

HS

STUDIES IN ACUTE CARDIAC FAILURE (CARDIOGENIC SHOCK)
USING CONTROLLED GLOBAL REDUCTIONS IN CORONARY PERFUSING PRESSURE

By

Gerald C. Taichman

A Thesis Submitted in Partial Fulfillment
of the Requirements for the Degree of

Doctorate in Philosophy

in the

Department of Physiology
School of Medicine
Faculty of Health Sciences
University of Ottawa
Ottawa, Ontario

August 1984



UMI Number: DC53583

INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

UMI[®]

UMI Microform DC53583
Copyright 2011 by ProQuest LLC
All rights reserved. This microform edition is protected against
unauthorized copying under Title 17, United States Code.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

ACKNOWLEDGEMENTS

The author would like to acknowledge the participation and assistance of a number of individuals who contributed to this project. First, I would like to acknowledge Dr. B. Korecky who acted as my graduate supervisor and Dr. Y. Akyurekli whose surgical ability and unbelievable patience helped me develop this preparation. To the research technicians of Experimental Surgery, Ottawa Civic Hospital, I would like to thank Mrs. V. Temple and Mr. K. Sheldrick for their technical assistance and expertise. To Mrs. J. Freda, Mrs. E. Masson, and Mrs. S. Menzies, I would like to thank them for their clerical help in the production of this thesis and the various manuscripts which arose from this work. I would like to acknowledge a special thanks to Doctors W. J. Keon and J. S. Cowan for their encouragement, sincerity, and friendship which they have always shown me. Lastly, the author wishes to dedicate this work to my wife Joan and our daughter Marsha who made everything worthwhile.

CONTENTS	PAGE #
Introduction - Background	3
- Specific questions	12
Methods - Background	15
- Anaesthesia and surgery	17
- Instrumentation	18
- Blood analysis	22
- Extracorporeal circuit	23
- Protocol: Series I	28
Series II	29
Series III	30
Results - Background	32
- Series I	34
- Series II	53
- Series III	69
Discussion	76
- Summary	86
References	88
Appendix	96

INTRODUCTION-Background:

Cardiogenic shock or acute cardiac failure is initiated by an impairment in myocardial function and is usually associated with severe anatomic lesions of the heart. Acute myocardial infarction (AMI) and cardiovascular surgery are common contents in which cardiogenic shock occurs(1-3). Noncardiogenic shock may be caused by hemorrhage(4), trauma(5), fluid loss(6), sepsis(7), anaphylaxis(8), anaesthesia(9) and stimulation of neural reflex mechanisms (neurogenic)(10). Although noncardiogenic shock is initiated by factors involving the peripheral vascular system, secondary myocardial involvement frequently occurs when shock is severe and prolonged. Under these conditions functional and anatomic derangements of the heart often develop.

Coronary Care Unit management of patients suffering from AMI has been associated with a progressive decline in mortality. This decline in mortality follows the better prevention, recognition and management of acute rhythm disturbances(1). However, acute cardiac failure or cardiogenic shock in association with AMI continues to be a most serious therapeutic challenge with a mortality rate of 80% or higher once diagnosed(1-3).

The term cardiogenic shock simply implies severe impairment of the pumping function of the heart leading to progressive circulatory deterioration and death. This inability of the heart to maintain an adequate level of cardiac output necessary for organ perfusion is clinically expressed in a number of ways (outlined by the AHA Council on Cardiovascular Surgery) including a systolic arterial blood pressure less than 90 mmHg, or 80 mmHg below the previous basal level, and evidence of reduced blood flow as shown by a substantial reduction in urinary outflow to less than 20 ml/min, impaired mental function, and peripheral vasoconstriction evidenced by cold clammy skin. Experimentally, numerous authors have extended these criteria to include a 30% or greater reduction in mean arterial pressure, the maintenance of this reduction for at least 30 minutes, electrocardiographic changes consistent with acute myocardial infarction, a 50% or greater reduction in cardiac output and an elevation of left ventricular end-diastolic pressure(11). Any of the above must also meet the constraint of the absence of arrhythmias that could themselves account for the arterial hypotension.

As noted earlier, extensive myocardial injury may result from a number of causes(3-10), any of which may progress to circulatory collapse. Most commonly however, cardiogenic shock is a consequence of ischemic heart disease with AMI(1-3). In the pathogenesis of cardiogenic shock, it is likely that the critical initial factor is the severe loss of pump function(3). This can be, in part, related to the loss of contracting units as suggested by the correlation between infarct size and circulatory dynamics. Thus, the hemodynamics may remain normal if less than 20% of myocardial mass is involved. If, however, the loss were between 20 to 30%, congestive failure would likely develop. In most instances, cardiogenic shock or acute cardiac failure will ensue if 35 to 40% of the ventricular mass has been damaged(3,12).

Numerous pathological studies have confirmed that cardiogenic shock occurs when at least 40% of the left ventricular myocardium has been damaged by AMI and associated ischemia(12-14). A very common cause of such an extensive area of necrotic and ischemic myocardium occurs when occlusive thrombotic elements reduce the amount of blood flow the heart receives(1,12). In general, four distinct groups of patients hospitalized for AMI, frequently develop cardiogenic shock. The first group of patients are relatively young (35-50 years old) in which the first documented episode of infarction is associated with an extensive myocardial lesion with occlusive disease of the proximal portions of the coronary arteries. In the second group, the recent myocardial infarction need not necessarily involve a large area of the myocardium but occurs in a heart already damaged by previous infarctions. Eventually a large enough mass of the heart is affected and cardiogenic shock ensues. In the third group of patients, myocardial infarction from occlusive coronary artery disease is associated with, or is soon followed by, one or more of the following "mechanical lesions": rupture of the ventricular septum, acute aneurysm or large dyskinetic or akinetic ventricular segments, acute and persistent severe mitral valve regurgitation. It has been frequently noted that these three mechanical lesions often occur in combination (1) and will (even with less than 40% of a loss in functioning myocardium) lead to cardiogenic shock. In the last group of patients who develop cardiogenic shock, myocardial infarction is associated with recurrent refractive rhythm disturbances. With each episode of dysrhythmia more areas of the heart

are rendered ischemic until cardiogenic shock supervenes.

The value of clinical investigations relating to the pathophysiology and therapy of cardiogenic shock is limited by a lack of standardization. For example, in the clinical setting it is not possible to standardize the ischemic episode producing shock nor is it possible to have an untreated control group. Laboratory studies, therefore, are necessary in which groups are easily obtainable, lesions are reproducible and multiple variables can be studied over a prolonged period of time. The development of experimental models of cardiogenic shock, however, has been difficult because of the failure on the part of investigators to adhere to common strict criteria for the definition of shock. As outlined above Agress (15) in 1952 clearly laid down reasonable criteria, nevertheless, the term "shock" continues to be used to describe a variety of experimental situations ranging from transient declines in mean aortic pressure or cardiac output to precipitous hemodynamic deterioration followed by ventricular fibrillation and death.

No one experimental model has thus far gained general acceptance. In general, investigators have usually resorted to one of three methods for producing myocardial injury: Coronary ligations, coronary embolization, and direct myocardial injury. A few attempts have also been made at reproducing coronary artery thrombosis.

Chirac (16) in 1698 first made observations that ligation of a coronary artery in experimental animals results in cardiac arrest. Further studies of the coronary circulation continued at about the turn of the century with Harrison (17), Samuelson (18), Hirsch and Glick (19). Samuelson (18) first described the clinical manifestations of acute myocardial infarction evolving into cardiogenic shock and tried to reproduce the clinical syndrome in rabbits. He observed that occlusion of the left coronary artery produced a state of reduced contractility followed by acute dilatation of the left ventricle and atrial standstill. As a result of this pioneering study, occlusion-ligation of a major coronary artery became the most used approach to the experimental production of acute myocardial infarction.

The functional consequences of coronary ligation were studied in Wigger's laboratory in the 1930's. There, Orias (20) noted that ligation of the left anterior descending (LAD) coronary artery in open

chest dogs did not have the same effect in all animals. In fact, it had no hemodynamic effect in one-third, caused immediate death in 13%, and produced a hypodynamic state of the LV in approximately one-half of his studies. The hypodynamic state was characterized by a reduction of the aortic pressure concomitant with an elevation of the left ventricular end-diastolic pressure. This was explained as a reduction of contractile power of the ischemic LV coupled with an increased tension of the nonischemic portion of the heart.

Tennant and Wiggers (21) using a similar type of preparation developed an optical myograph for recording localized contractions of the left ventricle and first demonstrated that a paradoxical outward movement occurs within the ischemic left ventricular wall. In 1939, as a result of the work of Harrison (22), cardiogenic shock became a clinical entity distinguished from other forms of shock. A controversy immediately began as to whether this form of shock had a solely central mechanism or also involved peripheral factors. Wiggers (23) concluded from his experiments that the crux of the circulatory failure which follows AMI is represented by myocardial failure. Wiggers also demonstrated myocardial depression occurs in all forms of shock, and established the concept that regardless of whether central or peripheral circulatory failure initiates the development of shock, the reduction of cardiac output and aortic pressure below a critical level sets into motion a vicious cycle of hemodynamic deterioration. Kupfer (24) noted a rise rather than a decline in the filling pressure of the heart after coronary artery ligation and concluded that "the circulatory failure of myocardial infarction cannot be peripheral in origin". More importantly he also noted that since only one of eleven dogs subjected to ligation of the LAD coronary artery developed severe circulatory failure, "experimental cardiogenic shock cannot be induced by coronary ligation".

The inability to produce cardiogenic shock by ligation of a single large coronary artery was explained by Eckstein (25) as due to an extensive and variable collateral circulation. Therefore, Ellis et al (26) proposed a method of sequential coronary ligations that would interrupt all the blood supply to the anterolateral wall of the left ventricle and produce an area of uniform ischemia. According to this method, first the ventricular branches of the circumflex artery, then

the branches of the LAD are suture ligated at 15 minute intervals. The procedure is continued until the filling pressure of the left ventricle rises above 13 mmHg and remains elevated for more than 30 minutes. In similar experiments Feola (27) found that this technique leads to LV ischemic failure but not to shock. In fact, an extensive review of the literature by Feola (10) concerning the reports of Ellis and others (26,28,29) revealed that shock according to the criteria outline by Agress (15) was rarely produced.

Thus ligation of coronary arteries produces AMI of variable extent and severity, depending mainly on the level of the occlusion and on the extent of the collateral circulation. Hemodynamically transient declines in cardiac output and arterial blood pressure (20,23,30), congestive heart failure (6) and severe arrhythmias (6,31) can be produced, but not protracted shock. The lesions are either precipitously lethal or compensatory mechanisms are activated that restore stable and relatively normal hemodynamics.

Why and how do these animal experiments differ from the clinical situation? Clearly substantial differences exist between the dog, in which non-occluded coronary arteries and the myocardium are normal, and patients in whom obstructive coronary atherosclerosis is a diffuse disease in which extensive fibrosis may already exist. In order to approximate the human situation more closely, newer models were developed.

Although coronary embolization was attempted as early as 1862 by Panum (32), it was developed and popularized as a method for producing cardiogenic shock by Agress in the 1950's. Agress and associates (33) first found in anaesthetized open-chest dogs that embolization of the coronary arteries by the injection of plastic microspheres into a transiently occluded ascending aorta produced widespread sublethal myocardial infarctions, resulting in prolonged hypotension. They then developed a double-lumen stainless steel cannula that could be inserted under local anaesthesia through the left carotid artery into the ascending aorta (34). A balloon near the tip of the cannula could be distended with saline injected through the outer lumen, whereas the microspheres could be injected through the inner lumen. Thus, coronary embolization could be carried out without general anaesthesia and without thoracotomy. Numerous experiments

have been carried out by the Agress method (35-38). In fact, this had become perhaps the most commonly used method for two reasons: it avoids general anaesthesia and thoracotomy, and the procedure can be carried out without any special equipment except a double-lumen catheter. Most recently, Sivarajian and Amory (37) used a modification of the original technique in monkeys. In their experiments they injected microspheres of smaller size (50 as opposed to 300 to 400 microns and in 5 mg increments five to ten minutes apart until shock was produced instead of injecting a predetermined dose based on body weight). According to these authors, the method was capable of producing shock in a majority of animals.

Despite its advantages Agress' microsphere embolization technique has been criticized for several reasons: (a) in dog experiments, at least, the method produced protracted shock in only about 20% of the animals studied, (b) acute shock is produced so that diffuse coronary ischemia is a much slower process clinically than abrupt occlusion of a major coronary artery as is the case in man with AMI, (c) a large number of microspheres reach the systemic circulation producing embolization in distant organs, and (d) the method does not allow selectivity of the region of the myocardium to be rendered ischemic.

A variant of coronary embolization is represented by the selective intracoronary injection of mercury. The method was first described by Hermann and Dechard (39) in 1934 and developed by investigators from Katz's laboratory in the late 1960's (19,40-42). Under fluoroscopy, a catheter is inserted through a carotid artery and the ascending aorta into the ostium of the circumflex artery, and 0.2 ml of mercury is injected into the terminal branches of the circumflex and blocks the collateral channels from the adjacent coronary arteries. This produces a characteristic myocardial infarction involving the posterolateral wall of the left ventricle including the posterior papillary muscle, the posterior portion of the interventricular septum, and a portion of the posterior wall of the right ventricle. Hemodynamically, a syndrome similar to cardiogenic shock often develops which is characterized by severe hypotension, tachycardia, severe oliguria or anuria, depressed sensorium, and death within 48 hours.

With this method, Lluck and his associates (40) noted that shock appears to develop in three stages. A first stage of

approximately 30 minutes, is characterized by a rapid drop in cardiac output and of arterial blood pressure, a reduction in left ventricular contractility as measured by LV dp/dt, and a reduction in heart rate. In their interpretation of the results the above changes were seen as a direct loss of contracting myocardium and the attenuation of the sympathetic drive of the heart. The second stage, which lasts approximately six to ten hours, is characterized by the intervention of compensatory mechanisms stimulated by the baroreceptors. Thus, during this phase, cardiac output and blood pressure tend to recover, heart rate increases and total peripheral resistance rises. Left ventricular end-diastolic pressure also rises which may represent another compensatory mechanism destined to improve the overall performance of the ventricle by way of the Starling's effect. During the third phase, the compensatory mechanisms gradually fail. Heart rate, LV dp/dt, and total peripheral resistance gradually decline along with the cardiac output and blood pressure. This progressive deterioration leads to death within one hour. The mechanism by which this deterioration comes about has not been completely elucidated. Haddy and Scott (43) suggested that the final waning of peripheral vasoconstriction is due to an autoregulatory escape caused by the buildup of vasodilating metabolites in peripheral blood and tissues from protracted underperfusion. It is also possible, as suggested by Rushmer et al (44) for all forms of shock, that the final deterioration results from a vicious cycle involving the depression of CNS and vasomotor centre function.

The model of mercury embolization has not been extensively used however, a number of important studies have utilized this technique. Edelman et al (41) found a redistribution of blood flow away from dependent portions of the lungs. Gorfinkel et al (42) found significantly less reduction of renal blood flow in animals in cardiogenic shock than with hemorrhagic shock. Hirsch and Glick (19) demonstrated an active participation of the mesenteric vascular bed in the compensatory vasoconstriction taking place during the second stage of shock. Glenn and his associates (45) studied the production of a myocardial depressant factor (MDF) during shock: "The injection of mercury led to a chain of events: myocardial damage - reduction of cardiac output - splanchnic ischemia - lysosomal disruption in

ischemic organs - entrance into the circulation of MDF. The production of a MDF by virtue of its negative inotropic effect, could further aggravate the shock condition." A similar observation was recently made by Senges et al (46) who found cardiogenic shock to cause the release of humoral factors into the circulation which were different from MDF but nonetheless had a direct depressant effect upon the heart.

This model indicated the importance of the splanchnic circulation in the pathophysiology of shock and emphasized the fact that the protection of cellular lysosomes might be critical in the maintenance of the integrity of the vascular as well as cardiac function.

Direct myocardial injury allows the production of lesions of controllable size and at specific sites. In 1908, Lohman (47) tried the topical application of sponges saturated with formalin. In 1909 Eppinger and Rothberger attempted to produce injury by freezing with ethylchloride (48). Other attempts to produce myocardial damage have included electrocautery (49), radon seeds (50) and localized hypothermia (51). All these methods, however, failed to produce significant and repeatable changes in cardiac output and blood pressure to mimic cardiogenic shock.

Recently, Maggs et al (52) reproduced in dogs a two-component theoretical model of myocardial infarction proposed by Swan and his associates (3). Under general anaesthesia and cardiopulmonary bypass large portions of the left ventricle were resected and replaced with patches of Dacron material. The patch would simulate the nonfunctioning and non compliant ischemic component, while the normal myocardium would represent the residual component. In experiments on dogs, the left ventricular end-diastolic pressure rose in proportion to the size of the patch, but the overall function of the left ventricle was well compensated and remained close to normal, owing to an increased contractility of the residual myocardium. With patches greater than 25% of the left ventricular wall most dogs died. With this technique, as with other models, cardiogenic shock was infrequently produced. More recently, Koo et al (53) reported a rat model in which the left chest is opened under general anaesthesia and a 5 mm² area of the left ventricle is electrocoagulated. The

hemodynamic changes observed 30 to 60 minutes after this injury were compatible with the criteria of shock, however, the frequency of shock was low and the technique has never been repeated by other investigators.

A good replica of human coronary atherosclerosis can be produced in dogs by a high cholesterol diet in combination with thyroid-suppressing agents (54). Such thyroid suppression, however, is not necessary in species such as the chicken, rabbit or monkey. This technique, obviously, is time-consuming and lacks predictability in terms of the extent of atherosclerosis, the development of myocardial infarction, and mortality. Vineberg and his co-workers (29) first tried to produce a slow obstruction of one or more coronary arteries leading to spontaneous occlusion by thrombosis. In their studies a steel-mantled cylinder of casein ameroid was inserted around the artery and would slowly absorb the water leading to a progressive constriction of the vessel and thrombosis within 2 or 3 weeks. The method failed to gain popularity, first because it required a preliminary thoracotomy, then because it appeared to be well tolerated by the animal, and thirdly, the slow restriction of the coronary artery activated the development of an effective collateral circulation. Salazar (55) devised a coronary catheter that allowed the passage of a stainless-steel electrode into the lumen of the left coronary artery and either of its branches. By passing a low grade electric current through the electrode Salazar was able to induce coronary thrombosis. Myocardial infarctions of varying size were produced in the areas downstream from the occluded arteries, however, no hemodynamic studies were reported. Murphy et al (56) used a modification of Salazar's method to produce coronary thrombosis in dogs pretreated with bretylium tosylate. Of the animals which did not die from ventricular fibrillation, AMI and shock was documented hemodynamically in about 40% of his animals. Unfortunately there has been no follow-up to the preliminary experiments carried out with this technique.

In reviewing the material reported on experimental myocardial infarction, one is struck by the fact that cardiogenic shock has been produced only occasionally. The usual sequelae of AMI in animals are arrhythmias, decreases in cardiac outputs, and elevations of

ventricular end-diastolic pressure; severe, protracted arterial hypotension occurs in an unpredictable manner in a minority of experiments. When cardiogenic shock does supervene, it generally develops in three stages: (a) a phase of acute power failure of the left ventricle followed by (b) a phase of partial recovery resulting from various compensatory mechanisms and finally (c) a phase of progressive circulatory failure.

In general, standardized animal models for cardiogenic shock have not been universally accepted. Although the criteria for shock are well stated, the development of a consistent animal preparation remains to be defined. The ideal experimental model should be as close as possible to the clinical condition in the sequence of coronary occlusion - AMI - acute left ventricular failure - shock, reproducible without general anaesthesia and thoracotomy, reproducible without excessive mortality from ventricular fibrillation, stable, without fluctuations toward spontaneous recovery or sudden deterioration, for adequate periods of time to permit valid observations. Obviously, this has not been simple to achieve. On the other hand the ideal model is not necessary for every type of experiment.

Specific Questions:

Myocardial mechanical function is dependent primarily on its blood supply, since in the normal heart oxygen extraction is near maximal and anaerobic reserves are minimal (57,58). Although it is generally recognized that reductions in myocardial blood flow will result in an impairment in mechanical function, the precise relationship between reduction in blood flow and function remain to be defined. It is of particular value to determine (a) how much blood flow can be reduced without an apparent reduction in function, (b) at what levels of flow reduction is myocardial function significantly impaired (acute cardiac failure or cardiogenic shock) and (c) at what levels of reduced flow is myocardial function completely lost.

Myocardial cell acutely deprived of coronary blood flow as a consequence of coronary occlusion will quickly become hypoxic and acidotic progressing eventually to irreversible damage depending upon the magnitude of the flow reduction, the duration of ischemia, and the metabolic demands of the ischemic tissue (59,60). Peripheral cells

of the hypoperfused zone, where there is less of a reduction of blood flow will undergo necrosis more slowly. As mentioned earlier the production of large areas of myocardial damage may be analogous to the clinical events preceeding cardiogenic shock however, the evolution of heterogenous flow patterns (61) and the subsequent development of a mixed population of normal to irreversibly damaged cells (62) precludes a close inspection of the inter-relationship between coronary supply and myocardial demand.

In the first series of experiments an alternative experimental preparation was developed in which the coronary circulation was separated from the systemic circulation and perfused under carefully controlled conditions. In this situation reductions in flow were globally experienced by all parts of the heart and the ensuing hemodynamic response could be assessed from the working heart in situ in terms of standard hemodynamic measurements. Furthermore, the steps between reductions in flow and depression in mechanical function were also studied by means of monitoring the changes in myocardial oxygen extraction and oxygen consumption.

With the advent of clinical means of reversing myocardial ischemia (i.e., coronary bypass surgery, intracoronary thrombolysis) the need arose to define the tolerable limits of ischemia. As a result numerous laboratories have placed a high priority upon determining the conditions under which the restoration of coronary blood flow is likely to be beneficial or harmful to the ischemic heart (59,63,64). Based mostly on coronary occlusive type experiments followed by reperfusion, it is only possible to state that the damage which occurs between 20 minutes or earlier and 3 hours of ischemia may be reversible by reperfusion but as the duration of ischemia increases the chance of recovery is reduced and the reperfusion damage is increased.

Since most of the reperfusion literature is based on the responses to the regional insult of temporarily occluding a coronary artery, a second series of experiments were performed in which the flow to the heart was globally reduced for various periods of time (15 to 120 minutes) while recoverability was assessed following 60 minutes of reperfusion.

Although the primary purpose was to resolve the recoverability of function with this type of experimental model, the results

were also intended to serve as baseline data in which the efficacy of various modalities (pharmacological agents) of treatment could be evaluated at some later date.

In the treatment of cardiogenic shock, drug therapy alone has not significantly altered patient mortality (1). In the present situation the most favoured modalities of treatment include temporary circulatory assistance (65) combined with drug support as needed and with corrective cardiac surgery (66), if feasible.

One such circulatory assist device is the intra-aortic balloon pump (IABP) which was first used in the treatment of cardiogenic shock in 1962 by Moulopoulos (67). Since then, the indications for its use have been extended to include a wide variety of clinical situations requiring temporary circulatory support (66,68).

In spite of the overwhelming clinical evidence of the beneficial effects of IABP treatment, the underlying mechanisms have not been clearly resolved (69,70). In theory, the beneficial effects of counterpulsation are achieved by the active displacement of aortic blood during the cardiac cycle which in turn is to reduce left ventricular work (systolic unloading) and increase coronary flow (diastolic augmentation) (71). Although both features would assist the failing heart, the presence and relative effects of either aspect during IABP treatment could not be independently appreciated. In the cardiac shock model developed, the coronary circulation is perfused from an extracorporeal source so the direct effects of diastolic augmentation can be separated from the hemodynamic responses to systolic unloading. In the third series of experiments this unique feature of the preparation was used to evaluate the systolic unloading effects of IABP treatment independent of diastolic augmentation in a variety of hypodynamic states.

METHODS-Background:

In the previous section of this thesis, is outlined not only the questions to be asked but also the various animal models most widely cited in the literature dealing with acute cardiac failure (cardiogenic shock). It is obvious from this outline that no universally acceptable model for cardiogenic shock currently exists. Clearly, the diversity of animal models reflects the specific needs of the questions under consideration. However, the decision on the most suitable model for investigations in this laboratory involved two major considerations: (a) can earlier models be easily adapted to answer the questions posed and (b) will the results clearly represent new information to the literature on cardiogenic shock?

The answers to both questions were obtained early in the project. In the first five experiments, the technique of multiple coronary ligation as outlined by Ellis et al (26) was used to induce cardiogenic shock in anaesthetized thoracotomized dogs. In spite of our attempts to keep the insult uniform, this procedure did not produce a stable preparation. First, the onset of cardiogenic shock was quite variable; in some animals the hypotensive state was reached within five minutes following the last coronary ligation while in others four to six hours were needed before the minimum requirements for shock were reached. Secondly, each coronary ligation produced an unstable situation progressing to either a state of recovery of arterial pressure or circulatory collapse due to ventricular fibrillation. Thirdly, it soon became obvious that the "failure state" is itself unstable, making the animal unsuitable for following any specific protocol of substantial duration. As has been observed before (11) systemic hypotension is a positive feedback situation in which the terminal events quickly ensue allowing insufficient time for careful inspection and/or the evaluation of various modalities of treatment. Lastly, in our five initial studies, irreversible ventricular fibrillation refractive to treatment terminated 80% of the experiments.

After these initial experiments, further attempts at coronary occlusion were abandoned and an alternate technique was sought. At about this time the study of Liedtke et al (72) in which an animal model in swine for the study of myocardial ischemia was presented in

which coronary perfusion to the entire heart was maintained at preselected flow rates with an extracorporeal roller pump while a wide variety of hemodynamic and metabolic parameters were measured. Of special note was the fact that this preparation could produce graded states of acute cardiac failure purely by the reduction in coronary flow alone. In two more pilot studies experiments on anaesthetized dogs a similar type of preparation with modifications to the method originally outlined by Liedke et al (72) were performed. Although some aspects of the surgical procedure were modified, the important observation was that the technique of controlling coronary flow to induce cardiogenic shock offered a clear experimental advantage over coronary occlusive procedures.

Before committing future experiments to this type of model it was decided to modify some aspects of the preparation as originally outlined. First, the procedure of right heart bypass was omitted, so that the in situ working heart should not be limited to just left heart failure but rather both sides of the heart should be involved in the expression of cardiogenic shock. Secondly, an alternative arrangement for the perfusion of the coronary circulation was made. Instead of perfusing the coronaries at predetermined flow rates, a more physiological approach was instituted in which coronary inflow pressure was the primary controlled variable while the resulting coronary flow was measured. In this situation, coronary flows reflected not only the present driving pressure, but any internal adjustments (57,58,73) in resistance to flow which resulted from changes in myocardial factors including demand.

In the next part of this method section a detailed outline of the surgical preparation and monitoring instrumentation of this animal model for cardiogenic shock will be presented. Although the model went through various modifications, the overall concept of controlling coronary perfusion was preserved. The developmental stages of the technique were minimal and by the fourteenth working preparation, a consistent protocol for both the surgery and instrumentation had been established. In the "protocol" part of this method section, three distinct series of experiments will be outlined. In the first, the developmental stages of the model will be presented along with the evaluation studies in which the feasibility and practicality of the

model were established. In the second part the experimental design for the myocardial responses to cardiogenic shock from 15 to 120 minutes followed by reperfusion will be set out in detail. In the final part of the protocol section, the experiments dealing with the analysis of therapeutic action of IABP on cardiogenic shock will be presented.

Anaesthesia and Surgery:

Acute experiments were performed on 109 mongrel dogs of either sex whose body weight ranged from 21 to 50 kg. Animals were fasted 24 hours prior to surgery but were given water ad libitum. The animal was premedicated with 0.4 mg. of atropine (Sterilab) intramuscularly to reduce the amount of bronchial secretions. Approximately ten minutes later anaesthesia was induced with sodium thiopental (Pentothal) administered intravenously through the cephalic vein. Once a plane II level of anaesthesia was achieved, the animal was shaved which usually required additional amounts of the thiobarbiturate, however, in general all animals received in total, approximately 20 mg/kg of the drug. The animal was then transported to the operating room and placed on a surgical table in the horizontal position with the limbs extended and secured. The trachea was intubated with a cuffed endotracheal tube and was thereafter positive pressure ventilated with a Harvard respirator (model 618) at a rate of 18 breaths/min. The tidal volume was adjusted according to the body weight based on a scaling factor recommended by Harvard Apparatus Company. While the chest was closed, no restriction was applied to the expired air flow; however, once the chest was opened a back pressure of 2 to 4 cm H₂O was instituted to maintain lung expansion. Throughout the remainder of the experiment a surgical level of anaesthesia (plane III) was maintained by means of a mixture of 30% nitrous oxide, 70% oxygen, and 0.25 to 0.75% halothane (Somnothane).

Core body temperature was monitored by means of a YSI oesophageal thermistor (series 600) in conjunction with a YSI electronic telethermometer (model 43), and maintained between 35^o and 37^oC by means of a thermoregulated water blanket. To minimize the incidence of ventricular arrhythmias, either induced from the manipulation of the heart or as a consequence of the experimental protocol, all animals received via the cephalic vein, a priming dose of 70 mg of lidocaine hydrochloride (Xylocaine) followed by a continuous

infusion of 1-2 mg/min throughout the experiment. If during the course of the study ventricular arrhythmias were encountered, additional 10-20 mg doses of lidocaine were administered as required; no other antiarrhythmic drug was given.

A thoracotomy was performed through the fifth left intercostal space. The wound was opened in layers and blood loss was kept to a minimum by means of electrocautery and carefully isolating and dividing large blood vessels (i.e. internal mammary artery and vein). The chest wound was extended from the neck of the 5th rib to the body of the sternum and kept open by a rib retractor. The pericardial sac was carefully opened with an incision which ran parallel and to the right of the left phrenic nerve from the pericardial attachment to the ascending aorta to its reflection on the diaphragm over the apex of the left ventricle. The edges of the pericardial incision were sutured to the border of the thoracic wound in order to cradle the heart but at the expense of compromising the venous return. Thus, when all cardiac instrumentation was completed, the sutures to the thoracic wall were cut and the heart allowed to fall back into the chest cavity with the pericardial sac partially covering the heart but left opened.

Instrumentation:

A standard three lead ECG arrangement was connected to the animals limbs to continuously monitor Lead II ECG. The signal was amplified by an ECG monitor (Electronics for Medicine, model VR-8) displayed on an eight channel Lexington semi-persistent monitoring scope (model DL 160). The ECG signal served four functions. First it monitored and measured heart rate, second the signal served as a timing trigger for the balloon inflation and deflation in the IABP study, third, to monitor and analyze various dysrhythmias and finally to follow the characteristic changes in the ECG waveform as ischemia was induced or evolved. In this study, changes in the configuration of the ECG tracings were noted but not recorded (i.e. S-T segment changes).

Haemodynamic measurements can be arbitrarily divided into pressure and flow parameters, some dealing with systemic measurements and others cardiac. For the assessment of aortic arterial pressure (systolic, diastole, and mean) the left brachial artery was isolated and cannulated with a 7F multipurpose Cordis catheter (model 521-742). This catheter was passed into the left brachiocephalic artery and

positioned at its opening into the arch of the aorta. Confirmation of the position of the tip of this catheter was done by palpation. Central venous pressure or mean right atrial pressure was measured by directly cannulating the atrial appendage and secured with 2-0 silk purse string sutures. The catheter was fashioned out of silastic tubing (1.57mm i.d. x 3.18mm o.d.) and connected to a 15G blunted needle. Pulmonary pressures (systolic, diastolic, mean, and capillary wedge) were measured from a triple lumen Swan-Ganz catheter (Edwards Laboratory, model 93-118-7F). The catheter was introduced into the right jugular vein or right brachial vein and followed the course of mixed venous blood by passing through the cavities of right atrium and right ventricle and eventually was positioned in the pulmonary artery with the tip of the catheter 3-4 cm past the pulmonary valve. This type of catheterization was accomplished by monitoring the pressure at the distal port of the catheter and guiding the catheter with the blood flow by means partially inflating the balloon, 1 cm back from the tip. This latter feature of the Swan-Ganz catheter was used to measure pulmonary capillary wedge pressures. In this situation the balloon was inflated until occlusive records were seen and measurements were taken within 30 sec during respiratory expiration.

Intracavitary pressures were measured from all four chambers of the heart. The catheter and catheterization technique described for mean left atrial pressures were similar to the methods described for mean right atrial pressure measurements. The catheter used to measure left ventricular intracavitary pressures (systolic and diastolic) was passed from the right brachial artery, down the right brachio-cephalic artery into the ascending aorta and manually guided across the aortic valve and into the left ventricle. In the initial 16 experiments, a Millar catheter tip manometer (model PC-470) was used in conjunction with a DC amplifier (Millar, model TC-100). In subsequent experiments pressures were recorded from a 7F multipurpose Cordis catheter (model 521-742) similar to the catheter used to measure aortic arterial pressure. Placement of the left ventricular catheter was closely scrutinized to minimize the amount of artifactual noise superimposed over the pressure signal and second to reduce the incidence of catheter induced arrhythmias. In addition to monitoring left ventricular pulse pressures, the electronic output signal was differentiated by means of

an analog device (Biotronex, model BL 620) to measure the maximum rate of developed pressure (max dP/dt). This signal was calibrated at the end of each study by means of triangular pulses of known amplitude. Right ventricular pressures (systolic and diastolic) were recorded from the distal port of a second Swan-Ganz catheter (Edwards Laboratory, model 93-118-7F) which was advanced as far as the right ventricle. All pressures were zero referenced to the height of the right atrium. Mean right and left atrial pressures were recorded directly by fluid manometry and expressed in terms of cm H₂O. All other fluid-filled catheters were used in conjunction with Statham P23Db pressure transducers and Electronics for Medicine SGM-2 signal conditioner and calibrated prior to and at the end of each experiment with a column of mercury, thus, vascular pressures were expressed as mm Hg. All fluid filled systems were heparinized (4 USP/ml) while automated flushing systems (Intraflow 2-03F) were used to keep a line free of clots. The frequency responses of this fluid filled catheter-transducer system was flat to: AP 28 Hz; LV 20 kHz with Millar and 28 Hz with 7F Cordis catheter.

Flows either regionally or systemically were measured by various techniques depending upon the information required. In the first 14 experiments aortic root flow velocity was measured by means of Statham electromagnetic circumferential flow probes (15-25mm in diameter) in conjunction with a Statham signal conditioner (model SP 2202). The probe was positioned around the ascending aorta, approximately 1 to 2 cm from its origin and calibrated by simultaneously determining the cardiac output via a thermodilution technique in the pulmonary artery. Eventually this latter technique became the method of choice for measuring systemic flows. With this technique, 5 mls of 4°C of 5% dextrose was rapidly injected into the right atrium and the resultant thermodilution curve was monitored by a thermistor positioned in the main pulmonary artery. The integration and computation of cardiac output was done by an Edwards cardiac output computer (model 9510) in conjunction with a specifically designed triple lumen catheter (Edwards model 93-118-7F) whose positioning has been outlined earlier. Data on systemic flows were reported as cardiac index in which minute volume flow was normalized by the body weight and expressed as ml/min.kg, or stroke index ml/beat.kg in which the cardiac index was divided by the heart rate. In addition, cardiac or stroke index were combined with mean arterial pressure to compute cardiac or stroke work (mmHg.ml/min.kg or mmHg.ml/beat.kg, respectively).

Blood flow to the heart was measured by two techniques. Since the essential feature of this preparation was the isolation of the coronary circulation from the systemic system, flows to the coronary arteries were measured in all experiments electromagnetically using two or three Biotronex extracorporeal flow probes (model BL C-2032) in conjunction with the appropriate signal conditioner (Biotronex, model BL-610). These probes were placed in line with the coronary perfusing catheters and were periodically calibrated against known blood flow rates and were found to deviate minimally once the gain setting had been initially established. Throughout the experiment, flow signals were periodically zeroed by stopping the flow of blood through the probe. A bypass system around each flow probe allowed this zeroing procedure to be performed without obstructing the flow to the coronary artery. The flow data from these probes were either reported as individual flow rates (ml/min) or combined with other flows from the accompanying coronary arteries and expressed as a percentage of the total flow or as the ratio of the left and right coronary flow rates. When flows through all probes (initially two for the first 13 experiments after which three probes were used) were combined, overall total coronary flow was normalized by weight of the heart (both atria and ventricles) and expressed as ml/min.g.

In analyzing these hemodynamic data, electronic signals were either recorded directly on a Beckman SII dynograph, or stored on a Bell and Howell VR-3200 FM magnetic tape recorder for later processing.

In addition to the coronary arterial flow data, radioactively labelled tracer microspheres were used in some of these studies as well. In the developmental stages of this preparation, microspheres were used to measure dispersion of the coronary extracorporeal source of flow while in later experiments they were used to measure the nutritive flow within the free wall of the left ventricle and its transmural distribution. In all studies in which microspheres were used, the size of the spheres was 15 ± 5 microns in diameter (3M Co, NEN) however, a variety of radionuclides were used (^{169}Yb , ^{141}Ce , ^{51}Cr , ^{85}Sr) depending on the number of flow measurements required. For each measurement, 1×10^5 microspheres were suspended in 15 mls of extracorporeal blood and mixed for at least 20 minutes on a vortex mixer. For flow measurements the microsphere

suspension was injected into an expansion - mixing chamber in line with the base of the coronary perfusing reservoir while a reference blood sample was withdrawn from a point downstream from the site of injection. This reference blood sample was taken with a Harvard withdrawal pump (model 901) which was started 15 sec. prior to injection and continued on for an additional 105 sec. after. The vast majority of reports in which microspheres have been used to measure flows, the tracer was injected systemically, usually in the left atrium or left ventricle and the proportional distribution would follow that of the cardiac output (61,74). In these experiments microspheres were only injected into a regional circulation; however, the same assumptions and calculations were used. In essence nonrecirculating microspheres became entrapped in the coronary microcirculation during the first pass through the heart: all microspheres that were able to pass across the coronary circulation were eventually filtered out by the pulmonary circulation. The calculation of myocardial blood flow was based on the assumption that the number of microspheres which are entrapped by an area of the heart is proportional to the arterial flow perfusing the region of the heart. The reference blood sample was used to calibrate the flow measurement so that the number of spheres or the amount of a specific radionuclide could be converted into absolute flows (ml/min) using the formula $F_m = F_b \cdot C_m \cdot C_b^{-1}$, where F_m is myocardial flow (ml/min), F_b is the withdrawal rate of the reference blood sample (ml/min). C_m is the net corrected radioactivity in the myocardial specimen (cpm), and C_b is the net corrected radioactivity in the reference blood sample (cpm). The final myocardial blood flows were normalized by the weight of the specimen (ml/min.g) as is done in more traditional applications of this procedure. The specific sampling techniques will be outlined in the various protocol sections to follow.

Blood Analysis:

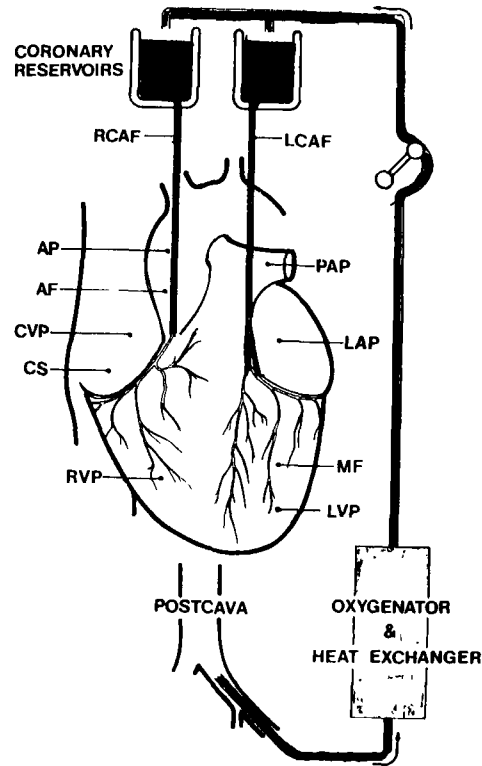
During the experiment, arterial blood gases (pH, pO_2 , and pCO_2) were periodically monitored either from the animal or the extracorporeal circuit using a Radiometer BMS-3 analyzer. Appropriate adjustments in pH were made either by altering the inspiratory CO_2 levels or by the administration of a 10% solution of sodium bicarbonate.

Myocardial oxygen data were obtained by measuring the uptake across the coronary circulation, arterial (extracorporeal) and coronary sinus blood (cannulated with a 7F multipurpose Cordis catheter) were drawn anaerobically and analyzed for their oxygen content ($[O]_a$ and $[O]_{cs}$, respectively)(ml/100 ml blood) by means of a Lexington analyzer (LEX-O₂-CON-TL). These values along with the normalized coronary blood flows (CBF) ml/min.100g) measured by the extracorporeal probes in series with the perfusing catheters were used to compute myocardial O₂ availability (ml/min.100g) = (CBF. $[O]_a$). $(100)^{-1}$, myocardial oxygen extraction (%) = ($[O]_a - [O]_{cs}$) ($[O]_a$) $^{-1}$. (100) , and myocardial oxygen consumption (ml/min.100g) = (CBF).($[O]_a - [O]_{cs}$) $(100)^{-1}$.

Extracorporeal Circuit:

The essential feature of the cardiogenic shock model is that coronary perfusing pressure is the controlled variable, with the resultant changes being recorded. To accommodate this procedure, animals were heparinized (300 USP/kg) and placed on total coronary bypass using a specifically designed extracorporeal circuit. In all experiments the system was primed with a mixture of citrated whole blood collected from donor dogs and a lactated Ringer's solution to which heparin (300 USP/L), potassium chloride (20 meq) and sodium bicarbonate (50 meq/L) were added. Into the extracorporeal circuit blood was collected from both femoral veins using wide-bore Bardic catheters (F-28) and collected in a venous reservoir whose overflow height maintained right atrial pressure at specific values selected between 9 and 16 cm H₂O. This procedure was instituted in order to maintain adequate preloading conditions to ensure that the ensuing hypotensive state did not result from insufficient amounts of circulating fluid (hypovolemia). After the venous reservoir, the blood passed through a Harvey H-200 bubble type oxygenator which aerated the blood with a gas mixture of 20% O₂ - 80% N₂ and heated the fluid to 36-38°C. Arterialized blood was then passed through a Harvey Q-100 filter and pumped to the coronary perfusing reservoirs. The delivery pressure to the coronary arteries was set on the basis of the height of these reservoirs above the left atrium, which was initially set equivalent to 120 mmHg. In the first 13 experiments (Figure 1), 2 reservoirs were used; one perfused the right coronary (RC) circulation

Figure I.



Extracorporeal circuit used for the first 13 experiments. The abbreviations represent the various parameters measured:

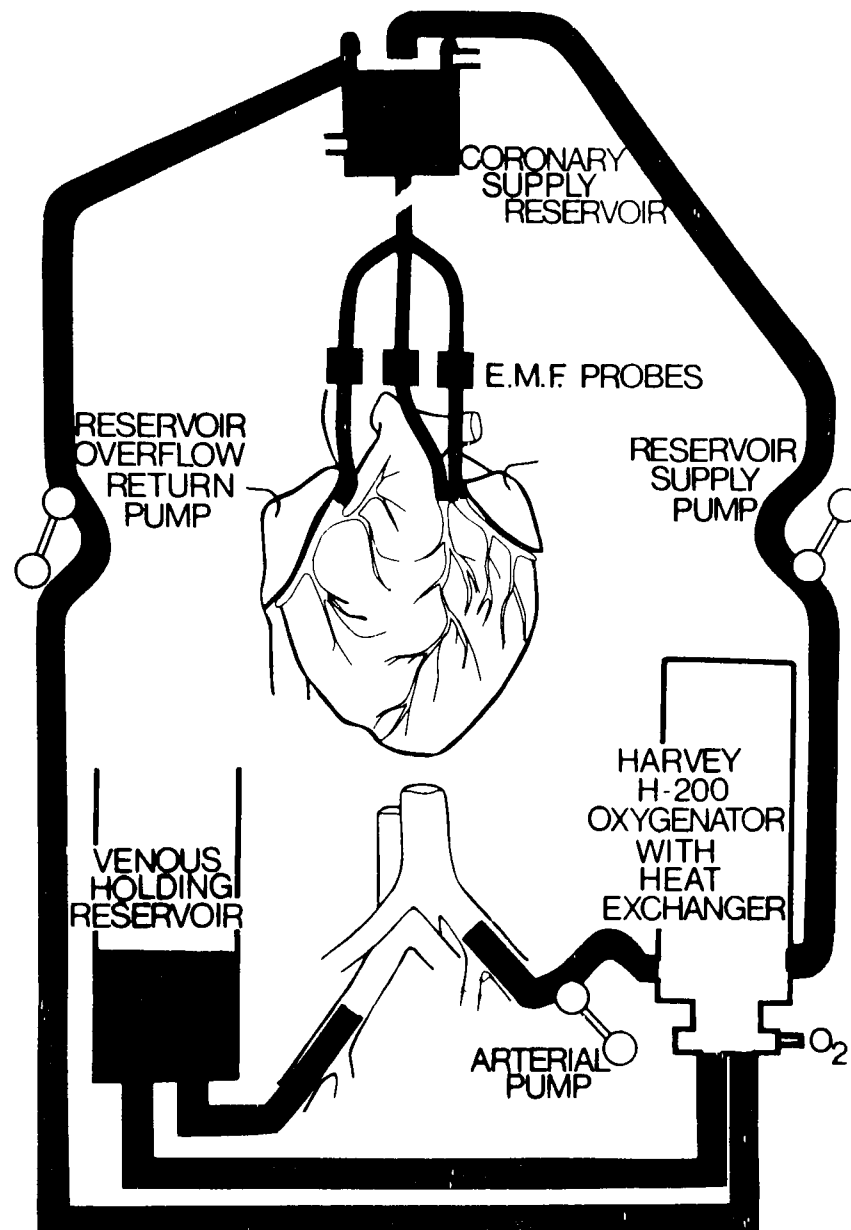
- RCAF = right coronary artery flow
- LCAF = left coronary artery flow
- AP = aortic (arterial) pressure
- PAP = pulmonary artery pressure
- AF = aortic flow
- CVP = central venous pressure (right atrial pressure)
- CS = coronary sinus sampling catheter
- RVP = right ventricular pressure
- LVP = left ventricular pressure
- MF = isometric muscle force (Walton Brodie stain gauge)

while the second perfused the left coronary system. After the thirteen experiments, a single chamber was used (Figure 2) which divided into 3 perfusing catheters. After passing out the bottom of the reservoir, the blood was reheated to 38°C via a heat exchanger (not shown in Figure 2) and the flow rate measured by extracorporeal flow probe for each perfusing catheter. Tapered catheters (Travenol 5M0287) were used as coronary cannulas whose unimpeded flows were minimally 600 ml/min at a driving pressure of 120 mmHg.

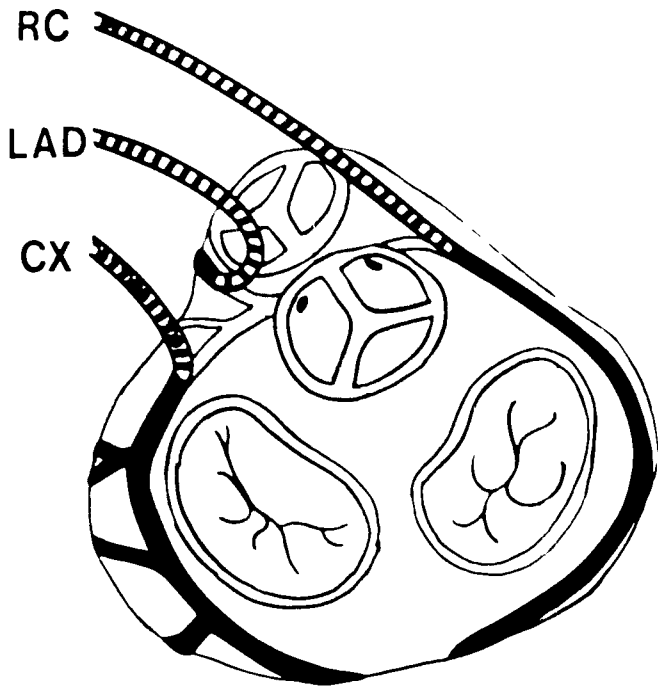
The three main coronary arteries (RC, LAD, and CX) were isolated by blunt dissection and 2-0 silk ties. The RC artery was cannulated 1-2 cm from its aortic origin while in the first 13 experiments the LAD and CX arteries were cannulated at their origins at the bifurcation of the left main coronary artery (Figure 3a,b). After the 13th experiment the method of catheterization and perfusion was altered to compensate for various inadequacies of this initial technique (Figure 3c,d). The specific reasons for these changes will be outlined in the results section. In the second technique, the extracorporeal system perfused the left main coronary artery and the septal artery as well as the vessels outlined before. In this procedure, the CX artery was cannulated both proximally and distally, 3-5 cm from its origin. The left main coronary artery was isolated by blunt dissection and a 3-0 silk tie at its aortic origin. By occluding the left main stem and retrogradely perfusing the proximal CX artery, all initial branches of the left coronary artery (septal artery) plus the LAD artery were perfused. Through the distal cannula on the CX branch the remaining portions of the artery were perfused. The RC artery was cannulated as before.

To minimize the episodes of systemic hypotension which were frequently encountered during coronary artery cannulation, the extracorporeal system was equipped with a partial bypass to temporarily support the systemic circulation. In this circuit, arterialized blood was infused into the left femoral artery which was cannulated with a 16F Bardic catheter. Once the perfused heart could maintain the blood pressure to within normal limits (mean pressures between 100-140 mmHg) this bypass support circuit was discontinued. In addition, excessive left ventricular pressures were avoided by

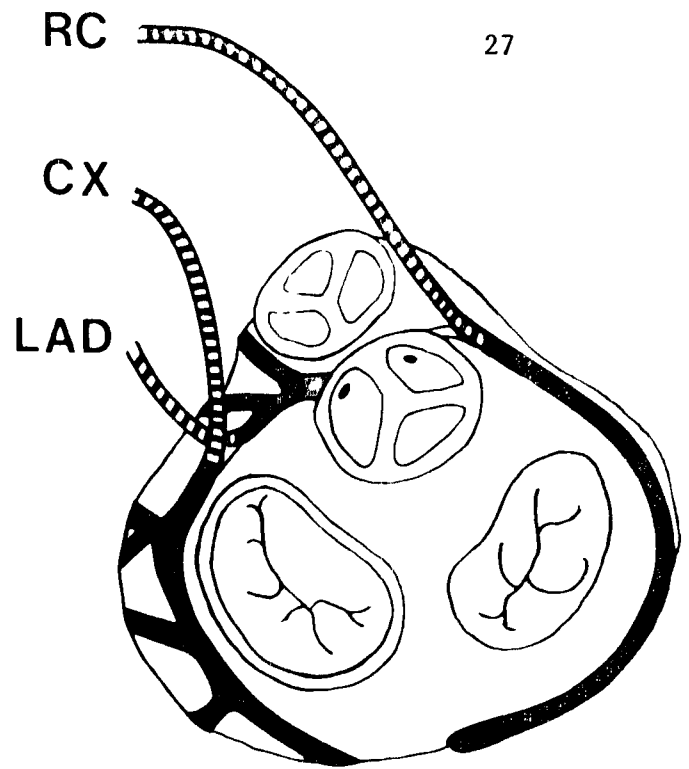
Figure 2.



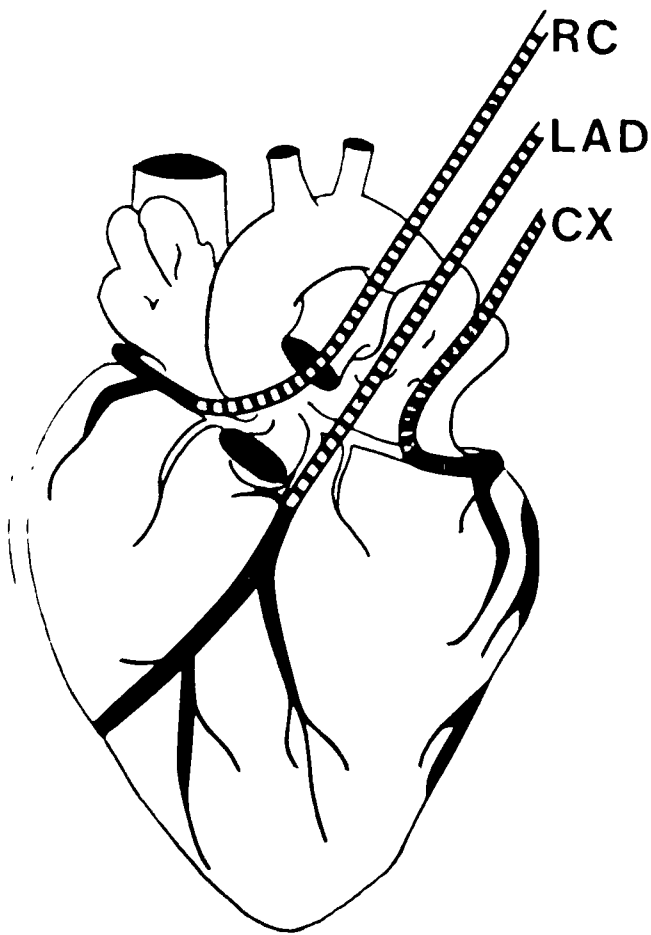
Extracorporeal circuit used in all studies beyond the first 13 experiments. Note the single coronary reservoir. For descriptive details of the circuit see text.



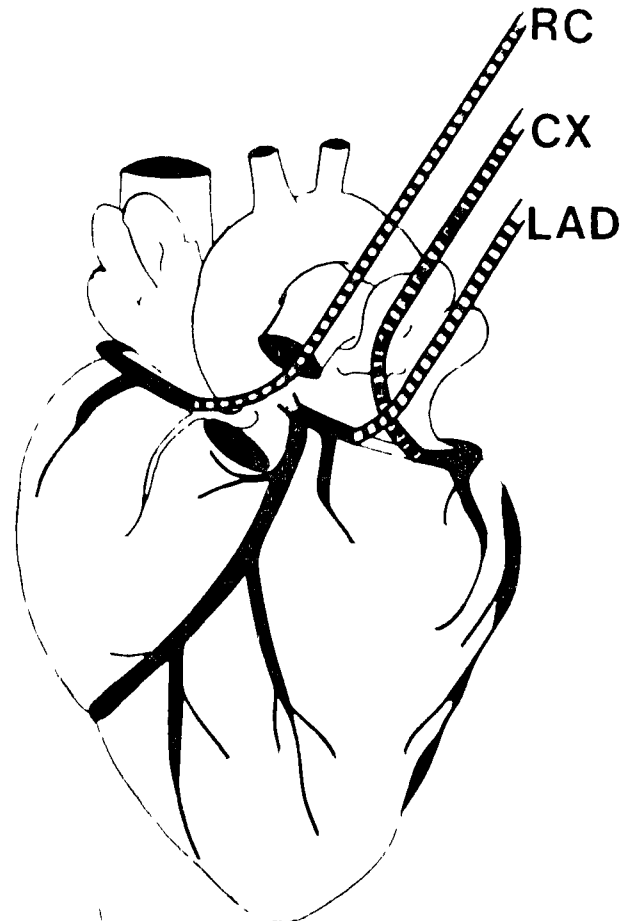
(a)



(c)



(b)



(d)

Coronary cannulation technique: (a) and (b) - type I, (c) and (d) - type II.
RC = right coronary; CX = circumflex, and LAD = left anterior descending.

cannulating the left atrium with a wide bore catheter in conjunction with a pressure reservoir. Adjustments in the height of this reservoir were done so that left atrial pressures would not exceed 30 cmH₂O.

Once coronary perfusion was established, animals were allowed to stabilize for at least 60 minutes at a coronary perfusing pressure (CPP) of 120 mmHg. During the period, pH and blood gases were measured and the appropriate corrections made. In addition, the plateau of the Frank-Starling curve was established by adjusting the height of the venous pressure until arterial pressure and cardiac output were maximal. Once the desired level was reached, no further adjustments to the venous reservoir were made. Towards the end of the stabilization period two sets of metabolic and hemodynamic values were gathered, 14 minutes apart. If values were consistent (in general, deviations less than 15% from initial value were considered consistent), both sets of data were averaged and used as control values for all subsequent maneuvers; if not, additional time was allocated for stabilization.

Protocol-Series I:

These initial experiments were designed to test the stability and the performance characteristics of this new preparation. In all, 31 preliminary experiments were performed during which time only the arrangement of the perfusing coronary catheters and the numbers of perfusing reservoirs were changed. In the first three animals, the stability of the preparation was documented by keeping the CPP at 120 mmHg and repeatedly taking hemodynamic measurements over a 2.5 hr. period. In two animals, the hemodynamic responses to changes in selective coronary hypotension were performed. In these studies, the RC artery CPP was maintained at 120 mmHg while the CPP to the left coronary system (LAD & CX) was rapidly dropped and returned to 120 mmHg. In all experiments to follow, decreases in CPP were performed uniformly on all three coronary arteries. In a group of nine animals the CPP was progressively reduced in 10 to 20 mmHg steps until an arterial systolic pressure of 75 mmHg or less was recorded. The time between reductions in CPP was usually 10 minutes. At the final perfusing pressure, coronary hypotension was extended until circulatory collapse ensued.

When the cannulation techniques were altered to accommodate

the perfusion of the left main coronary artery, two animals were used in stability studies. Starting ten minutes after the coronary cannulation had been completed, repeated hemodynamic observations were made over the next five hours while the CPP was maintained at 120 mmHg.

In nine dogs hemodynamic and myocardial oxygen responses to various levels of reduced coronary flow were studied. Accordingly, brief, three minute periods of reduced CPP's were used to decrease CBF. At the end of this period, hemodynamic and oxygen values were collected after which the CPP was returned to 120 mmHg. In all, eight different pressures were examined from 110 to 40 mmHg in a randomized fashion. Between these periods of reduced CPP, animals were allowed to recover for ten minutes: if at the end of this rest period control hemodynamics ($\pm 10\%$) were not re-established, no further studies were performed.

Protocol-Series II:

In these experiments 36 animals were used to estimate the myocardial impairment associated with a partial reduction rather than a complete obstruction of coronary flow. For these experiments hemodynamic and metabolic responses to global reductions in CBF for various durations were examined prior to and following 60 minutes of reperfusion. Before the experiment was begun, a 60 minute period of stabilization at a CPP of 120 mmHg, control measurements were taken. Acute cardiac failure was then induced by reducing the CPP until arterial systolic pressure had been reduced to at least 75 mmHg and the cardiac output had decreased by at least 50%. Animals were then divided into five groups based on the duration of coronary hypotension: 15 min (n = 6), 30 min (n = 8), 60 min (n = 7), 90 min (n = 8), and 120 min (n = 7). At the end of these various periods of hyperperfusion, a second set of measurements were made after which the CPP was returned to 120 mmHg. This recovery period lasted for 60 minutes after which a third set of data was gathered.

At the completion of the study, the animal was sacrificed with a lethal dose of sodium pentothal. The free wall of the left ventricle was removed and the fat and large epicardial vessels discarded. In four to six selected areas of the left ventricle, transmural blocks of tissue were removed and further subdivided into epicardial, midmyocardial, and endocardial tissue samples. These

samples were weighed and their radioactive content measured on a Beckman Biogamma counter at optimum window setting corresponding to the peak energies of each radionuclide. From these data, relative blood flows were calculated according to the procedures outlined earlier in this section.

Protocol-Series III:

In the final group of experiments the specific advantage that the coronary circulation could be separated from the rest of the systemic circulation was used to resolve the therapeutic mechanism of action of intra-aortic balloon counterpulsation (IABP). Specifically with the coronary circulation fed by extracorporeal sources the model was used to study the systolic unloading effects of IABP independent of direct coronary diastolic augmentation.

During stabilization an AVCO IABP balloon (n=3 for 12 ml capacity and n=10 for 10 ml capacity) was inserted into the left femoral artery passed up the abdominal aorta and positioned just distal to the origin of the left subclavian artery. The balloon was inflated by a helium-driven pumping system (AVCO, IABP-7) triggered by the R-wave of the ECG and synchronized to inflate at the closing of the aortic valve and to vent to atmospheric pressure immediately before left ventricular ejection. The timing and duration of balloon inflation was adjusted to produce the maximum augmentation of diastolic aortic pressure measured proximal to the balloon.

In 13 animals the effects of IABP treatment without direct augmentation of coronary flow were studied at various CPP. The perfusing pressure was reduced from 120 mmHg to one of a series of lower levels for 20 min. During the first ten minutes of coronary hypotension the balloon remained inactive, counterpulsation was then instituted during the final ten minutes. Data were collected before and after IABP treatment. The coronary perfusing pressure was then returned to 120 mmHg for a twenty minutes recovery period followed by another hypotensive episode, (hypotensive pressures called for in each animal were 80, 70, 60 and 50 mmHg with the order randomized). While the use of all four hypotensive levels was planned in each dog, if control levels could not be re-established after 20 minutes of recovery, the experiment was terminated.

In both Series II and III experiments, various statistical tests were applied. When the animal's initial response served as its own control of a Student's t-test for paired data was used; if the response between 2 groups of animals were being evaluated a Student's t-test for unpaired data was used. One-way and two-way ANOVA tests were used for the reperfusion study to evaluate whether any of the responses were duration dependent. In all cases, differences were considered significant at a P level of 0.05 or less.

RESULTS-Background:

In the course of these experiments, acute studies were attempted on 118 animals. The notations used to summarize elements of the various experimental designs are shown in Table I. The first nine animals were used in preliminary studies to evaluate two previously cited techniques for inducing cardiogenic shock (26,72). The results of these studies have been outlined in the Methods section and eventually led to the choice of perfusing the entire coronary circulation from an extracorporeal source at controlled perfusing pressures. The overall fate of the remaining 109 experiments is presented in Table I.

Of the 35 animals in group A which did not complete the required stabilization period, more than half (n=19) failed as a result of ruptured vessels in which repair was either impossible or experiments were terminated in the belief that subsequent data would have been affected by the repair. With type II method of cannulating the coronary circulation, 16 experiments terminated with the rupture of the left main coronary artery. As outlined in the Methods section, the isolation and occlusion of this vessel was an essential prerequisite of this technique however, this procedure proved to be technically difficult surgical procedure to perform. In some of these experiments the left coronary artery was short and deeply imbedded in the fat surrounding the root of the aorta which made isolation of the vessel difficult and hazardous. A second major cause of this type of rupture was due to anatomical considerations in which the septal artery which normally arose from the medial side of the left main coronary artery could not be seen during isolation and ruptured as a silk thread was passed around the left coronary.

In 16 of the experiments in group A, surgery and instrumentation was completed; however animals could not be stabilized during the equilibration period with a CPP set at 120 mmHg. Within this group eight animals suffered from repeated episodes of arrhythmias that were refractory to lidocaine therapy while in the remaining eight animals, arterial extracorporeal support could not be terminated without subsequent circulatory failure intervening. The reason(s) for these 16 failure(s) have never been clearly identified although an inadequate perfusion of the coronary circulation was probably the

TABLE I

A summary of the various groups involved in this study

- Group A - experiments which did not complete the required equilibration period.
- a) ruptured pulmonary artery (n=1)
 - b) ruptured right coronary artery (n=2)
 - c) ruptured left coronary artery (n=16)
 - d) uncontrolled arrhythmias (n=8)
 - e) could not be weaned from arterial support (n=8)
- Group B - experiments which did complete the required equilibration period and were used to collect experimental data.
- [a) type I coronary cannulation
 - [(i) stability studies, CPP maintained at 120 mmHg (n=3)
 - [(ii) hypotensive studies, only left coronary artery pressure reduced (n=2)
 - Series I- [(iii) hypotensive studies, entire coronary perfusing pressure reduced (n=9)
 - [
 - [b) type II coronary cannulation
 - [(i) stability studies, CPP maintained at 120 mmHg (n=2)
 - [(ii) hypotensive studies, entire coronary perfusing pressure reduced (n=9)
 - Series II- (iii) effects of global ischemia (5 sub-groups) and subsequent reperfusion (n=36)
 - Series III (iv) systolic unloading properties of IABP (n=13)

reason. In reviewing the experimental records of these 16 animals, coronary cannulation was usually difficult and was accompanied by prolonged periods of coronary ischemia. In addition, it was frequently noticed that initial coronary flows which should have been high due to a reactive hyperemic response were usually low and never substantially improved over the subsequent equilibration period.

Of the 74 animals which were successfully equilibrated and data collected (Group B) surgical preparation and instrumentation for these animals took from 2.0 to 3.5 hours depending on a number of factors. In general, animals whose coronary arteries were isolated for type II cannulation and perfusion required a somewhat longer period of surgery involving the isolation of the left main coronary artery. During cannulation of the coronary vessels using either type I or II arrangement, occlusion times without coronary perfusion ranged from eleven seconds to seven minutes with an over average time of 42 ± 7 sec (mean \pm SEM). Once the coronary extracorporeal bypass circuit was instituted and arterial support discontinued, equilibration averaged 72 ± 8 min. During this period arterial blood gases and pH readings were monitored from the animal and the oxygenator and the appropriate corrections made. Also during this period the catheters were flushed and their positions checked and both pressure and flow transducers repeatedly balanced to zero.

Series I:

In 14 animals cannulated with type I (Group B(a)(i),(ii),(iii)) arrangement systemic and coronary hemodynamic values measured at the end of the equilibration period at a CPP of 120 mmHg are presented in Table 2.

To evaluate the stability of the preparation cannulated with Type I arrangement, three animals were maintained at a CPP of 120 mmHg for an additional 2.5 hours beyond the end of the equilibration period (Group B(a) type II(i)). During this time none of the parameters outlined in Table 2 fluctuated by more than 12% from initial control levels with the exception of total coronary flow which steadily decreased in 3 experiments so that after 2.5 hours the relative decrease was 14, 15, and 21% respectively. A closer examination of the individual flows (LAD, CX, and RC) indicated that the reduction did not

TABLE 2

Control data for the first hypotensive study of Series I:
Group B a) type I (i) and (iii), (n=14)

Parameter	Measurement
Heart Rate (bpm)	134 \pm 10
Pressures (mmHg)	
Arterial-mean	119 \pm 9
-systolic	132 \pm 11
-diastolic	94 \pm 9
LV -systolic	123 \pm 11
-diastolic	14 \pm 4
Max dP/dt(mmHg/sec)	2014 \pm 187
Atrial-(cmH ₂ O)	
-right	7 \pm 1
-left	16 \pm 4
Flows	
Cardiac index (ml/min•kg)	134 \pm 12
Stroke index (ml/beat•kg)	1.09 \pm 0.09
Total coronary (ml/min•g)	0.86 \pm 0.08
Left: right coronary ratio	2.34 \pm 0.29

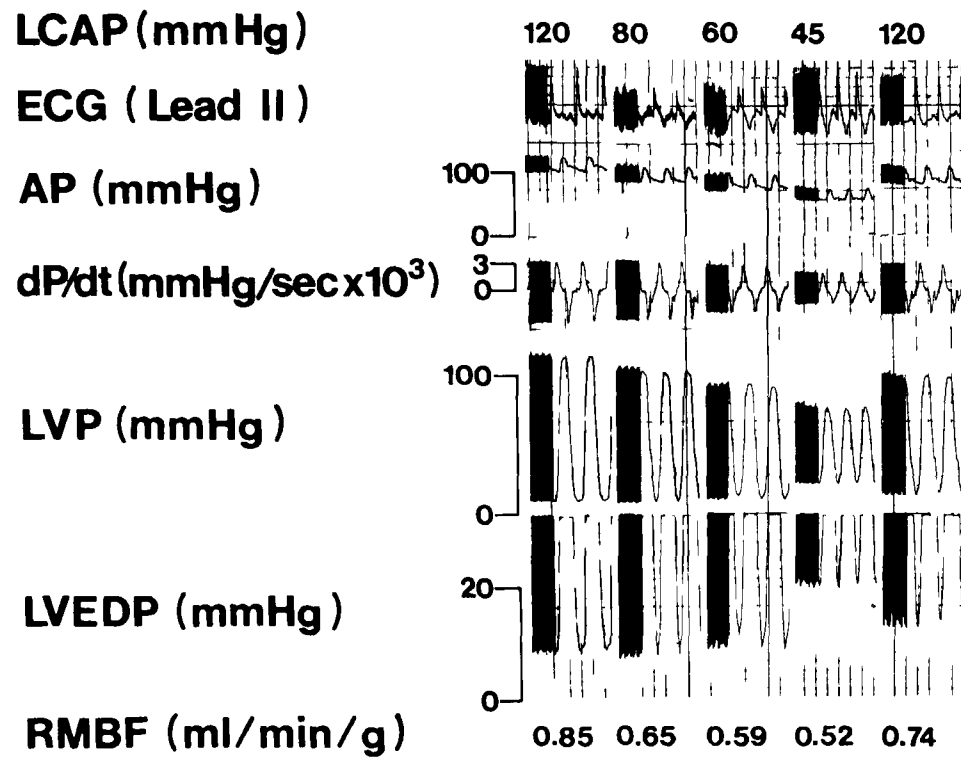
All values (mean \pm SE) were measured at the end of the stabilization period at a coronary perfusing pressure of 120 mmHg.

predominately originate in one particular part of the coronary circulation.

To assess the effectiveness of the type I coronary cannulation to perfuse the entire heart radioactively labelled microspheres were introduced in the coronary perfusing reservoirs of all three control animals at a CPP of 120 mmHg. At the end of the experiments the hearts were subdivided into counting samples (0.5 to 2.8 grams) and assayed for their radioactive content. In these three animals $78\% \pm 9\%$ of the nutritive flow to the heart appeared to have originated from extracorporeal sources while the remaining parts of the heart were either not perfused at all or were supplied by arterial blood originating from the aortic root.

In two animals (Group B(a), type I, (ii)) hypotensive studies were first performed in which only the height of the left coronary perfusing reservoir which supplied the LAD and CX arteries was reduced while the right coronary perfusing pressure was maintained at 120 mmHg. The results from one of these experiments are shown in Figures 4 and 5. In this study the left coronary perfusion was reduced from 120 to 80, 60, and 45 mmHg. After each reduction in CPP the preparation was allowed to stabilize for at least 10 min after which measurements were made. Figures 4 and 5 demonstrate that controlled reductions in the left coronary perfusing pressure alone caused concomitant reductions in coronary perfusing which in turn was expressed as progressive definable reductions in cardiac performance as monitored by the changes in ECG, arterial pressure, cardiac output, left ventricular systolic pressure and dP/dt . These reductions in performance were accompanied by increases in loading pressures (central venous pressure and left ventricular end-diastolic pressure) which between a CPP of 60 and 45 mmHg gave a situation clinically analogous to cardiogenic shock (acute cardiac failure). After 20 minutes at a CPP of 45 mmHg the left coronary perfusing reservoir was returned to a height equivalent to a perfusing pressure of 120 mmHg and a 20 minute recovery period was observed. The effectiveness of this reperfusion is also shown in Figures 4 and 5 in that some parameters returned to pre-hypotensive control levels (cardiac output, dP/dt) while other remained altered (left ventricular end-diastolic and systolic pressures). The results of the second study in this group were similar

Figure 4.

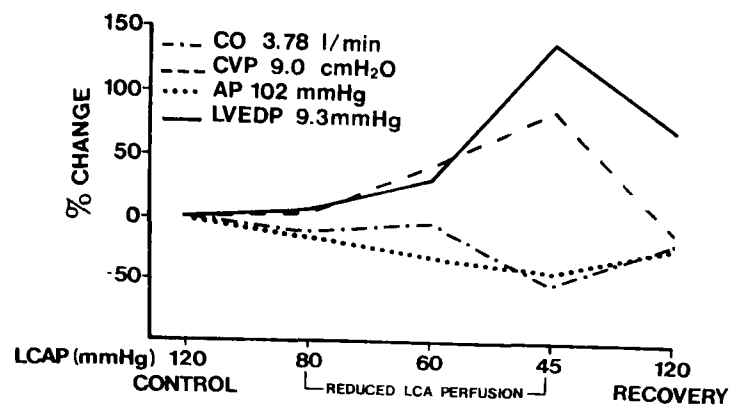


Experimental data from an animal (CSD-02) in which right coronary artery pressure was maintained at 120 mmHg while the left coronary artery pressure (LCAP) was reduced to 80, 60, 45 mmHg and returned to 120 mmHg. Abbreviations are:

- AP = aortic (arterial) pressure
- LVP = left ventricular pressure, and its rate of change (dP/dt)
- LVEDP = left ventricular end-diastolic pressure
- RMBF = relative myocardial blood flow

Series I a) type I (ii)

Figure 5.



The relative changes in 4 parameter measured from animal CSD-02 (Figure 4) are shown. Abbreviations are:

CO = cardiac output

CVP = central venous pressure

AP = mean aortic (arterial) pressure

LVEDP= left ventricular end-diastolic pressure

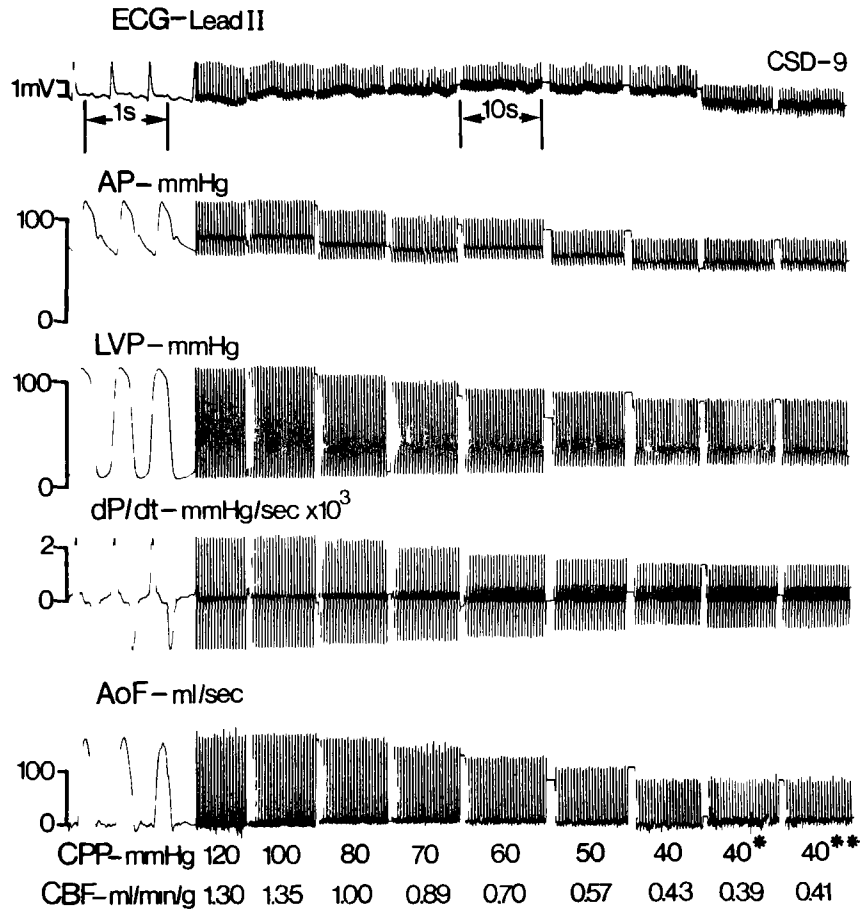
The values beside the abbreviations correspond to initial values measured when the coronary perfusing pressure to all three coronary vessels was 120 mmHg.

Series I a) type I (ii).

to the data from the first.

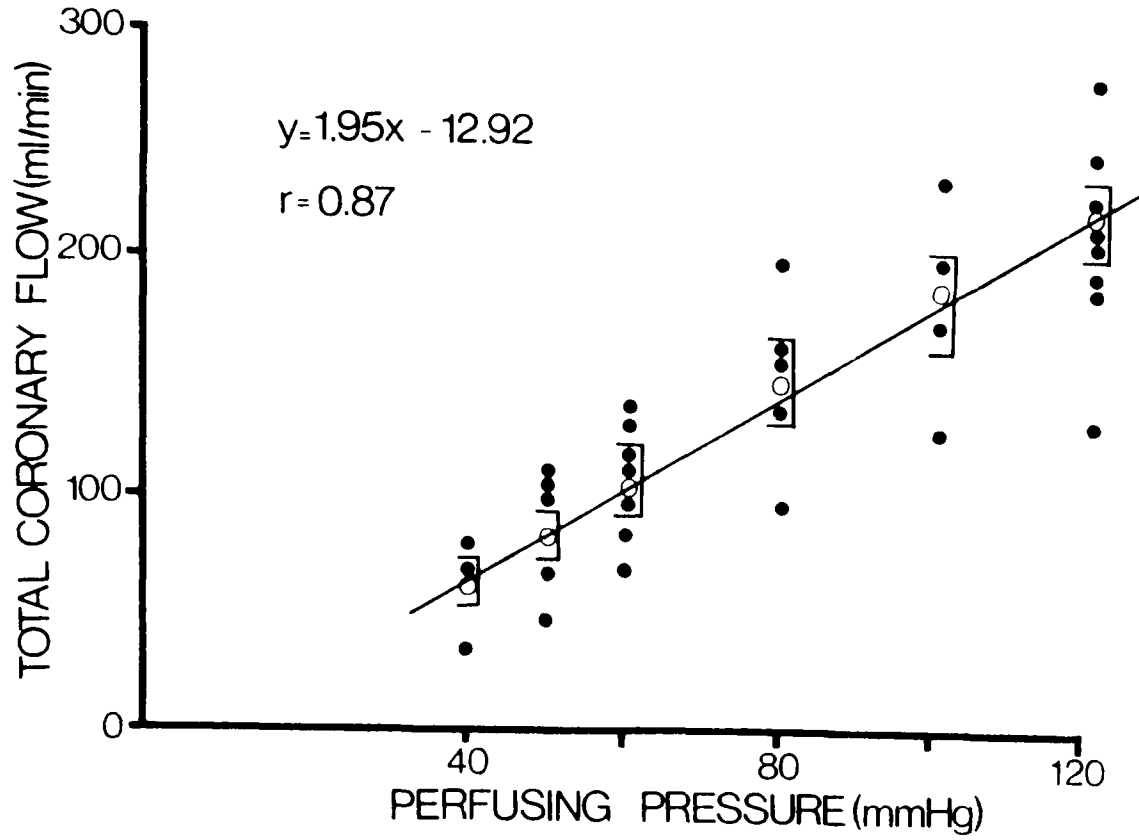
In the remaining nine animals with type I coronary cannulation the CPP was uniformly reduced to all three coronary vessels (LAD, CX, and RC) until an arterial systolic pressure of 75 mmHg or less was measured (Group B(a) type I(iii)). Figure 6 demonstrates such a protocol in which the CPP was reduced in 10-20 mmHg steps while the resulting hemodynamic changes were measured 10 minutes after the CPP was altered. In figures 7 and 8 the changes in total coronary flow have been plotted against perfusion pressure and effective perfusion pressure (CPP-LVEDP). In each case a least squares linear fit was calculated and a significant correlation ($p < 0.05$) found. In order to achieve the systemic hypotensive state of an arterial systolic pressure of 75 mmHg or less coronary perfusing pressure had to be reduced by $59.3 \pm 2.6\%$ from an initial level of 120 mmHg. With this reduction in CPP, total coronary flow decreased by almost an equal amount ($60.9 \pm 4.0\%$) which in turn reduced the various parameters of cardiac performance; cardiac index ($59.0 \pm 5.4\%$) Figure 9, max dP/dt ($52.5 \pm 3.3\%$) Figure 10, stroke index ($62.0 \pm 6.2\%$) Figure 11, stroke work ($74.8 \pm 8.7\%$) Figure 12, and mean arterial pressure ($37.6 \pm 3.7\%$) Figure 13. Figure 14(a)-(f) the relative reduction in total coronary flow versus the above mentioned hemodynamic parameters were plotted for the nine individual experiments. In each case a relatively predictable level of failure could be achieved by the controlled reduction in CPP alone. It should be noted that all experiments were performed under optimal loading conditions so that reductions in cardiac performance resulted from the underperfusion of the heart rather than hypovolemia.

At the lowest perfusing pressure the effects of protracted periods of coronary hypotension were also studied (Figure 6). Consistently in all nine experiments all hypodynamic values measured did not appreciably change from the start of this period until electrical instability developed which soon terminated in fibrillation and complete circulatory collapse. In seven dogs allowed to die in this manner, the mean survival time at the lowest CPP was 28 ± 4 min. In the remaining two animals, the CPP was returned to 120 mmHg after 30 min of severe ischemia. In these reperfusion studies a partial hemodynamic recovery was observed similar to the situation seen in Group B, (a) type I(ii); however within 2 and 5 min respectively,



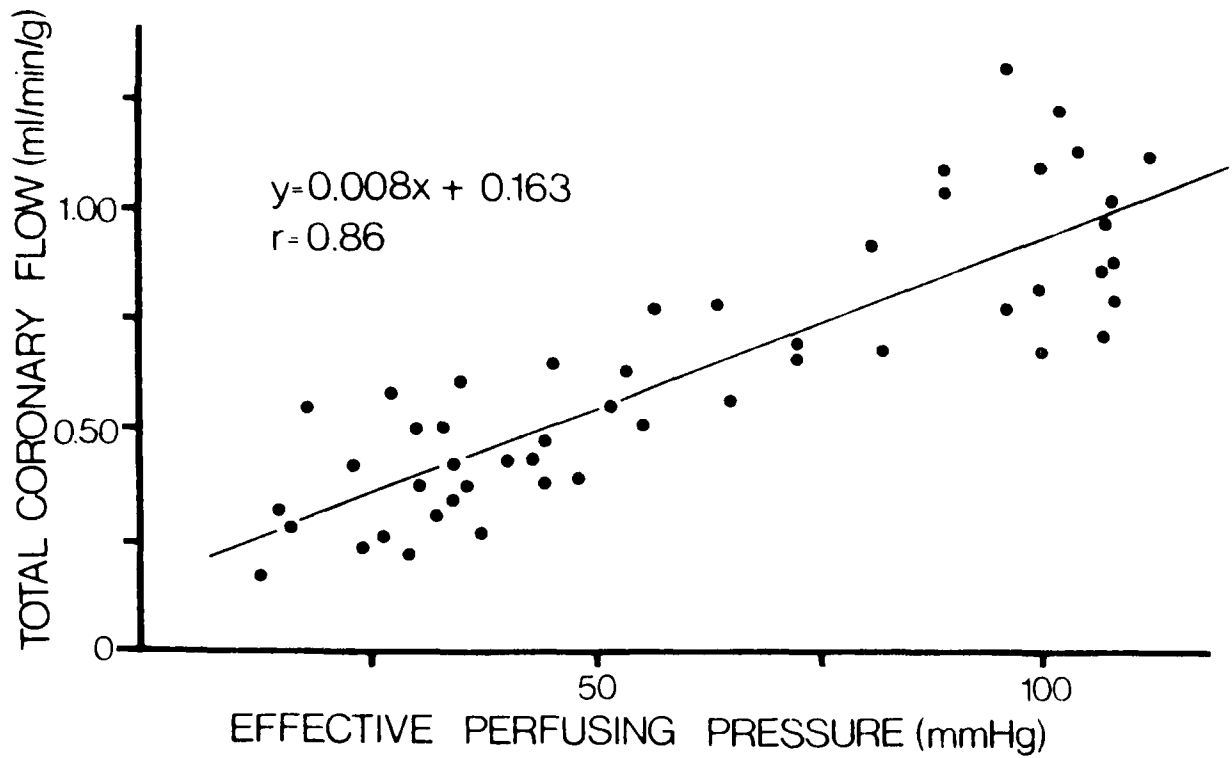
Hemodynamic responses from one animal (CSD-9) used in Series I a) type I (iii) experiments in which the coronary perfusing pressure was incrementally reduced to all 3 coronary arteries while the AP = aortic (arterial) pressure, LVP = left ventricular pressure and its derivative (dP/dt), AOF = aortic flow velocity, and CBF = coronary blood flow were monitored. All records were made 10 minutes after the pressure was reduced. At a CPP of 40 mmHg additional records were taken at the 20 minute (*) and 30 minute (**). points.

Figure 7.



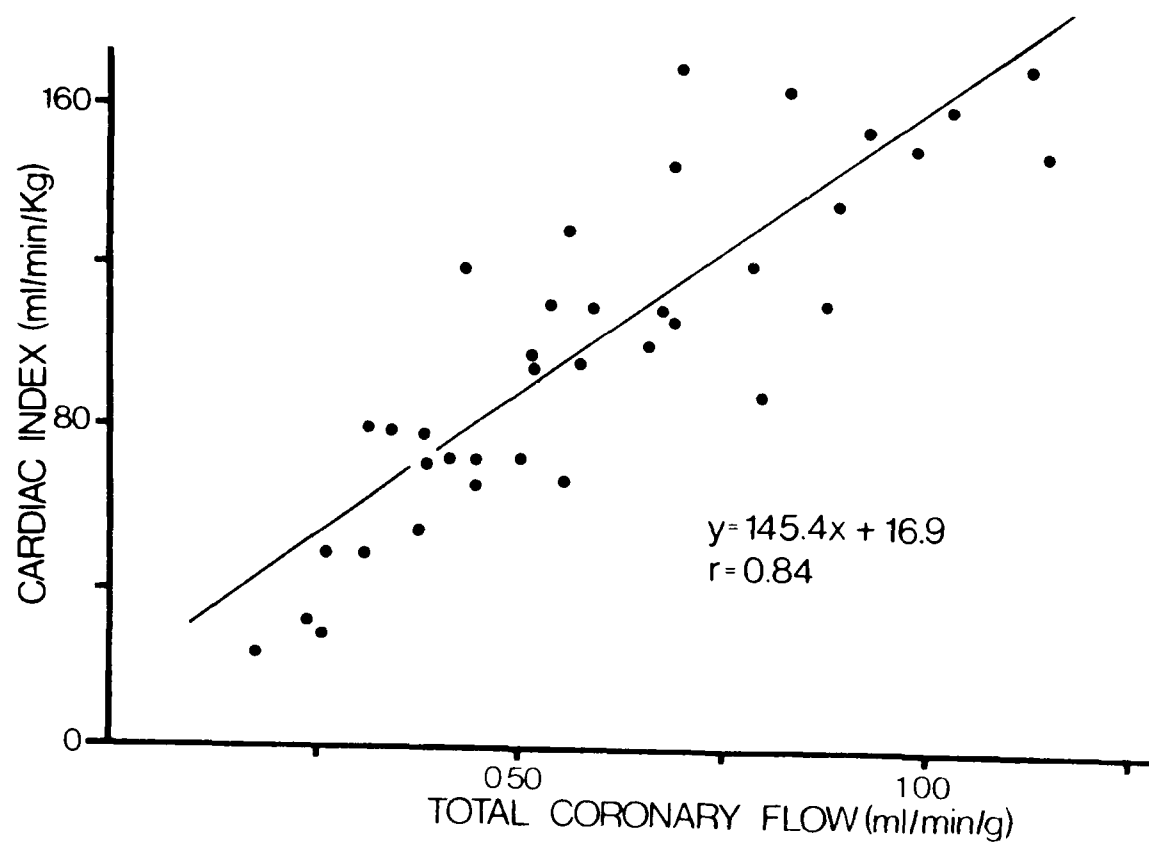
Total coronary flow versus perfusing pressure from animals (n=9) in Series I a) type I (iii) studies. Open circles and square brackets present mean \pm SE. Closed dots are individual data points.

Figure 8.



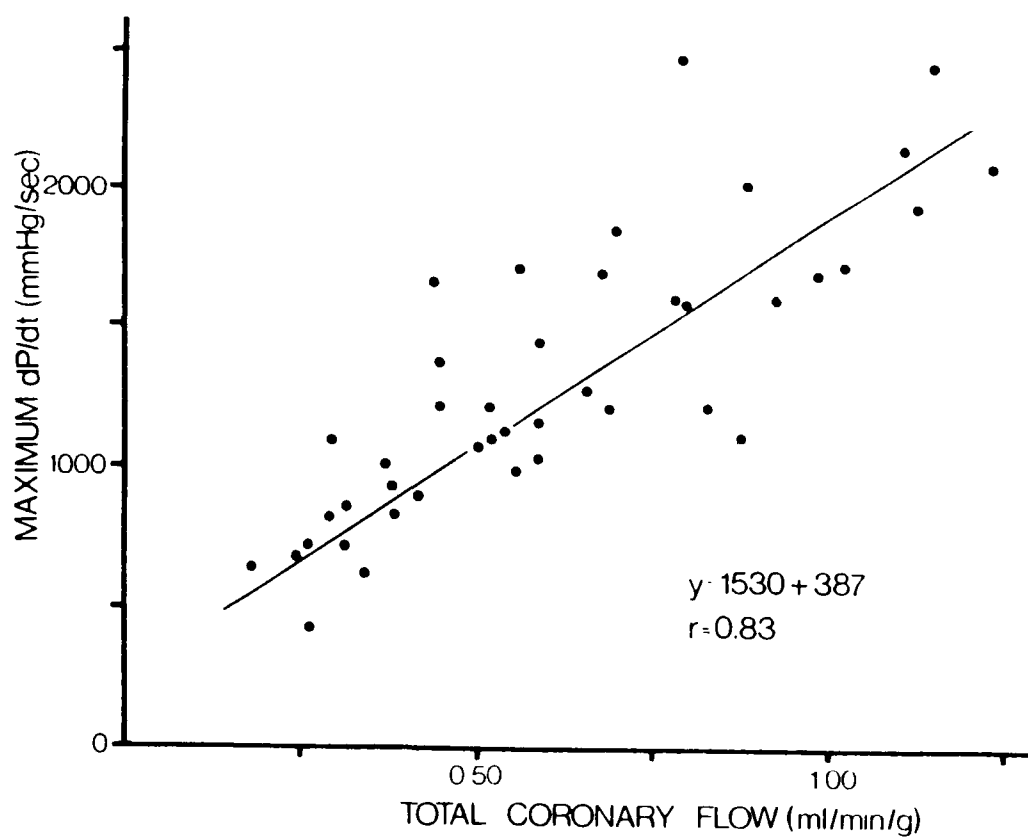
Total coronary flow versus effective perfusing pressure (CPP - LVEDP) for animals (n=9) in Series I a) type I (iii) studies. Closed dots are individual data points.

Figure 9.



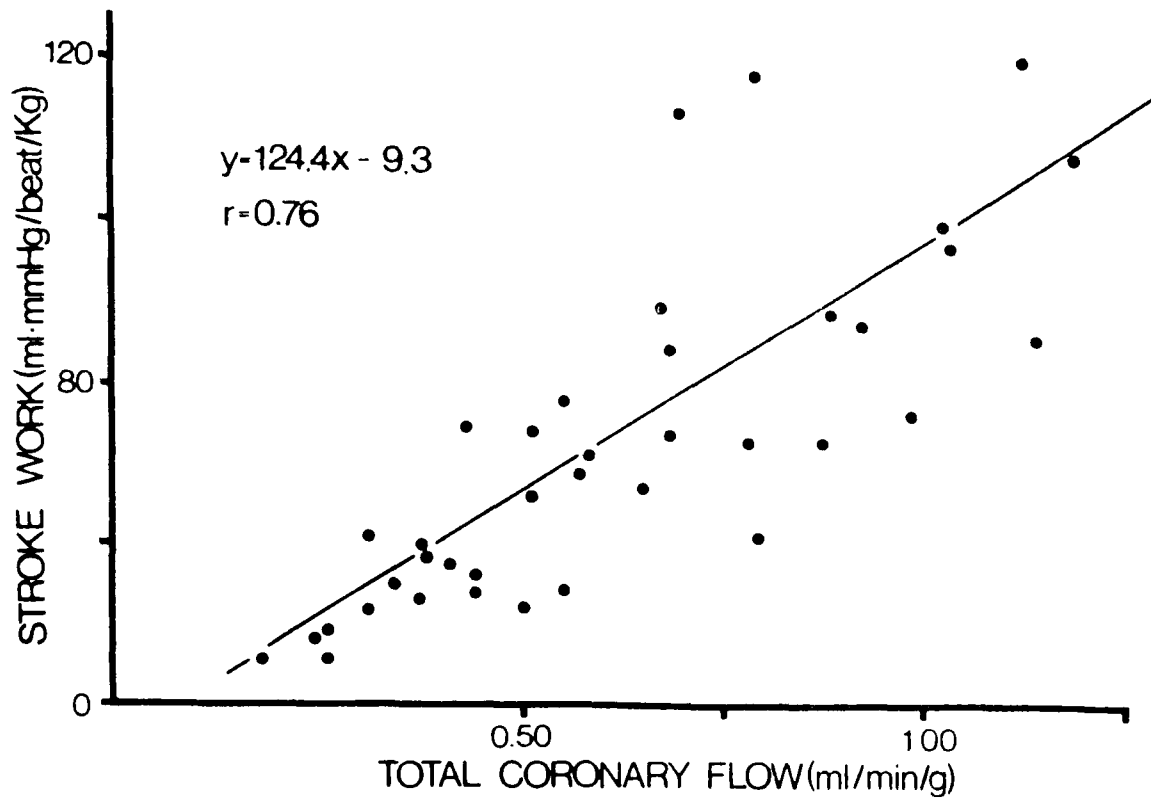
Relation between total coronary flow and cardiac index for animals (n=9) in Series I a) type I (iii) studies. Individual data points are shown.

Figure 10.



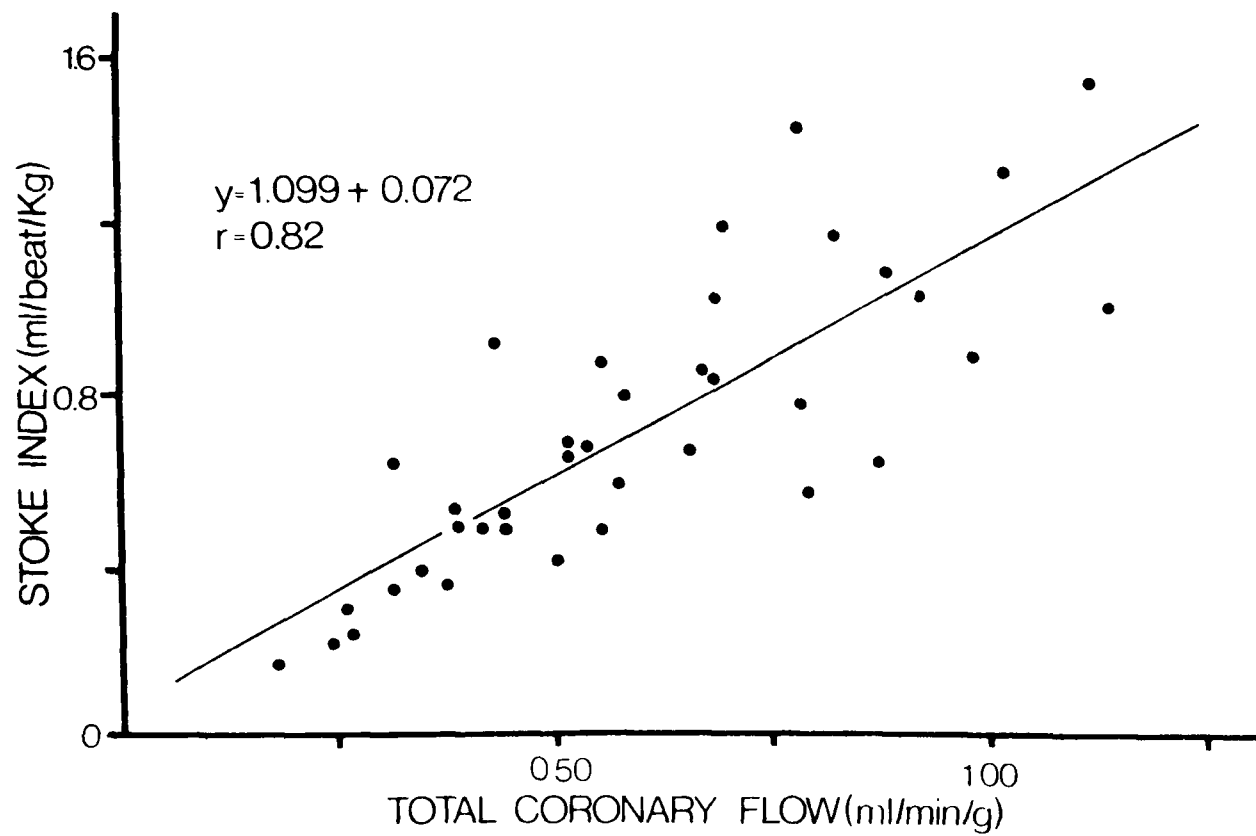
Relation between total coronary and LV maximum dP/dt for animals (n=9) in Series I a) type I (iii) studies. Individual data points are shown.

Figure 11.



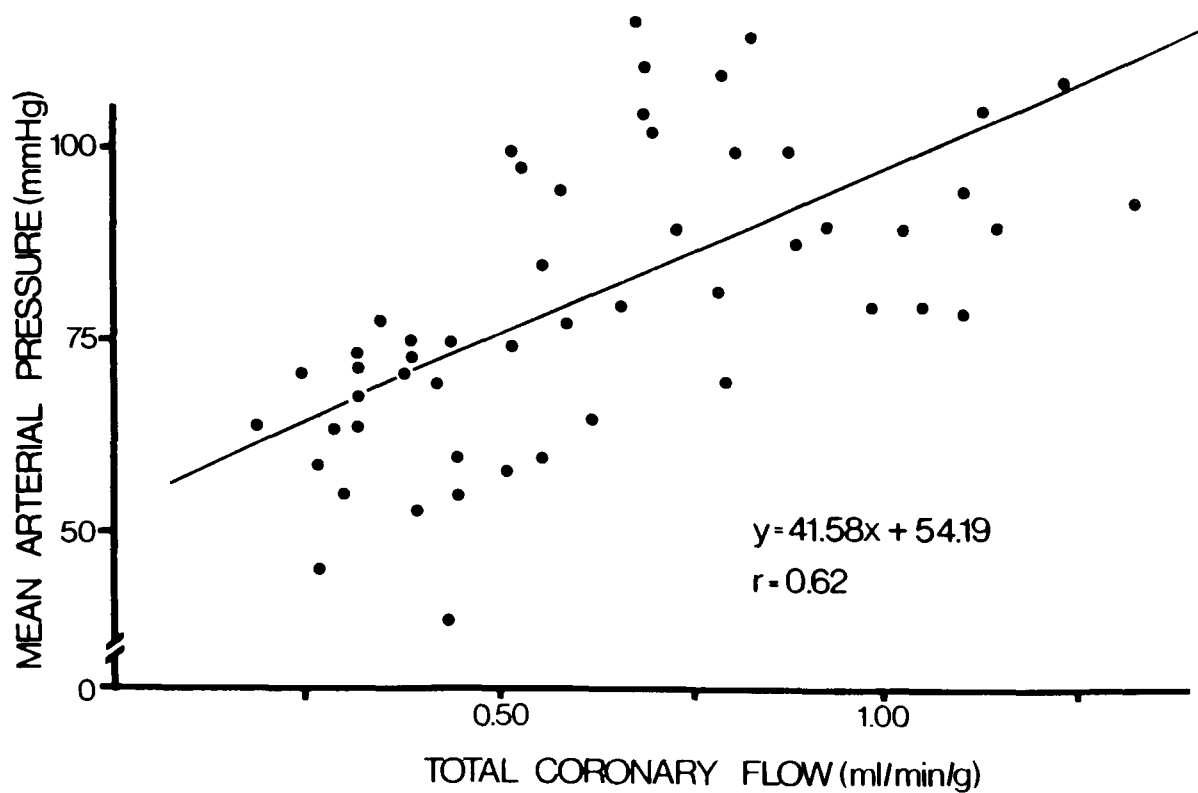
Relation between total coronary flow and stroke work for animals (n=9) in Series 1 a) type I (iii) studies. Individual data points are shown.

Figure 12.



Relation between total coronary flow and stroke index for animals (n=9) in Series I a) type I (iii) studies. Individual data points are shown.

Figure 13.

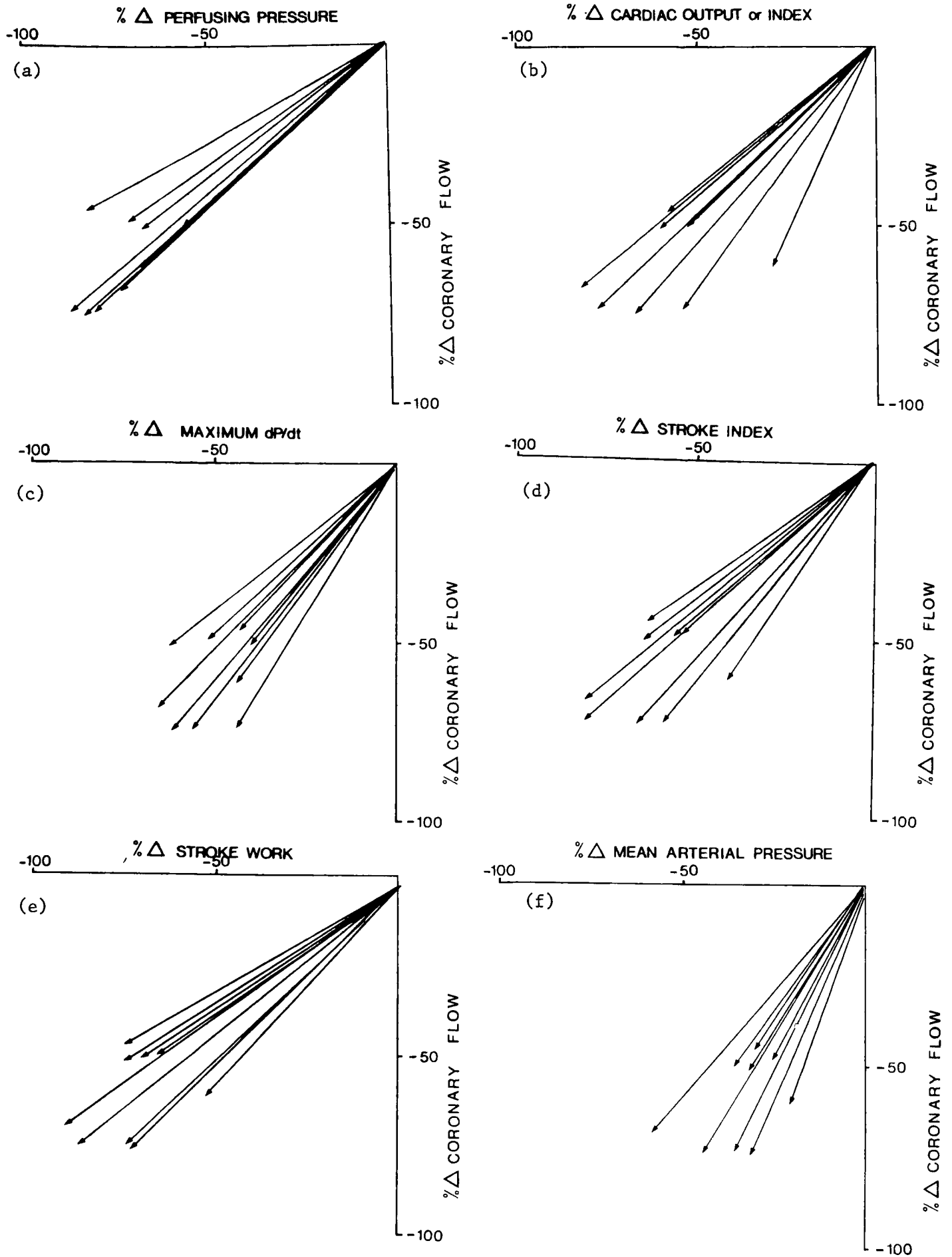


Relation between total coronary flow and mean arterial pressure for animals ($n=9$) in Series I a) type I (iii) studies. Individual data points are shown.

Text to Figure 14:

Relative reductions in coronary flow versus:

- (a) perfusing pressure
 - (b) cardiac output or index
 - (c) max dP/dt
 - (d) stroke index
 - (e) stroke work
 - (f) mean arterial pressure
- in order to produce acute cardiac failure in animals (n=9)
in Series I a) type I (iii) studies. See text for the
numerical values of the relative changes.



uncontrollable arrhythmias developed which soon terminated the experiment.

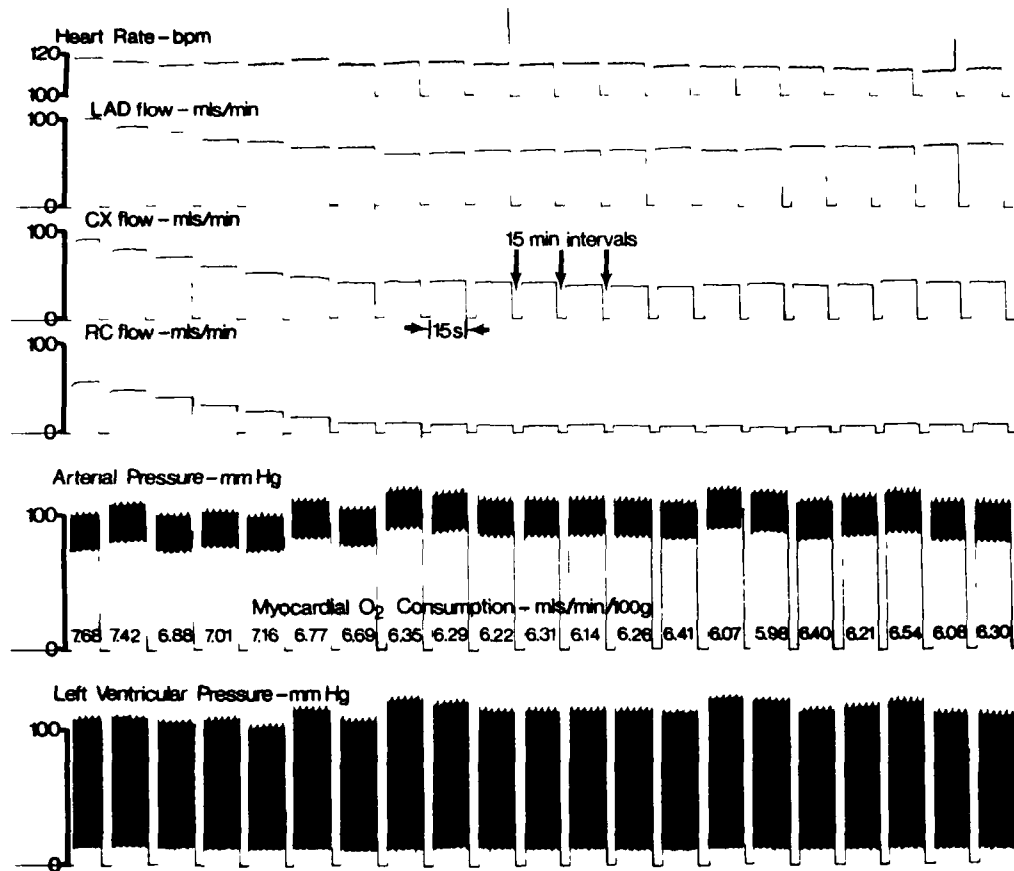
At the completion of the various protocols for all 16 animals with type I coronary cannulation, hearts were examined macroscopically. In all specimens a large, hemorrhagic, pale brown area was seen across the wall of the pulmonary conus. Occasionally this area encompassed the basal portion of the septum as well. The rest of the heart had scattered perivascular hemorrhages that were more prevalent in the hypotensive groups ((a) type I, (ii) and (iii)) than in the three control hearts (Group (a) type I (i)).

At this point in the study the technique for cannulating the coronary vasculature was changed from a type I arrangement (Figure 3a,b) to type II (Figure 3c,d). Although many factors were involved in this decision the results from the perfusion distribution experiments in Group (a) type I (i) clearly established that parts of the coronary circulation were not perfused by the extracorporeal circuit. In the first two experiments with this new technique, control time studies were performed (Group B(b) type II(i)) starting 10 min after coronary cannulation had been completed. Animals were monitored for 5 hrs at a constant CPP of 120 mmHg. The results from one of these control studies are shown in Figure 15. During the time when equilibration would occur, flows to all three coronary vessels slowly declined until a steady state was reached, with the exception of RC which more so in this experiment than in the second, continued to decrease slowly throughout the observation period. The reduction and developing steady state conditions seen in the coronary flows paralleled the changes in myocardial oxygen consumption while systemic hemodynamic values quickly recovered after coronary cannulation and remained relatively unchanged (range -17% to + 8%).

In these two experiments (Group B(b) type II (i)) and 9 additional studies (Group B (b) type II (ii)) control measurements were taken at the end of an equilibration period at a CPP of 120 mmHg. The results are shown in Table 3 and are similar to the values reported in Table 2 in which type I method for coronary cannulation was employed.

In Group B (b) type II (ii) experiments, nine animals were subjected to various levels of coronary hypotension for three minute periods after which the CPP was returned to 120 mmHg. In response to

Figure 15.



Results from a stability study on an animal (CSD-38) cannulated with type II arrangement (CPP = 120 mmHg). Records were started 10 minutes after coronary extracorporeal perfusion was established and continued with intermittent records for a 5 hour period. Abbreviations are LAD = left anterior descending, CX = circumflex, and RC = right coronary.

TABLE 3

Control data for the second hypotensive study of Series I:
Group B b) type II (i) and (ii), (n=11)

Parameter	Measurement
Heart Rate (bpm)	127 \pm 15
Pressures (mmHg)	
Arterial-mean	119 \pm 8
-systolic	131 \pm 10
-diastolic	97 \pm 9
LV -systolic	136 \pm 13
-diastolic	19 \pm 4
Max dP/dt(mmHg/sec)	2204 \pm 184
Atrial-(cmH ₂ O)	
-right	13 \pm 3
-left	23 \pm 6
Flows	
Cardiac index (ml/min·kg)	140 \pm 29
Stroke index (ml/beat·kg)	1.19 \pm 0.16
Total coronary (ml/min·g)	0.94 \pm 0.13
% LAD	44 \pm 3
% Cx	38 \pm 3
% RC	18 \pm 2
Left:right coronary ratio	4.51 \pm 0.49
Hemoglobin (g/dl)	10.9 \pm 0.3
Oxygen values	
Arterial content (ml/dl)	14.4 \pm 1.6
Coronary sinus content (ml/dl)	6.3 \pm 0.4
Myocardial availability (ml/min·100g)	14.8 \pm 2.0
Myocardial extraction (%)	59 \pm 6
Myocardial consumption (ml/min·100g)	8.7 \pm 0.9

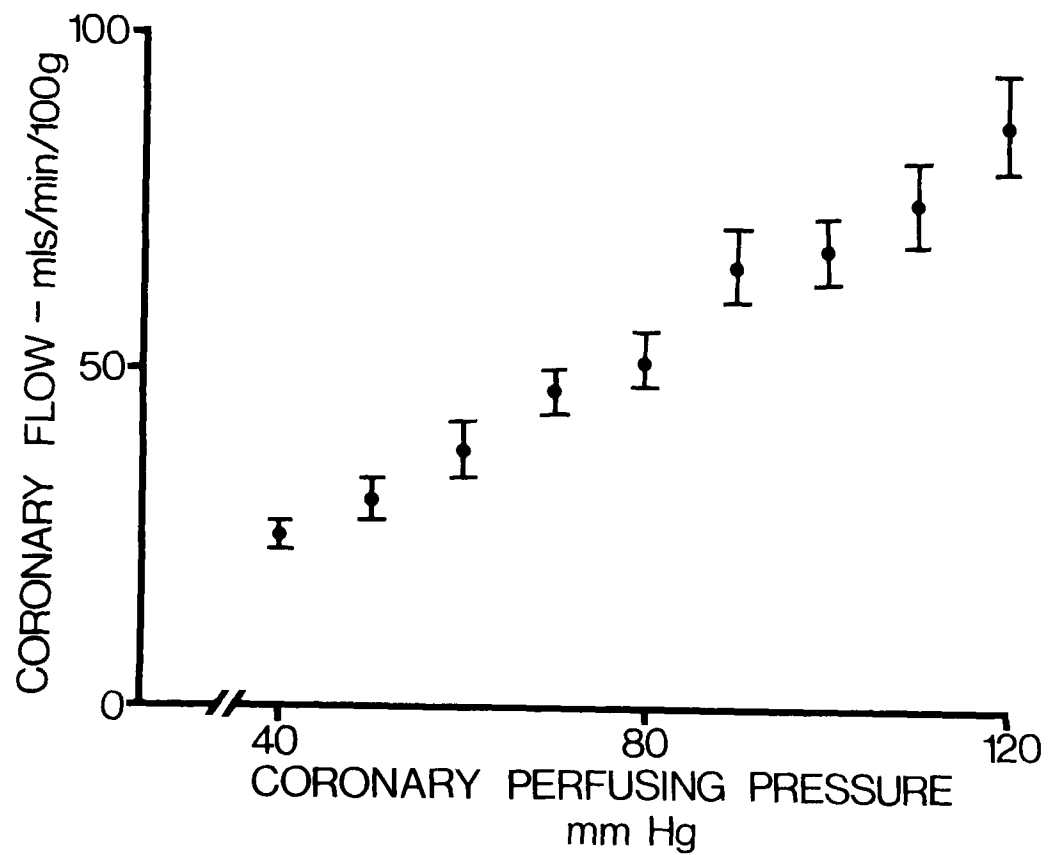
All values (mean \pm SE) were measured at the end of the stabilization period at a coronary perfusing pressure, of 120 mmHg.

these reductions in CPP, total coronary flow decreased as well. Figure 10 shows this interrelationship between coronary pressure and flow and is similar to results seen previously (Figures 7 and 8). Likewise at the lowest CPP the relative reduction in pressure (67%) was similar in magnitude to the relative decrease in flow ($71 \pm 3\%$). Figure 17 demonstrates that the decrease in total coronary blood flow was uniformly expressed by all three components of coronary circulation (LAD, CX, and RC). When reductions in total coronary flow were plotted against changes in myocardial oxygen availability (Figure 18), a significant positive correlation was found of 0.98 and is not unexpected since myocardial oxygen availability is the product of the total coronary flow and the arterial oxygen content. With decreases in coronary blood flow the heart appears to have extracted more oxygen from its limited supply (Figure 19). Although the correlation coefficient for total coronary flow versus myocardial oxygen extraction was low ($r=0.49$), the value was significant and can be attributed to a large variation in the absolute values among different animals, since individual trends for each animal (Figure 20) clearly demonstrate the presence of an inverse relationship. In addition to these observations, the magnitude of the reduction in myocardial oxygen extraction was considerable: at a CPP of 40 mmHg, oxygen extraction had increased to $79 \pm 3\%$ from $59 \pm 6\%$ at a CPP of 120 mmHg. In spite of this compensatory change in the ability of the heart to extract more oxygen, myocardial oxygen consumption decrease in a linear fashion ($r=0.92$) with total coronary flow (Figure 21). Although, at a CPP of 40 mmHg, the relative decrease in total coronary flow ($71 \pm 3\%$) was significantly greater than the relative reduction in oxygen consumption ($60 \pm 3\%$). The net result of these changes in flow and oxygen consumption was a decrease in cardiac performance. This positive correlation is shown in Figure 22 in which cardiac work is plotted against total coronary flow at all CPP values.

Series II:

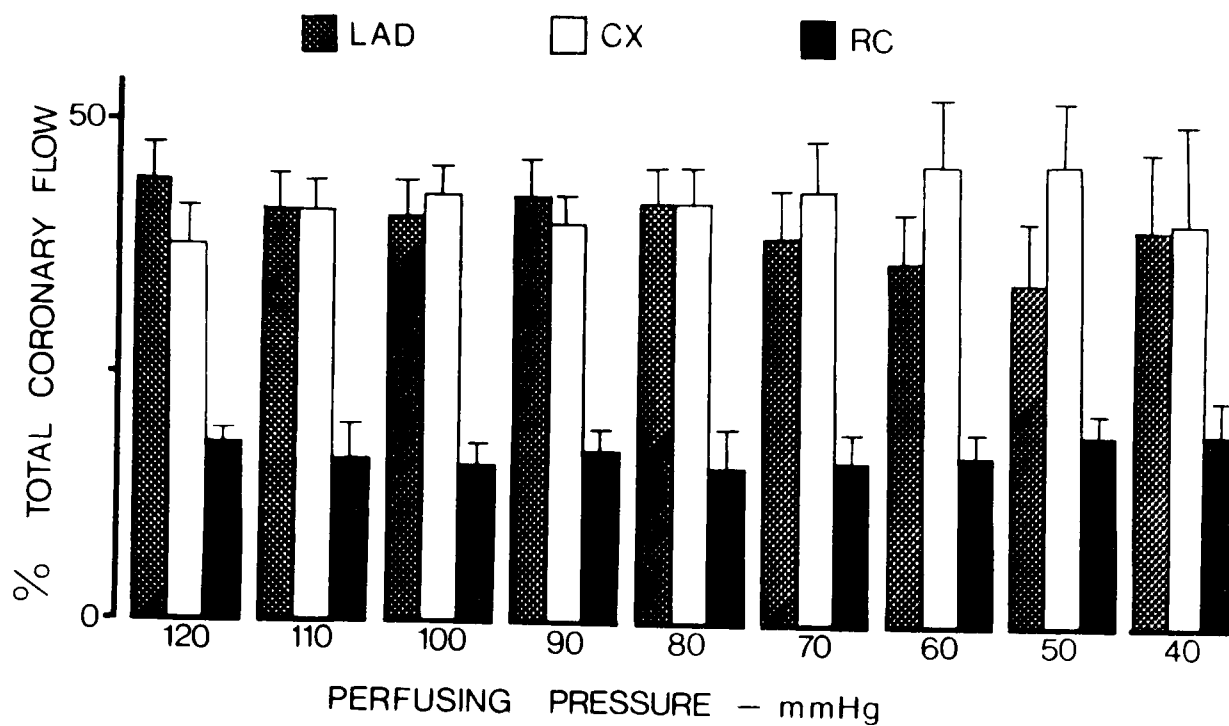
The objective in this series was to establish first, the effects of the duration of global ischemia and secondly, was there a hypoperfusion duration which could be reversed within 60 min of subsequent reperfusion (Group B(b) type II (iii)). For this study, 36 animals were divided into five subgroups in which cardiogenic shock was induced and sustained for a period of 15, 30, 60, 90, or 120 min after which the CPP was returned to 120 mmHg; recovery was monitored for the next 60 min.

Figure 16.



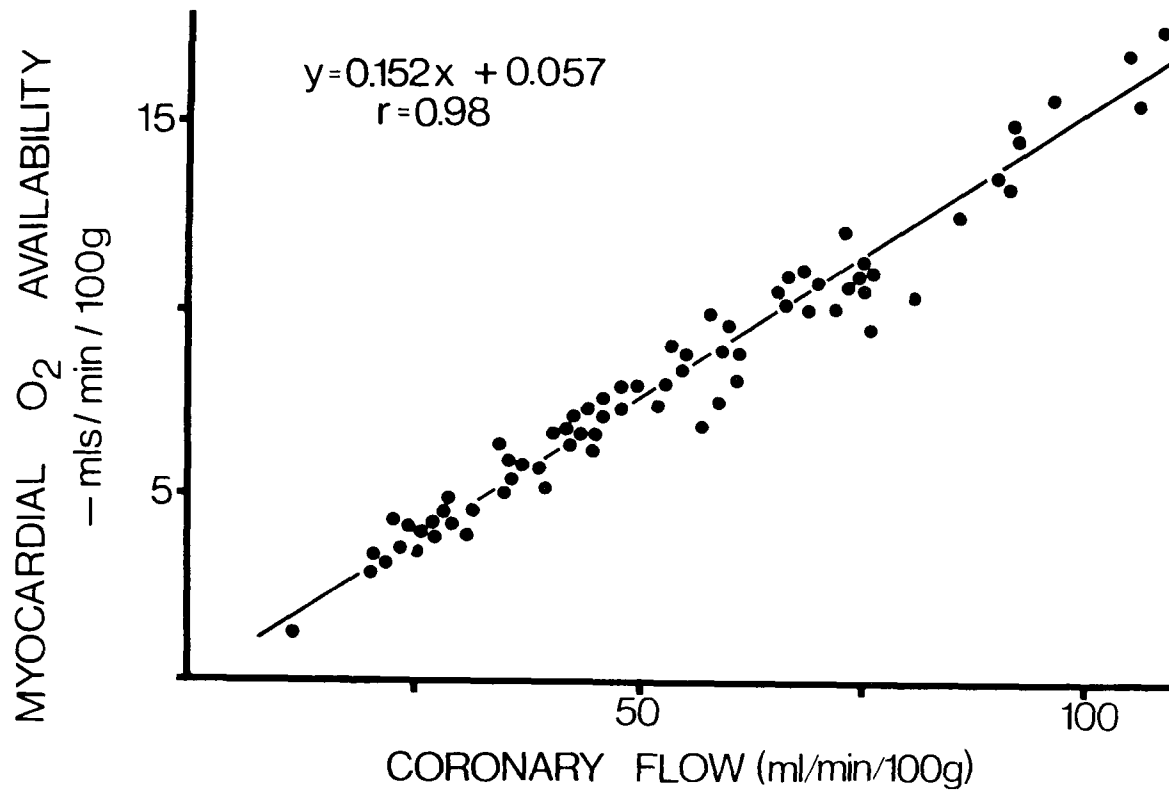
Coronary perfusing pressure versus coronary flow for animals (n=9) in Series I b) type II (ii) studies. Dots and lines represent mean \pm SE.

Figure 17.



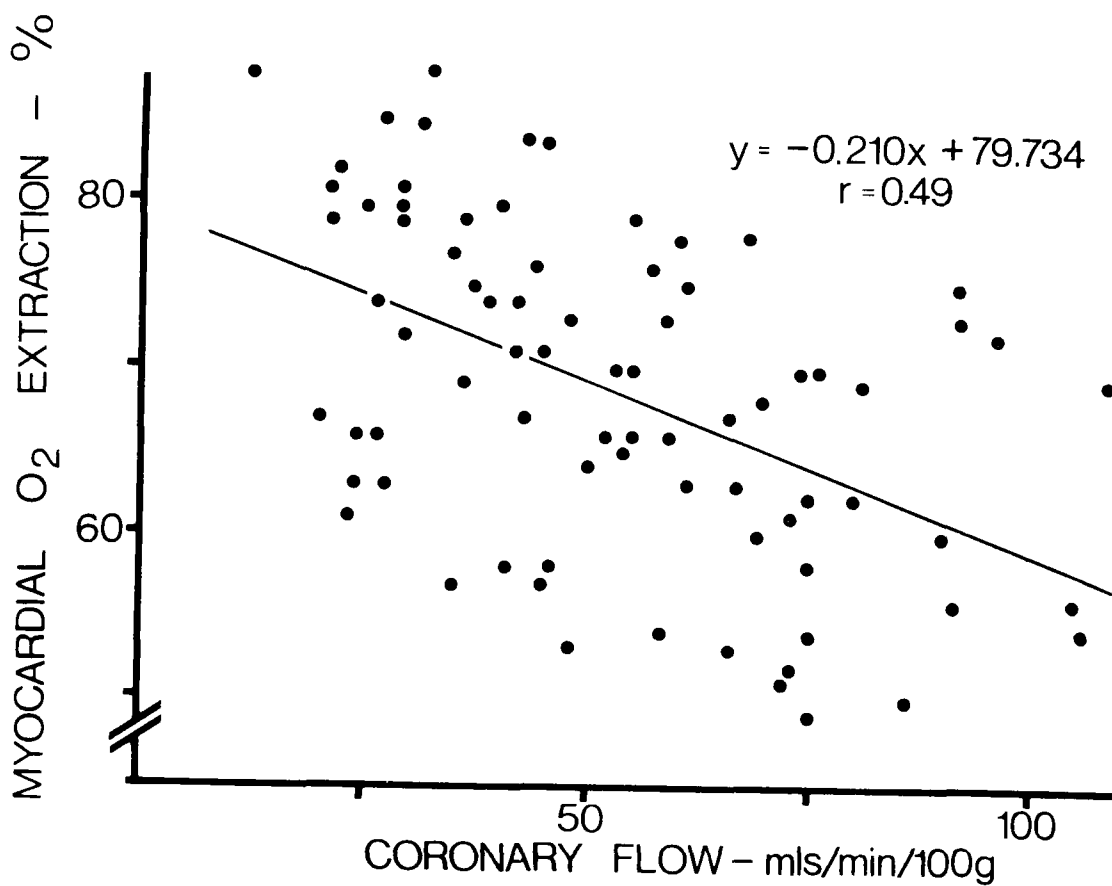
The distribution of total coronary flow into the 3 cannulated arteries (LAD = left anterior descending, CX = circumflex, and RC = right coronary) as a function of perfusing pressure for animals (n=9) in Series I b) type II (ii) studies. Values are expressed as mean \pm SE.

Figure 18.



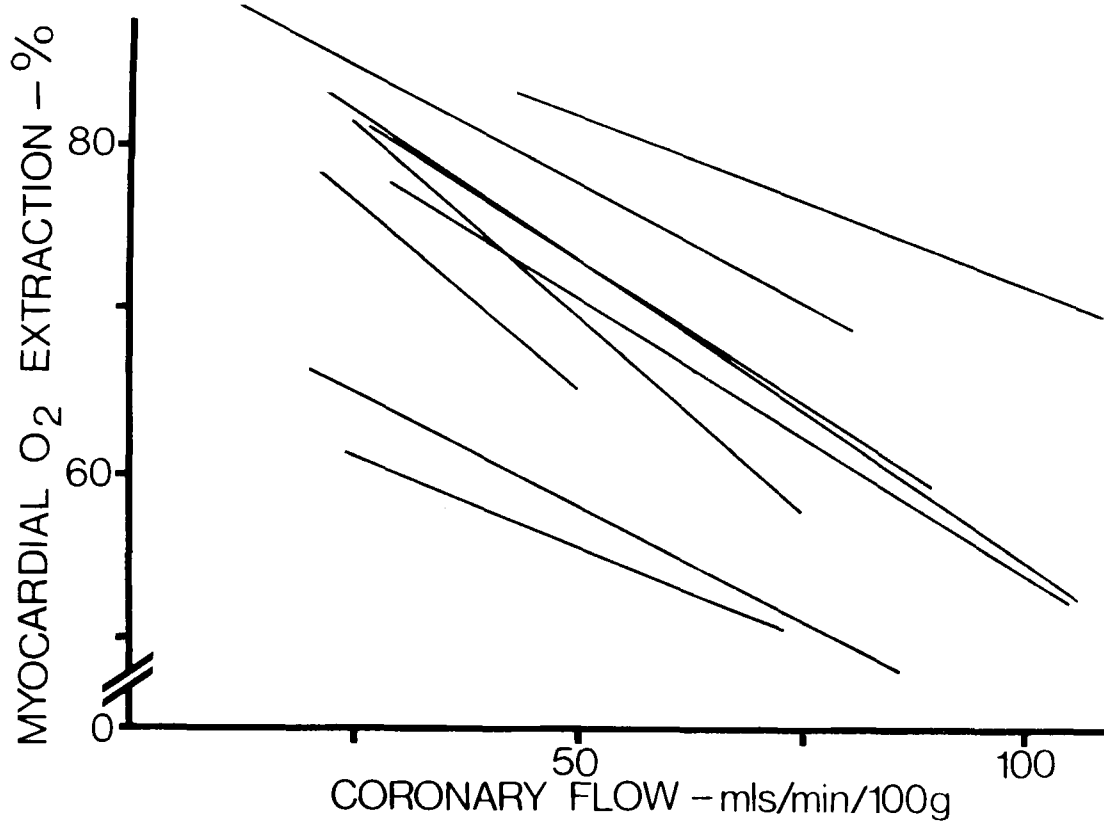
Relation between coronary flow and myocardial oxygen availability for animals ($n=9$) in Series I b) type II (ii) studies. Individual data points are shown.

Figure 19.



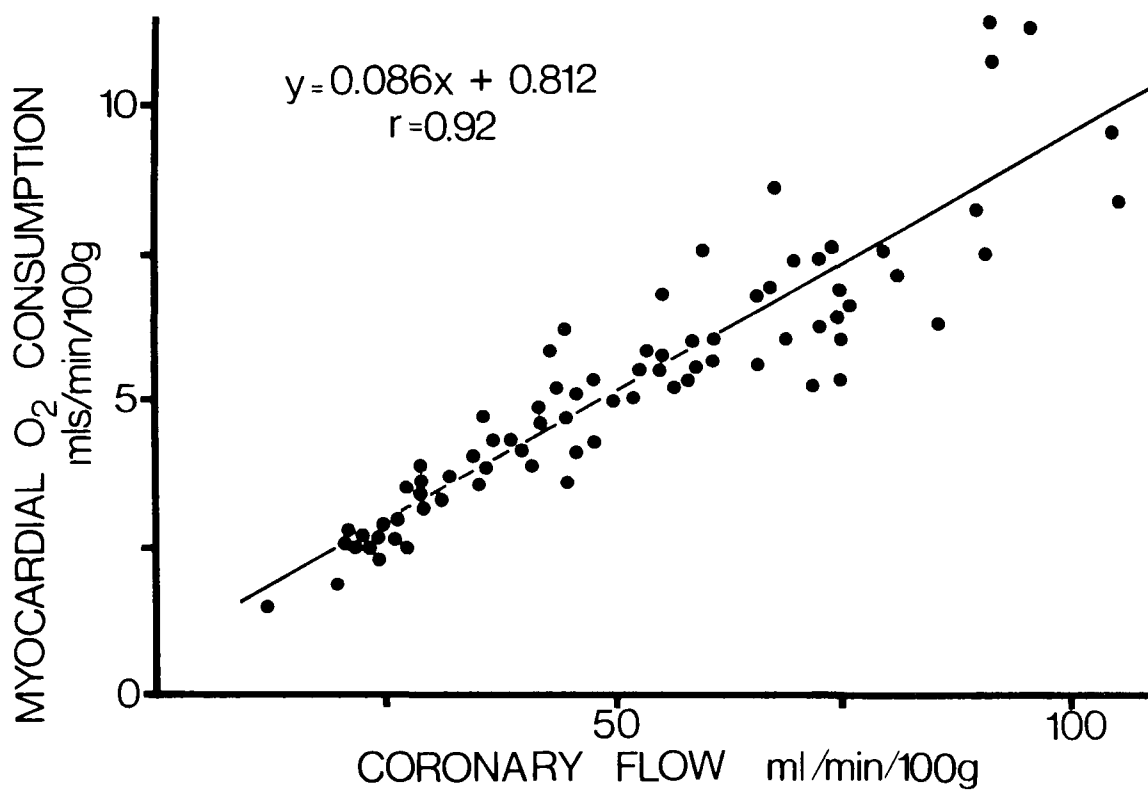
Relation between coronary flow and myocardial oxygen extraction for animals (n=9) in Series I b) type II (ii) studies. Individual data points are shown.

Figure 20.



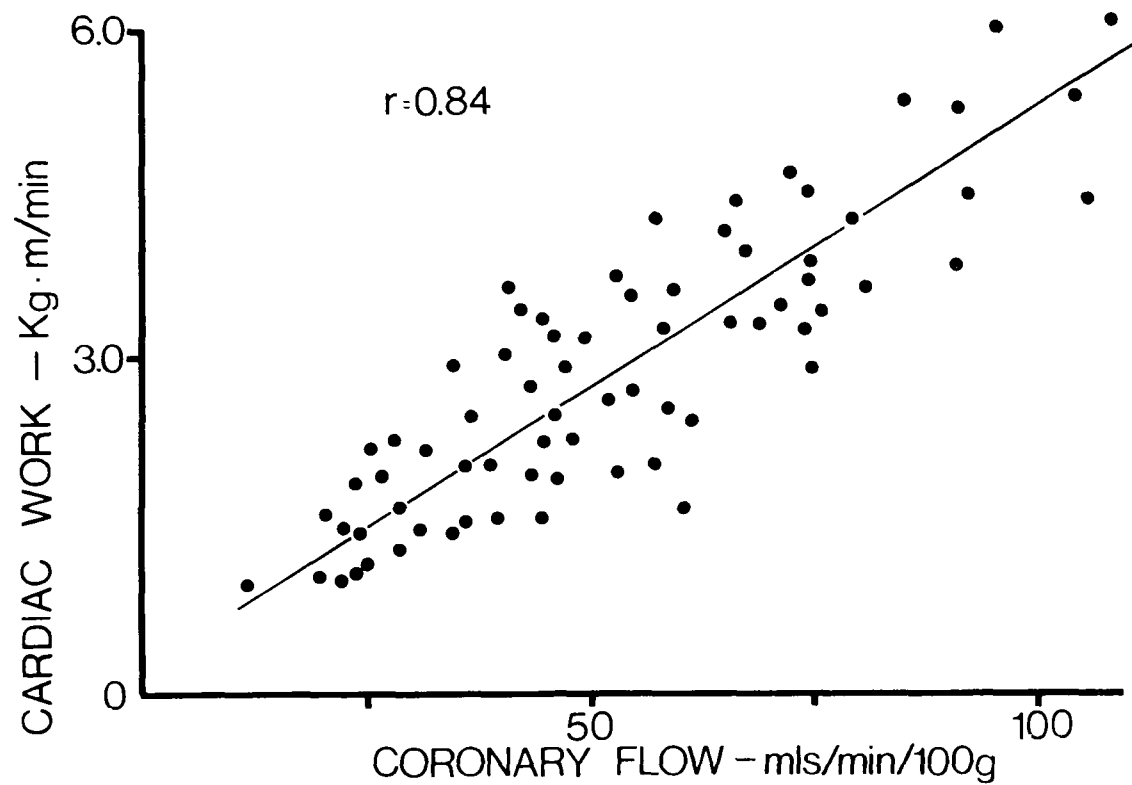
Relation between coronary flow and myocardial oxygen extraction for animals ($n=9$) in Series I b) type II (ii) studies. Every line is a linear least squares fit of the data from each animal.

Figure 21.



Relation between coronary flow and myocardial oxygen consumption for animal (n=9) in Series I b) type II (ii) studies. Individual data points are shown.

Figure 22.



Relation between coronary flow and cardiac work for animals ($n=9$) in Series I b) type II (ii) studies. The equation for the linear regression is $y = 0.051x + 0.277$ Individual data points are also shown.

In Table 4 control hemodynamic and metabolic values are presented for the 36 animals in this study. Based on a Student's t-test for unpaired data the results are not significantly different from the control data of earlier studies (Tables 2 and 3). Using a one-way ANOVA no significant differences could be found among the control data of the 5 groups. Thus, for simplicity all subsequent results were expressed as a percent change from control. The results from an individual experiment are presented in Figure 23. In this animal a 63% reduction in CPP was necessary to produce acute cardiogenic shock. As shown in Figure 23, changes in coronary flows, arterial and left ventricular pressures, and myocardial oxygen consumption were completed within 10 min of coronary hypotension and did not appreciably change throughout the period of global ischemia. The relative changes from their respective control values for a variety of parameters for each of the 5 subgroups are presented in Figure 24 a,b. With global hypoperfusion, heart rate remained unchanged while mean arterial pressure, cardiac index, max dP/dt, total coronary flow and myocardial oxygen consumption significantly decreased while left ventricular end-diastolic pressure, and myocardial oxygen extraction increased. Based on a one-way analysis of variance, no significant difference could be found in the magnitude of these changes when related to the duration of ischemia. The hemodynamic and metabolic responses to reperfusion are shown in Figure 25 a,b. With the exception of one parameter, animals exposed to the two shorter periods of ischemia (15 and 30 min) recovered with reperfusion: in animals who had sustained 15 minutes of ischemia, the cardiac index remained significantly depressed (Student's t-test for paired data). A closer examination of this depression revealed that a sustained increase in peripheral vascular resistance was present during reperfusion which was not seen in any of the other groups. Animals who had undergone longer (60 min) periods of ischemia could not, in general, reestablish control levels with reperfusion. But recoverability depended on the parameter chosen; systemic hemodynamic values (Figure 25a) were recoverable in animals who had sustained 60 min of ischemia while coronary flow and oxygen consumption remained significantly depressed in this same group of animals (Figure 25b). A comparison (2-way ANOVA) between reperfusion responses and the duration of ischemia showed that only coronary flow demonstrated a significant correlation: post-ischemic flow was inversely related to the duration of the insult.

The myocardial flow data shown in Table 5 were measured by

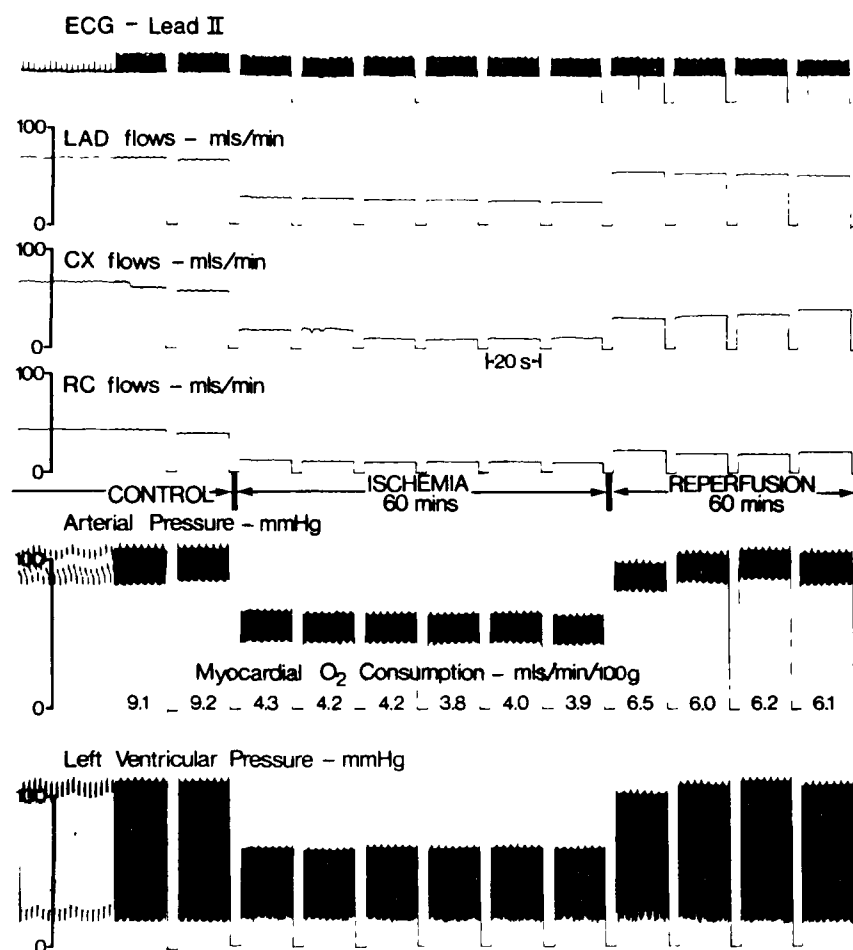
TABLE 4

Control data for global ischemia and reperfusion study of
Series II, (n=36)

Parameter	Measurement
Heart Rate (bpm)	119 \pm 16
Pressures (mmHg)	
Arterial-mean	109 \pm 8
-systolic	132 \pm 7
-diastolic	96 \pm 8
LV -systolic	135 \pm 9
-diastolic	15 \pm 2
Max dP/dt(mmHg/sec)	2117 \pm 221
Atrial-(cmH ₂ O)	
-right	10 \pm 1
-left	16 \pm 2
Flows	
Cardiac index (ml/min.kg)	97 \pm 11
Total coronary (ml/min.g)	0.91 \pm 0.06
% LAD	44 \pm 2
% Cx	35 \pm 2
% RC	21 \pm 3
Myocardial: LV free wall (ml/min.g)	107 \pm 10
Endocardial/epicardial ratio	1.11 \pm 0.17
Hemoglobin (g/dl)	12.1 \pm 0.4
Oxygen values	
Arterial content (ml/dl)	15.9 \pm 1.7
Coronary sinus content (ml/dl)	7.0 \pm 0.6
Myocardial availability (ml/min.100g)	16.1 \pm 2.0
Myocardial extraction (%)	59 \pm 5
Myocardial consumption (ml/min.100g)	8.5 \pm 0.7

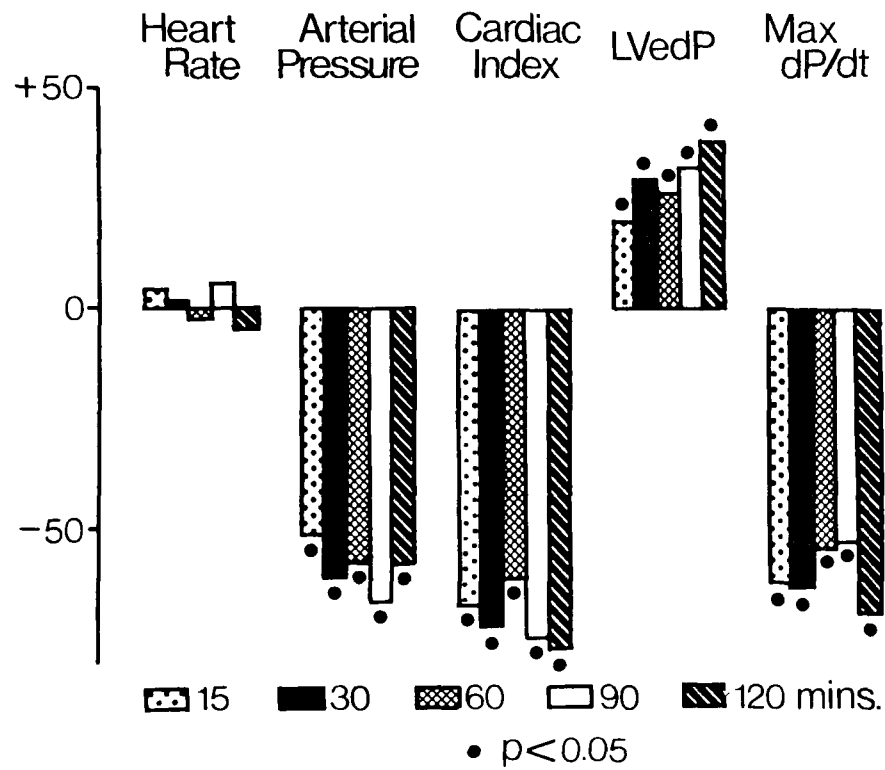
All values (mean \pm SE) were measured at the end of the stabilization period at a coronary perfusing pressure, of 120 mmHg.

Figure 23.



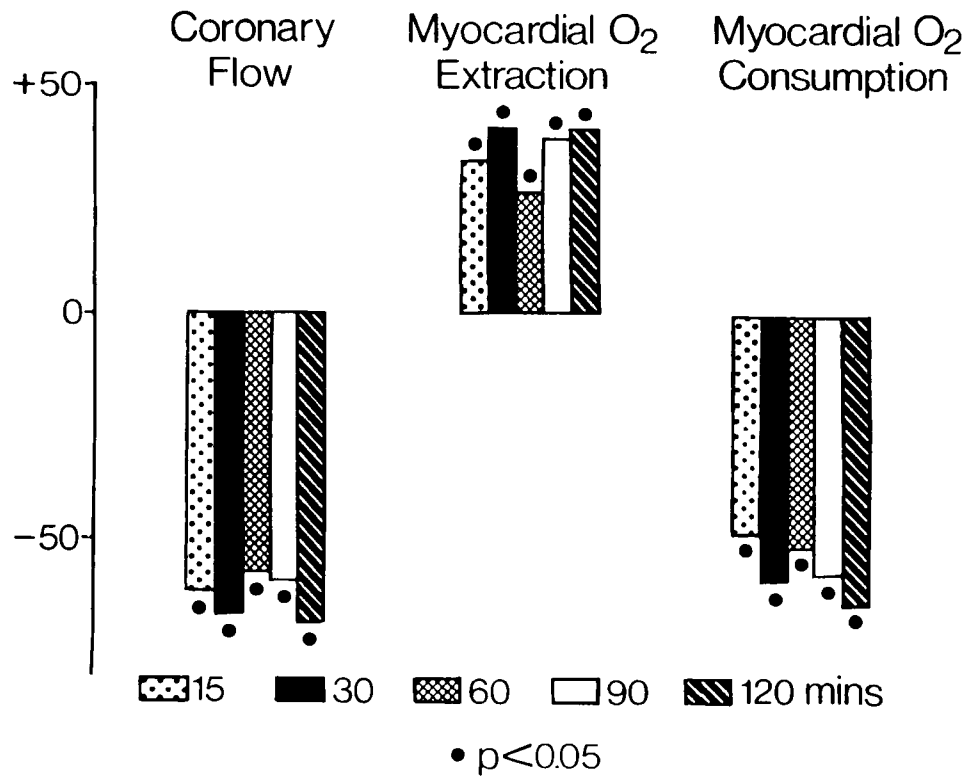
An example of the experimental protocol for animals in Series II studies. These are the hemodynamic records from an animal who had sustained 60 minutes of global ischemia followed by 60 minutes of reperfusion. During ischemia 20-second recordings were taken every 10 minutes while recordings during reperfusion were made every 15 minutes.

Figure 24(a)



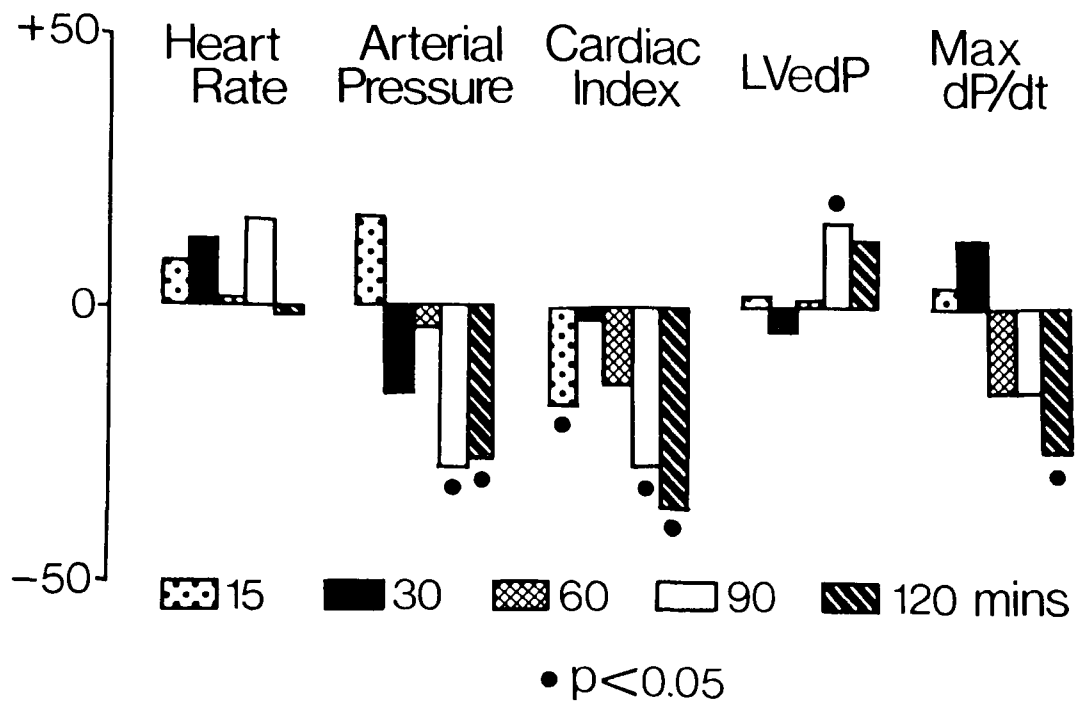
Relative change (%) from initial control values for heart rate, arterial pressure, cardiac index, left ventricular end-diastolic pressure (LVEDP), and max dP/dt after 15(n=6), 30(n=8), 60(n=7), 90(n=8), and 120(n=7) minutes of ischemia for animals in Series II studies. Dot indicates significant difference.

Figure 24(b)



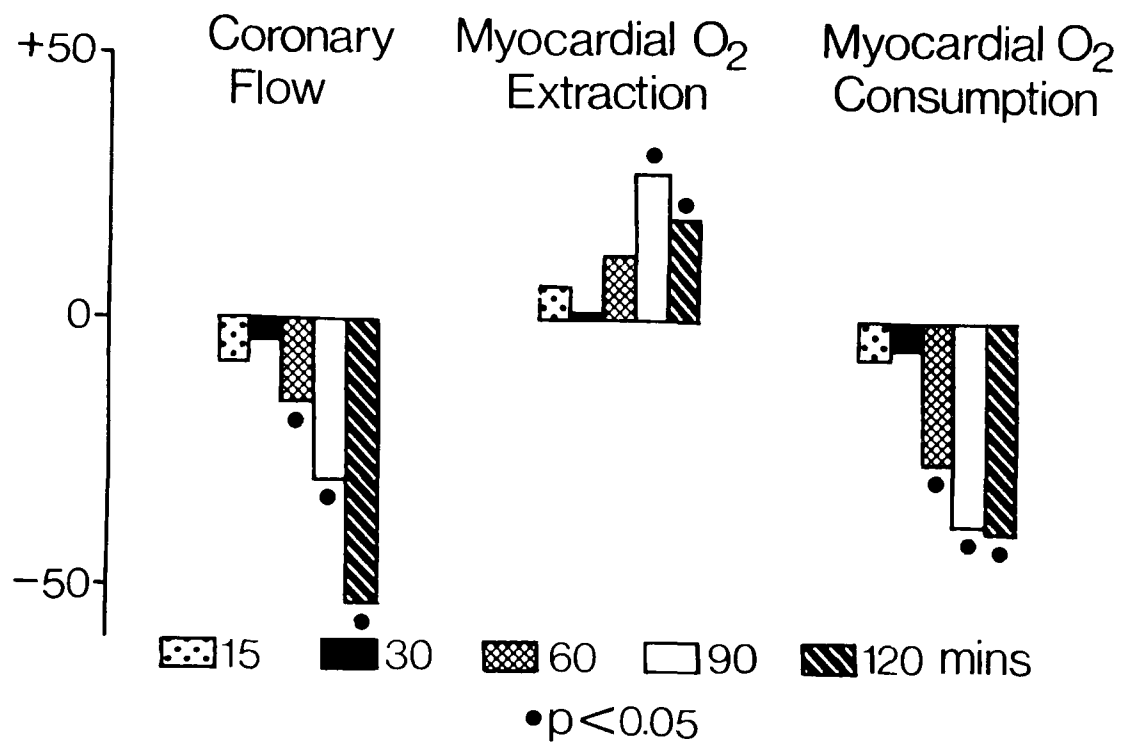
Relative change (%) from initial control values for coronary flow, myocardial oxygen extraction, and myocardial oxygen consumption after 15 (n=6), 30 (n=8), 60 (n=7), 90 (n=8), and 120 (n=7) minutes of ischemia for animals in Series II studies. Dot indicates significant difference.

Figure 25(a)



Relative change (%) from initial control values for heart rate, arterial pressure, cardiac index, left ventricular end-diastolic pressure, and max dP/dt after 15(n=6), 30(n=8), 60(n=7), 90(n=8), and 120(n=7) minutes of ischemia followed by 60 minutes of reperfusion for animals in Series II studies. Dot indicates significant difference.

Figure 25(b)



Relative change (%) from initial control values for coronary flow, myocardial oxygen extraction, and myocardial oxygen consumption after 15(n=6), 30(n=8), 60(n=7), 90(n=8), and 120(n=7) minutes of ischemia followed by 60 minutes of reperfusion for animals in Series II studies. Dot indicates significant difference.

TABLE 5

Myocardial flow responses to ischemia and reperfusion

		Duration of Ischemia			
		30 min (n=5)	60 min (n=6)	90 min (n=5)	120 min (n=5)
LV free wall flow (ml/min.g)	Control	1.06 ± 0.12	0.97 ± 0.10	1.01 ± 0.18	1.12 ± 0.19
	Ischemic	0.55 ± 0.07 \boxplus	0.42 ± 0.11 \boxplus	0.42 ± 0.13 \boxplus	0.46 ± 0.09 \boxplus
	Reperfusion	0.98 ± 0.15	0.81 ± 0.06	0.59 ± 0.12*	0.52 ± 0.16*
Endocardial/ epicardial flow ratio	Control	1.09 ± 0.16	1.13 ± 0.19	1.02 ± 0.26	1.17 ± 0.24
	Ischemic	0.36 ± 0.07 \boxplus	0.42 ± 0.10 \boxplus	0.31 ± 0.14 \boxplus	0.28 ± 0.09 \boxplus
	Reperfusion	0.96 ± 0.09	0.63 ± 0.12*	0.49 ± 0.16*	0.52 ± 0.11*

Values are presented as mean ± SE. Flows were measured by the distribution of microspheres.

* = p < 0.05, \boxplus = p < 0.01.

radioactively labelled microspheres. The results indicate that reperfusion after 60 minutes of hypoperfusion restored left ventricular free wall flow. In contrast, total coronary flow measured by the extra corporeal flow probes did not return to control levels with the same duration of insult (Figure 25b). Also in Table 5 the endo/epicardial flow ratio was found to be significantly reduced in all groups during ischemia but was recoverable with reperfusion only in those animals which underwent 30 minutes of ischemia (the shortest ischemic period for which this parameter was calculated).

Series III:

The objective of this series of experiments was to utilize the unique features of this cardiogenic shock model to determine the systolic unloading effects of IABP treatment independent of diastolic augmentation (Group B(b)type II(iv)).

In this study 13 animals were prepared as previously outlined. At the end of an equilibration period, various hemodynamic and oxygen measurements were recorded and are presented in Table 6. These control values are well within the range of the results from earlier experiments (Tables 2, 3, and 4). When the CPP was temporarily reduced from 120 mmHg, total coronary flow decreased. Eventually as the magnitude of the reduction in flow increased, the signs of cardiogenic shock ensued (Figure 26). Although the lower limits of normotensive pressures were measured, at a perfusing pressure of 80 and 70 mmHg, further reductions to 60 and 50 mmHg produced sustained periods of acute cardiac failure (Figure 26). Severe reductions in total coronary flow led to an increase in myocardial extraction; however, this increase was insufficient to maintain oxygen consumption which subsequently dropped as perfusing pressure was reduced. As had been noted earlier in Figure 17, the distribution of total coronary flow did not significantly change as the coronary perfusing pressure was reduced (Table 6).

When IABP was attempted in these animals on total coronary bypass, no unusual problems were encountered. As with intact animals the central aortic pulse pressure clearly monitored the operation of the balloon. During IABP treatment, aortic diastolic pressures were

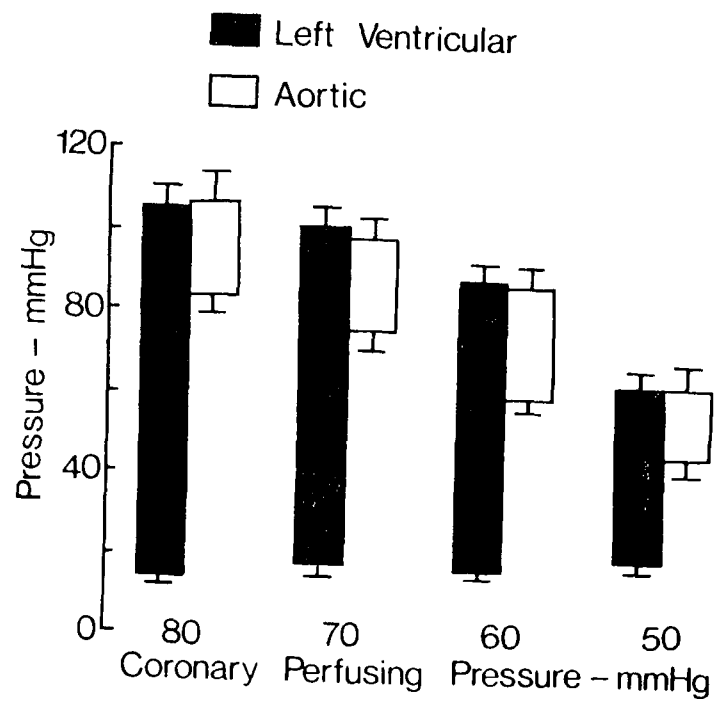
TABLE 6

Control data for the systolic unloading properties of IABP,
Series III, (n=13)

Parameter	Measurement
Heart Rate (bpm)	123 \pm 4
Pressures (mmHg)	
Arterial-mean	107 \pm 4
-systolic	124 \pm 6
-diastolic	93 \pm 3
LV -systolic	123 \pm 6
-diastolic	16 \pm 1
Atrial-(cmH ₂ O)	
-right	9 \pm 1
-left	16 \pm 1
Flows	
Cardiac index (ml/min•kg)	91 \pm 11
Total coronary (ml/min•g)	0.86 \pm 0.05
% LAD	47 \pm 1
% Cx	36 \pm 1
% RC	17 \pm 1
Myocardial oxygen extraction (%)	62 \pm 2
Myocardial consumption (ml/min•100g)	8.4 \pm 0.4

All values (mean \pm SE) were measured at the end of the stabilization period at a coronary perfusing pressure of 120 mmHg.

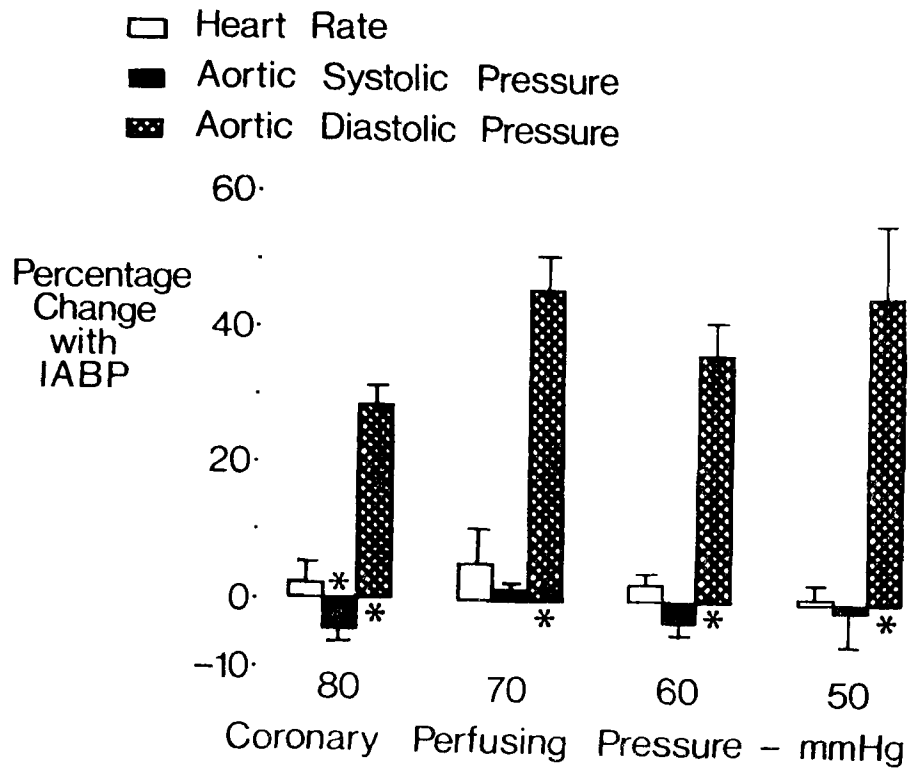
Figure 26



Changes in left ventricular (black bars) and aortic (white bars) systolic and diastolic pressures as a function of coronary perfusing pressure for animals (n=13) in Series III studies. Values are shown as mean \pm SE.

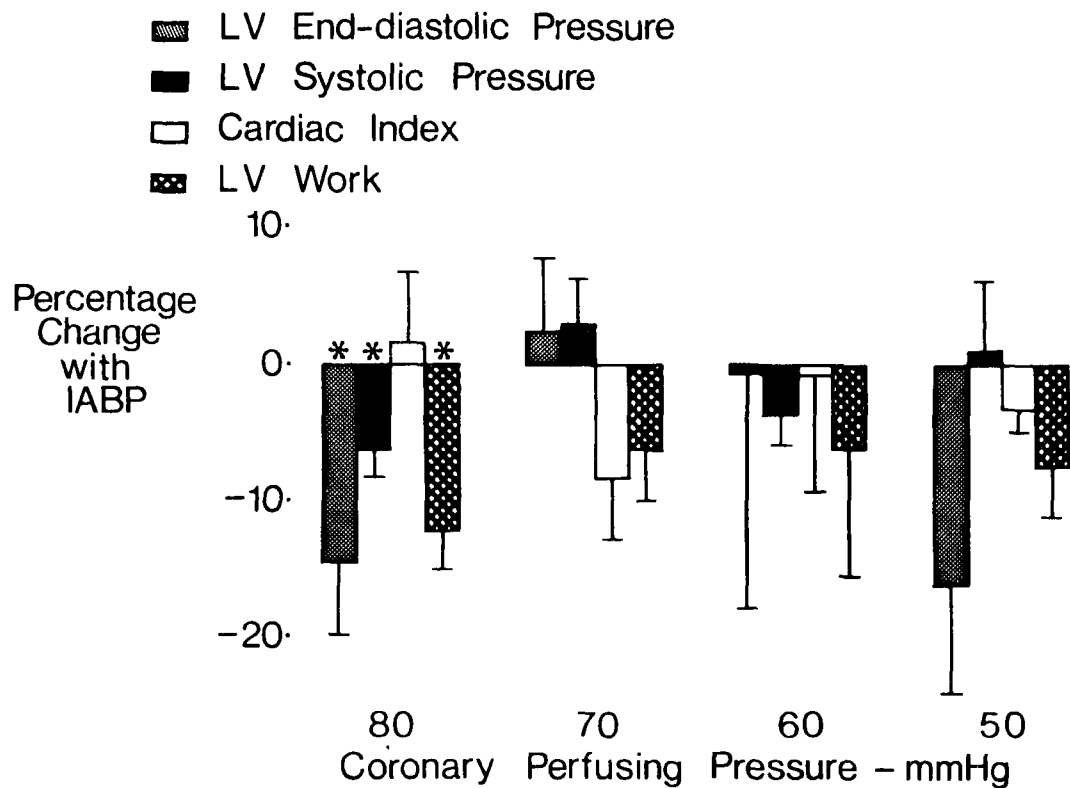
significantly ($p < 0.05$) augmented by $28 \pm 4\%$, $46 \pm 5\%$, $36 \pm 5\%$, and $46 \pm 11\%$ above the unassisted levels at coronary perfusing pressures of 80, 70, 60 and 50 mmHg, respectively (Figure 27). Likewise, mean arterial pressure also increased during the IABP treatment but to a lesser degree. Evidence of systolic unloading was only seen at a CPP of 80 mmHg. At this level, IABP significantly reduced systolic pressures in both the aorta by $4 \pm 2\%$ and the left ventricle by $6 \pm 2\%$, in addition, IABP significantly reduced left ventricular end-diastolic pressure by $14 \pm 5\%$ and left ventricular work by $12 \pm 3\%$; however, the cardiac index remained unchanged (Figures 27 and 28). At all other coronary perfusing pressures below 80 mmHg, IABP did not significantly alter any of the hemodynamic parameters. In terms of total coronary flow, a significant decrease was seen only when IABP was applied at a CPP of 80 mmHg (Figure 29) while oxygen availability, extraction and consumption were unaffected by the application of IABP at any CPP.

Figure 27



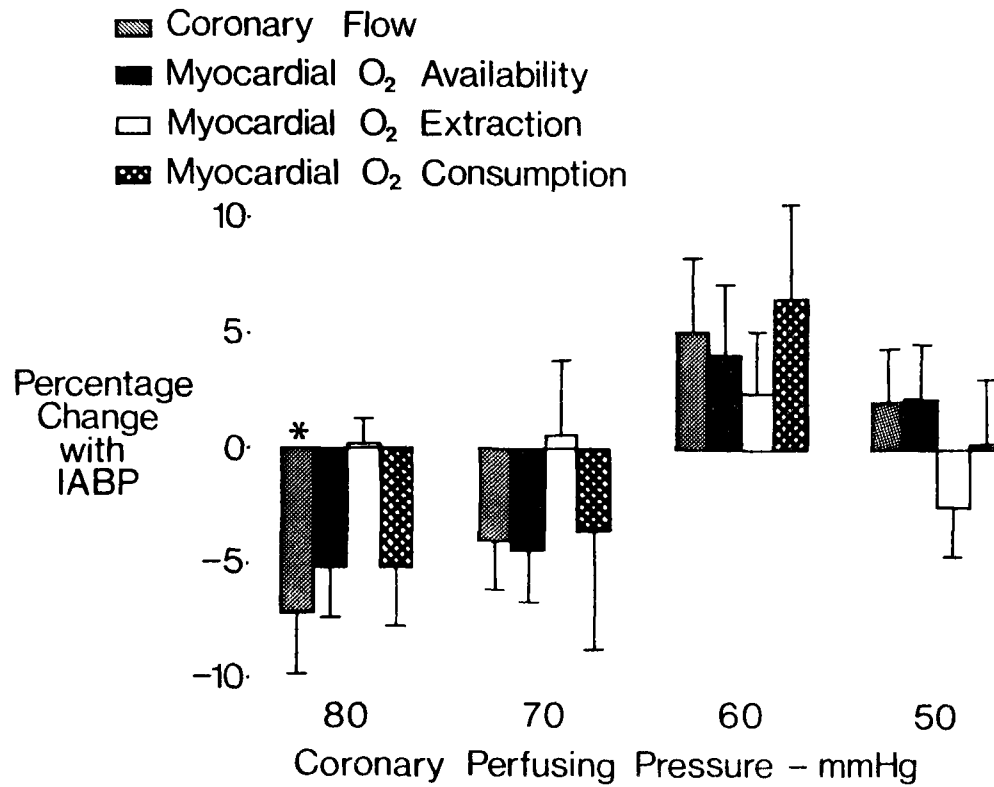
Relative change (%) from control values for heart rate, aortic systolic pressure, and aortic diastolic pressure with intra-aortic balloon pumping (IABP) treatment at a CPP of 80 (n=8), 70 (n=8), 60 (n=6), and 50 (n=9) mmHg for Series III studies. Values are mean \pm SE, asterisk indicates a significant change ($p < 0.05$).

Figure 28



Relative change (%) from control values for LV end-diastolic pressure, LV systolic pressure, cardiac index, and LV work with intra-aortic balloon pump (IABP) treatment at a CPP of 80 (n=8), 70 (n=8), 60 (n=6), and 50 (n=9) mmHg for Series III studies. Values are mean \pm SE, asterisk indicates a significant change ($p < 0.05$).

Figure 29



Relative change (%) from control values for coronary flow, myocardial oxygen availability, myocardial oxygen extraction, and myocardial oxygen consumption with intra-aortic balloon pump (IABP) treatment at a CPP of 80 (n=8), 70 (n=8), 60 (n=9), and 50 (n=6) mmHg for Series III studies. Values are mean \pm SE, asterisk indicates a significant change ($p < 0.05$).

DISCUSSION:

Within the last 20 years an intensive research effort has improved the management of patients suffering from acute myocardial infarction (75). In spite of this effort, statistical surveys (1-3,76) have clearly demonstrated that cardiogenic shock or acute cardiac failure, while complicating one in every six patients hospitalized for acute myocardial infarction, is associated with an 80 to 90% mortality (1-3). The clinical experience here at the University of Ottawa Heart Institute has shown that emergency revascularization in such situations will reduce the mortality (66) but further studies are needed to define the pathophysiology of this condition and to evaluate various modalities of treatment.

Although the onset of cardiogenic shock appears to be directly related to the extent of myocardial damage (12-14), irrespective of its temporal occurrence, the experimental production of animal models for cardiogenic shock has been difficult (10). As reviewed by Feola and Glick (11), in the majority of the experimental reports dealing with this topic, the occurrence of the desired hypodynamic state associated with a severe reduction in cardiac output and arterial pressure has been relatively unpredictable in all but a few experiments. In general, the preferred procedure has been to create large areas of myocardial damage either by coronary artery ligation (16-31); direct myocardial injury (47-53), coronary embolization (32-46) or coronary thrombosis (29,54-56). Although these insults may be analogous to the clinical events preceding cardiogenic shock, the presence of heterogenous flow patterns (61) and the subsequent development of a mixed population of normal to irreversibly damaged cells (62) makes precise mechanical, electrical, and metabolic analysis difficult and may account for the variability in the extent and duration of the shock-like state.

As an alternative approach an experimental model was developed in which the coronary circulation was separated from the systemic circulation and perfused from an extracorporeal system at controlled coronary perfusing pressure. Under normotensive conditions (CPP = 120 mmHg) these in situ working hearts were able to maintain normal hemodynamic values for extended periods of time. When the coronary perfusing pressure was reduced systemic hypotensive states developed for extended periods of time, which were hemodynamically

similar to the clinical syndrome of cardiogenic shock. Although this hypoperfusion model may mimic some of the features associated with cardiogenic shock, it is recognized that there are some important distinctions. First, the onset or induction of the insult is global in nature which is different from the regional disruptions in myocardial perfusion that eventually lead to cardiogenic shock. Secondly, the model itself is done in the anaesthetized state requiring an extensive amount of surgical intervention - both features are not components of the clinical state. Thirdly, the obvious stability of the preparation contradicts the hallmark feature of shock itself - that being the positive feedback qualities of the clinical state. In spite of these and other limitations, this model does have some specific advantages over earlier preparations. For example, in examining the therapeutic mechanisms associated with the use of IABP treatment, the model was able to separate the systolic unloading features from diastolic augmentation.

In the development of the production of this project, commonly used cardiovascular parameters, such as, arterial pressures and cardiac index were selected to assess the functional status of the heart. All measurements cited are easily measurable both in the animal laboratory and at the patient's bedside with a minimum amount of complexity. Secondly, these parameters reflect global responses of the heart as it tries to pressurize and perfuse the systemic circulation. However, in attempting to average the myocardial functional responses, the author is clearly aware that both parameters are affected by the periphery as well. In spite of this serious limitation a close correlation was found between changes in total coronary flow and overall cardiac function as reflected by these global variables. With respect to the question of the LV dP/dt being measured from a fluid-filled system with a limited frequency response, it should be noted that in various laboratories, this dP/dt is considered to be an essential index of cardiac contractility and as such has been measured with a catheter tipped manometer. In this study dP/dt measurements can be considered as a first order index of global myocardial contractility however, from our initial studies, this parameter did compare favourably with other variables of cardiac performance when the extent of myocardial dysfunction was compared (Figure 14).

Over the perfusing pressure range of 70 to 130 mmHg, Mosher and his associates (73) have shown that coronary flow can autoregulate while above and below this range coronary flow becomes pressure-dependent. Mosher et al (73) also demonstrated that autoregulation is not an instantaneous phenomena: a time dependent quality is also present so that the extent of autoregulation is not only determined by the perfusing pressure but also by the duration as well. In this animal preparation brief (3 minute) periods of reduced coronary perfusing pressure (Group B (b) type I (ii)) produced linear pressure-dependent changes in coronary flow. However, in earlier experiments (Group B (a) type I (iii)) in which longer periods (10 minute) of equilibration were imposed between changes in perfusing pressures a mild coronary autoregulatory response could be elicited in some animals. Part of this defect may be a result of the previous manipulations associated with coronary cannulation or may be a result of hemodilution imposed by the extracorporeal circuit since changes in arterial oxygen content by dilution (77) or by desaturation (78) may modify the autoregulatory response. What was noticed, however, is that brief (10 second) periods of temporary coronary occlusion at a CPP of 120 mmHg would evoke hyperemic responses which would indicate that some extent of autoregulation is still present. In the present study significant linear correlations were found between coronary flow, myocardial oxygen consumption and various indices of cardiac mechanical performance. This close correlation among these parameters has been known for some time but has been difficult to demonstrate precisely (79-81). With this preparation the balance and interrelationship between coronary supply and myocardial demand can be monitored over a wide range of values. Liedke et al (72) also demonstrated that cardiac performance can be carefully titrated by adjustments in coronary flow; however, in their experiments the coronary arteries were perfused to known rates of flow while in these current experiments coronary perfusing pressure was the only parameter adjusted while the resultant changes to flow and cardiac performance were measured.

These observations on the interrelationship between coronary flow and cardiac function are in agreement with earlier studies in which a number of different preparations were used. However, other reports have favored a different interpretation. In the experiments reported by Opie (82), Bacaner et al (78), the rate

of oxygen delivery rather than changes in coronary blood flow were considered primarily responsible for changes in cardiac performance by eventually limiting myocardial oxygen consumption (80,83). In addition, other researchers (84,85) have shown that perfusing pressure and coronary flow can independently alter the inotropic state of the heart. On the other hand Sarnoff et al (86) and Ross et al (83) both have reported that coronary flow and myocardial oxygen consumption were not interrelated when external work was held constant; however, these studies have been criticized not only in terms of methodology (81) but also in the interpretation of the data (78). Using miniature ultrasonic transducers, implanted on the left ventricular endocardial surface, Stowe and his co-workers (103) demonstrated in the regionally ischemic heart that a linear relationship exists between endocardial segmental stroke work and endocardial flow. However, the relationship was only evident with decreases in flow between 25 and 75% of control. Using a similar type of model, Vatner in 1980 (104) demonstrated as well that a good correlation exists between a reduction in endocardial flow and regional myocardial function; however, the best fit of the experimental data yielded an exponential expression rather than a linear fit. Both of these studies suggest that a threshold to a reduction in coronary flow exists, beyond which increased oxygen extraction cannot satisfy the energy costs of contractile function, leading to impaired function.

By definition, myocardial ischemia is said to exist when coronary flow proves insufficient to accommodate functional demands. Since over 90% of the energy normally produced by the consumption of substrates and oxygen is utilized to support the mechanical activity (87) any factor which would limit the supply of oxygen to the heart would eventually be expressed as a reduction in performance.

From the results of Series I experiments, the sequence of events associated with myocardial ischemia can be demonstrated. A reduction in the coronary perfusing pressure produced a significant decrease in total coronary flow of a somewhat similar magnitude. This reduction in coronary flow in turn produced an increase in myocardial oxygen extraction. However, this compensatory change was insufficient to maintain myocardial oxygen consumption which eventually fell and was finally expressed as a decrease in cardiac function. An unusual feature of the results from these experiments was the significant

linear correlations which could be observed between flow and cardiac performance. Previous experiments were usually limited to a much smaller range of values and could not verify the extent of this relationship (79-81).

In the initial stages of developing this preparation, flow distribution studies indicated that some of the nutritive flow to the heart was not originating from the extracorporeal system. With type I coronary cannulation the left main coronary remained opened to the aorta and as such could not be carefully pressurized as the rest of the coronary circulation. In addition, this flow was not included in the calculation of the total flow. The main stem of the left coronary artery is usually short and soon divides into the LAD and CX branches. In almost 90% of the dogs examined, the septal artery arose from the posterior wall of the main stem to supply the basal portions of the interventricular septum and part of the free wall of the right ventricle. In animals cannulated with type I arrangement, the septal artery was not perfused by the extracorporeal circuit, so that during hypotensive episodes associated with coronary cannulation and the induction of coronary bypass, myocardial areas supplied by the septal artery may have sustained longer periods of reduced flow. As a result, the initial experiments were prone to arrhythmias either during the stabilization period or the subsequent experimental protocol.

In order to overcome these problems inherent with type I arrangement, an alternative technique was developed which would supply the left main coronary artery and its initial branches with extracorporeal blood. This perfusion technique has not been previously outlined; however, slightly different arrangements have been proposed (88). Although this technique (type II) required more isolation of the left coronary artery, the losses due to surgical misadventures were relatively few and were substantially reduced as experience was gained.

In the experimental preparation developed in Series I, precise predictable levels of hemodynamic dysfunction could be easily derived by separating and controlling coronary perfusion from the rest of the systemic circulation. However, the temporal limits as to how long these fixed levels of hypotension could be tolerated still needed to be defined. In addition, the important clinical consideration of recoverability also needed to be resolved within the framework of this animal model (59,63,64,75).

In Series II experiments, all animals sustained a single reduction in the coronary perfusing pressure sufficient to satisfy the hemodynamic criteria for cardiogenic shock. As had been seen before, this reduction in perfusing pressure caused a significant reduction in total coronary flow, which in turn prompted an increase in the myocardial oxygen extraction. However, this compensatory change was insufficient to maintain myocardial oxygen consumption and eventually was expressed as acute cardiac failure (cardiogenic shock). As the period of global ischemia was extended to 120 minutes, no significant change in any of the hemodynamic or metabolic measurements was seen from their initial hypotensive response at 15 minutes. The stability of these measurements would indicate that within the framework of this animal preparation, standard parameters of functional activity may not be useful indicators for estimating the duration of the ischemic insult when the coronary perfusing pressure is held constant.

In animal experiments on reperfusion, there does not appear to be a clear demarcation between reversible and irreversible ischemic damage. Using the technique of temporary coronary artery ligation leading to nearly complete cessation of flow, the duration of both the insult (89-91) and the period of recovery (92,93) modify the results. In general, reports have ranged from 20 minutes to 3 hours as to the perfusion - deficit limiting myocardial integrity, although the question has not been satisfactorily resolved (105), some studies have shown that reperfusion itself may be deleterious to an ischemically damaged coronary bed leading to an extension of the original damage (63,64).

In the current experiments, global ischemia followed by 60 minutes of reperfusion could not easily distinguish the tolerable limits of the duration of the ischemic insult. Based on mean arterial pressure and cardiac index measurements, animals which had undergone 60 minutes of ischemia would recover, while 90 minutes could be tolerated when recoverability was based on max dP/dt data.

The correlation between the left ventricular end-diastolic pressure and recoverability appears to be inappropriate, since this parameter was significantly different from control in the 90 minute group but not in the 120 minute group. It appears that these parameters may have been affected by alterations in the status of the periphery as well as inherent changes in cardiac performance (94).

However, the oxygen data which may be less influenced by the periphery indicate that only 30 minutes of ischemia could be tolerated. Therefore, both partial reductions and complete obstructions of coronary flow appear to produce similar functional derangements in that the situation is reversible if the flow is restored within 30 minutes (89,90), although even with this brief ischemic episode, morphological alterations have been shown to persist (64).

In reperfusion studies, the removal of an obstruction from a coronary artery has not always assured the restoration of pre-ischemic levels of flow (95). This no-reflow phenomenon has been shown to be an inherent derangement in the vascular bed and is directly related to the duration of ischemia (63,64,89,90,96,97). The present study has shown that a sustained reduction in coronary flow can evolve a no-reflow response as well. This would imply that non-occluded as well as occluded areas of the heart in patients with acute coronary insufficiency accompanied by systemic hypotension (98), or those undergoing anoxia during cardiopulmonary bypass (99) may sustain enough ischemic damage which would limit the coronary flow during recovery.

In Series I experiments, global decreases in coronary perfusing pressure produced equal reductions in the flows to all 3 coronary arteries; however, the results from Series II experiments indicate that transmural flows are unequal. Under control conditions, myocardial nutritive flow has been shown to be evenly distributed across the left ventricular free wall (61,74,96); with global reductions in coronary perfusing pressures, decreases in endocardial flow were found to be greater than decreases in epicardial flow. With reperfusion, the significant decrease in endocardial flow persisted in animals who had sustained at least 60 minutes of ischemia. This uneven flow distribution with reperfusion appears to have resulted from the fact that the ischemic insult was not evenly expressed across the myocardial wall. It has been recognized that subendocardial necrosis, even in the regions supplied by non-occluded coronary vessels (98) is frequently encountered following cardiopulmonary bypass and can result in fatal postoperative myocardial failure in patients who have undergone an otherwise technically successful surgical procedure (99). Although the factors responsible for this condition have not been adequately defined, an imbalance between oxygen requirements and supply in the subendocardium has been suggested. These results support the view that the no reflow response was primarily expressed in the subendocardial layers of the heart.

Thus overall reductions in coronary flow for short periods of time appear to produce function derangements similar to the damage associated with temporarily obstructed coronary arteries. Therefore, myocardial areas other than those directly affected by an obstruction must be considered in acute hypotensive situations when estimating the extent of injury and the ability to recover with reperfusion.

Among the modalities of treatment for temporarily supporting the patient in cardiogenic shock is the assisted circulatory procedure of intra-aortic balloon counterpulsation (IABP) (1,2,65). The therapeutic action of arterial counterpulsation as applied by IABP is believed to result from the combined effects of increasing coronary supply while reducing myocardial demand (65,68,71).

Coronary supply occurs primarily during cardiac diastole, when the coronary vasculature autoregulates the flow depending on the myocardial demand (57,58). During ischemia the coronary vessels dilate so that coronary flow becomes primarily pressure dependent (73). One of the main effects of IABP is to elevate the diastolic pressure in the aorta and the coronary arterial bed, thus increasing the blood flow to the ischemic myocardium, hence the term diastolic augmentation (67).

As well as increasing coronary perfusion pressure, IABP is said to be capable of reducing left ventricular work (65,71). Balloon deflation just before ventricular ejection produces an appreciable negative intra-aortic pressure effect which should improve the emptying of the left ventricle (systolic unloading). Although balloon counterpulsation is dependent upon a number of physical factors such as balloon volume, placement, and the timing and duration of inflation and deflation (71), optimal conditions have not always assured the combined therapeutic effects of systolic unloading and diastolic augmentation (69,70). Part of the problem may be that IABP affects two interrelated systems (coronary supply and coronary demand) which cannot be separately investigated. Powell and his associates (69) attempted such independent studies by counterpulsating experimental animals on right heart bypass while perfusing a coronary vessel at a constant rate. Although the results and conclusions were similar to those of the present study, only one part of the entire coronary circulation was perfused from an extracorporeal source and thus collateral supply could not be excluded.

In our animal preparation, the entire coronary circulation was isolated from the aortic supply and perfused from an extracorporeal source at known perfusion pressures. Under these conditions, IABP might produce both systolic unloading and diastolic augmentation; however, direct alterations of coronary flow were excluded from the increases in aortic diastolic pressure with IABP. Previous studies in the development of this experimental model have shown that normotensive systemic hemodynamic measurements could be estimated at normal coronary perfusion pressures. As the perfusion pressure was reduced, acute cardiac failure developed which remained relatively stable for extended periods. When IABP was applied to this animal preparation at different levels of left ventricular performance, systolic unloading was only evident at normotensive states (coronary perfusion pressure of 80 mmHg), as shown by a reduction in left ventricular systolic and diastolic pressures and by a decrease in left ventricular work. Since augmented aortic diastolic pressure could not directly influence coronary perfusion, the significant decrease in total coronary flow appears to be an autoregulatory response brought about by a decrease in myocardial demand (57,58).

During acute coronary insufficiency and subsequent left ventricular failure, Tyberg et al (70) showed that in the face of systemic hypotension an increase in aortic compliance prevails which will reduce the volume of blood moved by the balloon during ventricular systole. Whereas at "normal" aortic pressures, compliance is lower, complimenting the systolic action of the balloon. Thus, IABP was not accompanied either by systolic unloading or by indirect changes in coronary flow and oxygen consumption. These results indicate that balloon unloading responses may be intimately related to the functional status of the circulatory system before IABP (69,70). Finally, reductions in ventricular loading with IABP during severe hypotensive episodes may be secondary to increases in coronary flow which accompany increases in aortic diastolic pressure (69,70,100,101). Previous experiments with this coronary bypass model have clearly shown that coronary flow and myocardial function are closely related over a wide range of perfusion pressures. In relatively normotensive states with a coronary perfusion pressure of 80 mmHg, balloon deflation effectively unloaded the left ventricle which in turn caused coronary flow to decrease. This autoregulatory response, which had been previously

inferred (100-102) could not be measured directly without isolated coronary perfusion as outlined in this current study.

Under low normotensive conditions IABP can effectively reduce myocardial demand by systolic unloading. In contrast, IABP in hypotensive states is unable to reduce further myocardial demand. Thus, the main therapeutic action of IABP to the compromised heart in hypotensive states is achieved by increasing coronary flow through augmentation of the aortic diastolic pressure rather than by systolic unloading.

Summary:

In acute experiments on anaesthetized dogs the effects of controlled global coronary hypotension were studied on in situ working hearts. With this new animal preparation predetermined levels of reduced cardiac performance could be achieved by decreasing total coronary flow solely by the reduction of the coronary perfusing pressure. After initial studies, it was subsequently shown that a reduction in coronary flow was partially compensated by an increase in myocardial oxygen extraction, however; myocardial oxygen consumption eventually decreased which was accompanied by a reduction in myocardial mechanical work. In a second series of experiments, animals were used to estimate the cardiac impairment associated with a single reduction in coronary flow sufficient to produce acute cardiac failure (cardiogenic shock). Once instituted this state was maintained for 15 to 120 minutes in five groups of animals after which the coronary perfusing pressure was returned to normal and reperfused for 60 minutes. In this model extended periods of hypoperfusion did not alter the initial hemodynamic dysfunction seen after only 15 minutes of ischemia. With reperfusion hemodynamic recoverability was quite variable and was dependent upon the parameter chosen. In general, animals who had sustained between 30-60 minutes of global ischemia were recoverable. In animals subjected to ischemia of 60 minutes and longer in duration a significant and progressively lower restoration of coronary flow was evident after 60 minutes of reperfusion. The production of a "no-reflow" response by means of a partial reduction in flow rather than a complete obstruction in a coronary artery has never been previously recorded and would imply that non-occluded areas of the heart which had sustained periods of prolonged hypotension may be susceptible to damage upon reperfusion. Furthermore, studies on the transmural distribution of blood flow indicate that global reductions in perfusing pressure will cause a significant decrease in subendocardial flow during ischemia and reperfusion. In a third group of experiments the therapeutic properties of intra-aortic balloon pump (IABP) therapy was evaluated with this animal model. By perfusing the coronary arteries from an extracorporeal source the systolic unloading

responses could be analyzed at different levels of aortic pressure without directly affecting coronary flow through diastolic augmentation. The results from these experiments suggest that IABP treatment is effective only in reducing myocardial demands at normotensive levels; IABP during hypotensive states does not assist the failing heart directly by systolic unloading. Thus the therapeutic action of IABP treatment must result from increases in coronary blood flow by diastolic augmentation.

In conclusion, an animal model for cardiac failure has been outlined and evaluated in terms of its performance, recoverability and its ability to resolve some of the therapeutic aspects in the treatment of cardiogenic shock.

REFERENCES

1. Resnekov L: Cardiogenic shock. *Chest* 83: 893, 1983.
2. Rackley CE, Russell RO, et al: Cardiogenic shock. *Cardiovasc Clinics* 11: 15, 1981.
3. Swan HJC, Forrester JS, et al: Hemodynamic spectrum of myocardial infarction and cardiogenic shock. *Circulation* 45: 1097, 1972.
4. Lee JC, Downing SE: Myocardial oxygen availability and cardiac failure in hemorrhagic shock. *Am Heart J* 92: 201, 1976.
5. Courand A, Riley RL, et al: Studies of the circulation in clinical shock. *Surgery* 13: 964, 1943.
6. Facey FL, Weil MH, et al: Mechanism and treatment of shock associated with acute pancreatitis. *Am J Surg* 111: 274, 1966.
7. Hinshaw LB: Role of the heart in the pathogenesis of endotoxin shock: A review of the clinical findings and observations on animal species. *J Surg Res* 17: 134, 1974.
8. Austen KF: Systemic anaphylaxis in the human being. *New Engl J Med* 291: 661, 1974.
9. Britt BA: Malignant hypothermia: A pharmacogenetic disease of skeletal and cardiac muscle. *New Engl J Med* 290: 1140, 1974.
10. Feola M, Arbel ER, et al: Attenuation of cardiac sympathetic drive in, experimental myocardial ischemia in dogs. *Am Heart J* 93: 82 1977.
11. Feola M, Glick G: Experimental models of cardiogenic shock, in *Shock in Myocardial Infarction*, edited by Gunnar RM, Loeb HS, Rahimtoola SH, New York, Grune, 1974, p.23.
12. Page DL, Caulfield JB, et al: Myocardial changes associated with cardiogenic shock. *New Engl J Med* 285: 133, 1971.
13. Walston A, Hackel DB, et al: Acute coronary occlusion and the "power failure" syndrome. *Am Heart J* 79: 613, 1970.
14. Harnaryan C, Bennett MA, et al: Quantitative study of infarcted myocardium in cardiogenic shock. *Br Heart J* 32: 728, 1970.
15. Agress CM, Rosenberg MJ, et al: Protracted shock in the closed chest dog following coronary embolization with graded microspheres. *Am J Physiol* 170: 536, 1952.
16. Chirac P: *De Motu Cordis Adversaria Analytica*. Monspelii, 1698.

References cont'd.

17. Harrison TR: Failure of the circulation, 1st ed Williams & Wilkins, Baltimore, 1935.
18. Samuelson B: Uber den einfluss der koronar-arterien-verschliessung auf die herzaction. Z Klin Med 2: 12, 1881 .
19. Hirsch LJ, Glick G: Mesenteric circulation in cardiogenic shock with and without alph-receptor blockade. Am J Physiol 225: 356, 1973.
20. Orias O: The dynamic changes in the ventricles following ligation of the ramus descendens anterior. Am J Physiol 100: 629, 1932.
21. Tennant R, Wiggers CJ: The effect of coronary occlusion on myocardial contraction. Am J Physiol 112: 351, 1935.
22. Harrison TR: Failure of the circulation, 2nd ed p. 502, Williams & Wilkins, Baltimore, 1939.
23. Wiggers CJ: The functional consequences of coronary occlusion. Ann Int Med 23: 158, 1945.
24. Kupfer S: Can experimental shock be induced by coronary occlusions? Proc Soc Exp Biol NY 76: 134, 1951.
25. Eckstein RW: Coronary interarterial anastomoses in young pigs and mongrel dogs. Circ Res 2: 460, 1954.
26. Ellis PR Jr, Bailas NJ, et al: Experimental heart failure in dogs. Arch Surg 89: 299, 1964.
27. Feola M, Haiderer O, et al: Experimental graded "pump failure" of the left ventricle. J Surg Res 11: 325, 1971.
28. Kennedy JH, Bailas N, et al: Left heart bypass in left ventricular failure due to experimental coronary artery ligation. J Thorac Cardiovasc Surg 51: 797, 1966.
29. Vineberg A, Mahanti B, et al: Experimental gradual coronary artery constriction by ameroid constrictors. Surgery 47: 767, 1960.
30. Gross L, Mendlowitz M, et al: Hemodynamic studies in experimental coronary occlusion. 1. Open chest experiments. Am Heart J 13: 647, 1937.
31. Johnson FD, Hill IGW: The form of the electrocardiogram in experimental myocardial infarction. The early effects produced by ligation of the LAD artery. Am Heart J 10: 889, 1935.

References cont'd.

32. Panum PL: Experimentelle beitrage zur lehre von der embolie. Virchows Arch 25: 308, 1862.
33. Agress CM, Rosenberg MJ, et al: Blood volume changes in protracted shock resulting from experimental myocardial infarction. Am J Physiol 166: 603, 1951.
34. Agress CM, Binder MJ: Cardiogenic shock. Am J Cardiol 1: 231, 1958.
35. Bloch JH, Pierce CH, et al: Experimental cardiogenic shock. Effect of low molecular weight dextran. Arch Surg 91: 77, 1965.
36. Bing J, Castellanos A, et al: Experimental myocardial infarction: Circulatory, biochemical and pathological changes. Am J Med Sci 232: 533, 1956.
37. Sivarajan M, Amory DW: Effects of glucagon on regional blood flow during cardiogenic shock. Circ Shock 6: 365, 1979.
38. Beckman CB, Niazi Z, et al: Protective effects of epinephrine tolerance in experimental cardiogenic shock. Circ Shock 8: 137, 1981.
39. Hermann G and Decherd G: Creatinine mobilization in myocardial damage. Proc Soc Exp Biol Med 32: 477, 1934.
40. Lluch S, Moguilevsky HC et al: A reproducible model for cardiogenic shock in the dog. Circulation 39: 205, 1969.
41. Edelman NH, Gorfinkel HJ et al. Experimental cardiogenic shock: pulmonary performance after acute myocardial infarction. Am J Physiol 219: 1723, 1970.
42. Gorfinkel HJ, Szidon JP, et al: Renal performance in experimental cardiogenic shock. Am J Physiol 222: 1260, 1972.
43. Haddy FJ and Scott JB: Metabolically linked vasoactive chemicals in local regulation of blood flow. Physiol Rev 44: 688, 1968.
44. Rushmer RF, Van Gitters RH, et al: Definition and classification of various forms of shock. In: Shock: Pathogenesis and Therapy p.1, Springer-Verlag, Berlin.
45. Glenn TM, Lefer AM, et al: Production of a myocardial depressant factor in cardiogenic shock. Am Heart J 82: 78, 1971.
46. Senges J, Mizutani T, et al: Inotropic and electrophysiological action of humoral factors released in cardiogenic shock after acute myocardial infarction. Basic Res Cardiol 73: 147, 1978.

References cont'd.

47. Lohmann A: Uber die funktion der bruckesfasern die en stelle der grossen venen die fuhrung der herztatigkeit beim saugetierte zu ubernehmen. Arch Gesamte Physiol 123: 628, 1908.
48. Eppinger H, Rothberger CJ: Zur analyse des electrokardiogramms. Wien Klin Wochenschr 22: 1091, 1909.
49. Cushing EH, Feil HS et al: Infarction of the cardiac auricles (atria). Clinical, pathological and experimental studies. Br Heart J 4: 17, 1942.
50. Haney HF, Borman MC, et al: The relation between position of experimental myocardial lesions in the dog and changes in the RS-T segment of the ECG. Am J Physiol 106: 64, 1933.
51. Taylor CB, Davis CB Jr.: Controlled myocardial injury produced by a hypothermal method. Circulation 3: 239, 1951.
52. Maggs PR, Nener TPE, et al: Effect of left ventricular akinesis on cardiac performance. Experimental study using a new model. Circulation 59: 1019, 1979.
53. Koo A, Tse TF, et al: Hepatic microvascular effects of terbutaline in experimental cardiogenic shock in rats. Clin Exp Pharmacol Physiol 6: 495, 1979.
54. Roberts JC Jr and Straus R (Eds): Comparative atherosclerosis: The morphology of spontaneous and induced atherosclerotic lesions in animals and its relation to human disease. New York, Hoeber, 1965.
55. Salazar AE: Experimental myocardial infarction. Induction of coronary thrombosis in intact closed-chest dogs. Cir Res 9: 1351, 1961.
56. Murphy SD, Charrette EJP, et al: Experimental coronary artery thrombosis for production of cardiogenic shock. Can J Surg 13: 189, 1970.
57. Rubio R, Berne RM: Regulation of coronary blood flow. Prog Cardiovasc Dis 18: 105, 1975.
58. Weber KT, Scott G, et al: The normal regulation of coronary blood flow. Cardiovasc Clinics 41: 9, 1983.
59. Maroko PR, Deboer LWV et al: Infarct size reduction: A critical review. Adv Cardiol 27: 127, 1980.

References cont'd.

60. Hearse DJ, Yellon DM: The "Border Zone" in evolving myocardial infarction: Controversy or confusion? *Am J Cardiol* 47: 1321, 1981.
61. Becker LC, Ferreira R, et al: Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. *Cardiovasc Res* 7: 391, 1973.
62. Jennings RB, Sommers HM et al: Myocardial necrosis induced by temporary occlusion of coronary artery in dog. *Arch Pathol* 70: 68, 1960.
63. Hearse JD: Reperfusion of the ischemic myocardium. *J Molecular Cell Cardiol* 9: 605, 1977.
64. Kloner RA, Ellis SG, et al: Studies of experimental coronary artery reperfusion. Effects on infarct size, myocardial function, biochemistry, ultrastructure and microvascular damage. *Circulation* 68: I-8, 1983.
65. Amersterdam EA, Awan NA, et al: Intra-aortic balloon counterpulsation: Rationale, application and results. *Cardiovasc Clinics II*: 79, 1981.
66. Keon WJ, Bedard P, et al: Emergency aorto-coronary venous bypass graft in cardiogenic shock. *Can Med Assoc J* 105: 1293, 1971.
67. Mouloupoulos SD, Topaz S, et al: Diastolic balloon pumping in the aorta-mechanical assistance to the failing circulation. *Am Heart J* 63: 669, 1962.
68. Bregman D: Mechanical support of the failing heart. *Curr Probl Surg* 13: 1, 1976.
69. Powell WJ Jr, Daggett WM, et al: Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption and coronary blood flow in dogs. *Circ Res* 26: 753, 1970.
70. Tyberg JV, Keon WJ, et al: Effectiveness of intra-aortic balloon counterpulsation in the experimental low output state. *Am Heart J* 80: 89, 1970.
71. Weber KT, Janicki JS: Intra-aortic balloon counterpulsation. A review of physiological principles, clinical results and device safety. *Ann Thorac Surg* 17: 602, 1974.
72. Liedke AJ, Hughes HC, et al: Experimental model for studying myocardial ischemia. Correlation of hemodynamic performance and metabolism in working swine heart. *J Thorac Cardiovasc Surg* 69: 203, 1975.

References cont'd.

73. Mosher P, Ross J Jr, et al: Control of coronary blood flow by autoregulatory mechanism. *Circ Res* 14: 250, 1964.
74. Domenech RJ, Hoffman JIE, et al: Total and regional coronary blood flow measured by radioactive microspheres in conscious and anaesthetized dogs. *Circ Res* 25: 581, 1969.
75. Braunwald E, Maroko PR: Reduction of infarct size - idea whose time (for testing) has come. *Circulation* 50: 206, 1974.
76. Killip T, Kimball JT: Survey of coronary care unit: concept and results. *Prog Cardiovasc Dis* 11: 45, 1968.
77. Gregg DE, Green HD: Effects of viscosity, ischemia, cardiac output and aortic pressure on coronary blood flow measured under constant perfusion pressure. *Am J Physiol* 130: 108, 1940.
78. Bacaner MB, Lioy F, et al: Coronary blood flow, oxygen delivery rate and cardiac performance. *J Physiol (Lond)* 216: 111, 1971.
79. Bacaner MB, Connolly JE, et al: The coronary blood flow as a critical determinant of cardiac performance and cardiac size. *Am J Med* 30: 392, 1961.
80. Bacaner MB, Lioy F: Induced change in heart metabolism as a primary determinant of cardiac performance. *Am J Physiol* 209: 519, 1965.
81. Daniell HB: Coronary flow alterations on myocardial contractility, oxygen extraction and oxygen consumption. *Am J Physiol* 225: 1020, 1973.
82. Opie LH: Coronary flow rate and perfusion pressure as determinants of mechanical function and oxidative metabolism of the isolated perfused rat heart. *J Physiol (Lond)* 180: 529, 1965.
83. Ross J Jr, Klocke F, et al: Effects of alterations of coronary blood flow on the oxygen consumption of the working heart. *Circ Res* 13: 510, 1963.
84. Weisfeldt ML, Shock NW: Effect of perfusing pressure on coronary flow and oxygen usage of non-working heart. *Am J Physiol* 218: 95, 1970.
85. Fisher VJ, Martino RA, et al: Coronary flow as an independent determinant of myocardial contractile force. *Am J Physiol* 217: 1127, 1969.

References cont'd.

86. Sarnoff SJ, Gilmore JP, et al: Relation between coronary blood flow and myocardial oxygen consumption. *Circ Res* 13: 514, 1963.
87. Sarnoff SJ, Braunwald E, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 192: 148, 1958.
88. Brunsting JR, Visser KR et al: Simultaneous perfusion of both coronary arteries and drainage of the coronary sinus in the dog heart in situ. *Pflugers Arch* 356: 193, 1975.
89. Constantini C, Corday E, et al: Revascularization after 3 hours of coronary artery occlusion: Effects on regional cardiac metabolic function and infarct size. *Am J Cardiol* 36: 368, 1975.
90. Lang TW, Corday E, et al: Consequences of reperfusion after coronary occlusion. Effects of hemodynamic and regional myocardial metabolic function. *Am J Cardiol* 33: 69, 1974.
91. Parker PE, Bashour FA et al: Coronary hemodynamics during reperfusion following acute coronary ligation in dogs. *Am Heart J* 90: 593, 1975.
92. Puri PS: Contractile and biochemical effects of coronary reperfusion after extended periods of coronary occlusion. *Am J Cardiol* 36: 244, 1975.
93. Sharma GP, Varley K, et al: Alterations in energy metabolism and ultrastructure upon reperfusion of the ischemic myocardium after coronary occlusion. *Am J Cardiol* 36: 234, 1975.
94. Monroe RG, French GN: Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. *Circ Res* 9: 362, 1961.
95. Kloner RA, Ganole CE, et al: The "no-reflow" phenomenon following temporary coronary occlusion in the dog. *J Clin Invest* 54: 1496, 1975.
96. Cobb FR, Bach RJ, et al: Local effects of acute cellular injury on regional myocardial blood flow. *J Clin Invest* 57: 1359, 1976.
97. Krug A: Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 19: 57, 1966.

References cont'd.

98. Corday E, Kaplan L, et al: Consequences of coronary arterial occlusion on remote myocardium: effects of occlusion and reperfusion. *Am J Cardiol* 36: 385, 1975.
99. Buckberg GD, Towers B, et al: Subendocardial ischemia after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 64: 669, 1972.
100. Chatterjee S, Rosensweig J: Evaluation of intra-aortic balloon counterpulsation. *J Thorac Cardiovasc Surg* 61: 405, 1971.
101. Feola M, Haiderer O, et al: Intra-aortic balloon pumping at different levels of experimental acute left ventricular failure. *Chest* 59: 68, 1971.
102. Yahr WZ, Butner AN, et al: Cardiogenic shock dynamics of coronary blood flow with intra-aortic phase-shift balloon pumping. *Surg Forum* 19: 142, 1968.
103. Stowe DF, Mathey DG, et al: Segmental stroke work and metabolism depend on coronary blood flow in the pig. *Am J Physiol* 234:H597, 1978.
104. Vatner SF: Correlation between acute reductions in myocardial blood flow and function in conscious dogs. *Circ Res* 47:201, 1980.
105. Kloner RA, Ellis SG, et al: Studies of experimental coronary reperfusion. Effects on infarct size, myocardial function, biochemistry, ultrastructure, and microvascular damage. *Circulation* 68: Suppl I-8, 1983.

APPENDIX

For this section 4 reprints have been included in which the majority of the material presented in this thesis was previously published:

- (a) Keon WJ, Taichman GC, et al: Acute cardiac failure: The relation between coronary flow and cardiac function. *Can J Surg* 19:531, 1976.
- (b) Keon WJ, Akyurekli Y, et al: Acute cardiac failure: The relation between coronary flow and oxygen consumption. *Can J Surg* 21:114, 1978.
- (c) Akyurekli Y, Taichman GC, et al: Effectiveness of intra-aortic balloon counterpulsation on systolic unloading. *Can J Surg* 23:122, 1980.
- (d) Taichman GC, Keon WJ, et al: Myocardial responses to acute global ischemia and reperfusion. *Am Heart J* 104:1247, 1982.

ACUTE CARDIAC FAILURE: THE RELATION BETWEEN CORONARY FLOW AND CARDIAC FUNCTION*

W. J. KEON, MD, FRCS[C], G. C. TAICHMAN, PhD, Y. AKYUREKLI, MD, FRCS[C]
and B. V. KORECKY, MD, PhD

To study the effects of acute coronary hypotension on the working dog heart in situ, both coronary arteries were cannulated and perfused with oxygenated blood at controlled pressures (40 to 120 mm Hg). At a perfusion pressure of 120 mm Hg, total coronary artery flow appeared to be sufficient (0.95 ± 0.08 ml/min·g) to maintain normal cardiac performance for a 2.5-hour observation period. During incremental decreases in coronary perfusion pressure, significant linear correlations were found between coronary flow and cardiac index ($r = 0.84$), left ventricular maximum dP/dt ($r = 0.83$), stroke index ($r = 0.82$), stroke work ($r = 0.83$) and mean arterial pressure ($r = 0.62$). During simulated shock conditions (systolic arterial pressure, < 75 mm Hg), relative reductions in coronary flow ($-60.9 \pm 4.0\%$) paralleled changes seen in cardiac function and persisted for 28 ± 4 min.

Pour étudier les effets de l'hypotension coronarienne aigue sur le coeur de chien in situ, les deux coronaires sont cannulées et perfusées séparément avec du sang oxygéné à des niveaux de pression contrôlés (40 à 120 mm Hg). A une pression de perfusion de 120 mm Hg, le débit coronarien total semble suffisant (0.95 ± 0.08 ml/min·g) pour assurer la performance cardiaque durant une période d'observation de 2.5 heures. La pression de perfusion coronarienne est diminuée de façon progressive et on établit des relations linéaires entre le débit coronarien et l'index cardiaque ($r = 0.84$), la dP/dt maximum ($r = 0.83$), l'index d'éjection systolique ($r = 0.83$) et la pression artérielle moyenne ($r = 0.62$). Pendant des conditions de choc simulé (pression artérielle systolique, < 75 mm Hg), la diminution relative du débit coronarien ($-60.9 \pm 4.0\%$) a été suivie des changements de fonction cardiaque observés et s'est maintenue pendant 28 ± 4 minutes.

AN intensive research program has improved the management of patients suffering from acute myocardial infarction.¹ However, statistical surveys have shown that cardiogenic

shock complicating one in every six patients hospitalized for acute myocardial infarction^{2, 3} is associated with an 80 to 90% mortality. Our clinical experience has shown that direct revascularization of ischemic myocardium will improve prognosis in these patients,⁴⁻⁶ but further studies are necessary to define the correct timing for this procedure.

Although the onset of cardiogenic shock appears to be directly related to the total extent of damaged myocardium, irrespective of its temporal occurrence,⁷ the experimental production of cardiogenic shock has been difficult.⁸ The creation of large areas of myocardial injury by various means⁹⁻¹⁰ has only occasionally produced shock-like states, variable in extent and duration. In the present experiment we have used a different approach. In situ working dog hearts on total coronary bypass were subjected to controlled levels of coronary hypotension. As a result, systemic hypotensive states developed for extended periods of time. As a potential experimental shock model, the preparation appears to be both technically feasible and reasonably reproducible.

METHODS

Surgical

Short-term investigations were performed on mongrel dogs (weight, 21 to 50 kg). Animals were premedicated with atropine (4 mg, intramuscularly) and initially anesthetized with Pentothal (20 mg/kg, intravenously). After tracheal intubation the animals were ventilated with a mixture of 70% oxygen and 30% nitrous oxide using a Harvard volume respirator. For the remainder of the experiment, surgical anesthesia was maintained with 0.5 to 1.0% halothane.

A thoracotomy was performed through the fifth left intercostal space and the pericardial sac was opened to the right of the phrenic nerve. The heart was cradled in the pericardium by suturing the edges of the thoracic wall.

*From the University of Ottawa cardiac unit, Ottawa Civic Hospital, Ottawa, ON.

Supported by the Ontario Heart Foundation.

Reprint requests to: Dr. W. J. Keon, University of Ottawa cardiac unit, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, ON K1Y 4E9.

The three main coronary arteries were isolated by blunt dissection. The right coronary artery was dissected close to its origin, while the left anterior descending and circumflex branches were isolated at the bifurcation of the left main coronary artery. After heparinization (2 mg/kg, intravenously), all three vessels were cannulated and perfused by an extracorporeal circuit. Throughout these experiments, pH, P_{O_2} and P_{CO_2} values were periodically measured (Radiometer BMS-3) from the arterialized blood of the animal and the extracorporeal circuit, and appropriately adjusted by changing inspiratory carbon dioxide content on the respirator or by the administration of 0.5% sodium bicarbonate. During these experiments, arterial pH values from the animal-extracorporeal circuit ranged from 7.34 to 7.48, P_{O_2} from 90 to 135 mm Hg and P_{CO_2} from 32 to 49 mm Hg.

Instrumentation

Fig. 1 is a simplified representation of the experimental design. Continuous lead II electrocardiographic monitoring was used to compute heart rate (HR) and served as a time reference signal for other measurements. Fluid-filled vascular catheters in conjunction with Statham transducers (P23Db) and Electronics for Medicine amplifiers (SGM-2) were used to measure various pressures referenced to the level of the right atrium. A catheter was introduced into the common carotid or the right brachial artery to measure arterial pressure (AP) from the ascending aorta. From the jugular veins, two flow-directed catheters (Edwards, model 93-118-7F) monitored pressures in the right ventricle (RVP) and the pulmonary artery (PAP). Mean right and left atrial pressures were measured by water manometry, while a Millar catheter-tip manometer system passed across the aortic valve measured left ventricular pressure (LVP). The natural frequency responses of these systems were as follows: AP, 28 Hz; LVP, 20 kHz; PAP, 10.5 Hz; and RVP, 25 Hz. Mean pressures were achieved either by mechanical dampening or electronic filtering. A differentiating circuit was applied to the left ventricular pressure signal to compute the differentiated response (dP/dt).

Aortic root flow velocity was measured

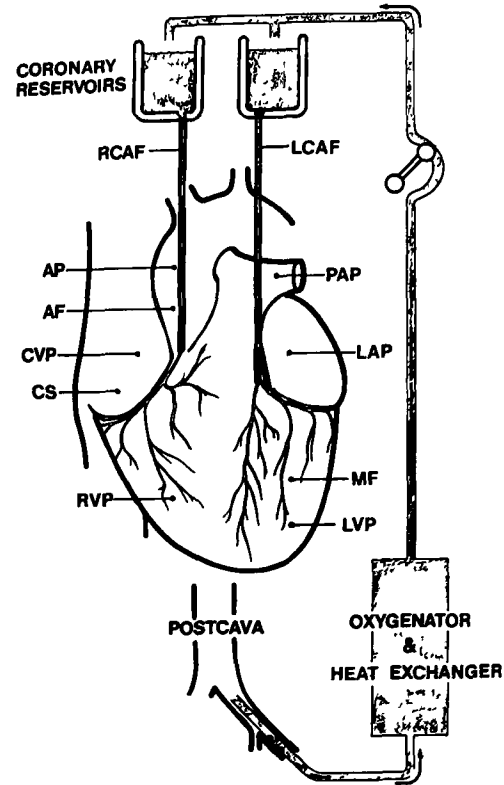


Fig. 1.—Total coronary bypass circuit. AP = aortic pressure; AF = aortic root flow; CVP = central venous pressure (right atrial); CS = coronary sinus sample; RVP = right ventricular pressure; LVP = left ventricular pressure; MF = mural force; LAP = left atrial pressure; PAP = pulmonary artery pressure; LCAF = left coronary artery flow; RAF = right coronary artery flow.

by a circumferential Statham flow probe and calibrated by simultaneous determination of cardiac output via a thermodilution technique in the pulmonary artery. Coronary venous samples were collected by catheterizing the coronary sinus. An uncalibrated isometric Walton Brodie strain-gauge device was sutured onto the anterior left ventricular surface to monitor changes in epicardial mural force. Signals were either recorded directly (Beckman S-11 Dynograph) or stored on tape (Bell and Howell VR-3200) for later processing.

Extracorporeal Circuit

The circuit (Fig. 1) was primed with heparinized (3 mg/kg) fresh whole blood from donor dogs and 5:1 Hartman's solution. During bypass, venous blood was collected from the femoral veins into a reservoir whose height regulated the venous pressure. This blood was then oxygenated (P_{O_2} , 100

to 130 mm Hg) and heated to body temperature (37 to 38°C) by an oxygenator (Harvey H200). Arterialized blood was returned to the animal through the cannulated coronary arteries. The coronary perfusion pressure was controlled by the height of a reservoir above the left atrium. Since separate right and left coronary reservoirs were used, pressures to either vasculatures could be altered individually or in unison. The right coronary reservoir fed the right coronary artery while the left reservoir supplied both the circumflex and the left anterior descending arteries. Flow to each coronary vessel was measured by extracorporeal flow probes (Biotronex). Tapered catheters (Travenol 5M0287) were used as coronary cannulas whose unimpeded flows were minimally 600 ml/min.

Experimental Protocol

Initially all animals were allowed to stabilize for at least 45 minutes. During this period the coronary perfusion pressure was maintained at 120 mm Hg. If consistent values could not be measured, then additional time was allotted for stabilization. At the end of this period, data were collected and used as control values for all subsequent maneuvers. In these experiments, the effects of coronary hypotension were examined both in terms of extent and duration. Hypotension was induced by step-wise decrements in the height of the coronary reservoirs while values were recorded at least 10 minutes after the pressure was changed. In order to assess all parameters at the peak of the heterometric autoregulatory curve (Frank-Starling relationship), the venous reservoir was adjusted during the stabilization period until no further increase in mean arterial pressure was achieved. Once optimal loading conditions were established, no further adjustments were made.

RESULTS

In these experiments 3 to 6.5 hours were required from induction of anesthesia to the start of experimental hypotension. In the course of cannulating coronary vessels, the average ischemic time was 48 ± 17 seconds (mean \pm SEM). During these maneuvers and the initial perfusion period, systemic hypotension was minimized by an arterial

TABLE I.—HEMODYNAMIC DATA (n = 12)*

Parameter	Measurement
Stabilization time (min)	68 \pm 10
Heart rate (beats/min)	131 \pm 11
Pressures (mm Hg)	
Arterial	
Mean . . .	116 \pm 8
Systolic . . .	127 \pm 11
Diastolic . . .	94 \pm 10
Right atrial (cm H ₂ O)	7.1 \pm 1.2
Pulmonary arterial (mean)	16.1 \pm 1.5
Left atrial (cm H ₂ O)	18.8 \pm 3.9
Left ventricular end-diastolic	1.22 \pm 2.1
dP/dt, max (mm Hg/s) . . .	1911 \pm 148
Cardiac index (ml/min·kg)	151 \pm 9
Stroke index (ml/beat·kg) . . .	1.12 \pm 0.10
Stroke work† (mm Hg/beat·kg)	121 \pm 14
Coronary flow, total (ml/min·g)	0.95 \pm 0.08
Left:right coronary flow ratio	2.59 \pm 0.31

*All values (mean \pm SEM) were taken at the end of the stabilization period.

†Stroke work = mean arterial pressure x stroke index.

support circuit. In addition arrhythmias that developed were treated by the administration of an intravenous 20-mg bolus of lidocaine. The stabilization period could not be completed in 4 of the 16 animals; we were not able to wean them from the arterial support. The control hemodynamic values of the remaining 12 animals are presented in Table I.

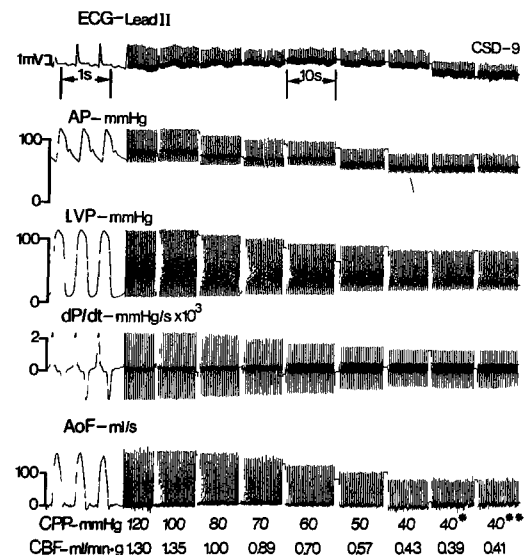


Fig. 2.—Hemodynamic effects of controlled coronary perfusion. Coronary perfusion pressure (CPP) was incrementally reduced while AP, LVP, derivative of LVP (dP/dt), aortic flow (AoF) and coronary blood flow (CBF) were monitored. All records were made 10 minutes after CPP was altered. At CPP 40 mm Hg, additional records were taken at 20 minutes (*) and 30 minutes (**).

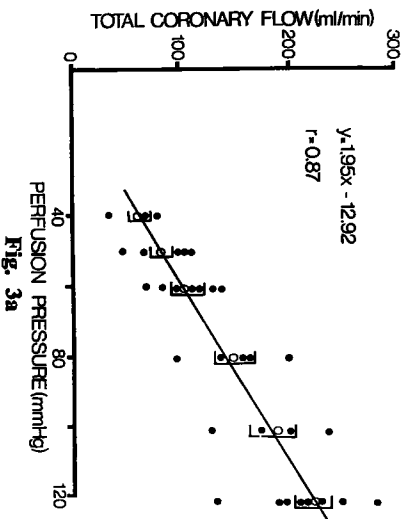


Fig. 3a

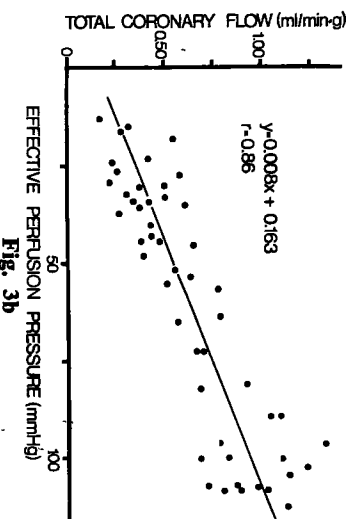


Fig. 3b

Fig. 3.—Coronary pressure-flow relations expressed as (a) perfusion pressure (hydrostatic driving pressure) v. total coronary flow (ml/min) and (b) effective perfusion pressure (perfusion pressure — left ventricular end-diastolic pressure) v. total coronary flow per gram of heart. In (a) open circles and square brackets represent mean \pm SEM.

In three animals, the effects of prolonged coronary perfusion at 120 mm Hg were evaluated. Over a 2.5-hour observation period, the parameters, with the exception of total coronary flow, fluctuated by no more than 12% from initial control values. The total coronary flow steadily decreased during this period; the greatest reduction was 21%.

In the remaining nine animals the coronary perfusion pressure was progressively reduced in 10 to 20-mm Hg steps until an arterial systolic pressure of 75 mm Hg or less was recorded (Fig. 2). In order to satisfy this criterion, the coronary perfusion pressure had to be reduced by $59.3 \pm 2.6\%$, which in turn caused the total coronary flow to decrease by $60.9 \pm 4.0\%$ (Figs. 3 and 4a). Though all hemodynamic parameters were measured under optimal loading conditions, the underperfusion of the heart limited its performance (Figs. 4b-f). When

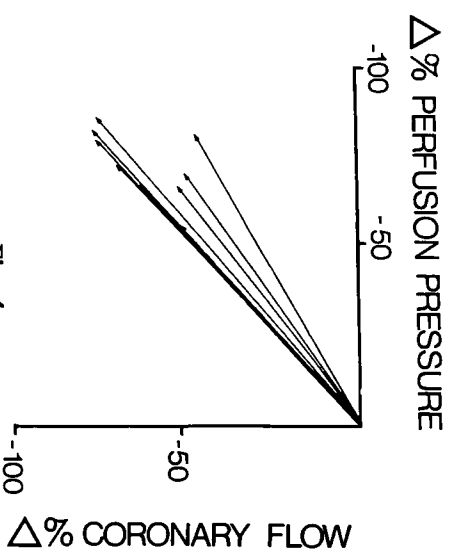


Fig. 4a

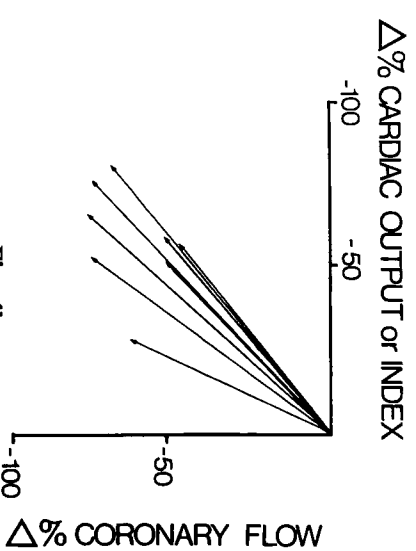


Fig. 4b

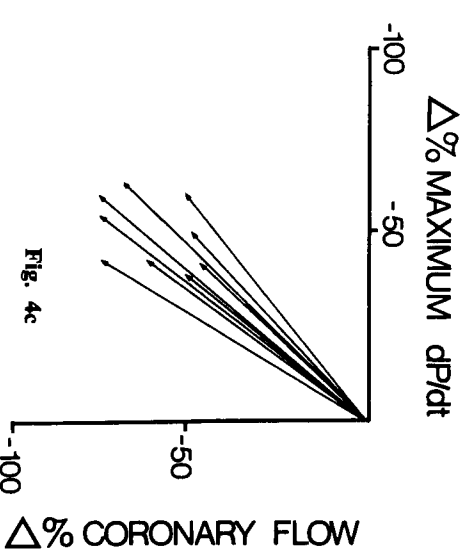


Fig. 4c

Fig. 4.—Relative reductions in coronary flow v. other hemodynamic parameters. In order to lower arterial systolic pressure to 75 mm Hg, a $59.2 \pm 2.6\%$ (mean \pm SEM) reduction in perfusion pressure (a) was needed to reduce coronary flow by $60.9 \pm 4.0\%$. Consequently cardiac output or index (b), maximum dP/dt (c), stroke index (d), stroke work (e) and mean arterial pressure (f) were reduced by $59.0 \pm 5.4\%$, $52.5 \pm 3.3\%$, $62.0 \pm 4.2\%$, $74.8 \pm 3.7\%$ and $37.6 \pm 3.7\%$ respectively. For control values see Table I.

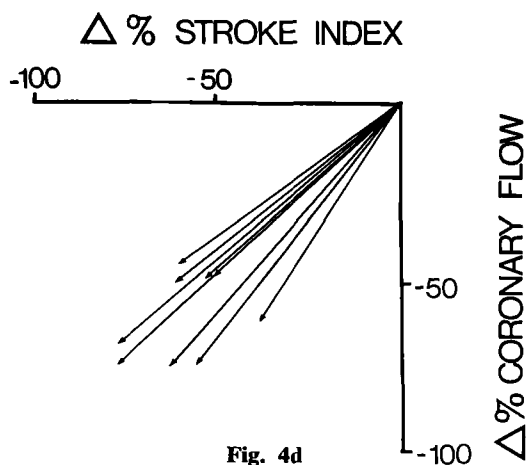


Fig. 4d

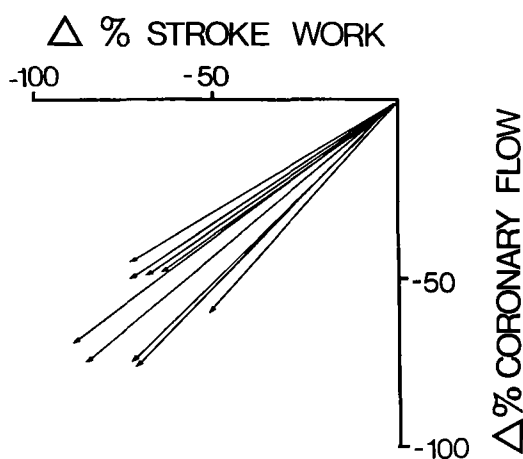


Fig. 4e

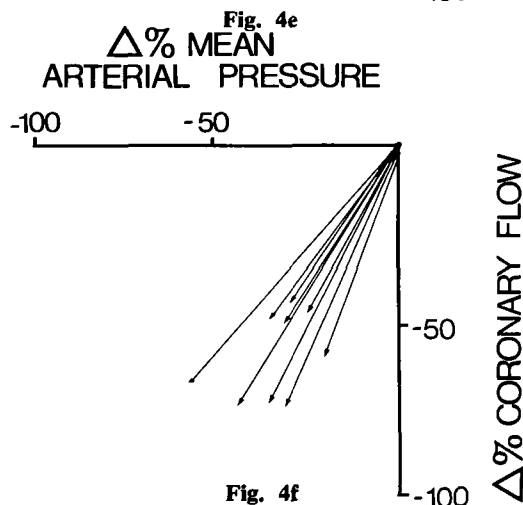


Fig. 4f

analyzed in detail at various hypotensive levels, linear correlations were found to exist (Fig. 5). In descending order of significance, they were cardiac index, maximum dP/dt , stroke index, stroke work and mean arterial

pressure. (In addition, preloading pressures such as left ventricular end-diastolic and left atrial pressures increased as the perfusion pressure was reduced.) Other parameters measured did not significantly correlate with coronary flow.

At the final perfusion pressure the effects of protracted periods of coronary hypotension were studied. Consistently, all values measured did not change appreciably from the start of this period (Fig. 2); in fact, fibrillation with subsequent complete circulatory collapse was usually abrupt in onset. In seven dogs allowed to die in this fashion, the mean survival time at the lowest perfusion level was 28 ± 4 minutes. Reperfusion at 120 mm Hg perfusion pressure in two animals who had sustained 30 minutes of severe ischemia resulted in a partial recovery; however, within 2 and 5 minutes, respectively, uncontrollable arrhythmias developed.

At the completion of the experiment, hearts were examined macroscopically. In all animals studied a large, hemorrhagic, pale brown area was found across the wall of the pulmonary conus. Occasionally this area encompassed the basal portion of the septum. The rest of the heart had scattered perivascular hemorrhages that were more prevalent in the hypotensive group than in the three control animals.

DISCUSSION

In a recent review, Feola and Glick⁸ emphasized the problems encountered with animal experimentation in the study of cardiogenic shock. In the majority of reports cited, the occurrence of the desired shock-like state, associated with prolonged severe reduction in cardiac output and arterial pressure, was unpredictable in only a few experiments. In general, the preferred procedure has been the production of large areas of myocardial damage either by coronary artery ligation,⁹⁻¹² direct myocardial injury,^{13, 14} coronary embolization¹⁵⁻¹⁷ or coronary thrombosis.^{18, 19} Although these insults may be analogous to the clinical events preceding cardiogenic shock, the presence of heterogenous flow patterns²⁰ and the subsequent development of a mixed population of normal to irreversibly damaged

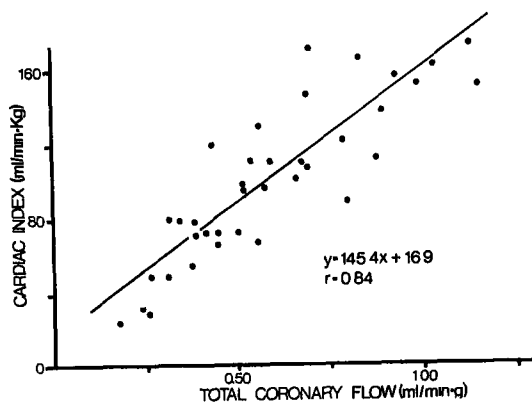


Fig. 5a

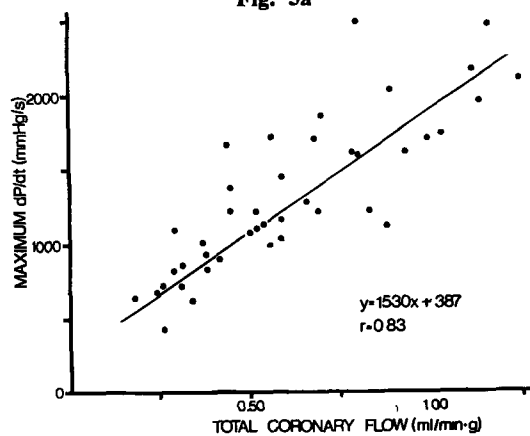


Fig. 5b

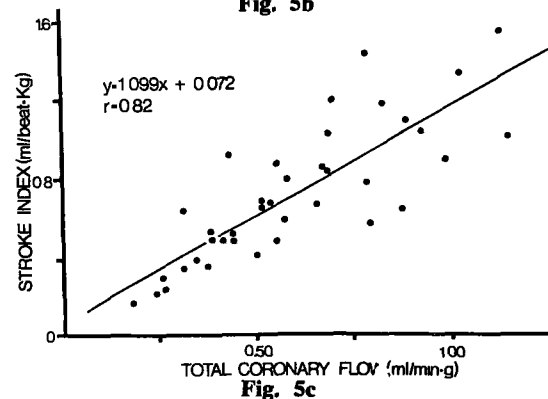


Fig. 5c

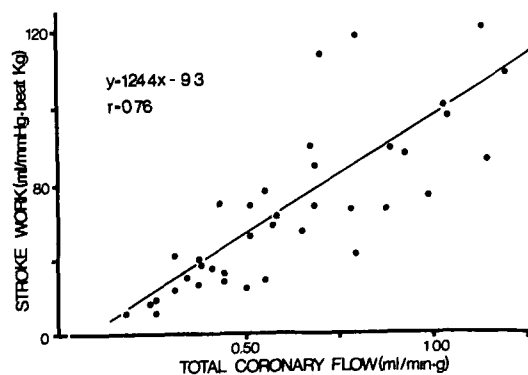


Fig. 5d

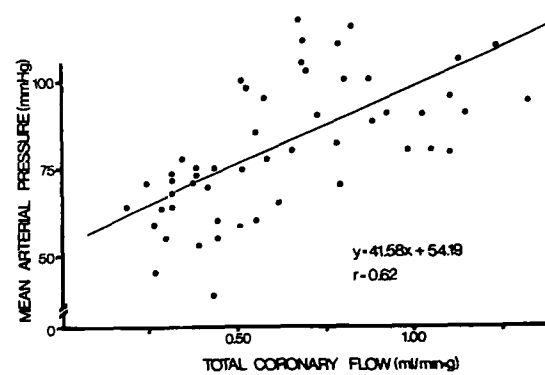


Fig. 5e

Fig. 5.—Relation between total coronary flow (ml/min-kg) and various hemodynamic parameters: (a) cardiac index; (b) maximum dP/dt; (c) stroke index; (d) stroke work; and (e) mean arterial pressure.

cells,²¹ make precise mechanical, electrical and metabolic analysis difficult. This may, partly, account for the variable response.

As an alternative approach, the technique of separating and controlling the coronary vasculature from the rest of the circulation may represent a more practical solution.²² In the present experiment total coronary flow was monitored while the coronary perfusion pressure and left ventricular filling pressure were arbitrarily set. At a perfusion pressure of 120 mm Hg the hemodynamics

appeared to be within normal limits and remained so for 2.5 hours of observation. With the exception of coronary flow, the increased resistance monitored was probably a result of cellular edema.^{2,3}

In the animals subjected to hypotensive coronary perfusion pressures, initial reductions evoked a mild autoregulatory response;²⁴ however, over most of the range of pressures investigated, coronary flow became pressure-dependent and decreased linearly with the driving pressure. In a recent study with a similar preparation, Liedke, Hughes and Neely²² showed that when coronary flow is reduced, the balance between supply and demand can no longer be maintained and cardiac performance decreases. In the present experiments, significant linear correlations were observed between coronary flow and the various indices of mechanical cardiac performance. In addition, these reductions appeared to be equal in magnitude: a $60.9 \pm 4.0\%$ reduc-

tion in coronary flow produced a similar reduction in cardiac index, stroke work and maximum dP/dt , and the balance was preserved. Although clearly detrimental to the rest of the animal, the reduction in mechanical function may have certain advantages for the ischemic myocardium, and the conservation of chemical energy by the reduction of external work may be important in preserving myocardial integrity. In this way tissue necrosis may be delayed.²⁵

In attempting to resolve the temporal limits and events of this shock-like state, we have observed that cardiac function remained unchanged, albeit hypodynamic, for 28 ± 4 minutes; reperfusion at this point appears to indicate the loss of myocardial integrity.

As an experimental model of cardiogenic shock, the present results indicate that a severe hypodynamic state can be achieved quickly and repetitively so as to permit the study of pathophysiologic and therapeutic experiments. In these initial experiments, the effects of a uniform reduction in total coronary flow was evaluated; however, the separate manipulation of individual coronary flows can easily be accommodated so as to parallel more closely the clinical situation. In subsequent studies we hope to examine this type of intervention in an effort to resolve the extent and temporal limitations of acute reductions in myocardial flow and to create an animal model to parallel our clinical experience with emergency revascularization surgery.⁴⁻⁶

We thank K. Sheldrick and the personnel of the department of research, Ottawa Civic Hospital, for their technical assistance.

REFERENCES

1. BRAUNWALD E, MAROKO PR: Reduction of infarct size — idea whose time (for testing) has come. *Circulation* 50: 206, 1974
2. KILLIP T, KIMBALL JT: Survey of coronary care unit: concept and results. *Prog Cardiovasc Dis* 11: 45, 1968
3. SCHEIDT S, ASCHEIM R, KILLIP T: Shock after acute myocardial infarction. Clinical and hemodynamic profile. *Am J Cardiol* 26: 556, 1970
4. KEON WJ, ABBAS SZ, SHANKAR KR, et al: Emergency aorto-coronary venous bypass graft in cardiogenic shock. *Can Med Assoc J* 105: 1293, 1971
5. KEON WJ, BÉDARD P, SHANKAR KR, et al: Experience with emergency aorto-coronary bypass grafts in presence of acute myocardial infarction. *Circulation* 48 (suppl 3): 151, 1973
6. IDEM: Experience with emergency aorto-coronary bypass grafts. *Can J Surg* 16: 268, 1973
7. PAGE DL, CAULFIELD JB, KASTOR JA, et al: Myocardial changes associated with cardiogenic shock. *N Engl J Med* 285: 133, 1971
8. FEOLA M, GLICK G: Experimental models of cardiogenic shock, in *Shock in Myocardial Infarction*, edited by GUNNAR RM, LOEB HS, RAHIMTOOLA SH, New York, Grune, 1974, p 23
9. ELLIS PR, BAILAS NJ, VISKOS JD, et al: Experimental heart failure in dogs. *Arch Surg* 89: 299, 1964
10. GOLDFARB D, CONTI CR, BROWN BG, et al: Treatment of severe cardiogenic shock by diastolic augmentation after ligation and division of left circumflex coronary artery in dogs. *J Thorac Cardiovasc Surg* 51: 783, 1966
11. SMALL ML: Standardized experimental preparation of cardiogenic shock. *Surgery* 60: 1051, 1966
12. FEOLA M, HAIDERER O, KENNEDY JH: Experimental graded "pump failure" of left ventricle. *J Surg Res* 11: 325, 1971
13. HANEY HF, BORMAN MC, MEEK WJ: Relation between position of experimental myocardial lesions in dog and changes in RS-T segment of electrocardiogram. *Am J Physiol* 106: 64, 1933
14. TAYLOR CB, DAVIS CD, VAWTER GF, et al: Controlled myocardial injury produced by hypothermal method. *Circulation* 3: 239, 1951
15. HAMBURGER WW, PRIEST WS, BETTMAN RB: Experimental coronary embolism. *Am J Med Sci* 171: 168, 1926
16. BING J, CASTELLANOS A, GRADEL E, et al: Experimental myocardial infarction: circulatory, biochemical and pathologic changes. *Am J Med Sci* 232: 533, 1956
17. LLUCH S, MOGUILJEVSKY HC, PIETRA G, et al: Reproducible model of cardiogenic shock in dog. *Circulation* 39: 205, 1969
18. SALAZAR AE: Experimental myocardial infarction. Induction of coronary thrombosis in intact closed-chest dog. *Circ Res* 9: 1351, 1961
19. MURPHY SD, CHARRETTE EJ, LYNN RB: Experimental coronary artery thrombosis for production of cardiogenic shock. *Can J Surg* 13: 189, 1970
20. BECKER LC, FERREIRA R, THOMAS M: Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. *Cardiovasc Res* 7: 391, 1973
21. JENNINGS RB, SOMMERS HM, SMYTH GA, et al: Myocardial necrosis induced by temporary occlusion of coronary artery in dog. *Arch Pathol* 70: 68, 1960
22. LIEDKE AJ, HUGHES HC, NEELY JR: Experimental model for studying myocardial ischemia. Correlation of hemodynamic performance and metabolism in working swine heart *J Thorac Cardiovasc Surg* 69: 203, 1975
23. SCHEEL KW, BANET M, OTT C, et al: Quantitative approach to collateral and antegrade flows after coronary occlusion. *Am J Physiol* 222: 687, 1972
24. MOSHER P, ROSS J, MCFATE PA, et al: Control of coronary blood flow by autoregulatory mechanism. *Circ Res* 14: 250, 1964
25. KATZ AM: Effects of ischemia on contractile processes of heart muscle *Am J Cardiol* 32: 456, 1973

Acute Cardiac Failure: The Relation Between Coronary Flow and Oxygen Consumption*

W.J. KEON, MD, FRCS[C], Y. AKYUREKLI, MD, FRCS[C], G.C. TAICHMAN, PH D AND B. KORECKY, MD, PH D

In an initial study with dog hearts functioning in situ on total coronary bypass, we demonstrated that predetermined levels of reduced cardiac pump function could be achieved by reducing total coronary flow through changes in the perfusing pressure. In subsequent experiments, oxygen values were measured so that changes in myocardial aerobic consumption in response to brief (3 minute) alterations in coronary perfusing pressure could be determined as well. As a result significant linear correlations were found between coronary flow and myocardial oxygen availability ($r = 0.98$), oxygen extraction ($r = 0.49$) and oxygen consumption ($r = 0.92$). These changes in oxygen values paralleled those in cardiac function (stroke work, $r = 0.84$).

Au cours d'une étude initiale sur le coeur de chien in situ en dérivation coronarienne complète, nous avons démontré que des niveaux prédéterminés de fonction cardiaque diminuée pouvaient être obtenus en réduisant le débit coronarien total par des changements de la pression de perfusion. Dans des expériences subséquentes, les concentrations d'oxygène ont été mesurées de façon à ce que les changements de la consommation aérobique du myocarde en réponse à de brèves (3 minutes) altérations de la pression coronaire de perfusion puissent également être décrits. Comme résultat, des corrélations linéaires significatives ont été trouvées entre le débit coronarien et la disponibilité d'oxygène myocardique ($r = 0.98$), l'extraction d'oxygène ($r = 0.49$) et la consommation d'oxygène ($r = 0.92$). Ces changements dans les concentrations d'oxygène ont été parallèles à ceux de la fonction cardiaque (travail systolique, $r = 0.84$).

*From the University of Ottawa cardiac unit, Ottawa Civic Hospital, Ottawa, Ont.

Presented at the annual meeting of the Canadian Cardiovascular Society, Toronto, Ont., Oct. 19-22, 1977

Supported by the Ontario Heart Foundation

Reprint requests to: Dr. W.J. Keon, University of Ottawa cardiac unit, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ont. K1Y 4E9

In reviewing the literature on the regulation of coronary blood flow (CBF), Rubio and Berne¹ stated that several factors can influence the quantity of blood passing through the heart. A primary determinant, they noted, was myocardial oxygen consumption. Although it is generally accepted that coronary flow is highly responsive to conditions of myocardial oxygen demand under physiologic conditions, certain pathologic states may diminish this autoregulatory process so that CBF may become a critical determinant of cardiac pump function. Within the physiologic range of flow there is a lack of agreement on the determinant effects of coronary flow on cardiac pump function and myocardial oxygen consumption. In thoracotomized animals^{2,3} and isolated hearts⁴ decreases in coronary flow produced similar changes in cardiac work and oxygen consumption. However, both Ross and colleagues,⁵ using perfused hearts at a constant level of work, and Sarnoff and associates,⁶ using isolated supported hearts at controlled levels of activity, observed that alterations in flow did not alter myocardial oxygen consumption. In a previous report⁷ we demonstrated with dog hearts working in situ that there was a significant linear relation between changes in coronary flow and various hemodynamic indices of cardiac pump function. The present study was undertaken to define the changes in aerobic consumption associated with these induced hypodynamic states.

Methods

Short-term experiments were performed on male mongrel dogs (body weight, 23 to 47 kg). As previously described⁷ animals received premedication of atropine (0.4 mg, intramuscularly) and were anesthetized with sodium thiopental (20 mg/kg, intravenously). Tracheal intubation was performed and positive-pressure ventilation with a Harvard pump (Harvard Apparatus, Millis, MA) initiated. Animals were maintained at a surgical plane of anesthesia with a mixture of 30% nitrous oxide and 70% oxygen plus 0.25% to 0.75% halothane. Animal core tem-

perature was maintained between 35° and 37°C with a thermoregulating water blanket. As a precautionary measure against ventricular arrhythmias, all animals received a priming dose of lidocaine hydrochloride (70 mg) followed by continuous infusion (2 mg/min) throughout the experiment. The heart was exposed through the left fifth intercostal space and the pericardial sac opened and sutured to the walls of the thoracic wound in order to cradle the heart.

The major components of the coronary arterial circulation were isolated, after blunt dissection, with 2-0 silk ties. In our initial study,⁷ the left coronary system was perfused through cannulas introduced into the circumflex (CX) and left anterior descending (LAD) arteries at the distal end of the left main stem (Fig. 1a); in the present experiment the technique was modified to perfuse the initial branches of the left main coronary artery as well.⁸ The CX artery was cannulated proximally and distally at a point 3 to 5 cm from its origin, and the left main coronary artery was isolated at its aortic origin with 3-0 silk. By occluding the left main stem and perfusing the proximal CX artery, we perfused all initial branches of the left main stem (septal artery) plus the LAD artery; through the distal cannula on the CX branch we were able to perfuse the remaining portion of the CX artery (Fig. 1b). The right coronary (RC) artery was perfused from a catheter introduced at its aortic origin.

During these experiments various hemodynamic variables were monitored. Heart rate was computed from the electrocardiographic (lead II) signal. Arterial (systolic, diastolic and mean) and left ventricular (systolic and diastolic) pressures were measured from fluid-filled catheters (Cordis, no. 521-742, Cordis Corporation, Miami, FL) in conjunction with Statham P23Db transducers (Statham Instruments, Oxnard, CA) and Electronics for Medicine SGM-2 amplifiers (Electronics for Medicine, White Plains, NY). Right and left mean atrial pressures were determined by direct cannulation and water manometry. All pressures were referenced to the level of the right

atrium. Flow through the pulmonary artery (cardiac output) was measured periodically by means of a thermodilution technique using a Swan-Ganz catheter (no. 93-118-7F, Edwards Laboratory, Santa Ana, CA) in conjunction with an Edwards computer (model 9510). Coronary flows were measured by three extracorporeal electromagnetic flow probes (Biotronex BLC-2032, Biotronex Laboratories, Silver Spring, MD) in series with perfusing Travenol 5M0287 cannulas (Travenol Laboratories, Deerfield, IL). At the end of each experiment, flow probes were calibrated by means of timed samples. In deriving total CBF, blood flows to all three vessels (LAD, CX and RC) were added together and normalized per 100 g of ventricular weight measured

at the completion of the experiment. In analysing these hemodynamic data, electronic signals were either recorded directly on a Beckman S-11 dynograph (Beckman Instruments Inc., Schiller Park, IL), or stored on Bell and Howell VR-3200 magnetic tape (Bell and Howell, Pasadena, CA) for later processing. Myocardial aerobic data were obtained by measuring the uptake of oxygen across the coronary circulation. Accordingly, arterial (extracorporeal) and coronary sinus blood samples were drawn and analysed for their oxygen content ($[O]_A$ and $[O]_{CS}$, respectively) with a Lexington analyser (LEX-O₂-CON-TL, Lexington Instruments, Waltham, MA). These data, in combination with CBF values, were then used to compute

1. myocardial oxygen availability (mL/min·100 g) = $(CBF)([O]_A)/(100)$;
2. myocardial oxygen extraction (%) = $([O]_A - [O]_{CS})(100)/([O]_A)$;
3. myocardial oxygen consumption (mL/min·100 g) = $(CBF)([O]_A - [O]_{CS})/(100)$.

The extracorporeal circuit was primed with heparinized (3 mg/kg) citrated whole blood from donor dogs and Hartmann's solution in a 1:1 ratio. During coronary bypass, venous blood was collected from both femoral veins into a reservoir whose height regulated the venous pressure (9 to 16 cm H₂O). This blood was then oxygenated and heated to body temperature (37°C) by a Harvey H-200 oxygenator (W. Harvey Research Corp., Santa Ana, CA). Arterialized blood was then pumped to a second reservoir, which subsequently drained into the three coronary perfusing catheters. Flows to the coronary arteries were established on the basis of the height of this reservoir above the left atrium. To minimize the systemic hypotensive states encountered during coronary artery cannulation, the extracorporeal system was equipped with a partial bypass. This circuit was used only during the initial phases of coronary bypass and was discontinued early during the stabilization period. In addition, excessive left ventricular pressures were avoided by cannulating the left atrium with a wide-bore catheter in conjunction with the pressure reservoir. Adjustments were made in the reservoir height so that the left intra-atrial pressure would not exceed 30 cm H₂O.

Once coronary perfusion was established, animals were allowed to stabilize for at least 60 minutes at a coronary perfusing pressure (CPP) of 120 mm Hg. During this period the plateau of the Frank-Starling curve (myocardial heterometric relation) was established by adjusting the venous pressure until arterial pressure and cardiac output were maximal. Once the desired level

was achieved, no further alterations were made throughout the experiment. Towards the end of the stabilization period, two sets of biochemical and hemodynamic values were obtained, 15 minutes apart. If values were consistent, both sets of data were averaged and used as control values for all subsequent maneuvers; if not, additional time was allocated for stabilization.

Arterial blood-gas samples were analysed periodically for pH and oxygen and carbon dioxide pressures (P_{O₂} and P_{CO₂}) by means of a Radiometer BMS-3 analyser (Radiometer, Copenhagen, Denmark) and appropriate adjustments were made to the animal or to the extracorporeal circuit by altering the inspiratory content of carbon dioxide or by the administration of 10% sodium bicarbonate. Arterial blood values from animal sources ranged from 7.33 to 7.47 for pH, 93 to 146 mm Hg for P_{O₂} and 28 to 36 mm Hg for P_{CO₂}, while arterialized blood from extracorporeal sources ranged from 7.37 to 7.43 for pH, 83 to 136 mm Hg for P_{O₂} and 32 to 48 mm Hg for P_{CO₂}.

In these experiments nine dogs were used to investigate myocardial oxygen consumption at various rates of reduced CBF. Accordingly, brief (3 minute) reductions in CPP were used to reduce CBF. At the end of this period hemodynamic and oxygen values were ascertained, after which the CPP was returned to 120 mm Hg. In all, eight different hypotensive pressures were examined from 110 mm Hg to 40 mm Hg in a randomized fashion. Between these hypotensive periods the animals were allowed to recover for 10 minutes; if at the end of this period control hemodynamics ($\pm 10\%$) were not re-established, the data from these animals were excluded from further analysis.

Results

Since the dogs in this experiment were cannulated in a different manner from that previously described,⁷ two were monitored for a 5-hour period (starting 10 minutes after cannulation) at a constant CPP of 120 mm Hg (Fig. 2). During the stabilization period flows to all coronary vessels slowly declined until a steady state was reached, with the exception of RC flow which continued to decrease throughout the observation period. However, RC flow represented the smallest component of the total CBF. The reduction and developing steady state conditions seen in the coronary flows paralleled changes in myocardial oxygen consumption, while systemic hemodynamic values quickly recovered after cannulation and remained relatively unchanged (range, -17% to +8%). Hemodynamic values obtained towards the end of the stabi-

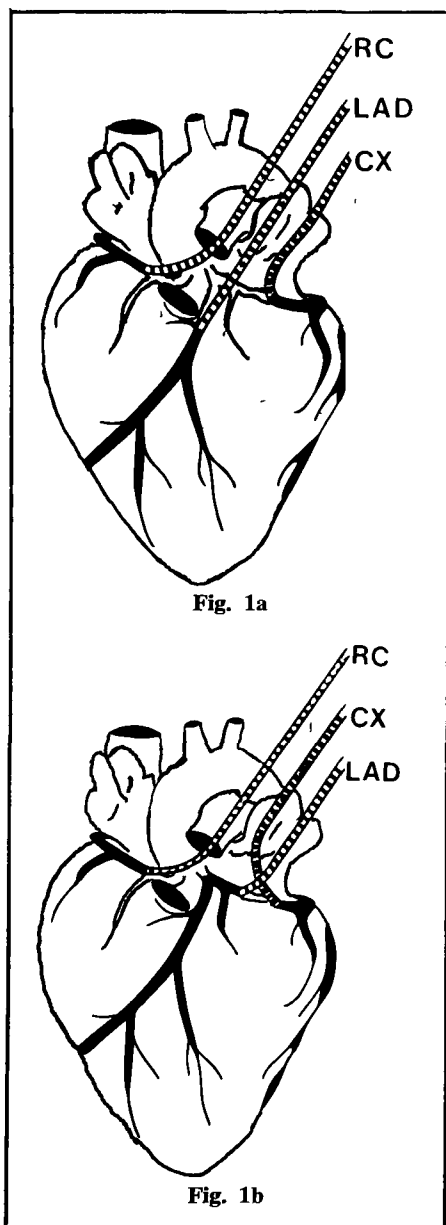


FIG. 1—(a) Initial method of cannulating and perfusing coronary vasculature.⁷ (b) Current method, left main coronary stem ligated. LAD = left anterior descending, CX = circumflex, RC = right coronary.

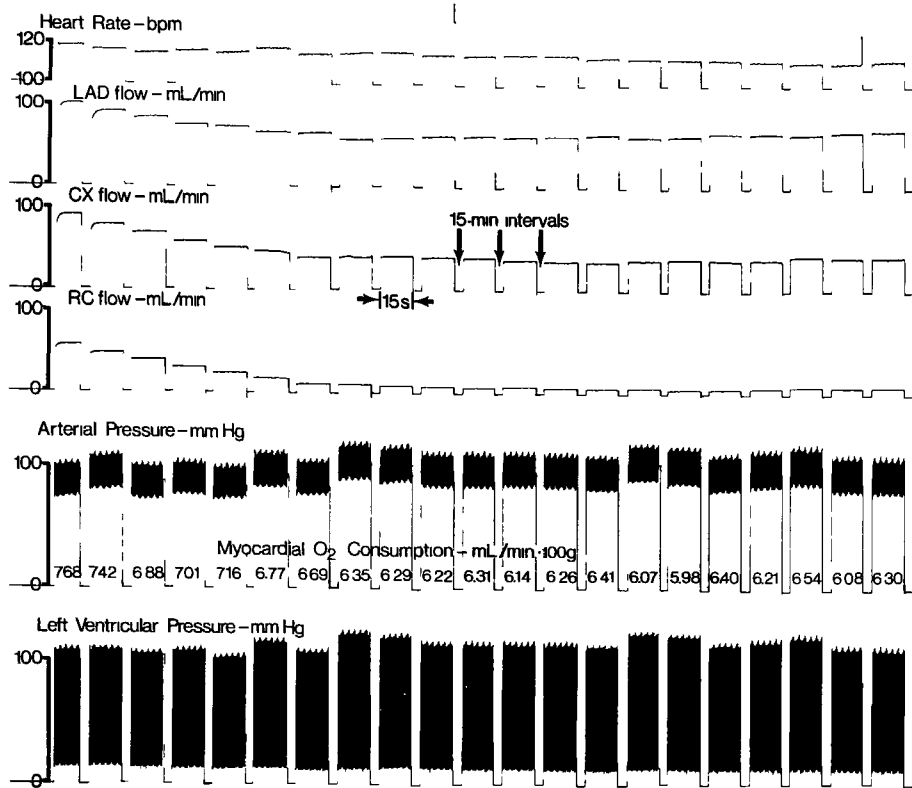


FIG. 2—Coronary flows and hemodynamic data from one dog in control study. Records were started 10 minutes after coronary perfusion was established.

lization period (control) are presented in Table I for the 11 animals in this study. The results are in agreement with those previously reported. Brief (3 minute) reductions in CPP evoked similar reductions in CBF (Fig. 3), of approximately equal magnitude (a 71% ± 3% reduction in CBF resulted from a 67% decrease in CPP). Fig. 4 demonstrates that the decrease in total CBF was

sustained equally by all three components of the coronary circulation (based on our current method of cannulation and perfusing the heart). Fig. 4 also demonstrates that most coronary flows at all levels of CPP were predominantly left coronary (LAD and CX) in origin. As a result of sharp reductions in CBF, myocardial oxygen availability decreased (Fig. 5) with a

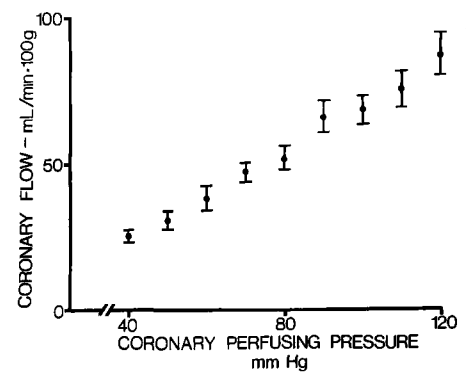


FIG. 3—Pressure-flow relation.

significant degree of linear correlation ($r = 0.98$). The decrease in CBF caused the heart to extract more oxygen from its limited supply (Fig. 6). Although the correlation coefficient for CBF versus oxygen extraction was low ($r = 0.49$), the value was significant and can be attributed to a large variation between different animals, since individual trends for each animal (Fig. 7) demonstrated similar inverse relations. In addition, the magnitude of the change in oxygen extraction was considerable: at the lowest CPP (40 mm Hg) the value had increased to $79\% \pm 3\%$ from $59\% \pm 6\%$ at a CPP of 120 mm Hg. In spite of this compensatory change in the ability of the heart to extract more oxygen, myocardial oxygen consumption decreased in a linear fashion ($r = 0.92$) with blood flow (Fig. 8); however, the magnitude of the decrease ($-71\% \pm 3\%$) was greater than the reduction in oxygen consumed ($-60\% \pm 3\%$). The net result of these changes, whereby a significant linear correlation ($r = 0.84$) was established between CBF and myocardial pump function (expressed as cardiac work), is shown in Fig. 9.

Table I—Hemodynamic Data in 11 Dogs*

Variable	Measurement
Heart rate, beats/min	127 ± 15
Pressures	
Arterial — mean, mm Hg	119 ± 8
systolic, mm Hg	131 ± 10
diastolic, mm Hg	97 ± 9
Right atrial, cm H ₂ O	13 ± 3
Left atrial, cm H ₂ O	23 ± 6
Left ventricular end-diastolic, mm Hg	19 ± 4
Maximum rate of left ventricular pressure (max dP/dt), mm Hg/s	2204 ± 184
Flows	
Cardiac index, mL/min·kg	140 ± 29
Coronary flow, mL/min·100 g	94 ± 13
% left anterior descending artery	44 ± 3
% circumflex artery	38 ± 3
% right coronary artery	18 ± 2
Left/right ratio	4.51 ± 0.49
Stroke work, kg-m/min	5.1 ± 0.4
Hemoglobin, g/dL	10.9 ± 0.3
Oxygen values	
Arterial content, mL/dL	14.4 ± 1.6
Coronary sinus content, mL/dL	6.3 ± 0.4
Myocardial availability, mL/min·100 g	14.8 ± 2.0
Myocardial extraction, %	59 ± 6
Myocardial consumption, mL/min·100 g	8.7 ± 0.9

*All values (mean ± SEM) were taken at end of stabilization period (control values).

Discussion

In these studies, the major problem of electrical instability, which was evident in our initial report,⁷ was overcome by modifying three aspects of the animal model: first, an alternative method of cannulating the left coronary artery was used; second, left atrial pressure was partially regulated; and third, lidocaine hydrochloride was infused continuously. Previously, the left coronary circulation was perfused from extracorporeal sources distal to the main stem. In an effort to assess the effectiveness of this type of cannulation (Fig. 1a), radioactive-labelled (ytterbium-169) microspheres, $15\mu \pm 5\mu$ in diameter, were introduced into the coronary reservoir and the distribution was measured.⁹ In three animals cannulated as in Fig. 1a and perfused at a CPP of 120 mm Hg, $78\% \pm 9\%$ of the nutritive flow originated from extracorporeal sources (unpublished

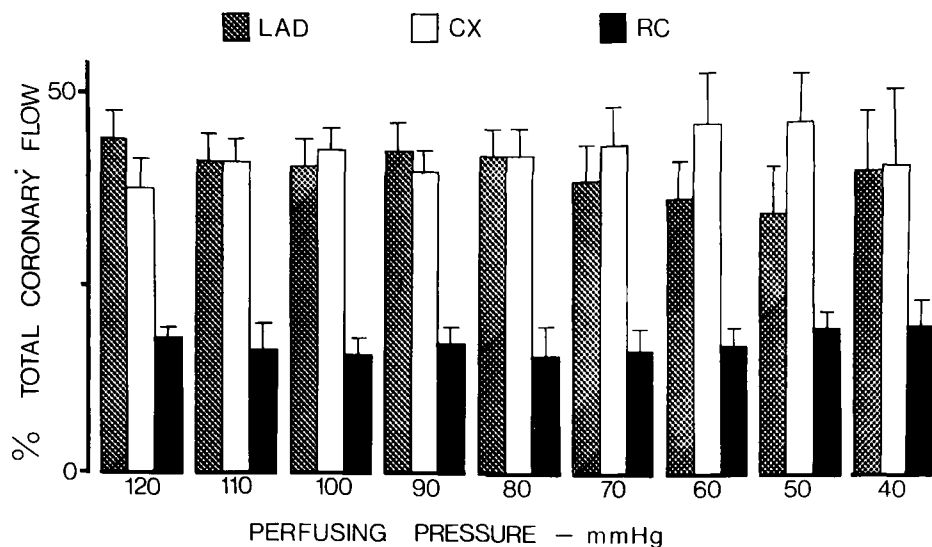


FIG. 4—Distribution of coronary blood flow (CBF) as function of perfusing pressure.

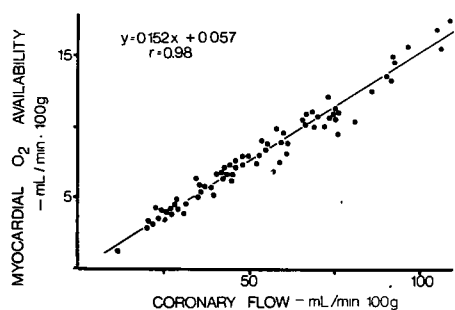


FIG. 5—Relation between myocardial oxygen availability and total CBF.

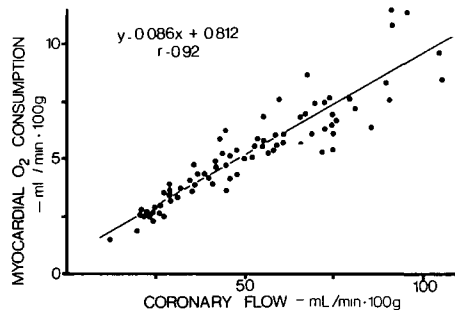


FIG. 8—Relation between myocardial oxygen consumption and total CBF.

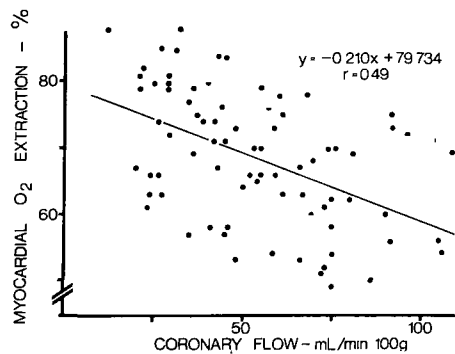


FIG. 6—Relation between myocardial oxygen extraction and total CBF.

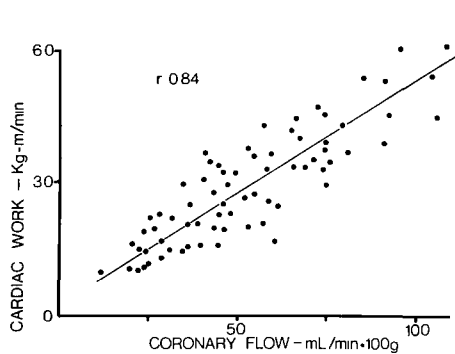


FIG. 9—Relation between cardiac work and total CBF.

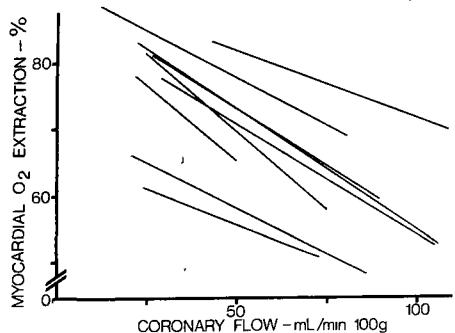


FIG. 7—Relation between myocardial oxygen extraction and total CBF. Each line is a linear regression line for each animal.

data), while the remaining parts of the heart presumably either were not perfused at all or were perfused from the aortic root. In the dog, the left coronary artery carries the largest portion of the total supply¹⁰ and usually arises from the aortic root as a single vessel, although double openings are occasionally present (12%). The main stem of the left coronary artery is usually short and soon divides into LAD and CX branches. In 83% of the animals studied, the septal artery arose from the posterior wall of the main stem to supply the basal portions of the inter-ventricular septum and part of the

free wall of the right ventricle.¹⁰ In our initial study,⁷ the septal artery was not perfused by the extracorporeal circuit; thus, during hypotensive episodes associated with coronary cannulation and the induction of bypass, myocardial areas perfused by the septal artery may have sustained longer periods of reduced flow. As a result, our initial model was susceptible to ventricular arrhythmias during either stabilization or the subsequent experimental period.

In the present study changes in coronary flow were induced by 3-minute alterations in CPP. Over the perfusing pressure range of 70 to 130 mm Hg Mosher and associates¹¹ have shown that coronary flow remains constant (autoregulates), while below and above this range coronary flow becomes pressure-dependent. Our results (Fig. 3) indicate that such a response could not be elicited; however, our earlier study⁷ demonstrated that longer periods (10 minutes) of reduced CPP were associated with a mild autoregulatory response. Part of the defect may be a result of the hemodilution imposed by the extracorporeal circuit, since changes in arterial oxygen by dilution¹² or desaturation¹³ may modify the response.

Our observations provide evidence that cardiac pump function as well as myocardial oxygen consumption can be greatly influenced by reductions in coronary flow. These observations on dog hearts working in situ agree with those of earlier studies^{2-4,13} and emphasize the range and linearity of the correlation. In the experiments reported by Opie¹⁴ and Bacaner, Liroy and Visscher¹⁵ the rate of oxygen delivery rather than changes in CBF were considered primarily responsible for the alterations in myocardial performance by eventually limiting myocardial aerobic consumption.^{4,5} In addition, other authors have shown that perfusing pressure¹⁵ and coronary flow¹⁶ can independently affect the inotropic state as well. On the other hand, Sarnoff and associates⁵ and Ross and colleagues⁵ have reported that CBF and myocardial oxygen consumption were not interrelated when external work was held constant; however, both studies have been criticized not only in terms of methodology³ but also interpretation of data.¹³ In the present study the primary mechanism responsible for decreases in cardiac pump function appears to be a reduction in myocardial oxygen consumption caused by a decrease in oxygen availability.

Myocardial ischemia is said to exist when coronary arterial flow proves insufficient to accommodate functional demands. Since over 90% of the energy normally produced by the consumption of substrates and oxygen is utilized to support mechanical activity,¹⁷ a substan-

tial reduction in oxygen consumption is primarily expressed as a decrease in mechanical activity. Although our results are in agreement with this hypothesis, current experiments¹⁸ indicate that the correlations between coronary flow and myocardial oxygen consumption, and pump function may be significantly altered during the period of recovery following prolonged ischemia.

We thank K. Sheldrick and the personnel of the department of research, Ottawa Civic Hospital, for their technical assistance.

References

1. RUBIO R, BERNE RM: Regulation of coronary blood flow. *Prog Cardiovasc Dis* 18: 105, 1975
2. BACANER M, CONNOLLY JE, BRUNS D, et al: The coronary blood flow as a critical determinant of cardiac performance and cardiac size. *Am J Med* 30: 392, 1961
3. DANIEL HB: Coronary flow alterations on myocardial contractility, oxygen extraction, and oxygen consumption. *Am J Physiol* 225: 1020, 1973
4. BACANER MB, LIOY F, VISSCHER MB: Induced change in heart metabolism as a primary determinant of cardiac performance. *Am J Physiol* 209: 519, 1965
5. ROSS J JR, KLOCHE F, KAISER G, et al: Effect of alterations of coronary blood flow on the oxygen consumption of the working heart. *Circ Res* 13: 510, 1963
6. SARNOFF SJ, GILMORE JP, SKINNER NJ JR, et al: Relation between coronary blood flow and myocardial oxygen consumption. *Ibid*, p 514
7. KEON WJ, TAICHMAN GC, AKYUREKLI Y, et al: Acute cardiac failure: the relation between coronary flow and cardiac function. *Can J Surg* 19: 531, 1976
8. BRUNSTING JR, VISSER KR, ZIJLSTRA WG: Simultaneous perfusion of both coronary arteries and drainage of the coronary sinus in the dog heart *in situ*. *Pflugers Arch* 356: 193, 1975
9. WARLTIER DC, HARDMAN HF, LADDU AR, et al: Myocardial distribution of coronary blood flow in the isolated supported heart preparation. *Cardiovasc Res* 9: 634, 1975
10. FEHN PA, HOWE BB, PENSINGER RP: Comparative anatomical studies of the coronary artery of canine and porcine hearts. II. Interventricular septum. *Acta Anat* 71: 223, 1938
11. MOSHER PA, ROSS J JR, MCFATE PA, et al: Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 14: 250, 1964
12. GREGG DE, GREEN HD: Effects of viscosity, ischemia, cardiac output and aortic pressure on coronary blood flow measured under a constant perfusion pressure. *Am J Physiol* 130: 108, 1940
13. BACANER MB, LIOY F, VISSCHER MB: Coronary blood flow, oxygen delivery rate and cardiac performance. *J Physiol (Lond)* 216: 111, 1971
14. OPIE LH: Coronary flow rate and perfusion pressure as determinants of mechanical function and oxidative metabolism of the isolated perfused rat heart. *J Physiol (Lond)* 180: 529, 1965
15. WEISFELDT ML, SHOCK NW: Effect of perfusing pressure on coronary flow and oxygen usage of nonworking heart. *Am J Physiol* 218: 95, 1970
16. FISHER VJ, MARTINO RA, HARRIS RS, et al: Coronary flow as an independent determinant of myocardial contractile force. *Am J Physiol* 217: 1127, 1969
17. SARNOFF SJ, BRAUNWALD E, WELCH GH JR, et al: Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 192: 148, 1958
18. AKYUREKLI Y, KEON WJ, TAICHMAN GC, et al: Recovery from acute reductions in coronary supply. Paper presented at the annual meeting of the Canadian Cardiovascular Society, Toronto, Ont., Oct. 19-22, 1977

Effectiveness of Intra-aortic Balloon Counterpulsation on Systolic Unloading

Y. AKYUREKLI, MD, FRCS[C], G.C. TAICHMAN, PH D AND W.J. KEON, MD, FRCS[C]

The therapeutic benefit of intra-aortic balloon pumping (IABP) is believed to result from the combined action of reducing myocardial demand (systolic unloading) while improving myocardial supply (diastolic augmentation). However, the relative importance of these aspects has not been fully understood. Accordingly, the systolic unloading responses to IABP were studied in 13 dogs on total coronary bypass. By perfusing the coronary circulation from an extracorporeal source at a controlled pressure the authors were able to analyse the systolic unloading responses without diastolic augmentation directly altering coronary flow. The results suggest that IABP is effective only in reducing myocardial demand at normotensive levels; IABP during hypotensive states did not assist the failing heart mechanically by systolic unloading. Therefore the therapeutic action of IABP must result from increases in coronary blood flow by diastolic augmentation.

On croit que les gains thérapeutiques de la contre-pulsion diastolique par ballonnet intra-aortique (CPBIA) résultent de l'action combinée d'une réduction de la demande myocardique (délestage systolique) et de l'amélioration de l'apport myocardique (augmentation diastolique). Toutefois, l'importance relative de ces aspects n'a pas été complètement élucidée. En conséquence, le délestage systolique en réponse à la CPBIA a été étudié chez 13 chiens sous pontage coronarien

From the University of Ottawa Cardiac Unit, Ottawa Civic Hospital, Ottawa, Ont.

Presented at the 32nd annual meeting of the Canadian Cardiovascular Society, Québec, PQ, Oct. 19, 1979

Supported by the Ontario Heart Foundation grant 5-1

Accepted for publication, Jan. 30, 1980

Reprint requests to: Dr. Y. Akyurekli, University of Ottawa Cardiac Unit, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ont. K1Y 4E9

complet. En perfusant la circulation coronarienne à partir d'une source extracorporelle à pression contrôlée, nous avons été capables d'analyser la réponse de délestage systolique sans que l'augmentation diastolique ne modifie directement le débit coronarien. Les résultats indiquent que la CPBIA n'est efficace qu'à réduire la demande myocardique à des niveaux de tension normale; la CPBIA durant les états hypotensifs ne soulagea pas mécaniquement le coeur défaillant par délestage systolique. L'action thérapeutique de la CPBIA doit donc résulter d'une augmentation du débit sanguin coronarien par augmentation diastolique.

Intra-aortic balloon pumping (IABP) for the treatment of cardiogenic shock was introduced in 1962 by Mouloupoulos, Topaz and Kolff¹ and popularized in 1968 by Kantrowitz and associates.² Since then, the indications for its use have been extended to include a wide variety of clinical situations requiring temporary circulatory support.^{3,4}

In spite of the overwhelming clinical evidence of the beneficial effects of IABP, the underlying mechanisms have not been clearly resolved.^{5,6} In theory, the beneficial effects of counterpulsation are achieved by the active synchronous displacement of aortic blood during the cardiac cycle which reduces left ventricular work (systolic unloading) and increases coronary flow (diastolic augmentation). Although both features would assist the failing heart, the presence and relative effects of either aspect during IABP have not been appreciated. The purpose of this study was to determine the systolic unloading effects of IABP independent of diastolic augmentation. This was accomplished by counterpulsating dogs while their coronary arteries were perfused from an extracorporeal source.

Methods

Short-term experiments were performed on 13 mongrel dogs ranging

in weight from 22 to 31 kg. Each animal was premedicated with atropine (0.4 mg, intramuscularly) and anesthetized with an intravenous injection of sodium thiopental (20 mg/kg). The trachea was intubated and positive-pressure ventilation (Harvard Apparatus Corp., Millis, Mass.) initiated. Throughout the remainder of the experiment, a surgical plane of anesthesia was maintained with a mixture of 30% nitrous oxide and 70% oxygen plus 0.25% to 0.75% halothane. As a precautionary measure against ventricular arrhythmias, lidocaine hydrochloride was administered intravenously as a priming bolus (70 mg) followed by a continuous infusion (2 mg/min).

The surgical procedure for total coronary bypass has been reported previously.^{7,8} The heart was exposed through the left fifth intercostal space. The three main coronary vessels were cannulated close to their aortic origins and perfused with arterialized blood at a controlled pressure while the remainder of the systemic circulation was left intact. The right atrial pressure was maintained within a limited range (7 to 11 cm H₂O) by means of a pressure-regulated system. The extracorporeal circuit was primed with a mixture of heparinized citrated whole blood from donor dogs and lactated Ringer's solution in a 1:1 ratio. During coronary bypass, venous blood was collected from the femoral veins and passed through a bubble oxygenator (W. Harvey Research Corp., Santa Ana, Calif.). The pH, oxygen pressure and carbon dioxide pressure of the oxygenated blood ranged from 7.36 to 7.42, 91 to 146 mm Hg and 32 to 46 mm Hg, respectively. The blood was then heated (35° to 38°C) and pumped to a perfusion reservoir which subsequently drained into the three coronary perfusion catheters. The driving pressure of the system was regulated by adjusting the height of the perfusion reservoir above the heart.

Of the 13 animals studied, 3 were counterpulsated with a 12-ml capacity single-segment intra-aortic balloon while in the remaining 10 a 20-ml

triple-segment balloon was inserted. The balloon (AVCO-Roche, Cranbury, NJ) was passed into the left femoral artery and positioned just distal to the origin of the left subclavian artery. It was inflated by a helium-driven pumping system (AVCO IABP-7, AVCO-Roche) triggered by the R-wave of the electrocardiogram and synchronized to inflate at the closing of the aortic valve and to vent to atmospheric pressure immediately before the left ventricular ejection. The timing and duration of balloon inflation were adjusted to produce maximum augmentation of diastolic aortic pressure measured proximal to the balloon.

During the experiments heart rate was computed from the electrocardiographic signal (lead II). Central aortic (systolic, diastolic and mean), left ventricular (systolic and diastolic) and mean pulmonary artery pressures were measured from fluid-filled catheters in conjunction with Statham P23Db transducers (Statham Instruments, Oxnard, Calif.) and Electronics for Medicine SGM-2 amplifiers (Electronics

for Medicine, White Plains, NY). Right and left mean atrial pressures were measured by direct cannulation and water manometry. All pressures were referenced to the level of the right atrium. Flow through the pulmonary artery (cardiac output) was measured periodically by a thermodilution technique using a Swan-Ganz catheter (model 93-118-7F, Edwards Laboratory, Santa Ana, Calif.) in conjunction with an Edwards computer (model 9510). Cardiac work was calculated as the product of cardiac output and mean ventricular ejection pressure. Coronary flows were measured by three electromagnetic flow probes (Biotronex Laboratory, Inc., Silver Spring, Md.) which were placed in series with the perfusion cannulas. Relative myocardial blood flow was derived by adding the flows from all three coronary vessels together and normalizing the value per 100 g of ventricular weight.

Myocardial oxygen data were obtained by measuring the uptake across the coronary circulation; arterial (extracorporeal) and coronary sinus blood

samples were drawn anaerobically and analysed for their oxygen content with an oxygen analyser (Lexington Instruments, Waltham, Mass.). These data in combination with myocardial flow values were used to compute myocardial oxygen extraction and consumption according to formulas outlined previously.⁷

At the end of the operation, the animal was stabilized for at least 60 minutes at a coronary perfusion pressure of 120 mm Hg. During this period the plateau of the Frank-Starling curve was estimated by adjusting the venous pressure until the arterial pressure and cardiac output were at their maximum levels. Once this was achieved, no further adjustments were made in the height of the venous reservoir.

At the end of the stabilization period, the effects of IABP without direct augmentation of coronary flow were studied at various coronary perfusion pressures. The perfusion pressure was reduced from 120 mm Hg to a lower level (80, 70, 60, or 50 mm Hg) for 20 minutes. During the first 10 min-

Table I—A Summary of the Hemodynamic and Metabolic Values (mean \pm SEM) Measured before (Con) and after Intra-aortic Balloon Pumping (IABP) at Four Reduced Coronary Perfusion Pressures*

	Coronary perfusion pressure, mm Hg									
	120 (n = 13)		80 (n = 8)		70 (n = 8)		60 (n = 9)		50 (n = 6)	
	Con	IABP	Con	IABP	Con	IABP	Con	IABP	Con	IABP
Heart rate, beats/min	123 ± 4	122 ± 6	125 ± 7	115 ± 6	121 ± 6	129 ± 4	133 ± 5	131 ± 6	131 ± 3	
Cardiac index, ml/min \cdot kg	90.8 ± 11.3	65.3 ± 13.2	70.0 ± 19.3	63.0 ± 12.4	57.3 ± 11.7	37.0 ± 3.0	36.2 ± 3.3	25.7 ± 3.4	24.6 ± 2.9	
Right atrial pressure, cm H ₂ O	8.8 ± 0.6	7.6 ± 0.8	7.4 ± 0.8	10.3 ± 0.7	9.9 ± 0.8	7.8 ± 0.9	7.9 ± 0.8	9.1 ± 0.8	9.3 ± 0.7	
Left atrial pressure, cm H ₂ O	15.6 ± 1.0	13.1 ± 1.0	12.9 ± 0.6	18.5 ± 1.6	20.8 ± 2.5	16.9 ± 2.1	18.1 ± 3.0	19.7 ± 1.9	18.8 ± 2.1	
Pulmonary mean pressure, mm Hg	20.0 ± 0.7	18.1 ± 1.2	17.6 ± 1.0	20.4 ± 1.0	22.7 ± 1.3	19.5 ± 1.7	21.8 ± 2.4	19.2 ± 2.2	19.5 ± 1.6	
Left ventricular diastolic pressure, mm Hg	15.6 ± 1.4	13.9 ± 1.2	11.9 ± 1.1	16.9 ± 2.1	17.0 ± 2.0	16.8 ± 2.0	16.6 ± 2.7	19.7 ± 2.4	16.5 ± 2.7	
Left ventricular systolic pressure, mm Hg	123.2 ± 5.8	105.3 ± 5.6	99.0 ± 6.4	101.4 ± 4.0	104.0 ± 3.2	80.0 ± 3.4	77.0 ± 3.6	63.0 ± 3.9	63.3 ± 4.2	
Aortic systolic pressure, mm Hg	123.6 ± 6.1	107.0 ± 7.0	102.4 ± 7.1	106.3 ± 4.6	107.1 ± 4.1	79.1 ± 3.8	77.1 ± 4.4	62.7 ± 5.5	61.5 ± 4.1	
Aortic mean pressure, mm Hg	106.6 ± 4.3	90.8 ± 4.7	96.0 ± 6.0	87.4 ± 4.2	97.0 ± 3.7	66.8 ± 3.8	73.4 ± 4.0	52.8 ± 4.8	57.3 ± 4.5	
Aortic diastolic pressure, mm Hg	92.9 ± 3.4	83.0 ± 3.7	107.3 ± 7.6	75.1 ± 4.2	108.7 ± 5.0	59.5 ± 3.0	81.0 ± 4.9	45.7 ± 4.9	64.8 ± 5.2	
Myocardial blood flow, ml/min \cdot 100 g	85.5 ± 4.8	59.4 ± 2.3	54.9 ± 1.6	56.1 ± 4.0	53.5 ± 2.9	38.7 ± 1.5	40.4 ± 1.3	36.2 ± 2.4	37.0 ± 2.7	
Left anterior descending-septal artery, % of coronary flow	46.5 ± 1.2	48.9 ± 1.8	50.0 ± 2.9	46.8 ± 1.3	46.3 ± 1.5	49.8 ± 1.9	48.6 ± 2.4	44.8 ± 3.6	43.5 ± 3.8	
Circumflex artery, % of coronary flow	36.5 ± 1.2	37.0 ± 1.8	37.8 ± 2.4	36.0 ± 1.0	35.6 ± 1.2	38.0 ± 2.1	36.7 ± 3.0	35.5 ± 3.7	35.3 ± 3.7	
Right coronary artery, % of coronary flow	16.9 ± 1.1	14.0 ± 1.0	12.0 ± 0.5	17.3 ± 0.9	18.1 ± 1.3	12.8 ± 1.4	14.8 ± 2.1	19.5 ± 4.3	21.2 ± 5.2	
Myocardial oxygen extraction, %	61.5 ± 2.4	67.5 ± 3.2	67.6 ± 3.4	73.0 ± 2.3	73.0 ± 1.4	78.7 ± 2.0	80.3 ± 2.1	84.7 ± 1.9	82.5 ± 2.1	
Myocardial oxygen consumption, ml/min \cdot 100 g	8.35 ± 0.43	6.25 ± 0.40	5.91 ± 0.37	6.40 ± 0.27	6.13 ± 0.30	5.06 ± 0.26	5.32 ± 0.16	4.83 ± 0.41	4.83 ± 0.41	

*Values in the first column were measured after stabilization at a coronary perfusion pressure of 120 mm Hg.

†Significant changes, $P < 0.05$.

utes of coronary hypotension, the intra-aortic balloon remained inactive; counterpulsation was instituted during the final 10 minutes. Data were collected before and after IABP. The coronary perfusion pressure was then returned to 120 mm Hg for 20 minutes of recovery followed by additional hypotensive episodes at different perfusion pressures. All four hypotensive pressures were attempted in each dog; however, if control levels (measured at 120 mm Hg) could not be re-established after 20 minutes of recovery, the experiment was discontinued. Hemodynamic and metabolic responses between control and counterpulsated states at each hypotensive level were statistically evaluated by means of the paired Student's *t*-test; differences were considered significant at $P < 0.05$.

Results

In our experiment, 13 animal preparations required 82 ± 18 minutes (mean \pm SEM) to stabilize at a coronary perfusion pressure of 120 mm Hg. At the end of this period, various hemodynamic and oxygen meas-

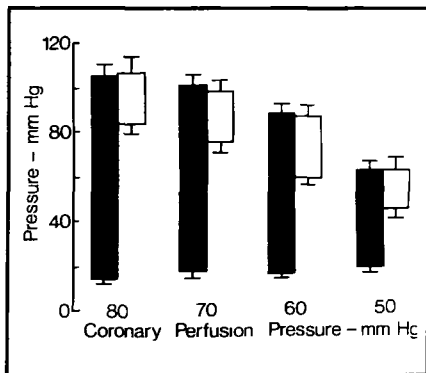


FIG. 1—Left ventricular (black bar) and aortic (white bar) intravascular pressures (systolic and diastolic) as function of four coronary perfusion pressures.

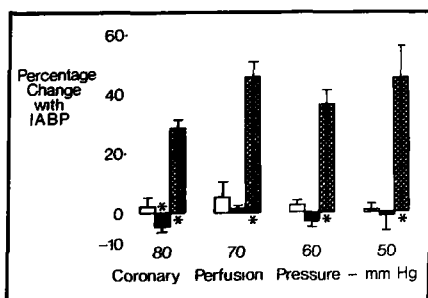


FIG. 2—Relative changes (%) in heart rate (white) and aortic systolic (black) and diastolic (dotted) pressures with intra-aortic balloon pumping (IABP) at four different coronary perfusion pressures. Asterisks above or below bars indicate significant alterations ($P < 0.05$).

urements were noted (Table I). When the perfusion pressure was temporarily reduced, coronary flow decreased and left ventricular power failure ensued (Table I, Fig. 1). Although the lower limits of normotensive pressures were measured at perfusion pressures of 80 and 70 mm Hg, further reductions to 60 and 50 mm Hg produced progressive degrees of systemic hypotension (Table I, Fig. 1). Severe reduction in coronary flow led to an increase in myocardial oxygen extraction; however, this increase was insufficient to maintain the oxygen consumption which subsequently dropped as the perfusion pressure was reduced (Table I). Although the total myocardial blood flow became severely reduced as the perfusion pressure was diminished, the flow distribution to the three main coronary vessels did not change significantly (Table I). When the average flows in the left anterior descending-septal, circumflex and right coronary arteries were measured at the four reduced perfusion pressures, the proportions (47%, 37% and 16%, respectively) relative to the total flow did not differ significantly from those at a driving pressure of 120 mm Hg.

When IABP was attempted in these animals on total coronary bypass no unusual problems were encountered. The central aortic pulse pressure clearly monitored the operation of the balloon. Diastolic pressures were significantly augmented ($P < 0.05$) by $28 \pm 4\%$, $46 \pm 5\%$, $36 \pm 5\%$ and $46 \pm 11\%$ above the unassisted levels at coronary perfusion pressures of 80, 70, 60 and 50 mm Hg, respectively (Table I, Fig. 2). Likewise, mean aortic pressure also increased during periods of IABP but to a lesser degree (Table I). Evidence of systolic unloading with IABP was seen only at a coronary perfusion pressure of 80 mm Hg. At this pressure, IABP significantly ($P < 0.05$)

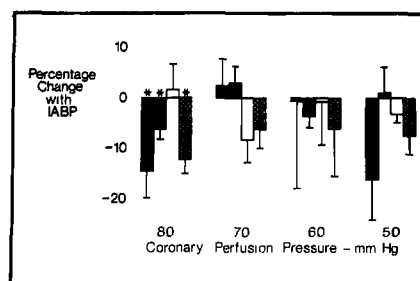


FIG. 3—Relative changes (%) in left ventricular end-diastolic (shaded) and systolic (black) pressures, cardiac index (white) and left ventricular work (dotted) with IABP at four different coronary perfusion pressures. Asterisks above bars indicate significant alterations ($P < 0.05$).

reduced systolic pressures in both the left ventricle and aorta by $6 \pm 2\%$ (Fig. 2) and $4 \pm 2\%$ (Fig. 3) respectively and left ventricular end-diastolic pressure by $14 \pm 5\%$ (Fig. 3); however, the cardiac index remained unchanged. When estimates of the combined action of left ventricular pressure and flow were calculated, cardiac work was significantly ($P < 0.05$) reduced by $12 \pm 3\%$ (Fig. 3) after 10 minutes of IABP. At all lower perfusion pressures (70, 60 and 50 mm Hg), the application of IABP did not alleviate depressed cardiac performance (Table I, Figs. 2 and 3). The uptake and consumption of oxygen were not significantly altered by the application of IABP to hypotensive animals on total coronary bypass. At all perfusion pressures, myocardial oxygen extraction and consumption were unaffected by IABP (Fig. 4). Similarly, the distribution of myocardial flow to the three main coronary arteries was not significantly altered by counterpulsation (Table I).

Discussion

The therapeutic action of arterial counterpulsation as applied by IABP is generally believed to result from the combined effects of increasing coronary supply while reducing myocardial demand.^{3,4}

Coronary supply occurs primarily during cardiac diastole, when the coronary vasculature autoregulates the flow depending on the myocardial demand.^{9,10} During ischemia the coronary vessels dilate so that coronary flow becomes primarily pressure dependent.¹⁰ One of the main effects of IABP is to elevate the diastolic pressure in the aorta and the coronary arterial bed, thus increasing the blood flow to the ischemic myocardium, hence the term diastolic augmentation.

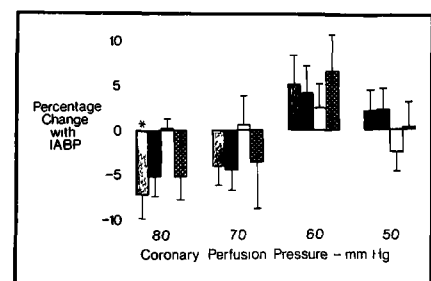


FIG. 4—Relative changes (%) in coronary flow (shaded) and myocardial oxygen availability (black), extraction (white), and consumption (dotted) with IABP at four different coronary perfusion pressures. Asterisk above bar indicates significant change ($P < 0.05$).

Increases in coronary blood flow ranging from 7% to 50% with IABP have been demonstrated in a number of experiments,¹¹⁻¹³ although other authors¹⁴ have been unable to demonstrate any significant change. In the experiments described by Powell and associates,⁵ IABP in hypotensive animals augmented coronary flow while the same procedure performed on normotensive animals did not significantly alter the flow; this was subsequently confirmed by Weber and Janicki.¹⁵ Others¹⁶⁻¹⁹ have shown that coronary sinus flow is increased by 5% to 100%. Gill and associates,²⁰ using radioactive microspheres, found that IABP in hypotensive animals increased subendocardial and transmural blood flow within the ischemic areas while Shaw, Taylor and Pitt²¹ using a similar technique found no increase in collateral blood flow to ischemic areas.

As well as increasing coronary perfusion pressure, IABP is said to be capable of reducing left ventricular work.^{22,23} Balloon deflation just before ventricular ejection produces an appreciable negative intra-aortic pressure effect which should improve the emptying of the left ventricle (systolic unloading). Some¹⁷ have obtained increases in cardiac output of 15% to 50% by this method, although others^{18,24} have been unable to demonstrate an unloading response. As a means of reducing myocardial demand, numerous studies^{2,15,19,23} have shown that IABP can decrease left ventricular systolic pressure by 4% to 20%, but others^{6,24} have been unable to demonstrate this response. Urschel and colleagues²⁵ and Weber, Janicki and Walker²⁶ calculated the change in mean ejection impedance and reported a 10% to 21% reduction with IABP while Mueller and associates²⁷ demonstrated a 46% reduction in left ventricular ejection resistance. In addition to the reduction in left ventricular afterload, Weber and Janicki¹⁵ presented evidence demonstrating that IABP can reduce left ventricular end-diastolic pressure (preload) as well, thus reducing ventricular volume and intramural compression. Although balloon counterpulsation is dependent upon a number of physical factors such as balloon volume, placement, and the timing and duration of inflation and deflation,²⁸ optimal conditions have not always assured the combined therapeutic effects of systolic unloading and diastolic augmentation.^{3-6,24} Part of the problem may be that IABP affects two interrelated systems (coronary supply and coronary demand)

which cannot be separately investigated. Powell and his associates⁵ attempted such independent studies by counterpulsating experimental animals on right heart bypass while perfusing a coronary vessel at a constant rate. Although the results and conclusions were similar to those of the present study, only one part of the entire coronary circulation was perfused from an extracorporeal source and thus collateral supply could not be excluded.

In our animal preparation, the entire coronary circulation was isolated from the aortic supply and perfused from an extracorporeal source at known perfusion pressures.^{7,8} Under these conditions, IABP might produce both systolic unloading and diastolic augmentation; however, direct alterations of coronary flow were excluded from the increases in aortic diastolic pressure with IABP. Previous studies in the development of this experimental model have shown that normotensive systemic hemodynamic measurements could be estimated at normal coronary perfusion pressures. As the perfusion pressure was reduced, acute cardiac failure developed which remained relatively stable for extended periods.^{6,7} When IABP was applied to this animal preparation at different levels of left ventricular performance, systolic unloading was only evident at normotensive states (coronary perfusion pressure of 80 mm Hg), as shown by a reduction in left ventricular systolic and diastolic pressures and by a decrease in left ventricular work. Since augmented aortic diastolic pressure could not directly influence coronary perfusion the measured decrease in flow (Table I, Fig. 4) appears to be an autoregulatory response, since myocardial demand has decreased.⁹

During acute coronary insufficiency and subsequent left ventricular failure, IABP was not accompanied either by systolic unloading or by indirect changes in coronary flow and oxygen consumption. These results indicate that balloon unloading responses may be intimately related to the functional status of the circulatory system before IABP.^{5,6} For example, an increase in aortic compliance at lower aortic pressures reduces the accompanying changes in aortic volume.²⁸ Also, Tyberg's group⁶ have shown that a lower arterial pressure causes the aortic wall to move with the balloon so that changes in balloon volume do not accompany changes in aortic blood volume. Finally, reductions in ventri-

cular loading with IABP during severe hypotensive episodes may be secondary to increases in coronary flow which accompany increases in aortic diastolic pressure.^{5,6,11,12} Previous experiments with this coronary bypass model have clearly shown that coronary flow and myocardial function are closely related over a wide range of perfusion pressures.^{7,8} In normotensive states with a coronary perfusion pressure of 80 mm Hg, balloon deflation effectively unloaded the left ventricle which in turn caused coronary flow to decrease. This autoregulatory response, which had been previously inferred,^{5,6,11,12,29} could not be measured directly without isolated coronary perfusion as outlined in our current study.

Under normotensive conditions, IABP can effectively reduce myocardial demand by systolic unloading. In contrast, IABP in hypotensive states is unable to reduce myocardial demand. Thus, the main therapeutic action of IABP to the compromised heart is achieved by increasing coronary flow through augmentation of the aortic diastolic pressure rather than by systolic unloading.

We thank Mr. K. Sheldrick and Mrs. V. Temple for their technical assistance and Mrs. E. Masson for her help in preparing the manuscript.

References

1. MOULOPOULOS SD, TOPAZ S, KOLFF WJ: Diastolic balloon pumping (with carbon dioxide) in the aorta—mechanical assistance to the failing circulation. *Am Heart J* 63: 669, 1962
2. KANTROWITZ A, TJONNELAND S, KRKAUER J, et al: Mechanical intra-aortic cardiac assistance in cardiogenic shock. Hemodynamic effects. *Arch Surg* 97: 1000, 1968
3. BREGMAN D: Mechanical support of the failing heart. *Curr Probl Surg* 13: 1, 1976
4. BOLOOKI H: *Clinical Application of Intra-aortic Balloon Pump*, Futura Publ, Mount Kisco, NY, 1977, p 353
5. POWELL WJ JR, DAGGETT WM, MAGRO AE, et al: Effects of intra-aortic balloon counterpulsation on cardiac performance, oxygen consumption, and coronary blood flow in dogs. *Circ Res* 26: 753, 1970
6. TYBERG JV, KEON WJ, SONNENBLICK EH, et al: Effectiveness of intra-aortic balloon counterpulsation in the experimental low output state. *Am Heart J* 80: 89, 1970
7. KEON WJ, TAICHMAN GC, AKYUREKLI Y, et al: Acute cardiac failure: the relation between coronary flow and cardiac function. *Can J Surg* 19: 531, 1976
8. KEON WJ, AKYUREKLI Y, TAICHMAN GC, et al: Acute cardiac failure: the relation between coronary flow and oxygen consumption. *Can J Surg* 21: 114, 1978

9. RUBIO R, BERNE RM: Regulation of coronary blood flow. *Prog Cardiovasc Dis* 18: 105, 1975
10. MOSHER P, ROSS J JR, MCFATE PA, et al: Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 14: 250, 1964
11. CHATTERJEE S, ROSENSWEIG J: Evaluation of intra-aortic balloon counterpulsation. *J Thorac Cardiovasc Surg* 61: 405, 1971
12. FEOLA M, HAIDERER O, KENNEDY JH: Intra-aortic balloon pumping (IABP) at different levels of experimental acute left ventricular failure. *Chest* 59: 68, 1971
13. YAHR, WZ, BUTNER AN, KRAKAUER JS, et al: Cardiogenic shock: dynamics of coronary blood flow with intra-aortic phase-shift balloon pumping. *Surg Forum* 19: 142, 1968
14. BROWN BG, GOLDFARB D, TOPAZ SR, et al: Diastolic augmentation by intra-aortic balloon. Circulatory hemodynamics and treatment of severe, acute left ventricular failure in dogs. *J Thorac Cardiovasc Surg* 53: 798, 1967
15. WEBER KT, JANICKI JS: Intraaortic balloon counterpulsation. A review of physiological principles, clinical results, and device safety. *Ann Thorac Surg* 17: 602, 1974
16. BREGMAN D, KRIPKE DC, GOETZ RH: The effect of synchronous unidirectional intra-aortic balloon pumping on hemodynamics and coronary blood flow in cardiogenic shock. *Trans Am Soc Artif Intern Organs* 16: 439, 1970
17. MUELLER H, AYRES SM, CONKLIN EF, et al: The effects of intra-aortic counterpulsation on cardiac performance and metabolism in shock associated with acute myocardial infarction. *J Clin Invest* 50: 1885, 1971
18. SWAN HJ, FORRESTER JS, DANZIG R, et al: Power failure in acute myocardial infarction. *Prog Cardiovasc Dis* 12: 568, 1970
19. TALPINS NL, KRIPKE DC, GOETZ RH: Counterpulsation and intra-aortic balloon pumping in cardiogenic shock. Circulatory dynamics. *Arch Surg* 97: 991, 1968
20. GILL CC, WECHSLER AS, NEWMAN GE, et al: Augmentation and redistribution of myocardial blood flow during acute ischemia by intraaortic balloon pumping. *Ann Thorac Surg* 16: 445, 1973
21. SHAW J, TAYLOR D, PITT B: Effects of diastolic augmentation on regional myocardial blood flow in dogs with acute myocardial infarction. *Clin Res* 21: 450, 1973
22. CORDAY E, SWAN HJC, LANG T-W, et al: Physiologic principles in the application of circulatory assist for the failing heart. Intraaortic balloon circulatory assist and venoarterial phased partial bypass. *Am J Cardiol* 26: 595, 1970
23. BOLOOKI H: *Clinical Application of Intra-aortic Balloon Pump*, Futura Publ, Mount Kisco, NY, 1977, p 12
24. SCHOTTLER M, SCHAEFER J, SCHWARZKOPF HJ, et al: Experimentally induced changes of arterial mean and aortic opening pressure by controlled variation of diastolic augmentation. *Basic Res Cardiol* 69: 597, 1974
25. URSCHEL CW, EBER L, FORRESTER J, et al: Alteration of mechanical performance of the ventricle by intraaortic balloon counterpulsation. *Am J Cardiol* 25: 546, 1970
26. WEBER KT, JANICKI JS, WALKER AA: Intra-aortic balloon pumping: an analysis of several variables affecting balloon performance. *Trans Am Soc Artif Intern Organs* 18: 486, 1972
27. MUELLER H, AYRES SM, GIANNELLI S JR, et al: Effect of isoproterenol, I-norepinephrine, and intraaortic counterpulsation on hemodynamics and myocardial metabolism in shock following acute myocardial infarction. *Circulation* 45: 335, 1972
28. WOLINSKY H, GLAGOV S: Structural basis for the static mechanical properties of the aortic media. *Circ Res* 14: 400, 1964
29. AUSTEN WG, BUCKLEY MJ, MUNDTH ED, et al: Assisted circulation: intraaortic balloon pumping. *Transplant Proc* 3: 1473, 1971

Reprinted from AMERICAN HEART JOURNAL, St. Louis
Vol. 104, No. 6, pp. 1247-1254, Dec., 1982
(Copyright © 1982 by The C. V. Mosby Company)
(Printed in the U.S.A.)

Myocardial responses to acute global ischemia and reperfusion

Effects of 15 to 120 minutes of global myocardial ischemia without coronary occlusion followed by 60 minutes of reperfusion were examined in anesthetized dogs on total coronary bypass. Thirty minutes or less of global ischemia was found to be fully recoverable, while longer periods of ischemia were associated with irreversible damage. Total and regional myocardial flows and myocardial oxygen consumption did not recover in animals subjected to 60 minutes of global ischemia, while hemodynamic dysfunction became apparent only after 90 minutes of global ischemia. These results indicate that global myocardial ischemia, like coronary artery ligation, will produce functional impairment during reperfusion which is dependent on the duration of the insult. (AM HEART J 104:1247, 1982.)

Gerald C. Taichman, B.Sc., Wilbert J. Keon, M.D., Yasar Akyurekli, M.D., and Borivoj Korecky, M.D., Ph.D. *Ottawa, Ontario, Canada*

Many of the problems associated with the pathophysiology and treatment of myocardial ischemia have been resolved through animal experimentation.¹ In the majority of these studies, the usual procedure has been to create areas of regional damage by selective coronary artery ligation and to

compare the ensuing responses to those of areas supplied by nonoccluded vessels.²⁻⁸ However, histologic damage has been shown to occur in these so-called normal areas, possibly as a result of transient periods of systemic hypotension which frequently accompany acute coronary insufficiency.⁹ The assumption that cardiac performance is also compromised in these control areas remains to be examined. In order to estimate the impairment associated with a partial reduction rather than a complete obstruction of coronary flow, an animal model was used in which total coronary flow was carefully controlled while the hemodynamic effects of various periods of global ischemia were examined prior to and following 60 minutes of reperfusion.

From the University of Ottawa Cardiac Unit, Ottawa Civic Hospital; and the Department of Physiology, University of Ottawa.

Received for publication Sept. 11, 1980; revision received Apr. 14, 1981; accepted June 2, 1981.

This work was supported by the Ontario Heart Foundation, Grant No. 5-7.

Reprint requests: G. C. Taichman, B.Sc., University of Ottawa Cardiac Unit, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9, Canada.

METHODS

Preparation and instrumentation. Acute experiments were performed on 36 mongrel dogs, 21 to 44 kg in body weight. The experimental preparation used in this study has been described in more detail in earlier reports.^{10,11} Briefly, each animal was premedicated with 4 mg atropine (intramuscular) and anesthetized with sodium thiopental (20 mg/kg, intravenously). The trachea was intubated and positive pressure ventilation (Harvard Apparatus, Millis, MA) was initiated. Throughout the experiment, a surgical level of anesthesia was maintained by a mixture of 30% nitrous oxide, 70% oxygen, and 0.25% to 0.75% halothane, and the core temperature was maintained between 35° and 37° C by a thermoregulated water blanket. To minimize the incidence of ventricular arrhythmias, all animals received a priming dose of 70 mg lidocaine hydrochloride followed by a continuous infusion of 2 mg/min.

A thoracotomy was performed through the fifth left intercostal space and the pericardial sac was opened to the right of the phrenic nerve. The edges of the pericardial incision were sutured to the walls of the thoracic wound in order to cradle the heart. The animals were placed on total coronary bypass utilizing an extracorporeal circuit primed with a mixture of heparinized citrated whole blood from donor dogs and lactated Ringer's solution. Venous blood was collected from both femoral veins into a venous reservoir whose height regulated right atrial pressure between 9 and 16 cm H₂O in order to maintain optimal loading conditions.¹⁰ A portion of this blood was then diverted to an oxygenator (W. Harvey Research Corp., Santa Ana, CA) and was pumped into a coronary perfusing reservoir which drained into three coronary catheters. The height of the latter reservoir above the left atrium established the coronary perfusing pressure, which was initially set at 120 mm Hg.

The left anterior descending, circumflex, and right coronary arteries were isolated with 2-0 silk ties and cannulated with tapered polyethylene catheters (Travenol Laboratories, Deerfield, IL). The left coronary vascular bed was perfused by two catheters, one oriented proximally and one distally into the circumflex artery 3 to 5 cm from its origin. By occluding the aortic opening of the main stem of the left coronary artery, the retrogradely directed cannula perfused the initial few branches of the circumflex artery, the left main stem, the septal artery, and the entire left anterior descending artery while the distal catheter perfused the remaining portion of the circumflex artery. The right coronary artery was perfused by a separate catheter introduced 1 to 2 cm beyond the vessel's aortic origin. Individual coronary flows were measured by extracorporeal flow probes (Biotronex Laboratories, Silver Spring, MD) placed in series with each coronary cannula.

During coronary artery cannulation, systemic hypotension was minimized by partial cardiopulmonary bypass which was discontinued during the subsequent period of stabilization. In addition, the left atrium was cannulated with a wide-bore catheter attached to a third reservoir

which did not allow the left atrial pressure to rise above 30 cm H₂O. During the experiment, arterial blood gases were monitored using a Radiometer BMS-3 analyzer (Radiometer, Copenhagen, Denmark). Appropriate adjustments were made in the systemic arterial or coronary arterialized blood by altering the inspiratory carbon dioxide levels by the administration of a 10% solution of sodium bicarbonate. Systemic arterial blood values ranged from 7.32 to 7.45 for pH, 193 to 360 mm Hg for P_{O₂}, and 28 to 36 mm Hg for P_{CO₂}, while arterialized blood from the extracorporeal circuit ranged from 7.35 to 7.45 for pH, 83 to 171 mm Hg for P_{O₂}, and 32 to 48 mm Hg for P_{CO₂}.

Heart rate was computed from the ECG (lead II) while arterial and left ventricular pulse pressures were measured from fluid-filled catheters (Cordis Corporation, Miami, FL) connected to Statham P23Db transducers (Statham Instruments, Oxnard, CA) and pressure amplifiers (Electronics for Medicine, White Plains, NY). Right and left atrial pressures were determined by direct cannulation and water manometry. All pressures were referenced to the level of the right atrium. A differentiating circuit was used to compute the maximum rate of pressure rise (max dP/dt) of the left ventricle. Cardiac output was measured periodically by means of a thermodilution technique using a Swan-Ganz catheter and computer system (Edwards Laboratories, Santa Ana, CA).

In addition to measuring total coronary blood flow (CBF), 21 of the 36 experimental animals were used to determine the changes in transmural myocardial blood flow across the left ventricular free wall by assessing the distribution of nonrecirculating radioactive microspheres.^{12,13} On three occasions during the experiment, 1×10^5 carbonized plastic microspheres, $15 \pm 5 \mu\text{m}$ in diameter, labelled with ¹⁴¹Ce, ⁵¹Cr, or ⁸⁵Sr gamma-emitting nuclides (3M Co., St. Paul, MN; and New England Nuclear, Boston, MA) were injected into the base of the coronary perfusing reservoir. In three animals coronary sinus samples were simultaneously drawn during microsphere injection to monitor the amount not trapped by the coronary vascular tree. During nine injections, the greatest amount of radioactivity that could be detected in sinus blood was 3.5% of the injected amount, with a mean \pm SEM of $0.8 \pm 0.3\%$.

Experimental protocol. In this study, approximately 2½ hours were required for surgery and instrumentation. Following a 60-minute period of stabilization at a coronary perfusing pressure of 120 mm Hg, control measurements were taken. Acute cardiac failure was induced by reducing the height of the coronary perfusing reservoir until the arterial systolic pressure had been reduced to 80 mm Hg and the cardiac output decreased by at least 50%. Animals were then divided into five groups based on the duration of coronary hypotension: 15 minutes (n = 6), 30 minutes (n = 8), 60 minutes (n = 7), 90 minutes (n = 8), and 120 minutes (n = 7). At the end of ischemia a second set of measurements was made, after which the coronary perfusing pressure was returned to control levels. This recovery period lasted for 60 minutes and terminated with a third set of data. All electronic signals were either

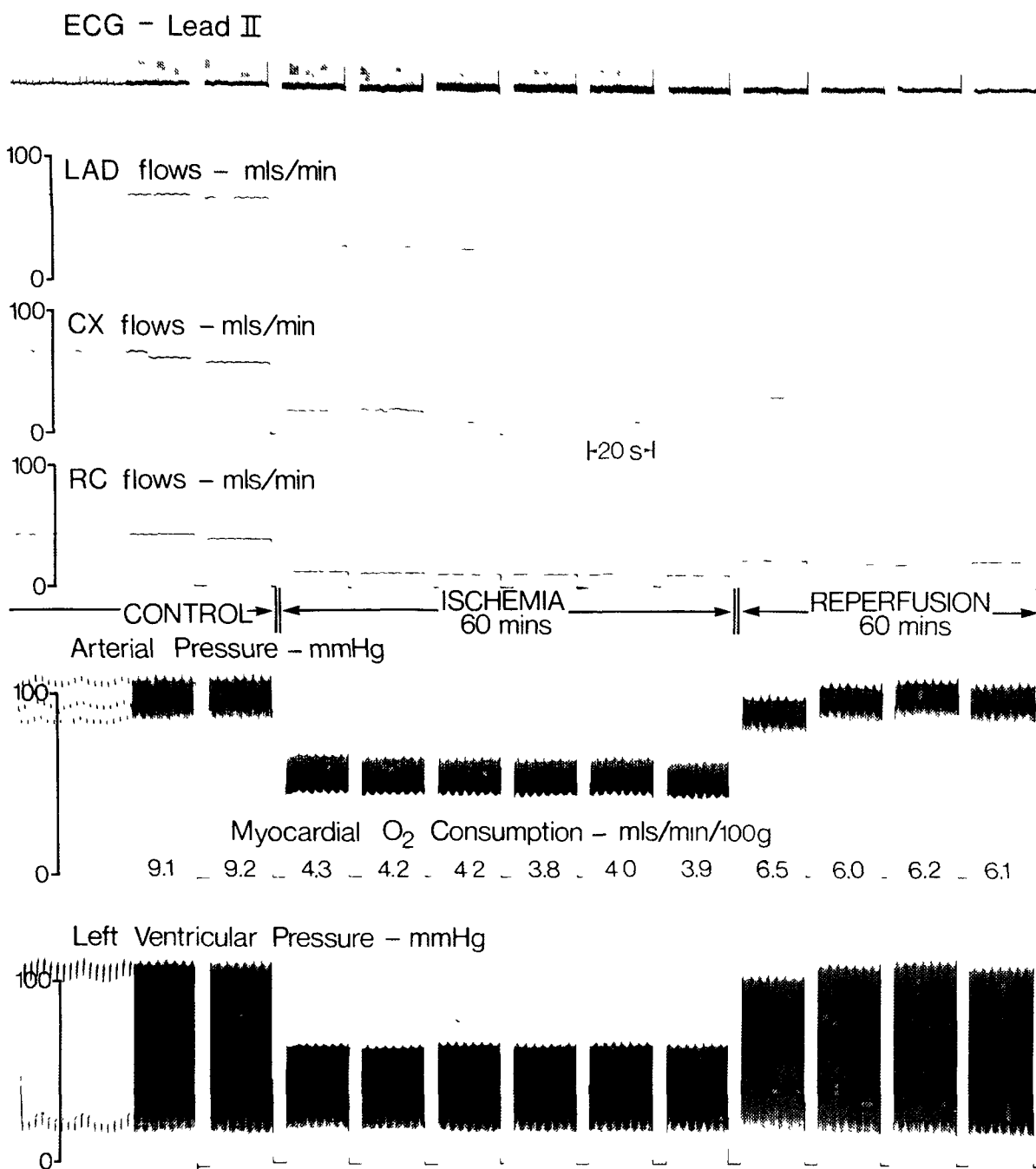


Fig. 1. The effects of 60 minutes of global ischemia followed by 60 minutes of reperfusion. During ischemia, 20-second recordings were taken at 10-minute intervals while recordings during reperfusion were taken every 15 minutes. LAD = left anterior descending, CX = circumflex, and RC = right coronary arteries.

recorded directly (Beckman Instruments Inc., Schiller Park, IL) or stored on magnetic tape (Bell and Howell, Pasadena, CA) for later examination.

The total coronary blood flow was calculated by summing individual coronary flows (anterior descending, circumflex, and right) and was normalized for each 100 gm of ventricular weight determined at the completion of the

experiment. Samples of arterialized blood from the bypass circuit and from the coronary sinus were periodically drawn and analyzed for oxygen content (Lexington Instruments, Waltham, MA). These data in combination with CBF values were used to compute myocardial oxygen availability, extraction, and consumption.¹¹

Postmortem measurements and calculations. At the

Table I. Control data (n = 36)*

Parameter	Measurement
Heart rate (bpm)	119 ± 16
Pressures (mm Hg)	
Arterial	
Systolic	132 ± 7
Diastolic	96 ± 8
Mean	109 ± 8
Left ventricular (LV)	
Systolic	135 ± 9
Diastolic	15 ± 2
Atrial (cm H ₂ O)	
Right	10 ± 1
Left	16 ± 2
Max dP/dt (mm Hg/sec)	2117 ± 221
Flows	
Cardiac index (ml/min/kg)	97 ± 11
Coronary†	
Total (ml/min/100 gm)	91 ± 6
% LAD	44 ± 2
% CX	35 ± 2
% RC	21 ± 3
Myocardial‡	
LV free wall (ml/min/100 gm)	107 ± 9
Endocardial/epicardial flow ratio	1.11 ± 0.17
Hemoglobin (gm/dl)	12.1 ± 0.4
Oxygen values	
Arterial (ml/dl)	15.9 ± 1.7
Coronary sinus (ml/dl)	7.0 ± 0.6
Myocardial availability (ml/min/100 gm)	16.1 ± 2.0
Myocardial extraction (%)	59 ± 5
Myocardial consumption (ml/min/100 gm)	8.5 ± 0.7

*Values measured at coronary perfusing pressure of 120 mm Hg.

†Flow values measured by extracorporeal probes.

‡Flow values calculated from the distribution of microspheres (n = 21).

completion of the study the animal was killed with a lethal dose of sodium pentothal. The free wall of the left ventricle was removed from the heart and the fat and large surface blood vessels were discarded. In four to six selected areas of the left ventricle, transmural blocks were removed and were further subdivided into epicardial, midmyocardial, and endocardial tissue samples. These were weighed and the radioactive content was measured (Beckman Instruments Inc., Schiller Park, IL) at optimum window settings corresponding to the peak energies of each radionuclide. Relative flow to each sample was then calculated using the following formula: $F_m = ([C_m][CBF])/C_i$ where F_m is the myocardial blood flow (ml/min), C_m is the counts per minute in the myocardial specimen, CBF is the total coronary flow, and C_i is the counts per minute of radiomicrospheres injected. The relative blood flows were normalized per unit mass (ml/min/100 gm). Myocardial transmural flow distribution was then expressed as a ratio between endocardial and epicardial flows across the left ventricular free wall.

Statistics. Statistical comparisons were made between control and hypotensive or reperfused states using Stu-

dent's *t* test for paired data, while relative responses between groups which had sustained different durations of ischemia were evaluated using an unpaired *t* test. A probability value (*p*) of less than 0.05 was termed significant.

RESULTS

Control data. The hemodynamic and metabolic data collected at the end of stabilization are presented in Table I. These results were measured at a coronary perfusing pressure of 120 mm Hg and served as control values for further comparisons. Global ischemia was then temporarily induced by lowering the coronary perfusing pressure for fixed periods of time; subsequent reperfusion was achieved by returning the perfusing reservoir to control levels.

Global ischemia. The results from an individual experiment are presented in Fig. 1. A 63% reduction in coronary perfusing pressure produced a proportional decrease in coronary flows, arterial and left ventricular pressures, and myocardial oxygen consumption. As illustrated, these ischemic responses were completed within 10 minutes of inducing coronary hypotension and did not appreciably change throughout the 60-minute period of global ischemia. The results from all experiments showing the relative responses after various periods of global ischemia are presented in Figs. 2 and 3. During global ischemia, heart rate remained unchanged, while mean arterial pressure, cardiac index, and max dP/dt decreased and left ventricular end-diastolic pressure increased. These responses did not appear to be affected by the duration of ischemia. Although a progressive increase in the relative changes of the left ventricular end-diastolic pressure (LVEDP) appears to have taken place, a statistical comparison among the groups showed no difference. A similar pattern was noted in the data shown in Fig. 4. The significant decrease in CBF and myocardial oxygen consumption and the increase in oxygen extraction were unaffected by ischemic intervals of up to 120 minutes.

Reperfusion. The hemodynamic responses following 60 minutes of reperfusion are seen in Fig. 4. With the exception of one parameter, animals exposed to shorter periods of ischemia (15 and 30 minutes) recovered with reperfusion; in animals who had sustained 15 minutes of ischemia, the cardiac index remained significantly depressed and this depression was caused by a sustained peripheral vascular constriction not seen in other groups. Animals who had undergone longer periods of ischemia could not in general reestablish control levels with reperfusion. Systemic hemodynamic values (Fig. 4) were

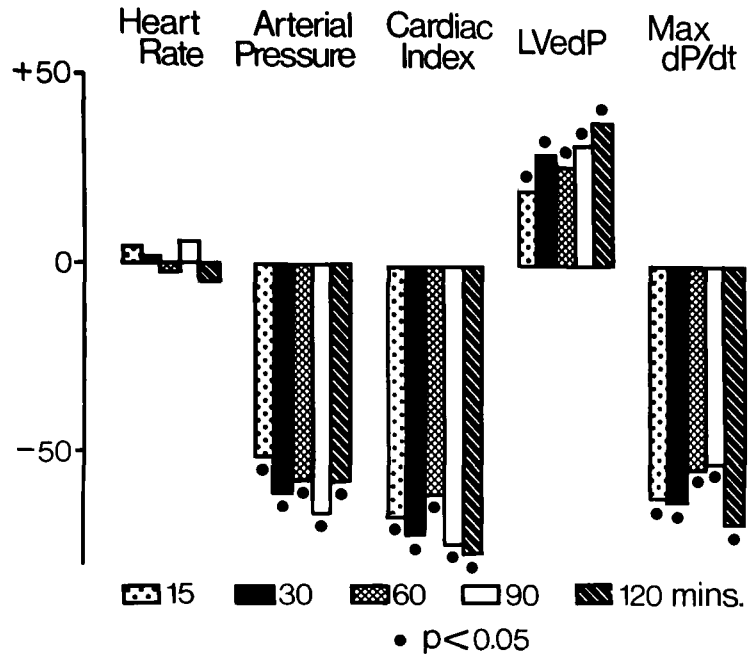


Fig. 2. Relative changes (%) in heart rate, mean arterial pressure, cardiac index, left ventricular end-diastolic pressure (*LVEDP*), and max dP/dt after various periods of ischemia. Differences between control and various periods of ischemia have been statistically evaluated.

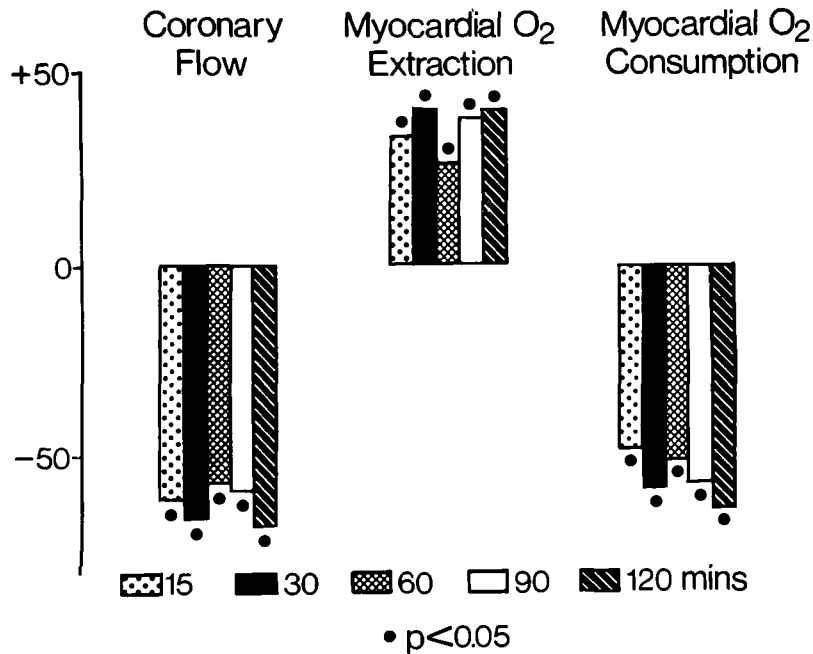


Fig. 3. Relative changes (%) in coronary flow, myocardial oxygen extraction, and myocardial oxygen consumption after various periods of ischemia.

recoverable in animals who had tolerated 60 minutes of ischemia while coronary flow and oxygen consumption remained significantly depressed (Fig. 5). A comparison between reperfusion responses and duration of ischemia showed that only coronary flow

demonstrated a significant correlation: postischemic flow was inversely related to the duration of the insult.

Myocardial flows. The myocardial flow data shown in Table II were measured by radioactive micro-

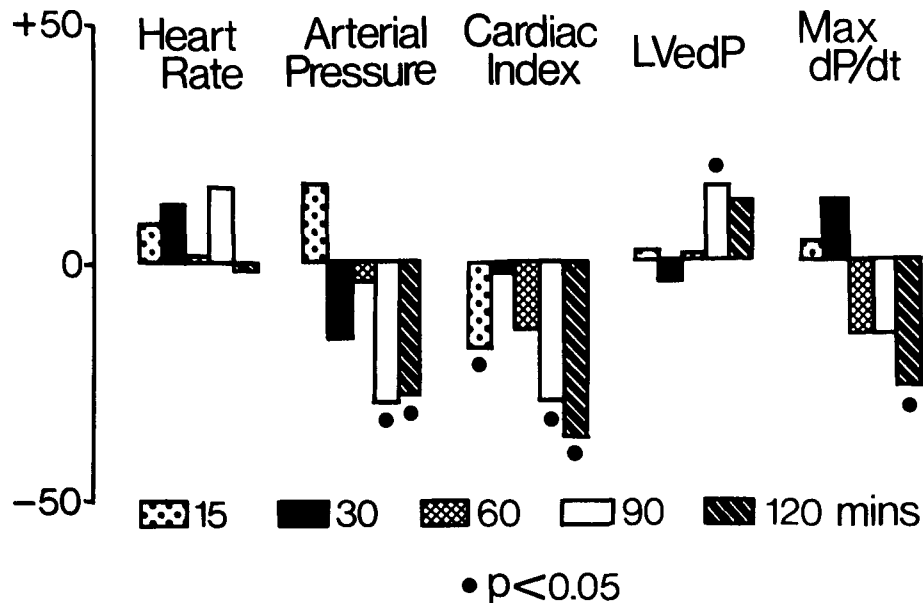


Fig. 4. Relative changes (%) in heart rate, mean arterial pressure, cardiac index, LVEDP, and max dP/dt after various periods of ischemia and 60 minutes of reperfusion.

sphere techniques. These results indicate that reperfusion after 30 or 60 minutes of ischemia restored left ventricular free wall flow. In contrast, total coronary flow measured in animals who had sustained 60 minutes of ischemia did not return to control levels with reperfusion (Fig. 5). As shown in Table II, the endocardial/epicardial flow ratio was significantly reduced in all groups with ischemia but was recoverable with reperfusion only in animals undergoing 30 minutes of ischemia.

DISCUSSION

Originally, we used the technique of global ischemia to investigate the relationship between coronary flow and various hemodynamic¹⁰ and metabolic¹¹ parameters. In these studies we found that overall reductions in coronary flow could be used to produce stable and predictable degrees of cardiac pump failure for extended periods of time. Traditionally, temporary coronary artery occlusion has been used to produce hemodynamic failure; however, in many studies, the desired shock-like state could not be consistently maintained.¹ The presence of heterogeneous flows within and around the ischemic areas^{13,14} and the subsequent development of a mixed population of normal to irreversibly damaged cells¹⁵ may account for this variable response. Also, it has been recognized that ischemic damage may not be limited to just the area beyond the occlusion; it has been demonstrated that remote, so-called "normal" areas of the heart may also be damaged by this procedure.⁹ The most likely explanation is that transient hypo-

dynamic episodes accompanying acute coronary insufficiency render previously well-perfused areas ischemic when regional mechanical demands exceed local supply.⁹ In order to study the changes occurring in these "normal" regions of the heart, it was our intention to reduce the nonuniformity of the ischemic damage by controlling the overall coronary perfusing pressure while examining myocardial performance.

Sequence of events accompanying myocardial ischemia. The sequence of events associated with myocardial ischemia¹⁶ is clearly evident in the present study. A reduction in the coronary perfusing pressure caused a significant decrease in total coronary flow, which in turn produced an increase in myocardial oxygen extraction. However, this compensatory change was insufficient to maintain myocardial oxygen consumption and eventually was expressed as a decrease in cardiac function. As the period of global ischemia was extended to 120 minutes, no significant changes from the initial response could be measured. The stability of these measurements indicates that standard hemodynamic and metabolic parameters may not be useful indicators of the duration of ischemia when the coronary perfusing pressure is held constant.

Recoverability following 30 minutes global ischemia. In animal studies on reperfusion, there does not appear to be a clear demarcation between reversible and irreversible ischemic damage. Using the technique of temporary coronary artery ligation, the duration of both the insult^{5,7,17} and the recovery

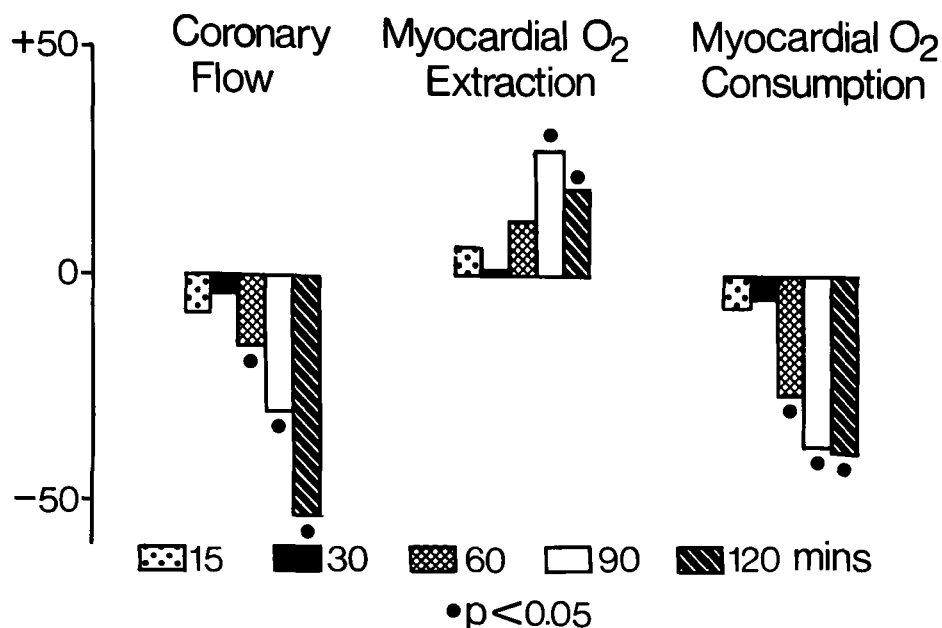


Fig. 5. Relative changes (%) in coronary flow, myocardial oxygen extraction, and myocardial oxygen consumption after various periods of ischemia and 60 minutes of reperfusion.

Table II. Myocardial flows*

		Duration of ischemia			
		30 min (n = 5)	60 min (n = 6)	90 min (n = 5)	120 min (n = 5)
LV free wall flow (ml/min/100 gm)	Control	106 ± 12	97 ± 10	101 ± 18	112 ± 19
	Ischemic	55 ± 7†	42 ± 11†	42 ± 13†	46 ± 9†
	Reperfusion	98 ± 15	81 ± 6	59 ± 12‡	52 ± 16‡
Endocardial/epicardial flow ratio	Control	1.09 ± 0.16	1.13 ± 0.19	1.02 ± 0.26	1.17 ± 0.24
	Ischemic	0.36 ± 0.07†	0.42 ± 0.10†	0.31 ± 0.14†	0.28 ± 0.09†
	Reperfusion	0.96 ± 0.09	0.63 ± 0.12‡	0.49 ± 0.16‡	0.52 ± 0.11‡

*Flows measured by the distribution of microspheres.

† = $p < 0.05$

‡ = $p < 0.05$

period^{6,8} modify the results. With the use of global ischemia followed by 60 minutes of reperfusion, the duration of the insult which could be tolerated was not easily identifiable. Based on mean arterial pressure and cardiac index measurements, animals undergoing 60 minutes of ischemia could recover, while 90 minutes could be tolerated according to max dP/dt data. The correlation between LVEDP and recoverability appears to be inappropriate, since this parameter was significantly different from control in the 90-minute group but not in the 120-minute group. It appears that these hemodynamic parameters were affected by alterations in the status of the periphery as well as by inherent changes in cardiac performance.¹⁸ However, the metabolic data which may be less influenced by the periphery

indicate that only 30 minutes of ischemia could be tolerated. Therefore both partial reductions and complete obstructions^{5,7} of coronary flow appear to produce similar functional myocardial damage; this damage can be reversed if flow is restored within 30 minutes, although morphological alterations have been shown to persist.¹⁹

No-reflow phenomenon. In reperfusion studies, the removal of an obstruction from a coronary artery has not always assured the restoration of preischemic levels of flow.¹⁹ This no-reflow phenomenon has been shown to be an inherent derangement in the vascular bed and is directly related to the duration of ischemia.^{14,17,20} The present study has shown that a sustained reduction in coronary flow can evoke a no-reflow response as well. This result would imply

that nonoccluded as well as occluded areas of the heart in patients with acute coronary insufficiency and hypotension, or those undergoing anoxic arrest during cardiopulmonary bypass, may sustain ischemic damage which would limit coronary flow during recovery.

Unequal transmural flows. Previously, we found that global decreases in coronary perfusing pressure produced equal reductions in the flows to all three perfusing catheters¹¹; however, the results of our current study indicate that transmural flows became unequal. Under control conditions, myocardial nutritive flow has been shown to be evenly distributed across the left ventricular free wall^{13, 14, 17}; with global reductions in coronary perfusing pressures, decreases in endocardial flow were found to be greater than decreases in epicardial flow. With reperfusion, the significant decrease in subendocardial flow persisted in animals who had sustained at least 60 minutes of ischemia. This uneven flow distribution with reperfusion appears to have resulted from the fact that the ischemic insult was not evenly expressed across the myocardial wall. It has been recognized that subendocardial necrosis, even in regions supplied by nonoccluded coronary vessels, is frequently encountered following cardiopulmonary bypass and can result in fatal postoperative myocardial failure in patients who have undergone an otherwise technically successful surgical procedure.²¹ Although the factors responsible for this condition have not been adequately defined, an imbalance between oxygen requirements and supply in the subendocardium has been suggested.²¹ Our results support this explanation in that the no-reflow response that we measured was primarily expressed in the subendocardium.

Conclusions. Overall reductions in coronary flow for short periods of time appear to produce functional myocardial damage similar to the derangements associated with temporarily obstructed coronary arteries. Thus, myocardial areas other than those directly affected by an obstruction must be considered when estimating the extent of injury and the ability to recover with reperfusion.

The authors thank Mr. K. Sheldrick and Mrs. V. Temple for their technical assistance and Mrs. B. Masson for her assistance in manuscript preparation.

REFERENCES

1. Feola M, Glick G: Experimental models of cardiogenic shock. In Gunnar RM, Loeb HS, Rahimtoola SH, editors: Shock in myocardial infarction. New York, 1974, Grune & Stratton, Inc, p 23.
2. Goldfarb D, Conti CR, Brown BG, Gott VL: Treatment of severe cardiogenic shock by diastolic augmentation after ligation and division of left circumflex coronary artery in dogs. *J Thorac Cardiovasc Surg* 51:783, 1966.
3. Small ML: Standardized experimental preparation of cardiogenic shock. *Surgery* 60:1051, 1966.
4. Ellis PR, Bailas NJ, Viskos JD, Wong SH, Hyland JW: Experimental heart failure in dogs. *Arch Surg* 89:299, 1964.
5. Constantini C, Corday E, Lang TW, Meerbaum S, Brasch J, Kaplan L, Rubins S, Gold H, Osher J: Revascularization after 3 hours of coronary arterial occlusion: Effects on regional cardiac metabolic function and infarct size. *Am J Cardiol* 36:368, 1975.
6. Puri PS: Contractile and biochemical effects of coronary reperfusion after extended periods of coronary occlusion. *Am J Cardiol* 36:244, 1975.
7. Lang TW, Corday E, Gold H, Meerbaum S, Rubins S, Constantini C, Hirose S, Osher J, Rosen V: Consequences of reperfusion after coronary occlusion. Effects of hemodynamic and regional myocardial metabolic function. *Am J Cardiol* 33:69, 1974.
8. Sharma GP, Varley K, Kim SW, Barwinsky J, Cohen M, Dhalla NS: Alterations in energy metabolism and ultrastructure upon reperfusion of the ischemic myocardium after coronary occlusion. *Am J Cardiol* 36:234, 1975.
9. Corday E, Kaplan L, Meerbaum S, Brasch J, Constantini C, Lang TW, Gold H, Rubins S, Osher J: Consequences of coronary arterial occlusion on remote myocardium: Effects of occlusion and reperfusion. *Am J Cardiol* 36:385, 1975.
10. Keon WJ, Taichman GC, Akyurekli Y, Korecky BV: Acute cardiac failure: The relation between coronary flow and cardiac function. *Can J Surg* 19:531, 1976.
11. Keon WJ, Akyurekli Y, Taichman GC, Korecky B: Acute cardiac failure: The relation between coronary flow and oxygen consumption. *Can J Surg* 21:114, 1978.
12. Domenech RJ, Hoffman JIE, Noble MIM, Saunders KB, Henson JR, Subijanto S: Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. *Circ Res* 25:581, 1969.
13. Becker LC, Ferreira R, Thomas M: Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. *Cardiovasc Res* 7:391, 1973.
14. Cobb FR, Bache RJ, Rivas F, Greenfield JC: Local effects of acute cellular injury on regional myocardial blood flow. *J Clin Invest* 57:1359, 1976.
15. Jennings RB, Baum JH, Herdson PB: Fine structural changes in myocardial ischemic injury. *Arch Pathol* 79:135, 1965.
16. Graham TP, Covell JW, Sonnenblick J, Ross J, Braunwald E: Control of myocardial oxygen consumption: Relative influence of contractile state and tension development. *J Clin Invest* 47:375, 1968.
17. Parker PE, Bashour FA, Downey HF, Kechejian SJ, Williams AG: Coronary hemodynamics during reperfusion following acute coronary ligation in dogs. *AM HEART J* 90:593, 1975.
18. Monroe RG, French GN: Left ventricular pressure-volume relationships and myocardial oxygen consumption in the isolated heart. *Circ Res* 9:362, 1961.
19. Meerbaum S, Corday E: Reperfusion during acute myocardial infarction. Part 1. *Am J Cardiol* 36:211, 1975.
20. Krug A, du Mesnil de Rochemont W, Korb G: Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 19:57, 1966.
21. Buckberg GD, Towers B, Paglia DE, Mulder DG, Maloney JV: Subendocardial ischemia after cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 64:669, 1972.