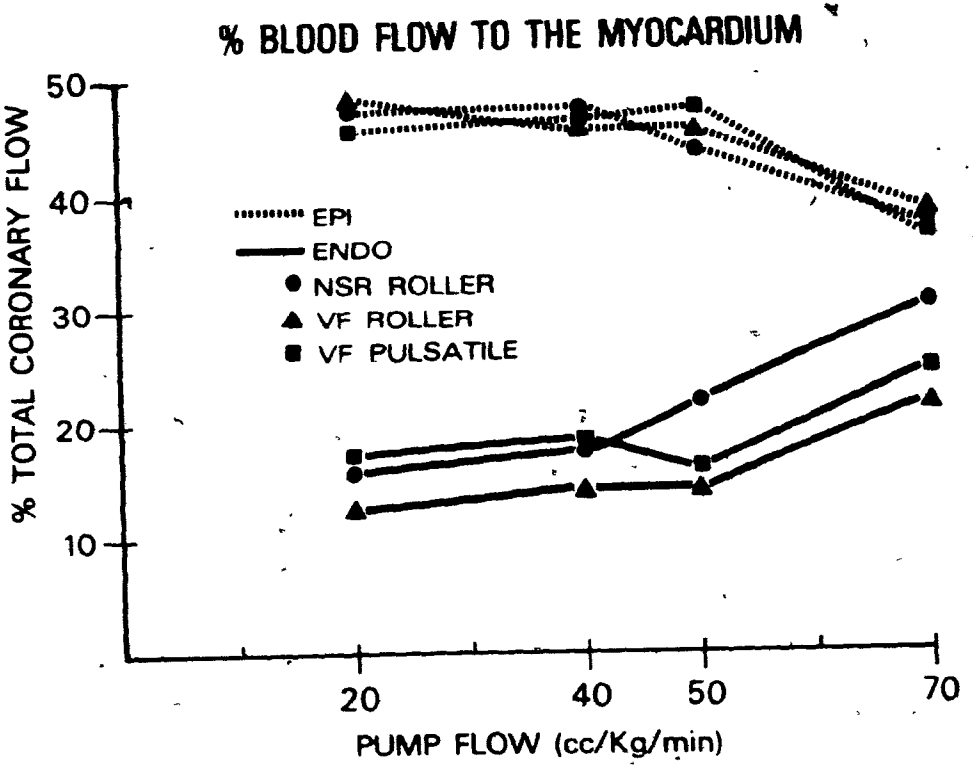

DISTRIBUTION OF MYOCARDIAL FLOW
(Pump rate 70 cc/Kg/min)
% TOTAL FLOW
60
40
20
EPI
MID
ENDO
SE
NSR Roller
VF Roller
VF Pulsatile

GRAPH C

DISTRIBUTION OF MYOCARDIAL FLOW
(Pump flow 20 cc/Kg/min)

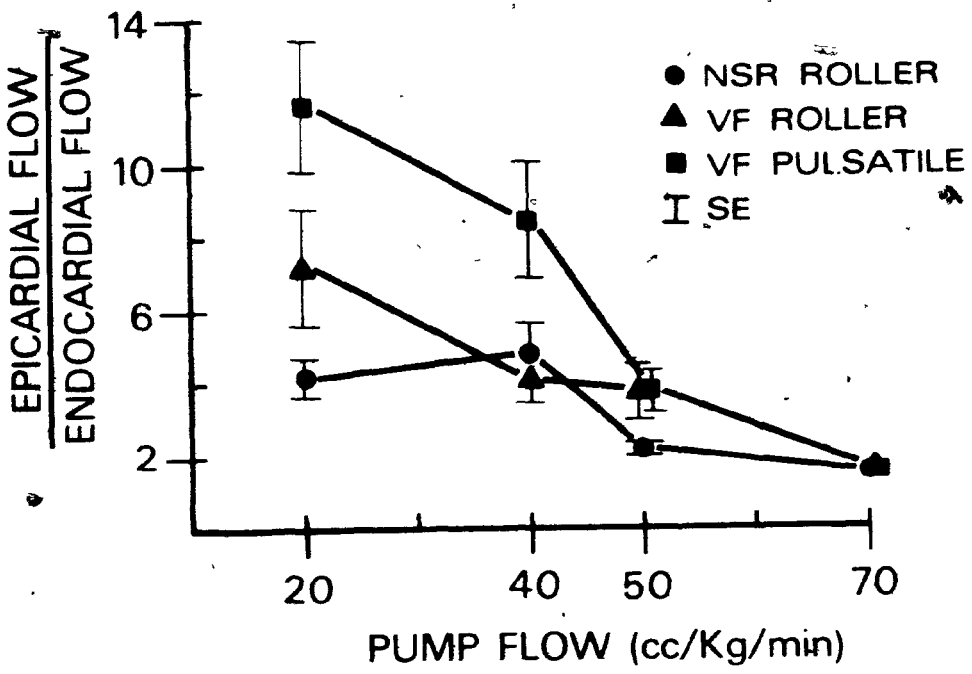


GRAPH D

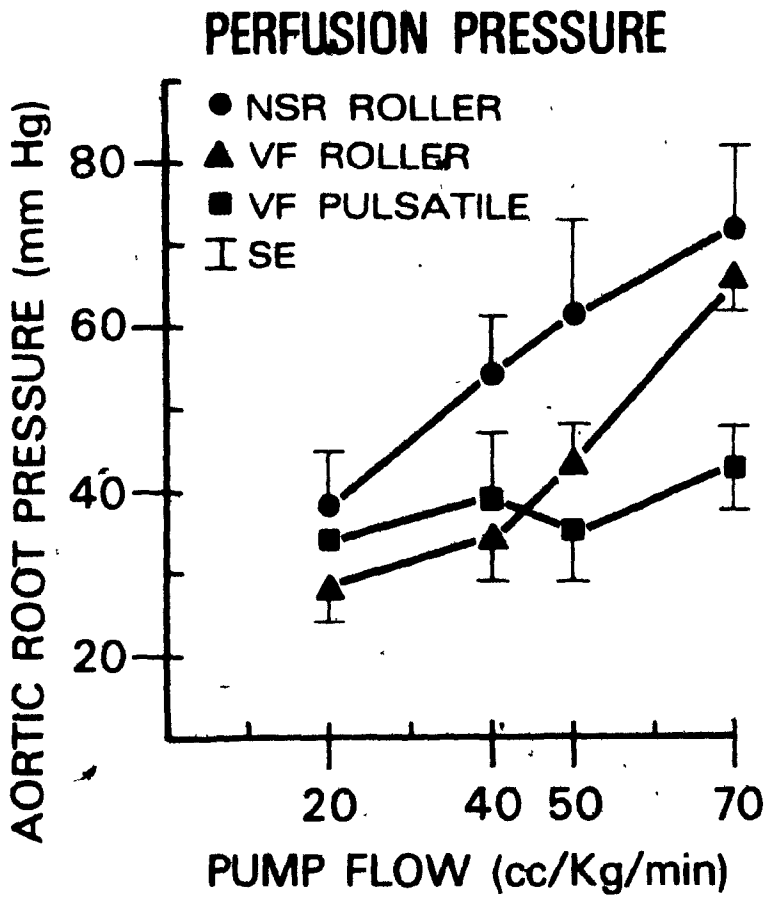

% BLOOD FLOW TO THE MYOCARDIUM
% TOTAL CORONARY FLOW
50
40
30
20
10
EPI
ENDO
NSR ROLLER
VF ROLLER
VF PULSATILE
20
40
50
70
PUMP FLOW (cc/Kg/min)

GRAPH E

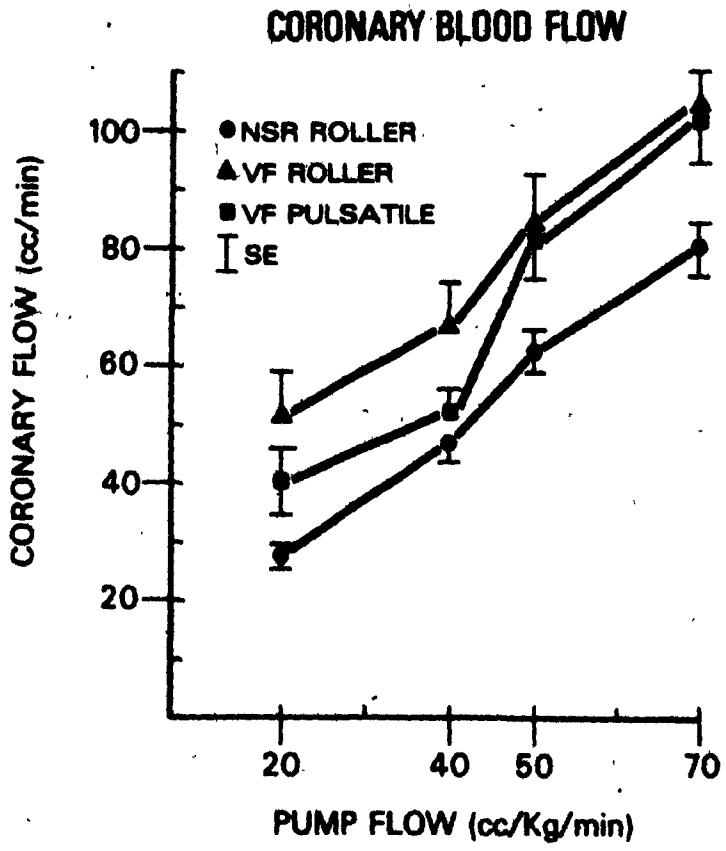
MYOCARDIAL BLOOD FLOW DISTRIBUTION



GRAPH F


PERFUSION PRESSURE
NSR ROLLER
VF ROLLER
VF PULSATILE
SE
AORTIC ROOT PRESSURE (mm Hg)
80
60
40
20
20
40
50
70
PUMP FLOW (cc/Kg/min)

GRAPH G


CORONARY BLOOD FLOW
CORONARY FLOW (cc/min)
100
80
60
40
20
NSR ROLLER
VF ROLLER
VF PULSATILE
SE
20
40
50
70
PUMP FLOW (cc/Kg/min)

GRAPH H