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STUDIES OF THE EFFECT OF EXPERIMENTAL MYOCARDIAL REVASCULARISATION ON VENTRICULAR FUNCTION

by

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To my wife Anne for her help and encouragement
and for making possible the completion of what
at times seemed an endless task.

"In Physiology, as in all other sciences, no discovery is useless, no curiosity misplaced or too ambitious, and we may be certain that every advance achieved in the quest of pure knowledge will sooner or later play its part in the service of man."

Ernest H. Starling

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SUMMARY

To evaluate the aorto-coronary bypass graft procedure two animal preparations were used. In the first the effect of myocardial revascularisation on the function of the chronically ischaemic ventricle was studied. The second preparation was used to study the effect on the ventricle of restoring blood flow after one hour of coronary occlusion.

Chronic myocardial ischaemia in dogs was produced surgically by implanted coronary constrictors. Revascularisation was performed using a cannula with a built-in flowmeter. Ventricular function curves were generated using the right heart bypass technique. The thirteen animals studied could be divided into two groups on the basis of the change in ventricular function produced by revascularisation. Group A comprised six dogs in which opening the graft produced an immediate improvement in ventricular function. Group B comprised seven dogs showing no immediate alteration in ventricular function on opening the graft. In Group A the mean graft flow: 48±7.3 ml/min, was greater than Group B, 26±4.0 ml/min ($P<0.05$). In Group A mean collateral flow: 16±0.3 ml/min was lower than Group B: 43±4.1 ml/min ($P<0.01$). With the passage of time after the graft had been opened collateral flow decreased, graft flow increased and the ventricle exhibited the "graft dependence effect", i.e. it became more dependent on the blood supply from the graft. It is concluded that the functional improvement brought about by revascularising

the chronically ischaemic ventricle is not large but is seen most clearly when graft flow is high and collateral flow low.

In the second series of experiments acute myocardial infarction was produced in awake dogs using an occluder implanted on the circumflex coronary artery. Release of the occlusion after one hour allowed reperfusion of the acutely ischaemic area. An acute increase in aortic pressure produced by phenylephrine administration was used to evaluate ventricular function.

In 10 normal dogs a sudden rise in aortic pressure to 190 mm Hg produced a rise in left ventricular end-diastolic pressure from 8 mm Hg to 20 mm Hg, a fall in stroke volume from 24 mls to 19 mls but no significant change in stroke work. The ventricular function curve produced by plotting stroke work against left ventricular end-diastolic pressure was thus approximately horizontal. Coronary occlusion increased left ventricular end-diastolic pressure from 7 mm Hg to 11 mm Hg, reduced stroke volume by 28%, systolic left ventricular pressure by 10% and stroke work by 37%. These changes were not accentuated by aortic pressure loading. The fall in stroke work was found to be the best measure of ventricular depression produced by coronary occlusion.

To assess the effect of revascularisation of an acute myocardial infarction, the coronary occlusion was released after one hour in seven dogs. This group was compared with a control group of nine dogs in which the occlusion was not released. The revascularised

dogs had a smaller mean infarct size: 9.0±2.3% of the left ventricle than the controls: 29.3±3.1% ($P<0.005$). Of the six revascularised dogs followed for one week, five were alive and four of these showed good recovery of ventricular function, whereas only three of the nine controls survived for one week with poor recovery of function. It is concluded that restoration of flow following one hour of acute coronary occlusion can reduce the size of the infarct and improve the function of the ventricle.

I hereby state that this thesis contains no material which has been accepted for the award of any other degree or diploma in any University and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except when due reference is made in the text of the thesis.

CONTRIBUTION OF THESIS TO ADVANCE OF MEDICAL KNOWLEDGE

This thesis is considered to contribute to the advance of medical knowledge as follows:

1. It was demonstrated in the dog that revascularising a chronically ischaemic ventricle produces only a relatively small improvement in its function. This finding suggests that coronary artery bypass grafting in patients with widespread ventricular akinesia secondary to chronic myocardial ischaemia would not improve clinical cardiac failure. This view is shared by many clinicians who consider chronic cardiac failure a relative contraindication to coronary artery surgery.
2. It was found in both Part A and Part B that measurements of ventricular function based purely on analysis of the rate of rise of left ventricular pressure, namely peak left ventricular dp/dt, "V_{PM}" and "V_{MAX}" were less sensitive indices of ventricular dysfunction due to myocardial ischaemia than left ventricular end-diastolic pressure and stroke work.
3. A relationship has been demonstrated between change in ventricular function following revascularisation on one hand and graft flow and collateral flow on the other. Such correlations are almost impossible to make in patients. It is difficult to extrapolate with great confidence from the relatively small number of simultaneous graft flow and ventricular function measurements in this study. However, the results suggest that revascularising

an area of the ventricle with a good collateral blood supply results in little functional improvement and low initial flow in the graft which could predispose to early graft thrombosis.

4. The phenomenon whereby the ischaemic ventricle may become dependent on a new blood supply provided by a graft has been described and the term "graft dependence effect" applied. While this effect has not been exhaustively evaluated in this study, its existence would explain the surprisingly marked effect on ventricular function sometimes observed when coronary artery bypass grafts are suddenly clamped on the operating table and the frequent observation of a myocardial infarction and deterioration in ventricular function following thrombosis of a bypass graft.
5. The response of the ventricle in the intact unanaesthetised dog to an acute increase in peripheral resistance has been described in detail including the unexpected fall in stroke volume.
6. Measurements have been made of the effect of coronary occlusion on ventricular function in the intact unanaesthetised dog. Measurements of stroke volume, stroke work, peak power, peak left ventricular pressure, peak left ventricular dp/dt, and left ventricular end-diastolic pressure have been made on a beat-to-beat basis and the changes produced in each parameter compared. Of all these parameters, stroke work depression has been shown to be the best indicator of ventricular dysfunction due to coronary occlusion. This knowledge finds application in the

coronary care unit where, using standard techniques for measuring cardiac output and arterial pressure, stroke work can be readily determined. Stroke work changes can thus be used as a guide to prognosis and response to therapy.

7. Pressure loading of the ventricle by administration of a pure alpha-adrenergic agent has been shown to be unhelpful in bringing out ventricular dysfunction due to ischaemia. This method of stress testing can therefore almost certainly be discarded as a useful diagnostic or prognostic test in the management of patients with acute myocardial infarction.

8. Restoration of blood flow following one hour of coronary occlusion has been shown to produce a functional and structural benefit to the ventricle. Thus revascularisation surgery performed upon patients very soon after acute coronary occlusion should be beneficial. Would revascularisation surgery performed after four hours, six hours, or more, also be beneficial? This question awaits further study.

INTRODUCTION

In the six years since its initial clinical application, the aorto-coronary vein bypass procedure has acquired astounding popularity in the treatment of coronary artery disease. Friedberg (1972) estimated that in the year 1971, 25,000 coronary artery bypass operations were performed in the United States alone.

Despite this enthusiasm, both the correct indications for the procedure and the precise benefit to be expected remain a subject of continuing debate and editorial comment. The original indication for the operation was intractable angina pectoris and relief rates up to 92% have been reported (Green et al., 1970; Morris et al., 1972). However, relief of such a subjective phenomenon as angina has been shown to be a somewhat unreliable index of successful myocardial revascularisation. Significant angina relief rates have been achieved even by a skin incision on the chest (Dimond et al., 1960). Patients with angiographically demonstrated occlusion of their vein grafts not infrequently describe relief of anginal pain. Clearly in evaluating the efficacy of the operation a less subjective measure is desirable.

Surgeons have employed vein bypass grafts for the relief of chronic congestive cardiac failure, secondary to coronary artery disease (Spencer et al., 1971; Mundth et al., 1971), and also for acute "pump failure" following myocardial infarction (Pifarre et al., 1971; Cohn et al., 1971; Dunkman et al., 1972). Some authors have

reported improved ventricular function following such surgery. However, others (Spencer et al., 1971; Rees et al., 1971; Saltiel et al., 1970; Dorchak et al., 1971) have described no improvement in ventricular function occurring in a substantial proportion of cases following successful bypass grafting, and a deterioration in cases with occluded grafts. Thus the effect of bypass grafting on ventricular function in patients is poorly understood.

The ultimate evaluation of the procedure in patients must be in terms of the reduction in mortality and incidence of myocardial infarction in surgically treated patients compared with a comparable control or medically treated group. No conclusive information on such a controlled clinical trial is available at present.

It was for these reasons that I became interested in studying revascularisation in animals since an animal preparation can offer a reproducible lesion and allow for more comprehensive measurements of physiological effects. There are many pitfalls in using such an approach. Many of the early operations for coronary artery disease, such as epicardial abrasion, which have now been universally discarded, were commended to clinicians on the basis of incorrect conclusions from animal experimentation. An interesting feature of the development of the aorto-coronary vein bypass procedure is the paucity of animal studies designed to evaluate its effects.

Improvement in ventricular function was chosen as the best measure of the efficacy of myocardial revascularisation in dogs.

Two separate clinical procedures had to be studied: firstly revascularisation of the chronically ischaemic ventricle and secondly revascularisation of the acutely ischaemic or recently infarcted ventricle. Two separate animal studies were carried out to investigate these two procedures.

In the first study the effects of revascularisation of the chronically ischaemic ventricle were examined. An animal model of chronic myocardial ischaemia was used to evaluate the early functional effects of revascularisation. There were three aspects to be considered in the design of this study. Firstly, the production of a reproducible model of myocardial ischaemia, secondly, finding an effective means of restoring blood flow to the ischaemic area and thirdly, the choice of a sensitive method of assessing ventricular function. Preliminary work was required to develop an animal preparation which fulfilled these requirements. Several different methods were used to produce ischaemia and to revascularise the ischaemic area before a workable system was developed.

Once developed by the author, this model of myocardial ischaemia and revascularisation was used in another study reported separately (Wechsler, Rosenfeldt et al., 1973). A catecholamine infusion was used to stress the heart and ventricular function was measured by force-velocity indices before and after revascularisation. This technique was applied in dogs and then in patients at the time of bypass graft surgery. This study showed an apparently large augmenta-

tion in contractility brought about by revascularisation. However, as the animal study described in Part A proceeded some doubt was cast on the results of the patient study by the possible role of the "graft dependence effect". Suddenly clamping the vein grafts after they had been perfusing the ventricle for an hour or two could have produced a depression of ventricular function larger than the actual benefit originally conferred by the grafts.

In the second study the effect on ventricular function and infarct size of restoration of coronary flow to an acute myocardial infarct was investigated. Awake dogs with an intact autonomic nervous system and implanted electromagnetic flow probes were utilised. It was decided to use the stress of increased aortic pressure to bring out impaired ventricular function. The first step was to examine the response of the intact heart to a sudden increase in aortic pressure and to determine whether this response pattern was altered by myocardial infarction. The haemodynamic response of the ventricle to the pressure load differed from that which might have been expected from a literal interpretation of Starling's Law of the Heart. This response pattern was analysed in detail. In the remainder of the project this information was used to compare the behaviour of revascularised with non-revascularised ventricles following coronary occlusion.

This thesis contains three parts. The first part is a description of ventricular function before and after revascularisation of a canine model of chronic myocardial ischaemia and the correlation

of graft flow and collateral flow with functional change. The second part describes a pressure loading technique for assessing ventricular function in the dog. Then follows a description of the effect of acute coronary occlusion on ventricular function in awake dogs. The effect on ventricular function of releasing the coronary occlusion after one hour is compared with the effect of a permanent occlusion. In the third part the conclusions from the first two parts are discussed and the clinical applications examined.

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It was with the help of Dr. Paul Ebert, now of Cornell University and the advice of Dr. Donald Gregg of the Walter Reed Army Institute of Research that the animal model of myocardial ischaemia and the means to revascularise it were developed.

Dr. Andrew Wechsler joined me in the laboratory towards the end of my first year there. He adapted the ischaemia-revascularisation model for use with force-velocity ventricular function analysis and gave me invaluable insight into muscle mechanics. I am also grateful to Dr. Wechsler and to Dr. Carl Gill for helping me finish the series of experiments using the right heart bypass technique.

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CHAPTER 1

HISTORY OF EXPERIMENTAL AND CLINICAL MYOCARDIAL REVASCULARISATION

Although chest pain due to myocardial ischaemia was referred to in the writings of the physician Coelius Aurelianus in 400 A.D., it was not until 1802 that the English physician William Heberden in his book "Commentaries of the History and Cure of Diseases" wrote a clinical description of the condition which can scarcely be bettered today and gave it the name, angina pectoris. The earliest treatments described by Heberden were medical: "quiet and warmth and spirituous liquors . . . opium taken at bed-time". It would appear that surgeons did not become involved in the treatment of this newly recognised disease for over 100 years.

The first surgical treatment of angina was directed at interruption of the pain pathways from the heart. In 1899 Francois-Franck, a professor of physiology in Paris, suggested sympathectomy as a cure for angina pectoris. The first successful cervico-thoracic sympathectomy for angina was performed by Jonnesco in Bucharest in 1916. More effective methods of surgical denervation of the heart were developed subsequently, including thoracic ganglionectomy, posterior rhizotomy and paravertebral sympathetic

block. By 1957 these procedures were approximately 70% effective in relieving anginal pain (White, 1957).

Another approach to the problem of myocardial ischaemia was to reduce the oxygen demands of the myocardium by thyroid ablation. In 1925 Boas and Shapiro performed subtotal thyroidectomies in a series of patients for relief of symptoms of myocardial ischaemia, but the results were unsatisfactory. The more radical approach of total thyroidectomy was then employed. In 1933 Blumgart et al. reviewed 95 patients in whom total thyroidectomy had been performed for relief of angina pectoris with a 47% success rate. However, this procedure subsequently lost popularity because of its significant mortality rate and the problems of tetany, recurrent laryngeal nerve damage and myxoedema.

A more modern approach to the reduction of myocardial oxygen consumption is the use of the carotid sinus nerve stimulator. This device, which is implanted surgically, can be activated by the patient himself at times of stress, thus producing a brady-cardia and a resulting decrease in myocardial oxygen consumption (Braunwauld et al., 1967).

However, surgical endeavour in the treatment of angina pectoris has centred mainly around procedures designed to increase the supply of oxygenated blood to ischaemic areas of the myocardium. These procedures can be classified as follows:

SURGICAL PROCEDURES FOR MYOCARDIAL REVASCULARISATION

1. Procedures to Increase or Redistribute Collateral Blood Supply

   (a) Cardiopericardiopexy.

   (b) Cardiomyopexy.

   (c) Cardiopneumopexy.

   (d) Cardio-omentopexy.

   (e) Internal mammary artery ligation.

2. Surgery of the Coronary Venous System

   (a) Production of coronary venous stasis.

   (b) Arterialisation of the coronary sinus.

3. Procedures to Implant a New Blood Supply Directly into the Myocardium

   (a) Internal mammary artery implantation.

   (b) Other implants bringing arterial blood into the myocardium.

   (c) Left ventricle-to-myocardium shunts.

4. Direct Surgery of the Coronary Arteries

   (a) Coronary endarterectomy.

   (b) Substitution of vein graft for obstructed segment.

   (c) Internal mammary artery-coronary anastomosis.

   (d) Aorto-coronary vein bypass graft.

1. Procedures to Increase or Redistribute Collateral Blood Supply

(a) Cardiopericardiopexy. The first procedure designed to increase the collateral blood supply to the heart by inducing adhesions between the heart and the pericardium was described by Claude Beck in 1935. The trial of this procedure was prompted by the observation that a patient with pericardial adhesions had survived complete occlusion of both major coronary arteries (Thorel, 1903). Beck's original experimental operation consisted of mechanically abrading the epicardium and inner surface of the pericardium in the dog with a burr or emery paper. The resulting adhesions conferred a protective effect against subsequent coronary artery occlusion. Compared with normal controls the abraded dogs showed a lower mortality rate and smaller infarct size in response to coronary artery ligation. In 1942 Thompson and Raisbeck reported a series of patients with angina in which talc induced pericarditis was used to improve the collateral blood supply to the heart. Schildt et al. (1943) subsequently reported the use of powdered asbestos for the same purpose.

(b) Cardiomyopexy. In 1935 Claude Beck used a pedicle of the pectoralis major muscle with an intact blood supply in the first operation to increase the blood supply to the human heart. Two years later Beck reported a series of 20 patients in which cardiomyopexy had been performed with increasing success.

(c) Cardiopneumopexy. In 1949 Carter et al. reported an experimental procedure in which the lingula of the lung was used as a source of collateral blood supply to the heart. Dogs prepared in this way showed a lower mortality rate and smaller infarct size following coronary artery ligation than did control dogs. Subsequently patients with angina were successfully treated using this technique.

(d) Cardio-omentopexy. O'Shaughnessey devised a revascularisation technique in which the omentum was made to adhere to the heart and pericardium, and in 1936 successful application to patients was reported.

(e) Internal mammary artery ligation. Bilateral ligation of the internal mammary arteries has been used in the belief that it could increase the collateral blood supply to the heart. As cited by Battezatti et al. (1955) this procedure was first performed by Zola and Bianchi in 1939. A high relief rate for angina has been claimed for this procedure (Battezatti et al., 1955; Glover et al., 1957). However, a well designed and executed double-blind trial to compare the results of internal mammary artery ligation and a sham operation consisting of a skin incision over the chest was reported by Dimond et al. in 1960. Both procedures produced identical relief rates for angina but neither altered the exercise electrocardiogram.

2. Surgery of the Coronary Venous System

(a) Production of coronary venous stasis. One of the more bizarre concepts in myocardial revascularisation was the idea that the production of coronary venous obstruction could improve myocardial blood flow. It was first suggested by Wearn et al. in 1933 that in the presence of coronary artery occlusion, venous blood could reach the ischaemic area by reversal of flow in the Thebesian veins. Robertson (1934) attempted to protect the myocardium of the dog against coronary occlusion by ligating the coronary sinus. It was hoped that increased coronary sinus pressure would cause backflow of blood into the capillaries of the ischaemic area. No protection of the myocardium due to coronary sinus ligation could be demonstrated. In a study of the effect of coronary sinus ligation on coronary haemodynamics Gregg and Dewald (1938) showed that retrograde flow from a divided coronary artery was increased by coronary sinus ligation. However, the increased retrograde flow was of highly desaturated blood. It had already traversed a capillary bed and therefore could not improve myocardial oxygenation. Also coronary sinus ligation failed to reverse paradoxical movement of the ventricle produced by occlusion of a coronary artery.

In spite of these findings the production of coronary venous obstruction found favour with surgeons for the treatment of angina. In 1946 Fateux reported a series of 16 patients with angina in which great cardiac vein ligation was combined with pericoronary neurectomy

to produce satisfactory relief of pain. Beck and Leighninger (1954) combined partial coronary sinus occlusion with cardiopericardiopexy and reported relief of angina in 85% of patients.

(b) Arterialisation of the coronary sinus. In 1898 Pratt demonstrated that if defibrinated arterial blood was forced into the coronary sinus of freshly extirpated cats' hearts ventricular contraction would continue for up to one and one-half hours. Hahn and Beck (1952) devised a procedure for supplying arterial blood to the coronary sinus. A vein graft was placed between the aorta and the coronary sinus. A few weeks later the coronary sinus was partially ligated near its orifice to reduce the shunt into the right atrium. When applied to patients this procedure resulted in relief of angina in 88% of cases (Beck and Leighninger, 1954).

3. Procedures to Implant a New Blood Supply Directly into the Myocardium

Before the advent of cardiopulmonary bypass it was virtually impossible to anastomose a vessel directly to a coronary artery. The only way to terminate a vascular graft to the heart was to bury it in the myocardium. Many different vessels were used as implants but the only technique to gain wide acceptance was the first to be described, i.e. the internal mammary artery implant of Vineberg.

(a) Internal mammary artery implantation. In 1946 Arthur Vineberg published an account of an experimental study in which the

internal mammary artery was implanted into the left ventricle of the dog. In one dog injection of the distal internal mammary artery after death outlined collateral vessels which anastomosed with the branches of the left coronary artery. This was the birth of the "Vineberg Operation". Application to patients followed in 1950. Following an initial period of scepticism the procedure gained wide acceptance by surgeons around the world (Vineberg, 1971). A review of the Cleveland Clinic experience of 665 internal mammary implants done between 1962 and 1967 showed a 5.4% hospital mortality rate, and a 79% rate of symptomatic improvement (Favoloro et al., 1967). Postoperative catheterisation showed patency in 92% of cases and varying degrees of runoff into the coronary circulation.

However, several physiological studies failed to find any objective evidence of benefit to the heart. In an experimental study of ischaemic dogs Barner (1968) could not demonstrate significant augmentation of total coronary blood flow or improvement of ventricular function in dogs with patent internal mammary artery implants. In a group of patients studied one year after internal mammary artery implantation McCallister (1970) found no correlation between clinical improvement and haemodynamics at the time of postoperative study. Improved ventricular performance following surgery was seen in only two out of fourteen patients with patent grafts. Dart and colleagues (1970) studied 139 patients who survived one year or longer following implantation of a single internal mammary artery into the left ventricular

myocardium. They found no correlation between angiographic patency or runoff and infarction rate or mortality. In 13 patients with existing internal mammary implants who were having further cardiac surgery, direct measurements of blood flow showed that the implants delivered an average of only 8.1 ml/min. (Dart et al., 1969).

(b) Other implants bringing arterial blood into the myocardium. As an alternative to the Vineberg procedure the following implants have been tried: gastro-epiploic artery implant (Bailey et al., 1967), carotid artery implant (Sabiston et al., 1957), implantation of a prosthetic tube connected to the thoracic aorta (Smith et al., 1957), and the subclavian artery implant (Fuquay et al., 1958). These procedures were evaluated mainly in dogs. However, the gastro-epiploic implant was used in 27 patients with subjective reduction of anginal pain in all but one of the 23 survivors (Bailey et al., 1967). Similarly Ferlic (1966) who implanted autogenous vein grafts from the thoracic aorta into a myocardial tunnel reported significant relief of angina in all 16 surviving patients.

(c) Direct left ventricle-to-myocardium shunt. A novel way of delivering oxygenated blood to the myocardium was devised by Massimo and Boffi (1957). A plastic T-tube was implanted into the left ventricular wall, the stem opening into the left ventricular cavity and the cross arms delivering blood into the substance of the myocardium. The device remained patent but its efficacy in relieving ischaemia was not demonstrated.

4. Direct Surgery of the Coronary Arteries

(a) Coronary endarterectomy. The first direct coronary artery surgery in man was reported by C. P. Bailey et al. in 1957, well before the days of coronary angiography. He performed a coronary endarterectomy in two patients. Both survived and in one angina was relieved. In 1961 Senning reported the successful use of endarterectomy combined with insertion of an autogenous vein patch for an occluded left anterior descending coronary artery.

(b) Substitution of vein graft for obstructed segment. The technique of excising an obstructed segment of coronary artery and replacing it with a venous autograft was first suggested by Murray in 1952. The technique was applied clinically by Favoloro in 1967 and the Cleveland Clinic series showed good correlation between angiographic patency of the graft and relief of angina (Favoloro et al., 1969).

(c) Internal mammary artery-coronary anastomosis. The next logical step following the implantation of the internal mammary artery into the myocardium was the direct anastomosis of the internal mammary artery to a coronary artery. This was carried out successfully in dogs as early as 1956 by Absolom, using a direct suture technique of anastomosis. An ingenious method of sutureless anastomosis was described by Goetz in which the internal mammary artery was fixed into a coronary artery by a tantalum ring (Goetz et al., 1961).

This technique was used in dogs with good patency rates and as early as May 1960 was applied successfully in one patient. However, it was Green who in 1968 began the systematic application of the internal mammary-coronary bypass technique. In Green's first series the patency rate was 97% at one year, and the rate of angina relief over 80 per cent. The appeal of the internal mammary artery over the saphenous vein graft is the better correspondence between the size of the graft and the grafted vessel and the lack of subintimal fibrosis which has been shown progressively to narrow vein bypass grafts (Vlodarver and Edwards, 1971).

(d) Aorto-coronary vein bypass graft. It was Murray who in 1952 performed the first experimental aorto-coronary bypass graft. In the dog he performed successful direct anastomoses between the coronary arteries and the internal mammary artery or other branches of the aorta (Murray, 1953). In 1966 Kahn performed the first clinical aorto-coronary bypass graft using a segment of saphenous vein (Effler, 1971). Subsequently Effler in Cleveland and Johnson in Milwaukee expanded the technique to include multiple grafts. Since then the operation has been performed many thousands of times in most parts of the world. As with its many predecessors, this operation is reported as being very successful: up to 92% of patients experiencing loss or reduction of angina (Green et al., 1970; Morris et al., 1972). However, the ultimate evaluation in terms of improved longevity and reduced infarction rate awaits the passage of time.

An immediate indication of benefit from vein bypass grafting would be improved ventricular function. The results to date are not clearly indicative of improvement. A number of studies have been done in which improved ventricular function was observed on the operating table at the time of vein bypass grafting (Wechsler et al., 1972; Bolooki et al., 1971; Anderson, 1972; Enright et al., 1972). These studies have been done after completion of up to three vein grafts and the discontinuation of cardiopulmonary bypass. As suggested in Chapter 4 of this thesis, the phenomenon of "graft dependence" could bring about a spurious depression of ventricular function immediately the grafts were clamped regardless of whether or not the graft initially augmented ventricular function. Thus these studies cannot be relied upon to measure true alterations in contractility produced by revascularisation. This conclusion was also reached by Anderson (1972).

More meaningful data are obtained by angiographic ventriculography performed before and after vein bypass surgery. Baroussa et al. (1972) showed that following surgery there was an improvement in the contractility of hypokinetic segments of the ventricle which correlated with graft patency. Chatterjee et al. (1973) reported marked improvement in ventricular function following revascularisation as evidenced by increased ejection fraction and reduced left ventricular end-diastolic pressure. However, Hamilton et al. (1972) in a similar angiographic study showed no change in ejection fraction or contractile pattern following revascularisation. Similar results were reported

by Lapin et al. (1973). Early postoperative studies may be misleading since they are influenced by the excessive levels of sympathetic stimulation present which raise heart rate and temporarily augment contractility (Boudoulas et al., 1973).

Exercise testing provides an evaluation of changes in overall cardiovascular function following coronary bypass surgery. Conversion from an ischaemic pre-operative exercise test to a normal test post-operatively was reported in 46% of patients by Bartel et al. (1973), and in 66% by Lapin (1973). A disturbing finding of these studies was that relief of angina following surgery often occurs in spite of persistence of electrocardiographic evidence of ischaemia during exercise testing.

As an extension from its use in the treatment of chronic myocardial ischaemia, the coronary artery bypass graft procedure has been employed in the management of the evolving acute myocardial infarction. Provided bypass grafting is carried out within the first few hours of the onset of coronary occlusion, myocardial damage can be prevented or minimised (Cohn et al., 1972). Experimentally it has been shown that if blood flow is not restored until five hours after coronary occlusion, extension of the infarct associated with myocardial haemorrhage may occur (Bresnahan et al., 1974).

The correct place (if any) of coronary artery bypass surgery in the management of acute myocardial infarction is not yet clear.

Probably bypass surgery should be restricted to the treatment of acute coronary occlusion occurring in the course of or soon after cardiac catheterisation.

CONCLUDING REMARKS

An overall view of the vast literature concerning surgical revascularisation of the ischaemic heart both in animals and patients reveals the interesting fact that nearly every one of the diverse procedures was initially assessed as being highly successful. There are probably two main reasons for this, apart from a surfeit of enthusiasm and lack of objectivity on the part of the originators of the procedures.

Firstly, angina pectoris in man has a large psychological component. Angina produces anxiety. Anxiety worsens angina by increasing heart rate and blood pressure and thus myocardial oxygen consumption (Howard J. C., 1971). Any operation performed under general anaesthesia has a large psychological and auto-suggestive effect which may break the vicious circle of anxiety and angina and thus produce a symptomatic improvement out of proportion to true reduction in myocardial ischaemia. The potency of this effect was clearly demonstrated in a study of patients with severe angina who reported marked improvement following a sham operation (Dimond et al., 1960).

Secondly, there is a non-specific effect of any form of surgery involving the surface of the heart and the pericardium in stimulating

the formation of adhesions containing collateral vessels. This phenomenon was well known to Beck who noted the effect of intra-pericardial dissection in producing a measurable increase in coronary collateral flow (Beck and Leighninger, 1954; Beck and Leighninger, 1955). Furthermore Robertson (1935) progressively tied off all coronary arteries in a group of dogs during six separate operations. The surviving animals had many vascular adhesions over the myocardium. Division of these adhesions resulted in death of the dogs from myocardial infarction. Similar naturally occurring cases have been reported in which humans with pericardial adhesions have been able to survive complete proximal occlusion of both main coronary arteries (Thorel, 1932; Leary and Wearn, 1930). Clearly if sufficient adhesions were present the resulting collateral circulation could completely replace the original coronary blood supply. Thus any surgical procedure to revascularise the heart can be expected at worst to result in pericardial adhesions which will provide a slightly increased blood supply even if the specific procedure itself is ineffectual.

Thus in the evaluation of any new surgical procedure to revascularise the heart these non-specific effects must be taken into consideration. More reliable indices of benefit are reduced annual mortality and infarction rates in patients with coronary artery disease. In experimental animals the efficacy of revascularisation is best gauged by a measurable improvement in ventricular function, increased coronary flow and reduced infarct size following coronary occlusion. It

was with these thoughts in mind that the project described in this thesis was undertaken.

PART A

REVASCULARISATION OF THE CHRONICALLY ISCHAEMIC VENTRICLE

CHAPTER 2

PRELIMINARY STUDIES

Preliminary work was required to develop an animal preparation suitable for revascularisation. Several different methods were used before a workable system was devised to produce chronic myocardial ischaemia and then to reverse this by surgical revascularisation.

(A) DEVELOPMENT OF A MODEL OF MYOCARDIAL ISCHAEMIA

High Cholesterol Diet

Ideally, in studying myocardial ischaemia, one should employ an animal with atherosclerotic heart disease. Atherosclerosis in dogs and rabbits was produced by the Lipid Group at Duke University under Dr. Per-Otto Hagan, by feeding the animals high cholesterol diets. These animals were used for the study of lipid content of vascular walls. Besides being expensive to produce by dietary means (about $700 per animal in the case of dogs), the disease is variable in its distribution in the coronary system. Thus, not all atherosclerotic animals are suitable for revascularisation and a very large number of animals would have to be fed the fatty diet to yield enough animals for a surgical study. Such a project could be done only with a major commitment of manpower and money, and in the end would still be subject to questions of species difference in its application to humans.

Coronary Artery Ligation

Initially, ligation of the proximal left anterior descending coronary artery was performed in three anaesthetised dogs. One animal died within a few minutes from ventricular fibrillation, another died as the chest was being closed and the third died on the day following surgery. A similarly high mortality had been described in a large number of dogs by Harris (1950) and therefore this method was abandoned.

Coronary Artery Snare

As reported in Chapter 7 it was possible with a low immediate mortality rate, to occlude acutely the circumflex coronary artery in the unanaesthetised animal using a previously implanted snare. However, at thoracotomy the dense fibrosis found around the snare and the adjacent coronary artery made the preparation unsuitable for surgical revascularisation.

Ameroid Constrictors

Finally it was decided to implant miniature "ameroid" constrictors (Vineberg et al., 1960) which gradually would occlude the circumflex coronary artery. The coronary artery became occluded seven to ten days after implantation of the constrictor.

In the first 13 dogs which were revascularised an average of 52 days after implantation, there was copious retrograde flow from the coronary artery when it was opened distal to the constrictor.

Also large epicardial collateral vessels could be seen running from the left anterior descending coronary artery to the distal circumflex coronary artery. Thus revascularisation had already been carried out by the animals' own collateral vessels. To reduce this effect, when the constrictor was implanted in the remainder of the animals, ligatures were applied to any branches of the left anterior descending coronary artery seen to be running near circumflex coronary artery branches. Also, the dogs were studied sooner, i.e. 14 to 25 days after implantation of the constrictor. This resulted in a standard amount of myocardial ischaemia at a predictable time.

(B) REVASCULARISATION

Vein Grafts in Dogs

Initially in a group of ischaemic dogs, long term revascularisation was attempted, using either an internal mammary artery to circumflex coronary artery anastomosis or aorto-coronary vein bypass graft. Nine dogs survived the operation. Of these, two died between two and three days post-operatively. In the remaining seven dogs, angiographic studies were done two to nine days post-operatively. Only one dog was shown to have a patent graft when studied two days after the operation (Fig. 1). The other six animals were found to have clotted grafts at the time of study, the occlusion usually being at the coronary end of the anastomosis. The main problem encountered was that of achieving a satisfactory anastomosis between the graft

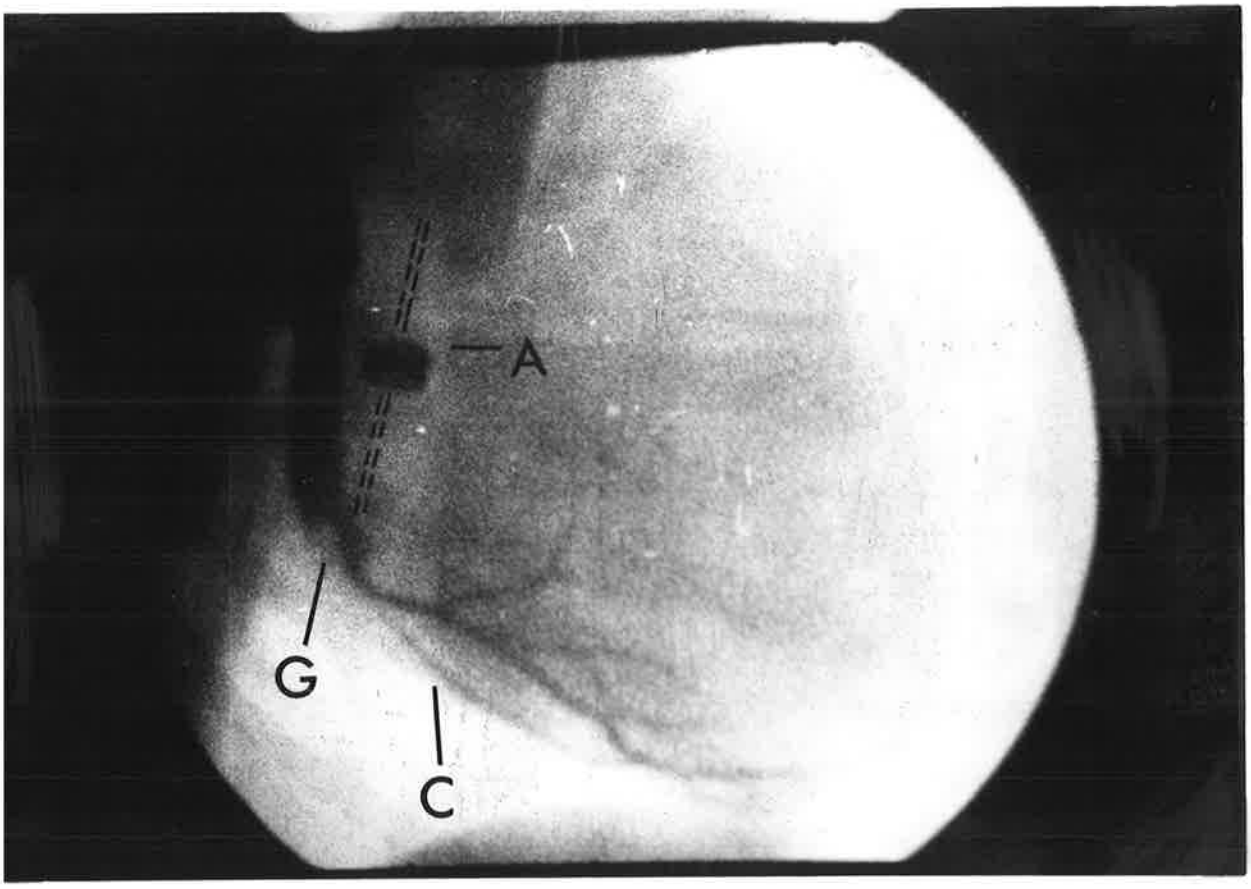


Figure 1. Single frame from a cineangiogram done in the right lateral projection showing an aorto-coronary vein graft (G) filling the circumflex coronary (C) distal to the occluded constrictor (A). The dotted lines indicate the unfilled circumflex coronary artery proximal to the anastomosis.

vessel and the circumflex coronary artery with the heart beating. Distal to the closed ameroid constrictor the circumflex coronary artery narrowed to a thin walled vessel one to two millimetres in diameter. It was found difficult accurately to suture the graft to this small vessel with the heart beating. This problem could have been overcome by the use of cardiopulmonary bypass and induced ventricular fibrillation to produce a quiescent heart while the anastomosis was performed. A simpler and very reliable method of revascularisation was finally developed using a polyethylene shunt with a built-in flow probe. This produced uniformly successful revascularisation but meant that the animal required anticoagulation and that the function study be done acutely.

(C) MEASUREMENT OF VENTRICULAR FUNCTION

During initial studies using chronic grafts, ventricular function was assessed using the angiographic ejection fraction measured from biplane cineangiograms (Dodge, 1962). For acute studies this method proved less suitable since repeated measurements resulted in the injection of a large volume of contrast material which is known to depress ventricular function (Behar, 1970). Also, this technique does not lend itself readily to measuring the response of the ventricle to stress. Finally, the stroke work vs left ventricular end-diastolic pressure ventricular function curve (Sarnoff, 1954) was chosen to measure ventricular function. A right heart

bypass technique was used to generate these curves. This method offered the advantage of speed, reproducibility, and the inclusion of a stress to the heart.

CHAPTER 3

EXPERIMENTAL METHODS

(A) PRODUCTION OF MYOCARDIAL ISCHAEMIA

The animals used were mongrel dogs weighing between 18 and 26 kilograms. Under pentobarbital anaesthesia (30 mg/kg) a left lateral thoracotomy was performed. An ameroid constrictor was placed around the proximal part of the circumflex coronary artery. Ameroid is a plastic product made of casein which swells when it absorbs water. The coronary artery ameroid constrictors are made from a bar of ameroid in which a central lumen has been drilled. Communicating with this lumen from the periphery there is a slot large enough to permit a coronary artery to be slid into the central lumen. The ameroid is enclosed in a slotted stainless steel cylinder. When the ameroid becomes wet with tissue fluid it swells, the central lumen is gradually narrowed and the coronary artery occluded in seven to fourteen days (Vineberg, 1960). To increase the severity of the ischaemia two to three lateral epicardial branches of the left anterior descending coronary artery were ligated (Fig. 2). The animals were allowed to recover for a period of 14 to 25 days at which time the circumflex coronary artery had become occluded.

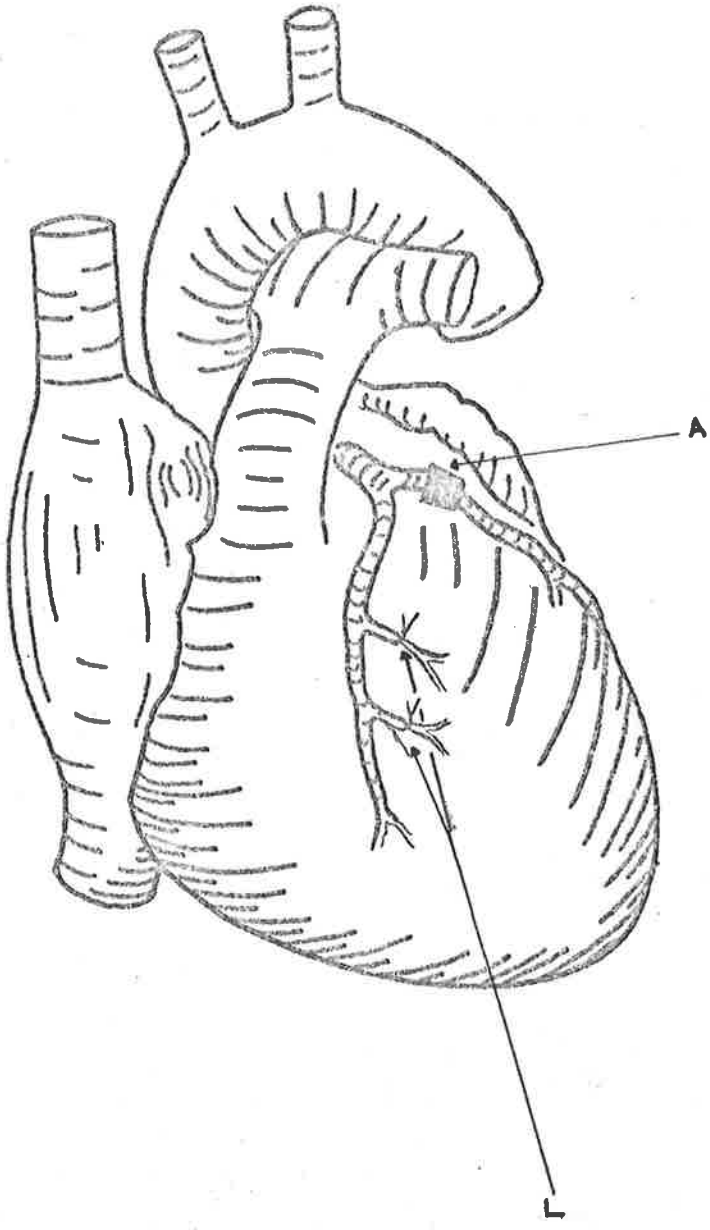


Figure 2. Ameroid constrictor (A) in place on the proximal portion of the circumflex coronary artery and the ligatures (L) on branches of the left anterior descending coronary artery.

(B) REVASCULARISATION

The animals were premedicated with morphine sulphate (1.5 mg/kg, IM), anaesthetised with chloralose (80 mg/kg, IV), intubated and ventilated with 100% oxygen. Through a median sternotomy the circumflex artery was dissected distal to the ameroid constrictor and an electromagnetic flow probe was placed temporarily around the vessel. Absence of flow confirmed that the constrictor had closed. The distal circumflex coronary artery was cannulated with a Teflon cannula of 2 mm internal diameter. Retrograde flow from the cannula against atmospheric pressure was measured by 30-second collections in a graduated cylinder. Collections were done in triplicate and the results averaged.

Revascularisation was performed using a polyethylene shunt with a built-in square wave electromagnetic flowmeter probe* connecting the left subclavian artery to the cannula in the circumflex coronary artery (Fig. 3). This compact and lightweight system was made specially for the study. It fitted snugly in the pericardium and performed reliably. The total length of the shunt was 25 cm and its internal diameter was 5 mm except at the flow probe head where it narrowed to 2.5 mm. The pressure gradient measured across this system between the aorta and the circumflex coronary artery was negligible. To

* Model RC-1000 Micron Instruments Incorporated, Los Angeles, California, U.S.A.

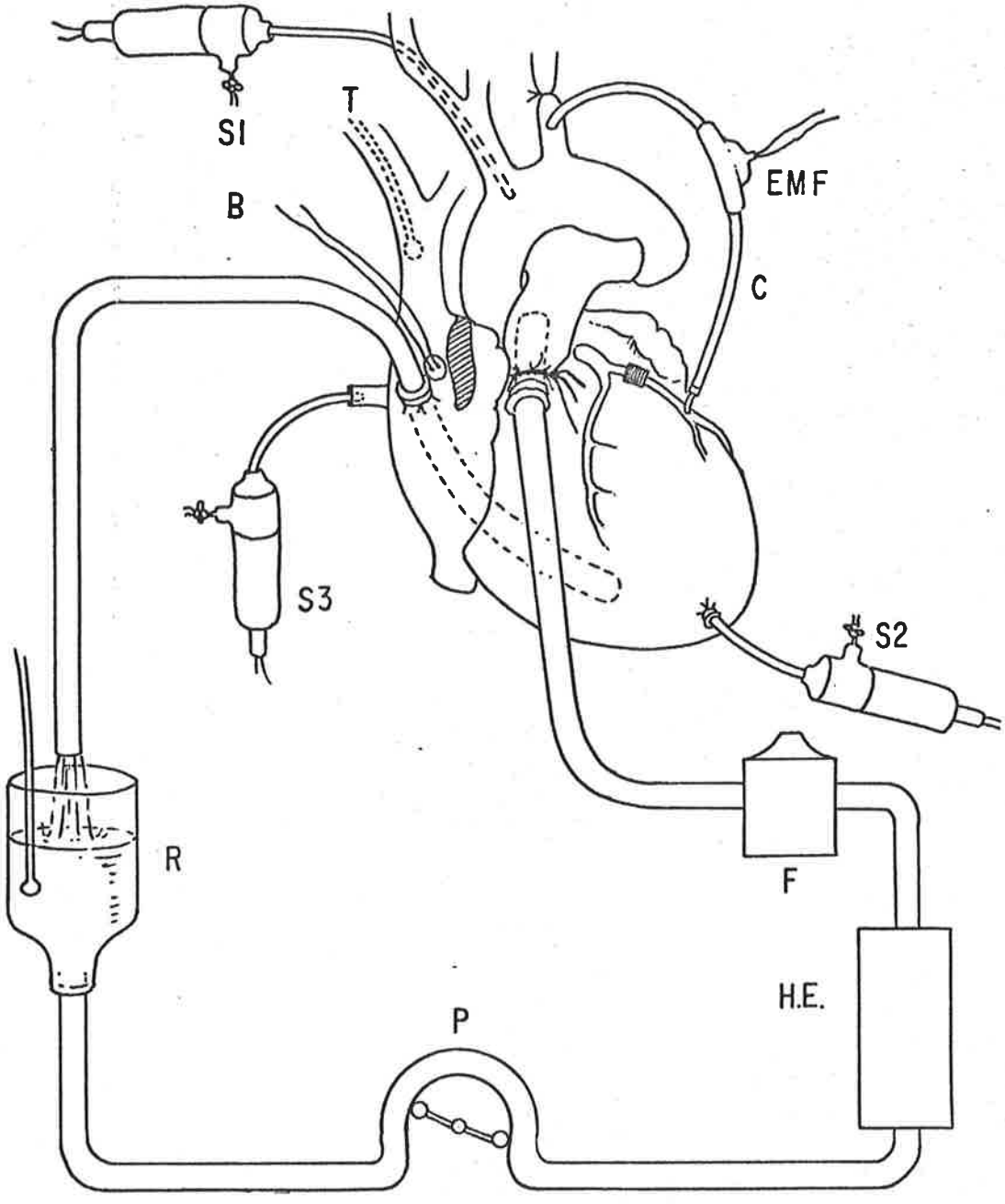


Figure 3. The right heart bypass circuit and the revascularisation shunt. S1, S2, S3 = strain gauges; T = thermistor; EMF = electromagnetic flow probe; C = shunt cannula; F = filter; HE = heat exchanger; P = roller pump; R = blood reservoir; B = bipolar pacing electrode.

obtain flow zeros from the flowmeter, the shunt tubing was clamped distal to the flow probe. The "electrical flow zero" which could be obtained from the flowmeter by a switch often differed from the true mechanical flow zero and was therefore not considered reliable. The flow probe was calibrated periodically by passing normal saline through it at a known rate (see Ch. 3(F)). Calibrations remained within a standard deviation of ±5% during the period of the studies.

(C) VENTRICULAR FUNCTION CURVES

Pressure monitoring catheters were inserted into the left atrium through the right superior pulmonary vein and into the aorta through the right common carotid artery. A short metal cannula of 3.5 mm internal diameter was passed into the left ventricle through the apex. All monitoring lines were connected to Statham P23Db transducers zeroed at the level of the left atrial appendage. Any animal showing in the left atrial pressure tracing evidence of mitral insufficiency was excluded from the study. The left ventricular pressure signal was used for the simultaneous measurement of the left ventricular end-diastolic pressure and full left ventricular pressure pulse. Bilateral vagotomy was performed, the sino-atrial node crushed and the heart paced at a constant rate with a bipolar electrode sutured to the right atrial appendage.

A right heart bypass technique was used to deliver a volume stress to the heart and to generate ventricular function curves.

Systemic and coronary venous return were drained from the right ventricle into a reservoir and pumped by a pre-calibrated roller pump through a heat exchanger and Dacron wool filter* to the pulmonary artery† (Fig. 3). The bypass circuit was primed with 500 ml of fresh heparinised donor blood and 1000 ml of normal saline.

A tendency of the animals to develop pulmonary oedema and hypoxia at the high pump flow rates was observed. This complication of the right heart bypass technique has been described previously and has limited maximum pump flow rates and thus the amount of stress able to be applied to the left ventricle (Covell et al., 1966). However, in this study it was found that this problem could be overcome by the addition of a positive end-expiratory pressure of 5 cm of water to the exit port of the ventilator once right heart bypass had been established. The efficacy of positive end-expiratory pressure in maintaining normal pulmonary function was proven in two dogs with normal hearts subjected to prolonged periods of right heart bypass at high flow rates and high left atrial pressures. Increasing the pump flow rate eventually produced hypoxia and pulmonary oedema. After the end-expiratory pressure was added the hypoxia and pulmonary oedema were reversed. Subsequently when the end-

* Pioneer Filters, Inc., Hillsboro, Oregon, U.S.A.

† For details of the roller pump and calibration procedure see Chapter 3(F).

expiratory pressure was removed, hypoxia returned and haemorrhagic pulmonary oedema ensued. A positive end-expiratory pressure was then used throughout the revascularisation studies. Blood gases were monitored at 20-30 minute intervals. No measurements of ventricular function were made if the arterial PO_2 fell below 70 mm Hg.

Blood temperature was monitored by a thermistor in the superior vena cava and maintained at 38^{0} C (normal canine blood temperature). Aortic pressure was not held constant, but was allowed to rise with increasing pump output, thus adding a pressure stress to the volume load. Stroke work vs left ventricular end-diastolic pressure ventricular function curves were generated by stepwise increases in the pump output until a cardiac output of 3L/min or a left ventricular end-diastolic pressure in excess of 30 mm Hg was obtained. An initial control curve was obtained without graft flow. In order to minimise any "graft-dependence effect" (see Chapter 4) initial control curves were obtained in dogs nos. 6, 8, 9, 10 and 11, before the graft was first inserted and in most of the other dogs only a short time after insertion. The graft was then opened and after two minutes a second ventricular function curve was obtained. The graft was clamped for two minutes and a second control curve generated. This procedure was then repeated until five to seven satisfactory curves were obtained or the preparation became unstable. Any curves generated with the graft open were discarded if the preceding and subsequent control curves with the graft closed were appreciably different.

In eight animals, to block the effects of sympathetic stimulation, function curves were also obtained after the addition of propranolol (0.2 mg/kg) to the perfusion system. Three additional animals (Nos. 1, 2 and 3) were given propranolol immediately after right heart bypass was begun, but then developed progressive ventricular failure. The beta-receptor blockade was reversed and the animals' condition stabilised for the study by the administration of a constant infusion of epinephrine or isoproterenol (0.3-0.8 µg/kg/min). Heparin (1.5 mg/kg) was administered intravenously prior to institution of bypass and thereafter 2 mg was added half-hourly to the perfusate. Left ventricular stroke work was calculated from the equation: LVSW = $\frac{SV(AoP-LVEDP)}{1000}$ x 13.6, where LVSW = left ventricular stroke work (gm-m), AoP = mean aortic pressure (mmHg), LVEDP = left ventricular end-diastolic pressure (mmHg) and SV = left ventricular stroke volume (ml/beat). All data were recorded on an eight-channel pen recorder model 7700 and also on seven channel analogue magnetic tape using a Hewlett-Packard recorder series 3955. Fig. 4 shows an original recording.

(D) FORCE-VELOCITY MEASUREMENTS

As an additional quantitation of the contractile state of the heart before and after revascularisation, an index of contractility was calculated from the first derivative of left ventricular pressure with respect to time (dP/dt). The first derivative was obtained

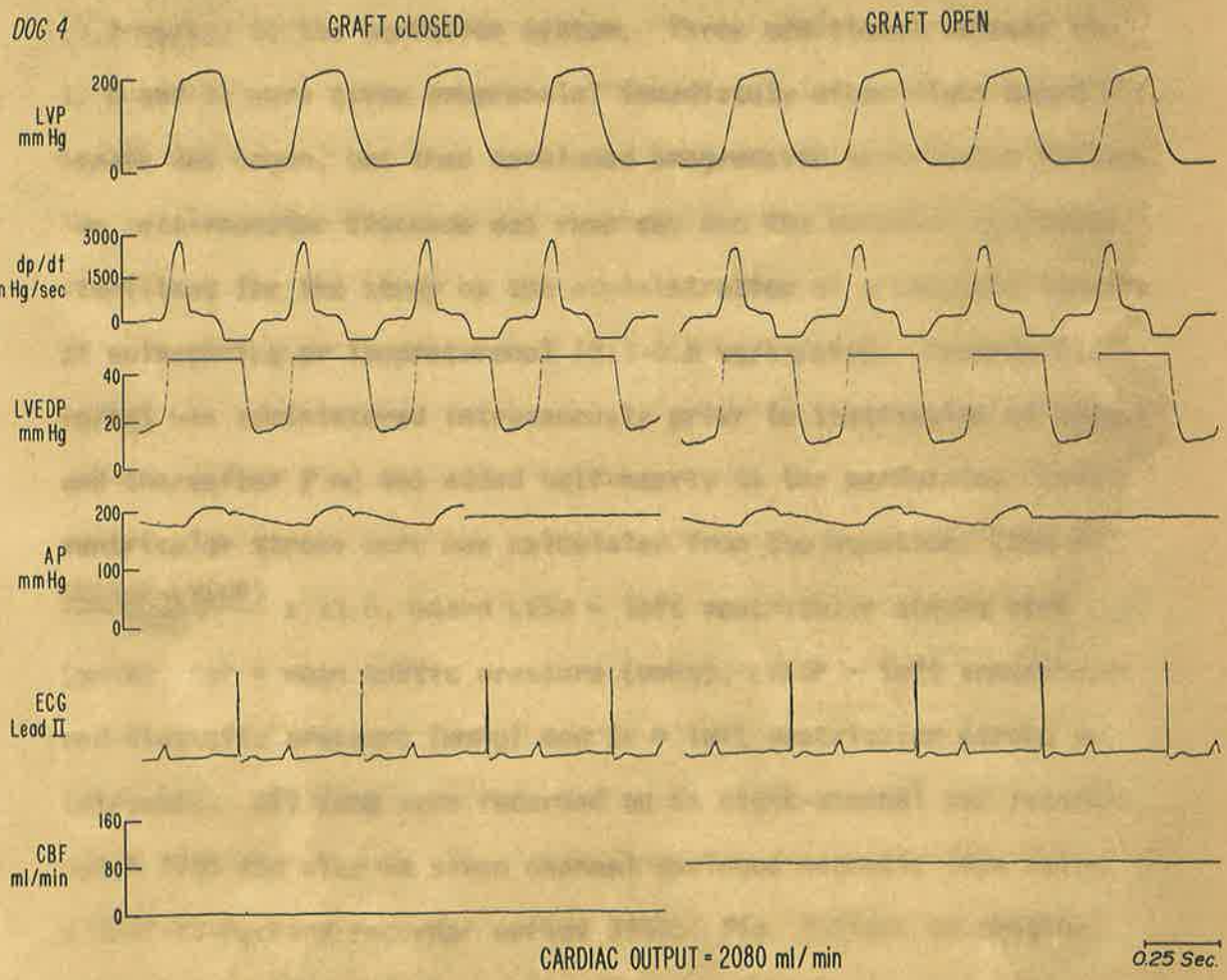


Figure 4. Original recordings from a dog during volume loading (high pump flow), showing from above downwards: left ventricular pressure, first derivative of left ventricular pressure, high gain left ventricular pressure, phasic and mean aortic pressure, lead II electrocardiogram showing pacing artefact and mean graft flow. Opening the graft produced a fall in left ventricular end-diastolic pressure from 16 mm Hg to 11 mm Hg.

from the left ventricular pressure signal by a Hewlett-Packard 350-16 RC Differentiator. This unit had a time constant of 0.29 sec and the output voltage increased linearly (within 5%) with frequency up to 20 c.p.s. The phase shift of the derivative produced with respect to the input signal was measured using a sine wave generator. Phase shift was found to vary linearly with frequency, being 90^{o} at 0 c.p.s. and 68^{o} at 5 c.p.s. The contractile element velocity index was calculated from the equation $V_{CE} = \frac{dP/dt}{KP}$ where V_{CE} is a measure of the contractile element velocity of the myocardium, P is isovolumic left ventricular pressure (mmHg), and the constant K = 28 (Sonnenblick et al., 1969). The left ventricular pressure and dP/dt were digitised from the magnetic tape recordings at 2.5 millisecond intervals and the calculations carried out by an IBM 1130 computer. A correction for phase shift was introduced. Four beats were plotted together to yield one composite pressure-velocity curve. V_{CE} was estimated by the peak measured value of contractile element velocity, V_{PM} (Nejad et al., 1971).

(E) PATHOLOGICAL EXAMINATION

At the conclusion of the study the dogs were put to death and the hearts removed. The ventricles were sliced transversely, any infarct present was noted and its extent recorded diagrammatically*.

* for sample record see Appendix.

Blocks were taken for microscopy from areas of definite and suspected infarction.

The ostium of the left coronary artery was cannulated and water injected to confirm closure of the ameroid constrictor.

(F) CALIBRATION PROCEDURES

(1) Calibration of Roller Pump

Description. The pump used was a Sarns Model 3600 roller pump. The roller head, which compresses flexible tubing, is driven by an electric motor powered by an adjustable voltage source. The voltage determining the roller speed and thus the pump output, can be varied continuously by a potentiometer and is read directly from the built-in voltmeter. The control section of the pump incorporates a feedback circuit which detects changes in the load and keeps the roller speed constant. In all studies and calibration procedures, 3/8" internal diameter plastic tubing was used in the roller head.

Calibration method. The calibration procedure was performed periodically between studies. For convenience, calibrations were routinely done using warm tap water. Comparison calibrations were done between water and blood at the same temperature, to estimate the error introduced by using water in the routine calibrations.

The pump inflow tubing was connected to a reservoir and the pump outflow was collected in a measuring cylinder during 20 or 30

second periods. Measurements were made in triplicate at each pump speed and the results averaged. Calibration curves of blood flow against motor voltage were plotted. Linear regression analysis was done on the data and the standard error calculated.

Results. Figure 5 shows the calibration curve obtained during three calibrations done several months apart. The calibration for water was found to be essentially linear. There was little variation in the calibrations for water done at different times, the standard error of ± 84 ml was only 3% of the average maximum flow rate used in the studies. At the high flow rate the calibration curve for blood is distinctly non-linear. At the average maximum flow used throughout the studies (2,500 ml/min) this non-linearity introduced an error of 100 ml/min or 4% into the flow readings.

It was found during calibration that the pump output was unaltered by placing resistances in the outflow tubing which produced pressure loads up to 200 mmHg. However, placing resistance in the inflow tubing to the pump by occluding 2/3 of its lumen markedly attenuated pump output.

Discussion. The convenience and accuracy of this pump made it useful for controlling the cardiac output in the right heart bypass circuit. The slight non-linearity for blood would not introduce significant error into the ventricular function measurements where left ventricular end-diastolic pressure or V_{PM} values were compared

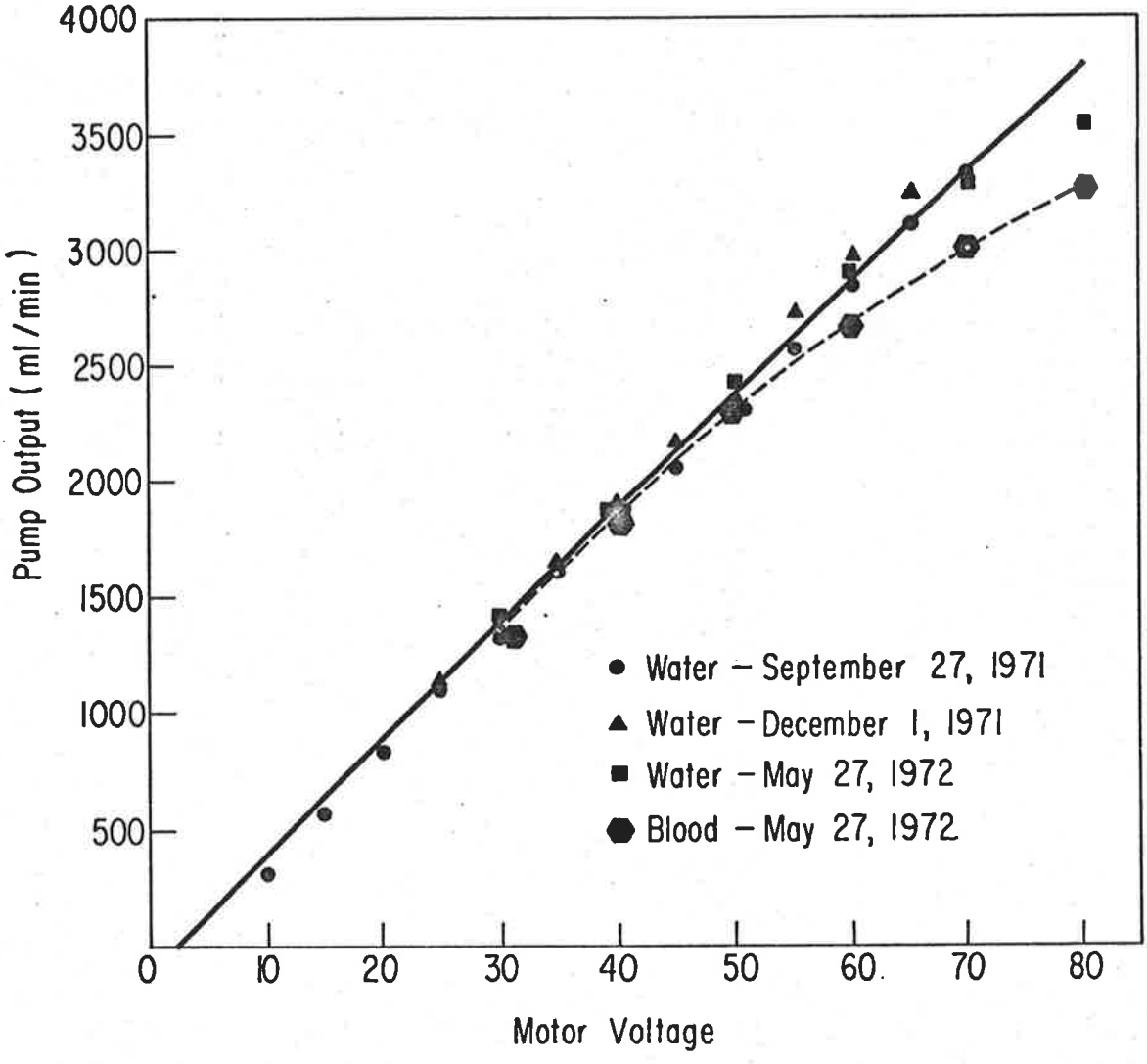


Figure 5. Calibration curves for the roller pump done on three separate occasions.

with the graft open and then closed, as comparisons were always done at the same pump settings.

During the course of studies using the right heart bypass circuit described, loading conditions would be unlikely to influence pump output. The outflow resistance of the filter and heat exchanger was low and the pulmonary artery pressure, when measured on several occasions, never approached 200 mm Hg even at the highest flow rates. Thus, outflow resistance did not affect pump accuracy. Resistance in the inflow tubing was always low, being the 50 cm column of blood between the pump and the blood level in the reservoir. This negative pressure was well below levels shown to alter pump output.

(2) Calibration of Flow Probe Shunt

Description. The special shunt used to bypass the occluded circumflex coronary artery was made from a short length of polyethylene tubing of 5 mm internal diameter. A 2.5 mm square wave electromagnetic flow probe* was sealed in the tubing so that all the blood passed between the contacts of the flow probe. The signal from the flowmeter was recorded by a Sanborn model 7700 pen recorder.

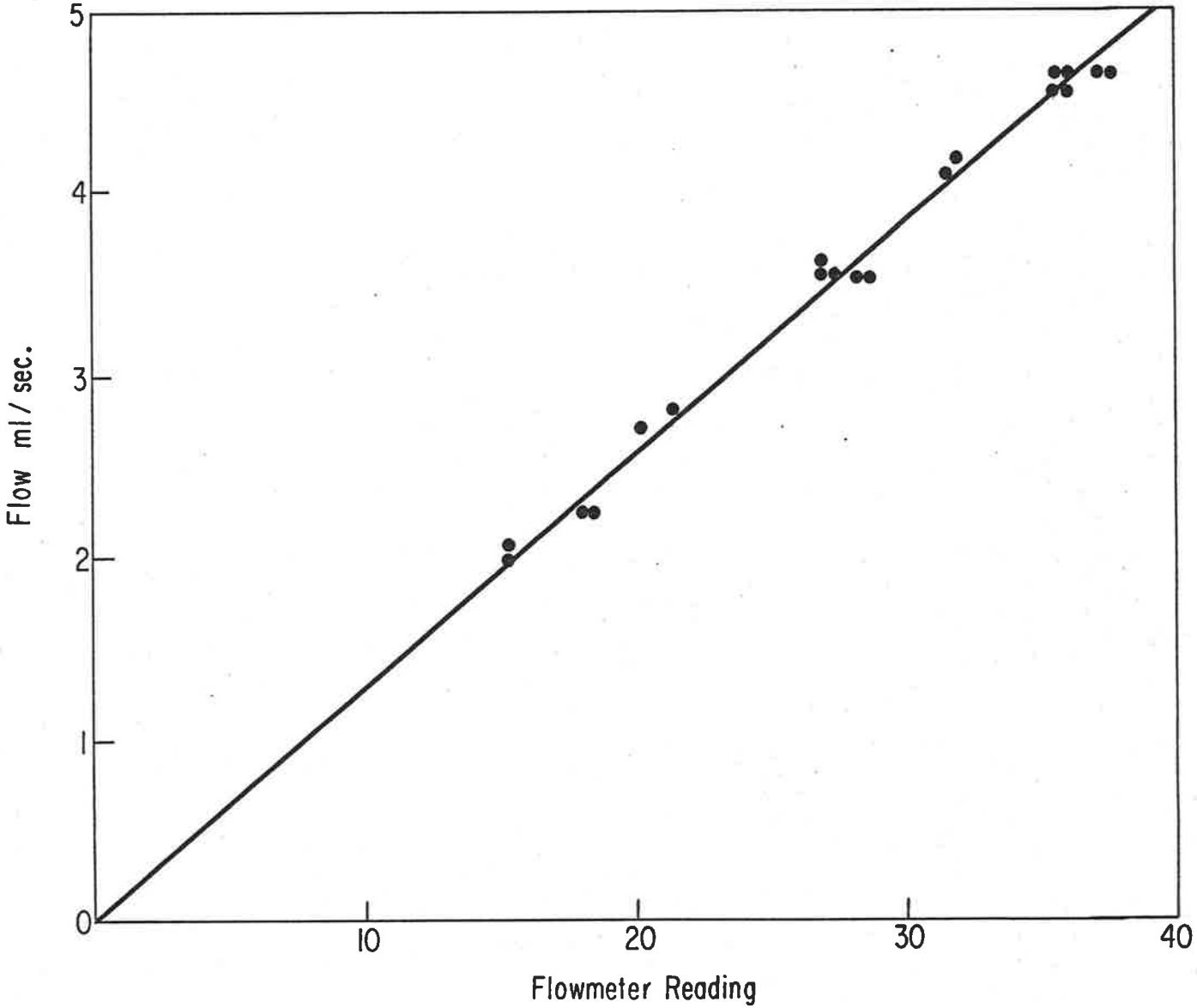
Calibration method. Normal saline was passed through the flow probe at a constant rate, a timed collection performed using a measuring cylinder and the flow signal was recorded. These measurements

* Micron Instruments, Inc., Los Angeles, California.

were carried out three times at each flow rate and the flowmeter readings were averaged. This procedure was then done at three different flow rates and a calibration curve plotted.

Results. Figure 6 shows a composite calibration curve produced by plotting together the results of three separate calibrations done on the same day. The plot of flow signal vs flow was always found to be linear over the range of flow tested. The calibration factor remained within a standard deviation of ±5% during the period of the studies. It has been shown previously that the use of saline instead of blood increases the signal output of the electro-magnetic flowmeter by approximately 5% (Greenfield et al., 1962). However, changing the haematocrit from 20 to 45% does not influence the calibration.

Figure 6. Calibration curve for electromagnetic flowmeter probe.


Flow ml / sec.
0
1
2
3
4
5
10
20
30
40
Flowmeter Reading

CHAPTER 4

RESULTS

(A) PATHOLOGY

The development of myocardial ischaemia produced a 26% mortality in the 35 dogs surviving surgery. Death usually occurred at seven to ten days post-operatively when the constrictors were almost completely closed. The most common histological finding at the time of death or sacrifice after study was small areas of chronic infarction at the sites of the ligatures on the branches of the left anterior descending coronary artery and more recent subendocardial infarction on the posterior left ventricular wall. Twenty-five per cent of dogs surviving surgery showed no evidence of infarction. There was no correlation between the presence or absence of infarction and the degree of functional improvement following revascularisation.

Of the 26 animals surviving coronary constriction, 24 were used in the ventricular function study and two (dogs 14 and 15) were used for measurements of graft flow and collateral flow only.

(B) VENTRICULAR FUNCTION CURVES

The ischaemic animals were often haemodynamically unstable and tolerated poorly the procedures necessary for revascularisation and institution of right heart bypass. Stable conditions and repro-

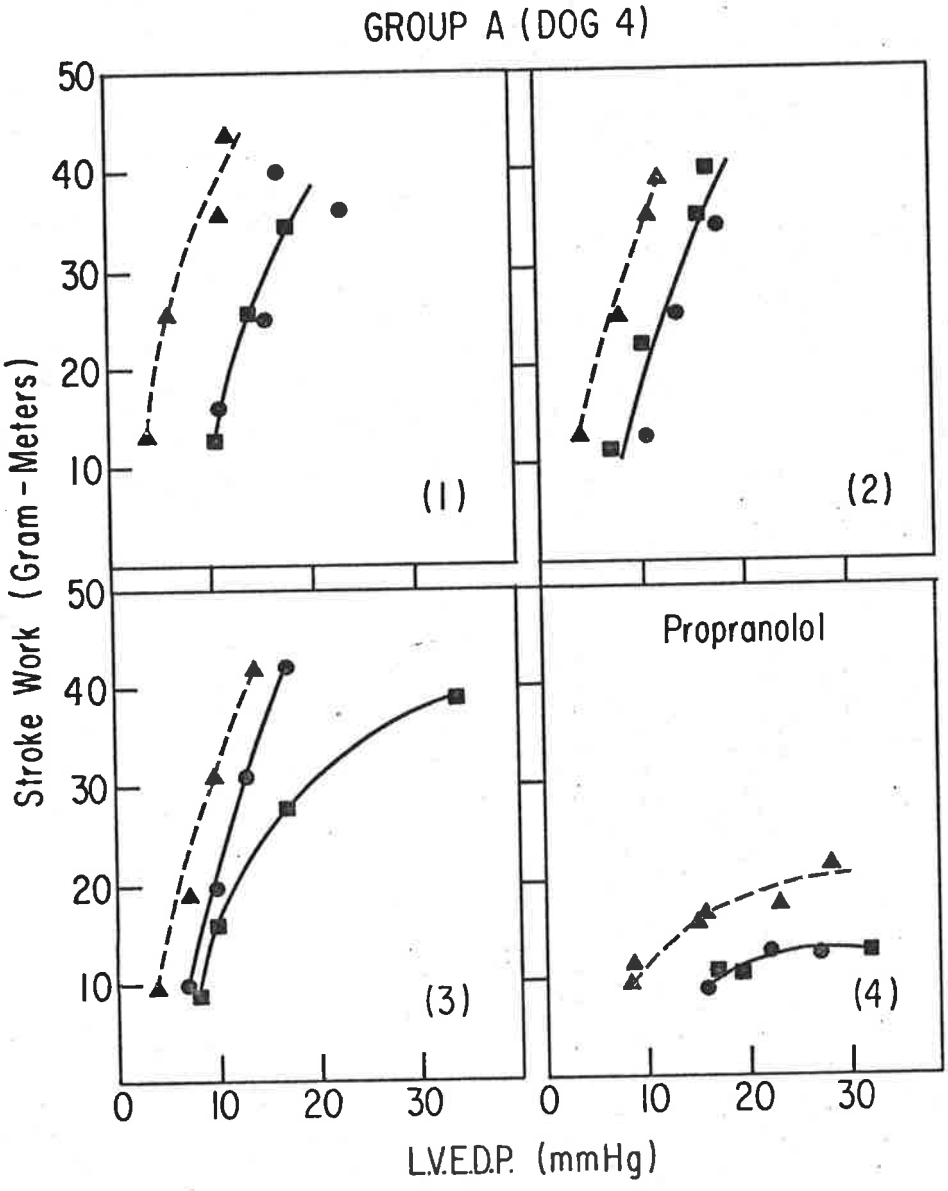


Figure 7. The effect of opening the graft on successive ventricular function curves in a representative animal from Group A (dog 4). Opening the graft produced an immediate improvement in ventricular function: Panels 1-3. This improvement was also seen after administration of propranolol: Panel 4. The circles and continuous lines represent the curve generated with the graft occluded. The triangles and broken lines represent the curve with the graft open. The squares and continuous line represent the curve with the graft re-occluded.

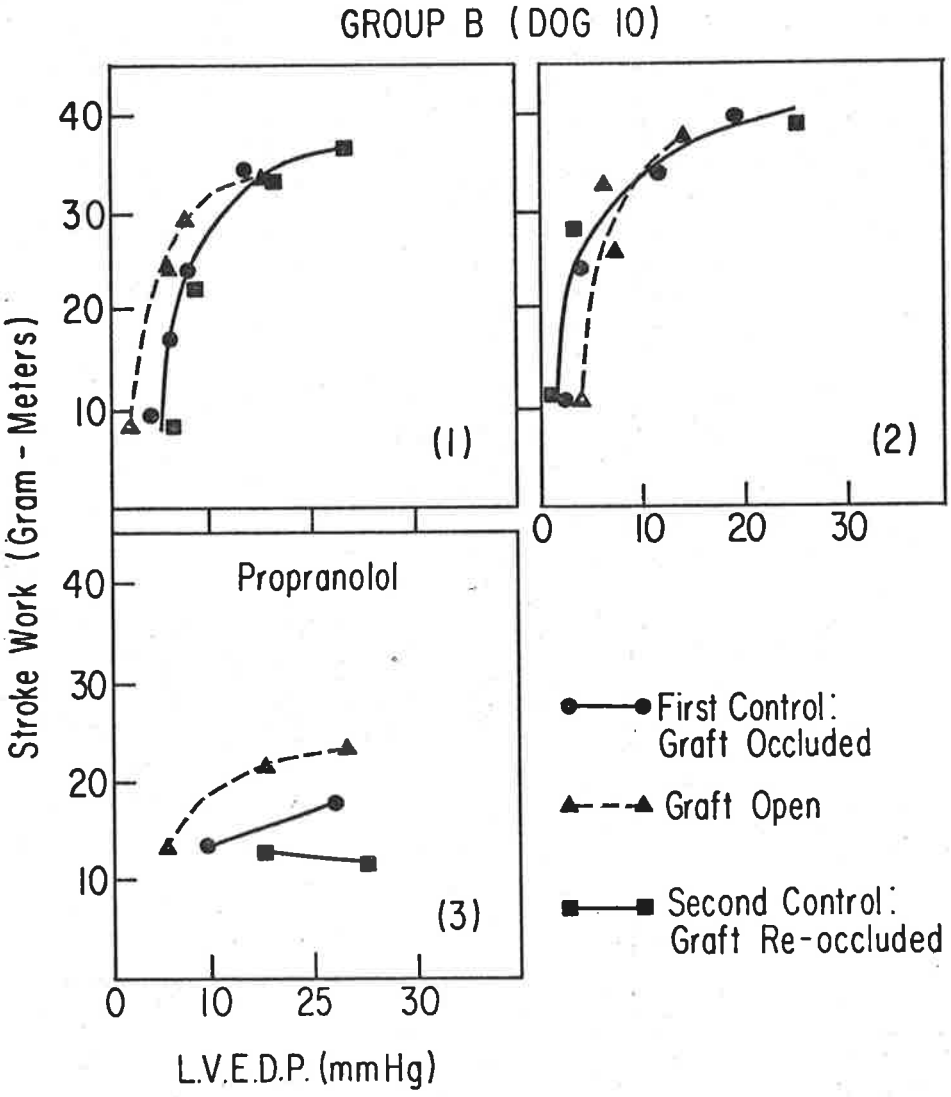


Figure 8. The effect of opening the graft on successive ventricular function curves in an animal from Group B (dog 10). Opening the graft produced no improvement in function: Panels 1 and 2, until after the administration of propranolol: Panel 3.

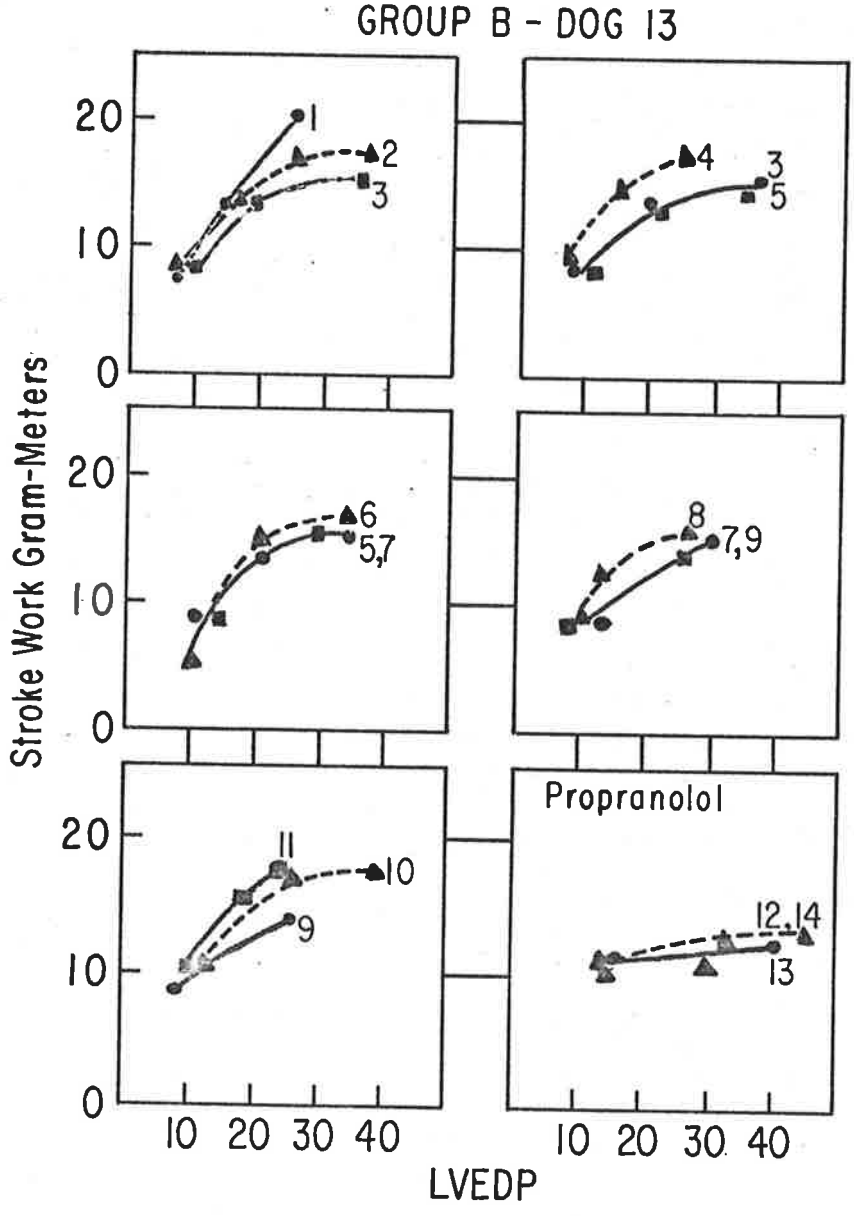


Figure 9. Consecutive ventricular function curves in a Group B dog showing no change in ventricular function on opening the graft before (curves 1-11) or after (12-14) beta-receptor blockade. The odd numbered curves were obtained with the graft open, the even numbered with the graft closed. The symbols used are the same as in Fig. 8.

ducible function measurements were obtained in only 13 animals. In these, a total of 114 function curves were obtained.

The animals could be divided into two groups on the basis of the effect of revascularisation on ventricular function. Group A consisted of six animals in which opening the graft produced immediate improvement in ventricular function manifested by a displacement of the ventricular function curve upwards and to the left as compared with the control curves. This improvement in ventricular function produced by opening the graft was also seen in curves obtained after the administration of propranolol in three of these dogs. Figure 7 shows ventricular function curves from a representative group A animal. Group B comprised seven animals showing no immediate alteration in the ventricular function curve on opening the graft. Five Group B dogs were given propranolol and subsequently three of these showed an increase in contractility when the graft was opened. Ventricular function curves from animals showing these two response patterns are shown in Figures 8 and 9.

Animals were compared with each other at high stress by comparing left ventricular end-diastolic pressure (LVEDP) measured with the graft open with that when the graft was closed at constant levels of aortic pressure, heart rate and the same high level of cardiac output (Table 1). In preparing Table 1, only those values of LVEDP (the graft open and then closed) were used where the corresponding aortic pressures were within 9% of each other. Each given value

TABLE 1

CHANGES IN LEFT VENTRICULAR END-DIASTOLIC PRESSURE PRODUCED BY OPENING THE GRAFT

DOG NO.	GRAFT	CO ml/min	LVEDP mm Hg	MAP mm Hg	CO ml/min	LVEDP mm Hg	MAP mm Hg
GROUP A: IMMEDIATE IMPROVEMENT IN FUNCTION FOLLOWING REVASCULARISATION							
1	Closed	840	29	107			
	Open	840	18	111			
2	Closed	2080	31	126			
	Open	2080	18	128			
3	Closed	1580	39	151	After Propranolol		
	Open	1580	31	161			
4	Closed	2330	17	200	1330	30	141
	Open	2330	12	190	1330	15	152
5	Closed	2330	28	117	1330	24	63
	Open	2330	8	116	1580	9	74
6	Closed	3230	34	172	2700	30	136
	Open	3230	27	172	2700	24	148
MEAN ± SE	Closed		30±3.0*	146		28±2.0	113
	Open		19±3.6	146		16±4.3	125
GROUP B: NO IMMEDIATE CHANGE IN FUNCTION FOLLOWING REVASCULARISATION							
7	Closed	2180	16	148			
	Open	2180	15	143			
8	Closed	2980	12	145	After Propranolol		
	Open	2980	10	136			
9	Closed	1830	15	123	1350	40	102
	Open	1830	12	120	1350	13	96
10	Closed	2840	11	162	1330	18	124
	Open	2840	11	165	1330	8	126
11	Closed	3230	12	133	2700	26	145
	Open	3230	12	130	2700	13	148
12	Closed	2350	11	130	2520	11	131
	Open	2350	12	136	2520	10	125
13	Closed	2080	29	103	1550	40	118
	Open	2080	29	105	1550	38	110
MEAN ± SE	Closed		15±2.4	135		27±5.8	124
	Open		14±2.5	134		16±5.5	121

TABLE 1 (CONTINUED)

ABBREVIATIONS

CO = Cardiac Output

LVEDP = Left Ventricular End-Diastolic Pressure

MAP = Mean Aortic Pressure

All "closed values are the means of readings taken before and after the graft was opened

* $p<0.01$

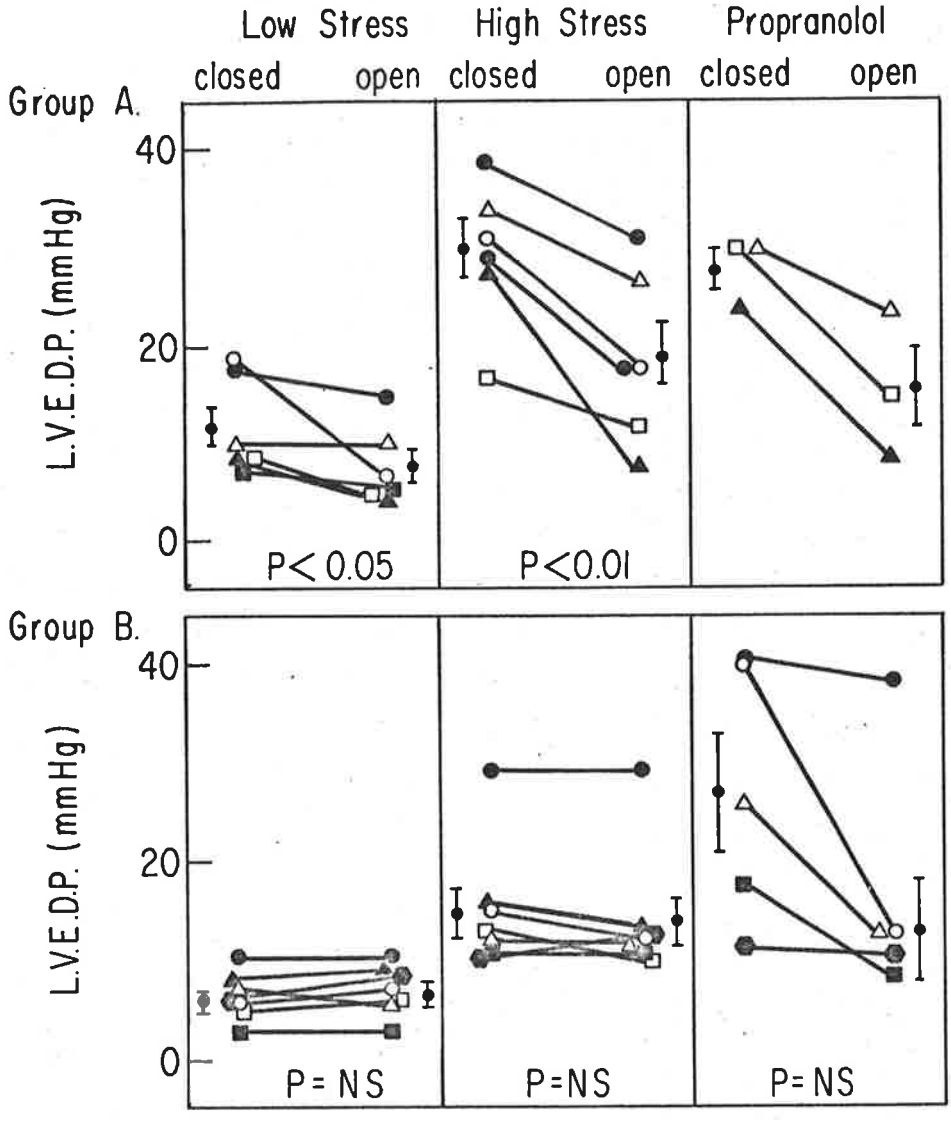


Figure 10. The effect of volume loading and propranolol in eliciting improvements in contractility produced by opening the graft. In Group A dogs (upper panels), the fall in left ventricular end-diastolic pressure (LVEDP) on opening the graft is greater after volume loading (high stress), and is also seen after propranolol. In Group B dogs (lower panels), there is no change in LVEDP on opening the graft even after volume loading. However, 3 of the 5 dogs receiving propranolol and a volume load showed a fall in LVEDP on opening the graft. The bars represent mean ± SEM.

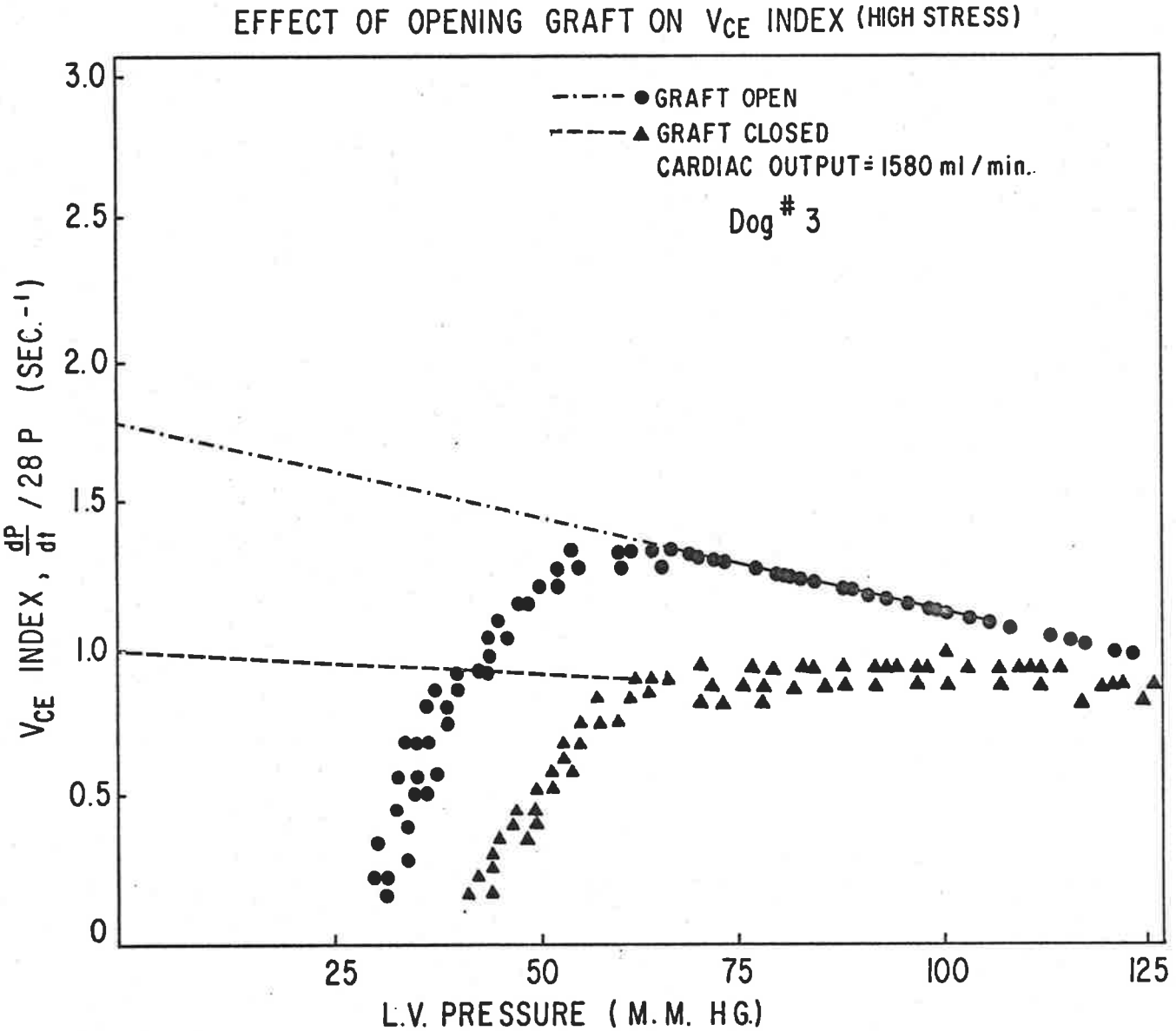
of LVEDP and aortic pressure represents the mean of all the corresponding values obtained during consecutive volume loading runs. In Group A during volume loading, the mean LVEDP with the graft open: 19±3.6 mmHg (SEM), was significantly lower than that with the graft closed: 30±3.0 mmHg ($P<0.01$). Readings obtained in three dogs (numbers 4, 5 and 6) after administration of propranolol also showed a lower LVEDP with the graft open than closed. In Group B there was no significant mean change in LVEDP when the graft was opened. However, in three animals (numbers 9, 10 and 11), after the administration of propranolol, opening the graft during stress caused a 42% mean fall in LVEDP. Figure 10 demonstrates these changes in graphic form and shows the effect of a volume stress and propranolol in eliciting differences not otherwise evident*.

(C) FORCE-VELOCITY MEASUREMENTS

The effect of revascularisation on contractility was measured by the V_{PM} index in 12 of the 13 dogs. Figure 11 shows force-velocity curves from a representative dog from Group A. Extrapolation of the linear part of each curve to the ordinate yields "V_{MAX}"; this value was not used in this study. Instead the peak value of V_{CE} i.e. V_{PM} was used, since this does not involve the error inherent in extrapolation. The curve plotted with the graft open is higher than that

* For table of values see Appendix.

Figure 11. Force velocity curves from a representative dog from Group A. On the ordinate is the contractile element velocity index V_{CE}. On the abscissa is instantaneous left ventricular pressure. Four beats were plotted together to obtain each of these curves.


EFFECT OF OPENING GRAFT ON V_{CE} INDEX (HIGH STRESS)
GRAFT OPEN
GRAFT CLOSED
CARDIAC OUTPUT = 1580 ml / min.
Dog # 3
V_{CE} INDEX, $\frac{dP}{dt}$ / 28 P (SEC.$^{-1}$)
3.0
2.5
2.0
1.5
1.0
0.5
0
25
50
75
100
125
L.V. PRESSURE (M.M. HG.)

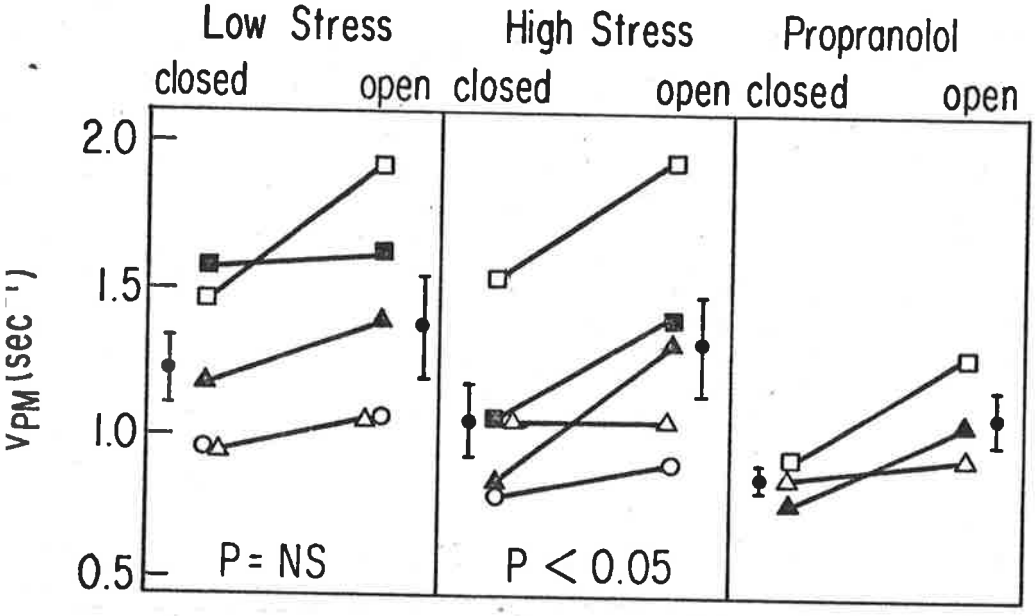


Figure 12. Contractile element velocity index (V_{PM}) in Group A dogs measured with the graft open and with the graft closed, at constant aortic pressure, cardiac output and heart rate. The values in the middle panel were obtained after volume loading. During volume loading (high stress) opening the graft produced an increase in contractility.

TABLE 2

CHANGES IN V_{CE} INDICES PRODUCED BY OPENING GRAFT

GROUP A	GRAFT CLOSED		GRAFT OPEN	
LOW STRESS				
DOG NO.	Vpm	Vmax	Vpm	Vmax
2	0.95	1.31	1.05	1.46
3	1.56	2.21	1.62	2.22
4	1.47	1.78	1.92	2.34
5	1.17	1.54	1.4	1.71
6	0.94	1.08	1.05	1.44
Mean	1.22	1.58	1.38	1.83
SE	±0.128 NS	±0.195 NS	±0.175	±0.189
HIGH STRESS				
2	0.80	1.15	0.90	1.27
3	1.06	1.32	1.41	1.77
4	1.54	1.91	1.95	2.21
5	0.83	1.18	1.34	1.78
6	1.07	1.21	1.07	1.29
Mean	1.06	1.35	1.33	1.66
SE	±0.132	±0.141	±0.179*	NS
PROPRANOLOL				
4	0.92	1.34	1.29	1.62
5	0.79	-	1.05	1.40
6	0.89	1.01	0.94	1.19
Mean	0.87	1.32	1.09	1.40
SE	±0.039 NS	±0.173 NS	±0.103	±0.124

* $p<0.05$

TABLE 2 (CONTINUED)

GROUP B	GRAFT CLOSED		GRAFT OPEN	
LOW STRESS				
DOG NO.	Vpm	Vmax	Vpm	Vmax
7	1.28	-	1.21	-
8	1.55	2.10	1.57	2.04
9	1.68	1.89	1.58	1.76
10	1.74	2.22	1.92	2.32
11	1.35	1.65	1.41	1.77
12	1.37	-	1.37	-
13	1.43	1.83	1.48	2.01
Mean	1.49	1.94	1.51	1.98
SE	0.066	0.100	0.084	0.103
P	0.59	0.52	-	-
HIGH STRESS				
7	0.95	1.29	1.04	1.46
8	1.78	2.15	1.65	2.07
9	1.48	1.86	1.44	1.84
10	1.82	2.18	1.59	2.00
11	1.41	1.67	1.40	1.61
12	1.46	-	1.34	-
13	1.02	1.51	1.26	1.74
Mean	1.42	1.78	1.39	1.79
SE	0.126	0.144	0.077	0.094
P	0.65	0.88	-	-
PROPRANOLOL				
9	0.58	0.58	1.48	1.80
10	0.99	1.32	1.15	1.59
11	1.16	1.41	1.48	1.77
12	1.42	-	1.55	-
13	0.82	1.11	0.79	0.98
Mean	0.99	1.10	1.29	1.53
SE	0.143	0.185	0.143	0.190
P	0.13	0.23	-	-

with the graft closed, indicating greater myocardial contractility. All values of V_{PM} which were compared with the graft open and then closed were measured at the same aortic pressure, heart rate and cardiac output. In Group A before volume stress, mean V_{PM}, measured with the graft open: 1.38±0.175, was not significantly different from that with the graft closed: 1.22±0.128. After volume loading, opening the graft increased mean V_{PM} significantly from 1.06±0.132 to 1.33±0.179 ($P<0.05$). Of the three dogs in which V_{PM} measurements were also obtained after propranolol, two showed increases in V_{PM} on opening the graft. Figure 12 shows these results diagrammatically. In Group B before or after volume loading, the mean V_{PM} value with the graft open was not significantly different from that with the graft closed. Of the five dogs in which measurements were obtained after propranolol administration and volume loading, four showed increases in V_{PM} on opening the graft, but the mean values were not significantly different. The complete results of the force-velocity measurements are shown in Table 2.

(D) GRAFT HAEMODYNAMICS

The data from the 11 dogs in which flow was measured are shown in Table 3, where the measurements obtained in Group A (immediate functional change) are compared with those obtained in Group B. Group A animals had significantly greater mean graft flow before stress (48±7.3 ml/min) than Group B (26±4.0 ml/min, $P<0.05$). In

TABLE 3

CORONARY BLOOD FLOW DATA

Dog No.	Time of Study	Collateral Flow	Graft Flow		Control Graft Flow / Collateral Flow	Peak Reactive Hyperaemic Flow
			Control	Maximum Stress		
	Days	ml/min	ml/min			% Control
Group A						
3	25	15	56	80	3.7	-
4	14	-	64	104	-	181
5	25	16	40	61	2.5	162
6	24	16	32	82	2.0	246
MEAN ± SE	22.0±2.7	16±0.3†	48±7.3*	82±8.8	2.7±0.5†	196±25.4
Group B						
7	24	-	17	36	-	132
8	23	53	34	72	0.64	175
9	16	-	30	100	-	235
10	23	48	18	94	0.38	-
11	22	45	45	80	1.0	180
12	22	29	24	60	0.83	-
13	24	40	17	36	0.43	114
MEAN ± SE	22.0±1.0	43±4.1†	26±4.0*	68±9.7	0.66±0.12†	167±21.1

Significant differences between means of two groups: *$P<0.05$, †$P<0.01$.

Group A, the mean collateral flow (16±0.3 ml/min) was significantly lower than Group B (43±4.1 ml/min, $P<0.01$). The best separation between the groups was provided by the ratio of control graft flow to collateral flow. Group A animals had a ratio of 2 or more, while Group B animals had ratios of 1 or less (Fig. 13). One animal from Group A (dog 2) had 20 ml/min of residual flow through the ameroid constrictor at the time of study. Connecting the graft augmented circumflex flow to 80 ml/min. All other animals had no measurable forward flow when studied.

(E) REACTIVE HYPERAEMIA

The reactive hyperaemic response of the circumflex coronary arterial bed was studied after occlusions of the graft for periods of 10 seconds. The response was quantitated using the percentage increase of the peak hyperaemic flow over control, and the percentage payment of the flow debt (Coffman and Gregg, 1960). The overall average values were 178±16% for the peak and 50±11.3% for the debt repayment. No significant differences between values for Group A and Group B were found. In five animals the reactive hyperaemic response was measured in the first five minutes after connecting the graft and again after an average of 92 minutes of graft perfusion (range 28-180 min). The peak flow response increased significantly from a mean value of 147±17% to 198 ±14% of control ($P<0.05$). This

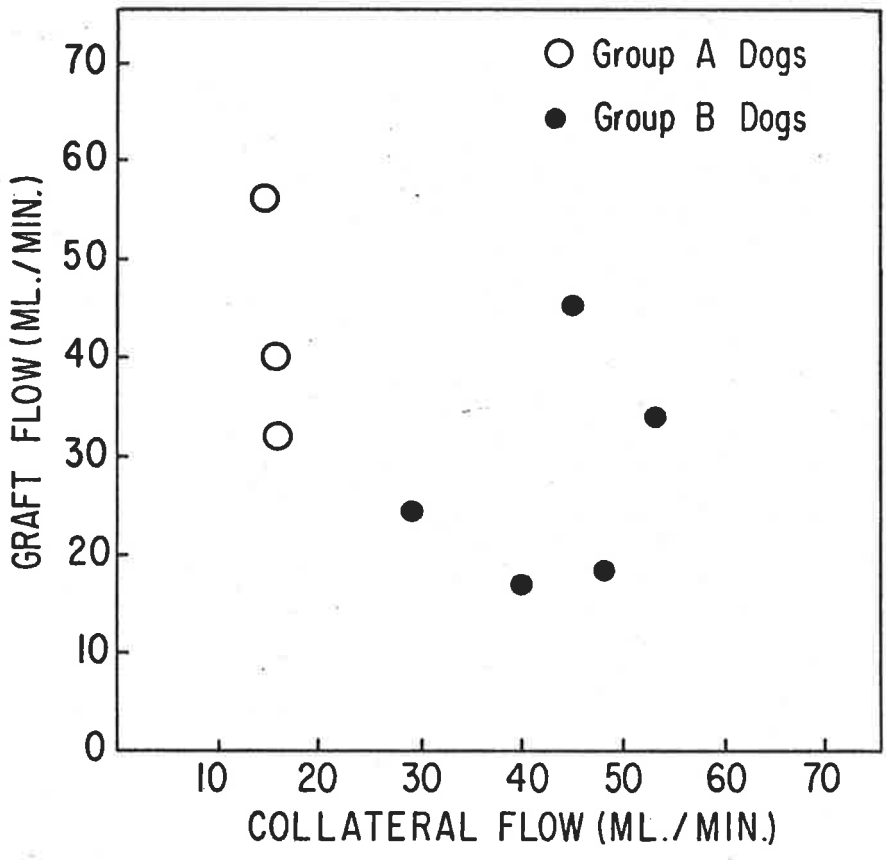


Figure 13. Graft flow and collateral flow as separators between Group A and Group B animals.

was accompanied by a significant increase in the graft flow measured at the same aortic pressure from 32±6 ml/min to 52±8 ml/min ($P<0.05$) (Table 4).

TABLE 4

CHANGES IN REACTIVE HYPERAEMIA AND GRAFT FLOW WITH TIME

	EARLY			LATE		
Dog	Graft Perfusion time	Peak R. H. Flow	Graft Flow	Graft Perfusion Time	Peak R. H. Flow	Graft Flow
	(min)	(% control)	(ml/min)	(min)	(% control)	(ml/min)
9	5	138	44	90	235	48
5	2	100	32	40	162	72
10	7	140	21	28	200	45
14	2	150	48	120	172	68
15	2	207	16	180	222	28
Mean	4*	147*	32*	92	198	52
S.E.	±1	±17	±6	±27	±14	±8

* $P<0.05$

CHAPTER 5

DISCUSSION

(A) PRODUCTION OF MYOCARDIAL ISCHAEMIA

In preliminary experiments the circumflex coronary artery was gradually occluded by an ameroid constrictor and the left anterior descending coronary artery system was left intact. After 28 days, the distal circumflex bed had an extensive collateral blood supply, including many enlarged easily visible epicardial collateral vessels. If epicardial branches of the left anterior descending coronary artery were ligated at the time of placement of the constrictor, epicardial collateral vessel enlargement was much less evident when the chest was re-opened for revascularisation. In animals prepared in this way, improved function brought about by revascularisation suggested that myocardial ischaemia was present at least under conditions of stress.

The time of study is also important. In a similar study reported by Marlon et al. in 1971, dogs were revascularised after 10 weeks of occlusion and no functional change due to revascularisation could be demonstrated. In the preliminary studies (Chapter 1) dogs restudied one to three months after placement of constrictors and ligatures were found to have abundant epicardial collateral vessels feeding the circumflex bed with copious retrograde flow from the circumflex coronary artery. Thus, revascularisation had already been performed

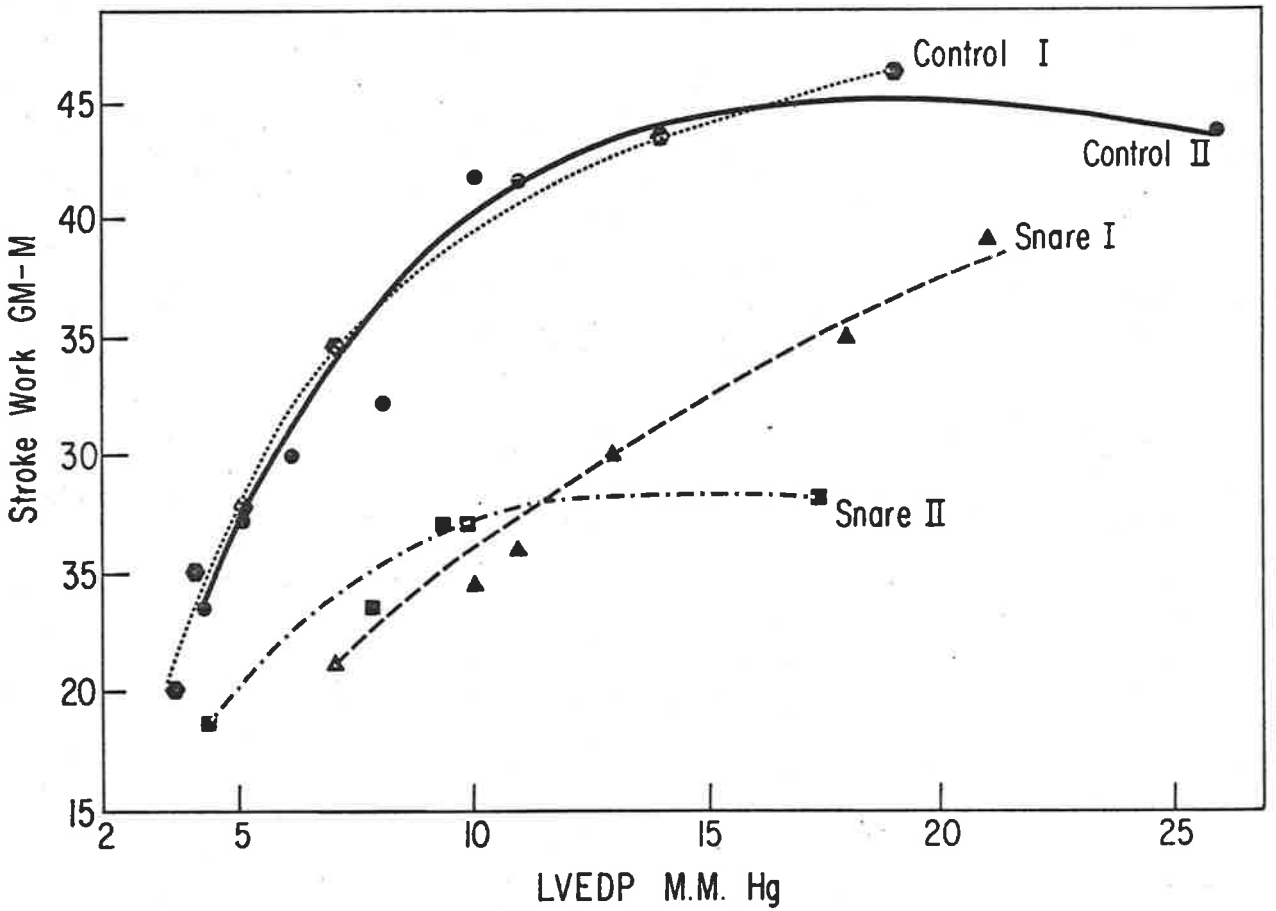
by the animals' own collateral vessels. However, between 14 and 25 days after surgery when the ameroid constrictor had closed and before marked collateral enlargement had occurred, there was an ischaemic period during which the effect of surgical revascularisation could be studied. Variation in the times taken for complete closure of the constrictors together with variation in the number of pre-existing collaterals normally found in mongrel dogs (Eckstein, 1954) provided differing amounts of collateral blood supply at the time of study.

(B) VENTRICULAR FUNCTION

In the dog, a profound depression of the ventricular function curve has been described if a major coronary artery is acutely occluded (Enright et al., 1970). This observation was confirmed by preliminary experiments in which the midportion of the left anterior descending coronary artery was acutely occluded in four anaesthetised open-chested dogs. Stroke volume-LVEDP curves were generated by volume loading during right heart bypass in two dogs and by pressure loading produced by constricting the arch of the aorta in two other dogs. In all cases, the coronary occlusion produced a curve profoundly depressed below control curves. Figure 14 shows typical curves from a volume-loaded dog.

In the revascularised dogs, upward shifts in the ventricular function curves brought about by revascularisation were small. Improved ventricular function was best demonstrated when the ventricle

Figure 14. Four consecutive ventricular function curves obtained in a normal dog placed on right heart bypass. The curve obtained 2 minutes after coronary occlusion (Snare 1) was depressed well below the control curve (Control 1). A second curve (Control 2) taken 25 minutes after release of the occlusion, shows full recovery of function. A second occlusion resulted in a more depressed curve (Snare 2) than the first occlusion. The occlusion was released after 10 minutes and this was followed by ventricular fibrillation.


Control I
Control II
Snare I
Snare II
Stroke Work GM-M
LVEDP M.M. Hg
45
40
35
30
35
20
15
2
5
10
15
20
25

was stressed. The depression of the ventricular function curve produced by clamping the graft,when present was also relatively small.

Increases in the contractile element velocity index, V_{PM}, when the graft was opened in Group A animals are suggestive of improved contractility and correlated with falls in LVEDP ($r = -0.81$). Using the peak measured value (V_{PM}) of contractile element velocity avoids the uncertainties of lengthy extrapolation of the pressure-velocity curve to the ordinate necessary at high end-diastolic pressures to obtain V_{MAX}. Nejad (1971) has shown in heart-lung preparations that V_{PM} is less sensitive to pre-load changes than V_{MAX}. However, Grossman (1972) has shown in the intact dog that V_{PM} and V_{MAX} are both lowered by a rise in LVEDP when contractility is constant, unless developed left ventricular pressure (LVP-LVEDP) is used in the calculations. Thus, in the present study where total left ventricular pressure was used, possibly some of the measured increase in V_{PM} on opening the graft was due to reduced pre-load per se.

In general when the graft was opened, the change in the contractile element velocity index was less than the change in left ventricular end-diastolic pressure. In Group A dogs before volume loading, opening the graft produced a significant fall in left ventricular end-diastolic pressure but no significant change in V_{PM}. Similarly after volume loading opening the graft produced a relatively smaller change in V_{PM} than in left ventricular end-diastolic pressure (Figs 10 and 12).

The improved function following revascularisation was seen after volume loading in six of the thirteen animals studied and in a further three only after beta-receptor blockade and volume loading. Application of a stress in the form of a volume load and high aortic pressure at a constant heart rate causes increased end-diastolic and systolic pressure, thus producing increased left ventricular wall stress, with resultant augmentation of myocardial oxygen demand (Braunwauld, 1971). If the collateral blood supply alone is inadequate to meet this demand, a depression in ventricular function reversible by opening the graft would be expected. The explanation of the contractility differences seemingly unmasked in three dogs by propranolol is not immediately obvious. The drug did reduce the incidence of arrhythmias during volume stressing and thus allowed greater stress to be applied to the ventricle in some dogs. Addition of propranolol to the perfusate of a dog on right heart bypass frequently produces progressive dilatation and failure of an already ischaemic ventricle. When an ischaemic ventricle is pushed towards this stage by propranolol even a small beneficial effect on function produced by opening the graft may become detectable.

(C) GRAFT HAEMODYNAMICS

The method of retrograde flow collection for measuring collateral flow (Anrep and Hausler, 1928) overestimates true intercoronary collateral flow since it measures flow draining against atmospheric

pressure instead of that flowing against the peripheral coronary resistance. Although measurements were obtained in only 8 of the 13 animals, the fact that those animals with good collateral flow exhibited no functional improvement after the graft was connected suggests that collateral flow was adequate to sustain the functional needs of the myocardium even during stress.

These findings indicate, not surprisingly, that revascularising an area of the left ventricle with an already abundant collateral supply does not improve the functional state of the heart in the dog. Whether this situation ever obtains in patients with coronary artery disease awaits clinical study. Patients in this category might be characterised by normal pre-operative exercise tolerance tests and on angiography good retrograde filling of obstructed coronary vessels from non-diseased vessels via large collaterals. At the time of operation there would be brisk coronary back-bleeding prior to attaching the vein graft and initial graft flow would be low. If the human situation matches the experimental model, such patients would be unlikely to obtain augmented function from coronary bypass surgery.

(D) REACTIVE HYPERAEMIA

The reactive hyperaemic response to a 10-second occlusion was much less than that found in anaesthetised dogs by Coffman and Gregg (1960). They found flow debt repayments of 200% and peak hyper-

aemic flows of 250-550% of control compared to values of 50±11.3% for the debt and 178±16% for the peak found in this study. These findings, however, are similar to those of Greenfield et al. (1972) in patients studied at the time of coronary bypass surgery. Occlusions of the vein grafts for 10 seconds resulted in a mean flow debt repayment of 51.5% and a peak response of 155 per cent. It has been shown in the canine hind-limb preparation that even a limited quantity of arterial blood available during occlusion is potent in reducing the reactive hyperaemic response (Bache, 1965). "Leakage" of collateral flow into the distal bed during the graft occlusion would thus explain the attenuated reactive hyperaemic response.

The increased reactive hyperaemic response observed after prolonged graft perfusion can be explained by the closure of collateral vessels with time. Reduced "competition" from collateral flow would also explain the increase in graft flow observed after prolonged perfusion. In the two additional ischaemic animals (dogs 14 and 15) not placed on right heart bypass, serial retrograde flow measurements were taken up to three hours after the graft had been connected. Measured collateral flow showed a steady decline while graft flow increased (Fig. 15). Collateral flow is brought about by the pressure gradient between the obstructed and non-obstructed coronary arteries. When this gradient is removed by bypass grafting, flow declines and some collateral vessels begin to close. The phenomenon of acute regression of coronary collateral vessels following the re-establishment

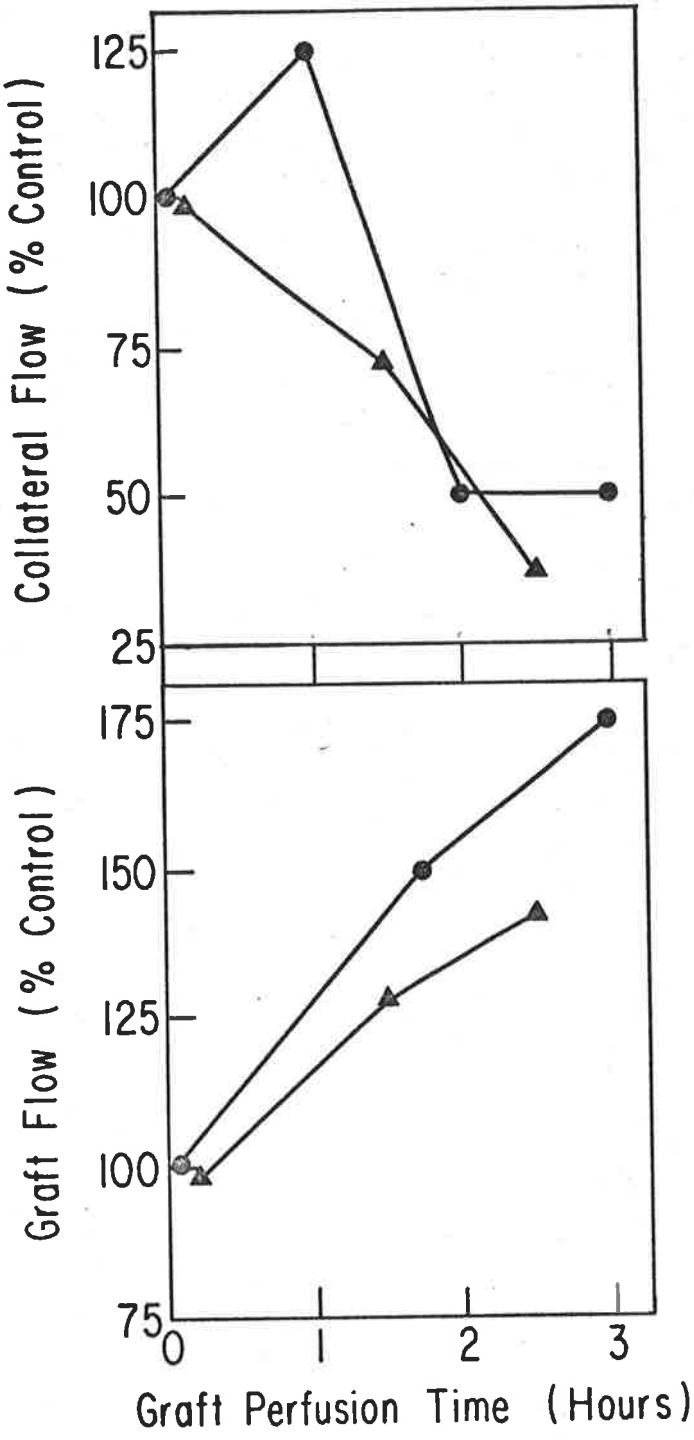


Figure 15. Changes in collateral flow and graft flow in two dogs (Nos. 14 and 15) in the first three hours after the graft was connected.

of flow in a previously occluded coronary artery has been demonstrated in awake dogs by Khouri et al. (1971).

(E) GRAFT DEPENDENCE

What would be the effect of collateral vessel regression on ventricular function? If, after prolonged graft perfusion and closure of collateral vessels the graft were re-occluded, a depression in ventricular function might be expected, unless collateral flow was re-established very rapidly. That reopening of collateral vessels was not a rapid phenomenon after prolonged graft perfusion in this preparation, was suggested by observations in three animals in which peripheral coronary pressure was measured. During graft occlusions of four to ten minutes toward the end of the experiment, no significant rise in peripheral coronary pressure was seen. Thus, the ventricle may have become at least temporarily dependent on its new blood supply. This situation of increasing dependence on the graft was notable in two dogs where it was observed that the depression in ventricular function produced by clamping the graft after one to two hours of perfusion was greater than the improvement in function brought about when the graft was first connected. Also, dog No. 7 and a further two animals not included in the function study actually developed ventricular fibrillation when the graft was clamped after prolonged perfusion. Bias introduced by the "graft-dependence effect" was minimised by taking control measurements of ventricular function early in the

study and in five dogs (Nos. 6, 8, 9, 10, 11) even before the graft was inserted. Several human studies designed to measure the acute effect of revascularisation on ventricular function at the time of aorto-coronary bypass surgery have been reported (Wechsler et al., 1972; Bolooki et al., 1971; Enright et al., 1972; Anderson, 1972). In these studies it is important to take the control measurements of ventricular function, if possible, before graft flow is established or at least after a minimal time of graft perfusion. Sudden interruption of flow in a graft which had been perfusing for an hour or more an area of the ventricle previously supplied by collateral vessels alone, might produce marked temporary depression in ventricular function. This would give an exaggerated impression of the true improvement conferred by the graft. The same considerations also apply to intra-operative measurements of flow or reactive hyperaemia in vein grafts as the values would be expected to increase with the passage of time after insertion of the graft.

If graft flow had been established for weeks or months, it might be expected that following reocclusion of the graft, collateral reappearance would be a correspondingly slower process. In the study by Khouri et al. (1971) following 3 to 90 days of re-established flow in a previously occluded circumflex coronary artery, the collateral indices required one hour to rise to the high values reached during the initial occlusion. Following bypass grafting there is a tendency for subtotal coronary obstructions proximal to the graft to progress

to total occlusion (Malinow et al., 1973). Thus, it might be expected that the sudden re-occlusion of a vein bypass graft in a patient weeks or months after its insertion might produce significant myocardial damage before collateral flow could be re-established. This would explain the observation (Rees et al., 1971) that following thrombosis of a bypass graft, ventricular function is usually poorer than before bypass surgery.

PART B

REVASCULARISATION FOLLOWING ACUTE MYOCARDIAL INFARCTION

CHAPTER 6

INTRODUCTION

Part A dealt with the effect of experimental revascularisation in the setting of chronic myocardial ischaemia. Part B describes a study of revascularisation following acute myocardial ischaemia.

A quantitative knowledge of the effect of revascularisation on ventricular function is essential when deciding whether or not to use surgical means to treat low output states including cardiogenic shock complicating acute myocardial infarction. For the survival of the patient an early improvement in ventricular function following revascularisation is essential.

Coronary occlusion in the anaesthetised, open-chested dog produces a poor model in which to study acute myocardial infarction in patients. Indeed sudden occlusion of a major coronary artery in the open-chested dog causes fatal arrhythmias in most cases (Harris, 1950). For this reason it was decided to study the effects of infarction in the intact unanaesthetised dog. The unanaesthetised animal has the advantage of intact autonomic responses following infarction and in this it closely parallels the patient with an acute myocardial infarction.

Having decided to use an unanaesthetised preparation, a suitable method had to be found for repeatedly quantitating ventricular function. Angiographic methods are unsuitable for use in unanaesthetised

animals unless heavy sedation is employed. The results of the first study suggested that in measuring ventricular dysfunction due to ischaemia, force-velocity indices might not be as useful as the hydraulic indices, stroke work and left ventricular end-diastolic pressure. Hence it was decided to use a stroke work vs. left ventricular end-diastolic pressure ventricular function curve, to measure contractility changes brought about by acute myocardial infarction and subsequent revascularisation.

Ventricular function curves are usually generated by varying venous return in the right or left atrium. This is easily achieved in the isolated supported heart (Sarnoff, 1958), the heart-lung preparation (Starling, 1918) or the right heart bypass preparations as described in Chapter 3. Ventricular function curves generated in awake animals have been reported (Stone et al., 1966; Keroes et al., 1969). In these studies the animals were given rapid infusions of electrolyte solution to produce increases in ventricular filling pressure and stroke work. However, using this technique, curves cannot be obtained in rapid succession, as many hours must be allowed for fluid excretion after each curve.

Pressure loading has been used to generate ventricular function curves in dogs (Goodyer et al., 1962; Hood et al., 1969) and in man (Ross and Braunwauld, 1964). A pressure loading technique was chosen for this study because it can be used repeatedly over a short time. Also since a pressure load applied to the ventricle produces

a marked augmentation of myocardial oxygen consumption (Braunwauld, 1971) it would be expected to bring out functional impairment due to ischaemia. A pharmacological means was chosen to raise aortic pressure since it caused little disturbance to the unanaesthetised animals and represented an intervention that could also be applied in patients. Phenylephrine was selected as the pressor agent because it has a minimal amount of beta-adrenergic activity (Goldberg et al., 1953).

Sixty minutes of coronary occlusion was used since it is greater than the minimum time necessary in the working heart at normothermia to produce myocardial infarction (30-45 mins) (Jennings et al., 1960) and therefore long enough to produce a reproducible lesion but short enough to allow maximum recovery of function following revascularisation.

CHAPTER 7

EXPERIMENTAL METHODS

(A) PREPARATION OF ANIMALS

Twenty-three mongrel dogs (25-33 kg) were anaesthetised with sodium thiamylal (15 mg/kg IV), intubated and ventilated with room air using a Harvard ventilator. Aseptic surgical technique was used as follows to prepare the animals as shown in Fig. 16. A thoracotomy was performed in the fourth left intercostal space through which a Statham sine-wave electromagnetic flow probe, series TTQ, was placed around the ascending aorta. A stiff polyvinyl catheter 2 mm in diameter was introduced into the aortic arch through the internal mammary and left subclavian arteries. A No. 8 French polyethylene catheter was introduced into the left atrium through the left atrial appendage. A bipolar epicardial pacing electrode was sutured to the right ventricle. A Statham electromagnetic flow probe, series ST, was placed around the proximal circumflex coronary artery and an inflatable occluder placed just distal to the flow probe. In the dogs in which the circumflex coronary artery was to be occluded permanently, the flow probe and cuff were replaced by a snare consisting of a loop of No. 4 silk which passed loosely around the circumflex coronary artery and then through polyvinyl tubing to a subcutaneous pocket on the anterior chest wall. The apical pericardium was loosely sutured to the adjacent chest wall to facilitate later

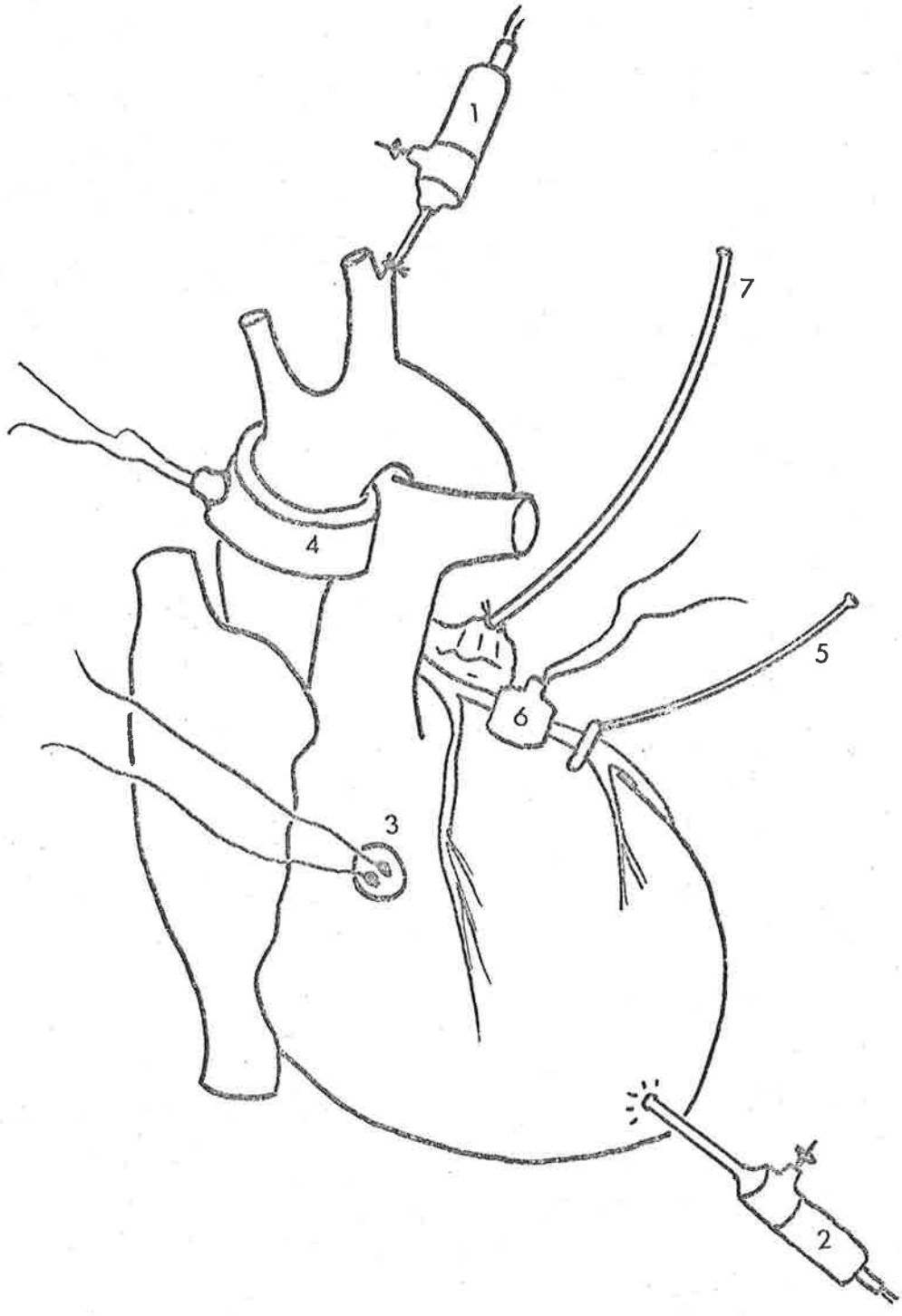


Figure 16. Preparation for awake dog studies showing pressure monitoring transducers and catheters in aortic arch (1) and left ventricle (2), epicardial pacing electrode (3), aortic flow probe (4), pneumatic occluder (5), coronary flow probe (6), left atrial catheter (7).

percutaneous puncture of the left ventricular apex. The ends of the connecting leads and catheters were led dorsally to a subcutaneous pouch at the base of the neck. The animals were given prophylactic antibiotics for the first three post-operative days.

(B) DATA COLLECTION

The animals were studied seven to ten days after full recovery from surgery. They were then without signs of infection or anaemia. An intramuscular injection of 15 mg of morphine sulphate was given on arrival at the laboratory and 15 minutes later each animal was placed on its right side on a padded table and restrained loosely. Under local anaesthesia using lidocaine, the leads, catheters, and the snare were exteriorised. Under local anaesthesia and fluoroscopic control, a Teflon catheter 15 cm long with in internal diameter of 2 mm was introduced into the left ventricle through the apex by percutaneous puncture. The frequency response of this catheter was flat (within 10%) to 6 c.p.s. and had a resonance frequency of 16 c.p.s. The aortic and left ventricular pressure catheters were connected to Statham P23Db strain gauges. The left ventricular pressure signal was used for the simultaneous recording of left ventricular end-diastolic pressure at high gain and the full left ventricular pressure pulse. The first derivative of left ventricular pressure was obtained using a Hewlett-Packard RC differentiator model 350-16 described in Chapter 3(D). Aortic and coronary flow were measured using Statham model M-4000 electromagnetic flowmeter.

All flow probes used in the study were regularly calibrated by passing normal saline through them at known rates (see Chapter 3(F)). The calibrations remained within a standard deviation of ±5% over the period of the study. The standard three-lead electrocardiogram was recorded before and after infarction and lead II monitored continuously.

All data were recorded using an eight-channel Hewlett-Packard chart recorder, series 7700, and on seven-channel analogue magnetic tape using a Hewlett-Packard recorder series 3955. When all instruments were giving satisfactory readings, the lights were dimmed and 30 minutes allowed for the animal to adjust to its surroundings. Most animals required no further sedation and many slept intermittently through the course of the experiment. Utilising these techniques, baseline measurements after the initial adjustment period remained stable for study periods of six to eight hours.

(C) PROCEDURE FOR MEASURING VENTRICULAR FUNCTION

In these animals the rise in arterial pressure following an injection of phenylephrine during sinus rhythm produced a pronounced reflex bradycardia. Therefore during measurements of ventricular function the heart rate was controlled by ventricular pacing usually at 120 beats per minute, using a Grass stimulator, model S88.

After taking control measurements, aortic pressure was increased by an intravenous injection of phenylephrine hydrochloride (Neosynephrine, Winthrop Laboratories). In the first four dogs in the series, phenylephrine was given as a constant intravenous infusion beginning

at 2 µgm/kg/minute and increasing the dosage in steps until mean aortic pressure reached 175 mm Hg, usually at a dosage of 5 µgm/kg/minute. Data were recorded under steady state conditions, i.e. after two to three minutes, at each level of aortic pressure. In the remaining 17 dogs, a bolus of phenylephrine (125-500 µg diluted in 5 cc of normal saline) was injected into the left atrium over five seconds. The injection of comparable volumes of normal saline produced no haemodynamic changes. Data were recorded during the rising phase of the pressor response which lasted approximately 15 seconds. Haemodynamic measurements were then allowed to return to control levels and a further 20 to 30 minutes elapsed before any further injections were given. The pressor response was considered satisfactory if the mean aortic pressure exceeded 175 mm Hg and left ventricular end-diastolic pressure increased 10 mm Hg above control. If a satisfactory response was not obtained with the first injection, the dose was increased. Once the appropriate dose had been determined (average 300 µgm), this was used throughout the study.

To examine the effect of altered sympathetic neurohumeral influences, ventricular function curves were obtained in four dogs before, and ten minutes after, beta-receptor blockade with propranolol (Inderal) 0.4 mg/kg intravenously and also during infusion of norepinephrine, 0.8 micrograms per kg per minute to maintain a constantly high level of sympathetic stimulation during the pressure increase.

The reproducibility of the haemodynamic measurements was determined by comparing the responses to two to three sequential injections of phenylephrine done on the same day and on different days.

In order to measure the response to a volume load, an infusion of Ringer's Lactate solution was given into the left atrium via the indwelling catheter in five of the seventeen dogs. The solution was infused as rapidly as possible and enough fluid given to raise the left ventricular end-diastolic pressure to 25 mm Hg. Between 200 ml and 400 ml of Ringer's Lactate was given over three to five minutes. During the infusion, heart rate was maintained at 120 beats per minute by ventricular pacing.

(D) CORONARY OCCLUSION

In 14 dogs after two to three control ventricular function curves had been obtained, the circumflex coronary artery was occluded gradually over five minutes using the snare or occluder. To reduce the incidence of arrhythmia following occlusion, lidocaine hydrochloride (Rochelle Laboratories) was given as a 2 mg/kg bolus immediately prior to occlusion and an additional 2 mg/kg infused over the first 15 to 20 minutes of occlusion. The lidocaine infusion was stopped at least 30 minutes prior to ventricular function measurements.

(E) REVASCULARISATION

The dogs with coronary occlusion were divided into two groups. In the control or permanent occlusion group, the occlusion of the coronary artery was maintained. In the "revascularised" or re-perfused group the coronary occlusion was released after one hour. Between 45 and 60 minutes after occlusion and also at two and four hours after occlusion, phenylephrine was given as before and the response recorded. Each animal which survived the occlusion was restudied approximately one week later, at which time two or three further ventricular function curves were obtained.

A single plane cineangiogram following injection of 10 cc of Renografin 76 (Squibb Laboratories) through the left ventricular catheter was obtained during ventricular pacing at the end of each day's study.

(F) PATHOLOGICAL EXAMINATION

All surviving animals were put to death with an overdose of sodium pentobarbital. The hearts of all animals were fixed in formalin for three to six days. The left ventricle was then sliced transversely at approximately 1 cm intervals and examined macroscopically for evidence of myocardial infarction. Areas of chronic infarction could be usually identified with assurance by the naked eye. Tissue samples were also taken for histological examination. Transparent plastic sheeting was placed over the slices of the left ventricle

and the areas of myocardial infarction and normal muscle were traced. The area of the infarct and the total area of each left ventricular section were measured by planimetry. Each of these areas was multiplied by the thickness of the slice from which it came and the total infarct volume thereby obtained was expressed as a percentage of the total left ventricular volume. The infarcted area was then excised, weighed, and expressed as a percentage of the total left ventricular weight.

In addition to the 14 dogs in which haemodynamic measurements were done following coronary occlusion, in four additional dogs (Nos. 7, 8, 9, 16) coronary occlusion was performed as described, no function measurements were made and the hearts were used after death or sacrifice at one week for measurement of infarct size.

(G) DATA ANALYSIS

The data were analysed using IBM model 1130 computing system in conjunction with a Redcor model 663 analogue-to-digital converter. Left ventricular pressure and aortic flow were digitised from the magnetic tape at 5 millisecond intervals and entered into the digital computer for processing. Stroke volume was obtained by integrating the forward aortic flow for each beat. Left ventricular end-diastolic pressure for each beat was read from the chart record and entered into the computer. Left ventricular power and stroke

work were calculated from the equations: $P = Q(t).p(t)$, $SW = 0.0136 \int_{t=0}^{t=T} Q(t) \left\{p(t)-LVEDP\right\} dt$, where P = left ventricular power in gm-m/sec, SW = stroke work in gm-m, Q(t) = instantaneous aortic flow rate in ml/sec, p(t) = instantaneous left ventricular pressure in mm Hg, LVEDP = left ventricular end-diastolic pressure in mm Hg, t = 0, t = T are the times of onset and termination of ejection, respectively. Data reported for each variable represent the mean values determined from eight to ten consecutive paced beats under control conditions and four to six consecutive paced beats for each observation during the pressor response. Statistical analysis was done using the student's t-test.

CHAPTER 8

RESULTS

(A) PRESSURE-GENERATED VENTRICULAR FUNCTION CURVES

Figure 17 illustrates the response of left ventricular pressure, left ventricular end-diastolic pressure, phasic aortic and coronary blood flow and left ventricular dp/dt as the aortic pressure increased following a bolus injection of 400 μg of phenylephrine into the left atrium of a normal dog (dog no. 13). Heart rate was controlled at 120 beats per minute by ventricular pacing. The mean aortic pressure increased from 80 to 150 mm Hg, left ventricular end-diastolic pressure increased from 9 to 20 mm Hg, mean coronary blood flow increased from 50 to 125 ml/min and stroke volume progressively decreased. Figure 18 illustrates the changes in stroke volume, left ventricular end-diastolic pressure and stroke work occurring in another normal dog (dog no. 1) as a function of increasing left ventricular systolic pressure, following a bolus injection of phenylephrine. Stroke volume showed a steady decline, left ventricular end-diastolic pressure a progressive rise, while stroke work remained fairly constant. Using these parameters, stroke work vs left ventricular end-diastolic pressure ventricular function curves were plotted.

Figure 19 illustrates two consecutive control ventricular function curves and a curve obtained one hour after coronary occlusion

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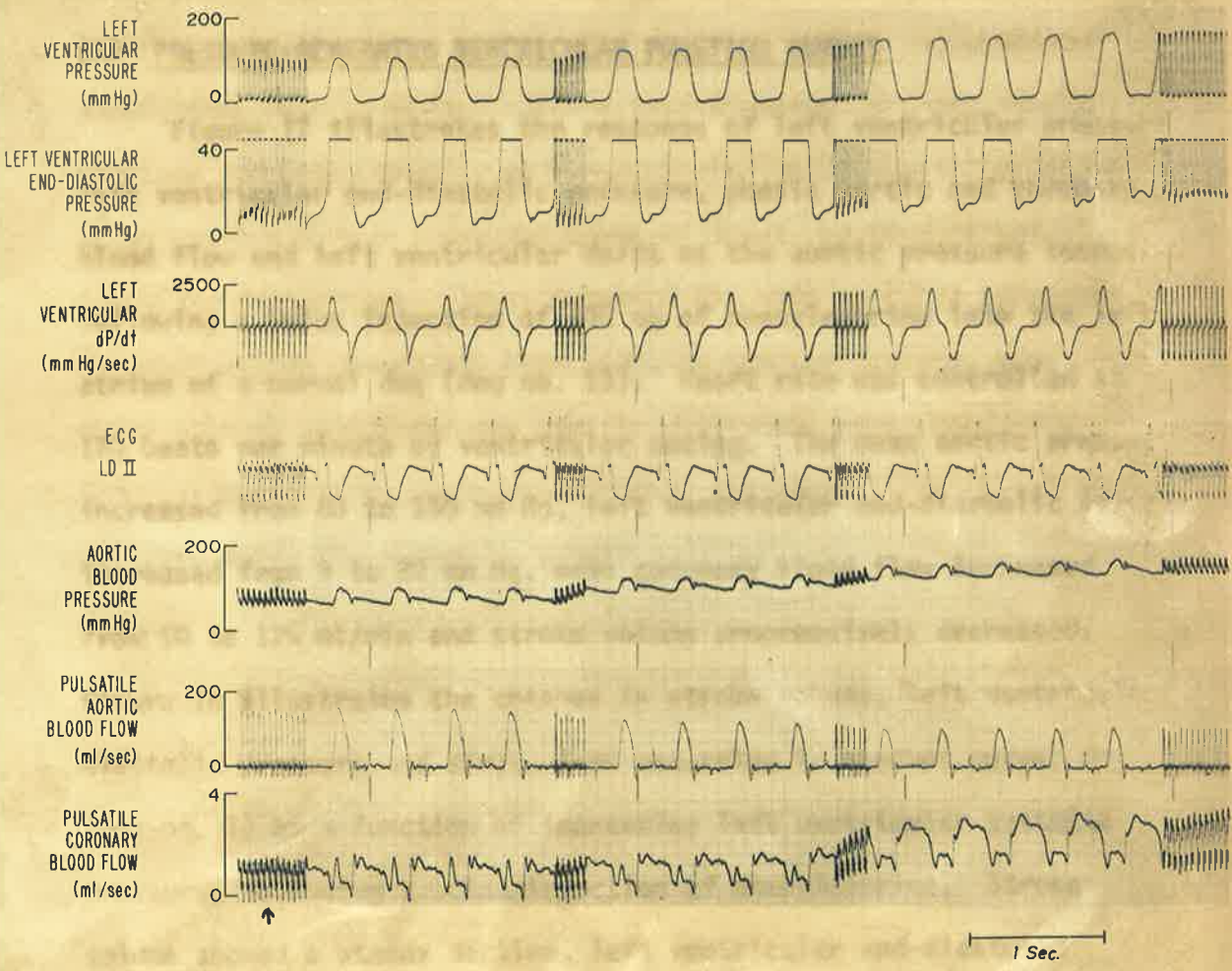
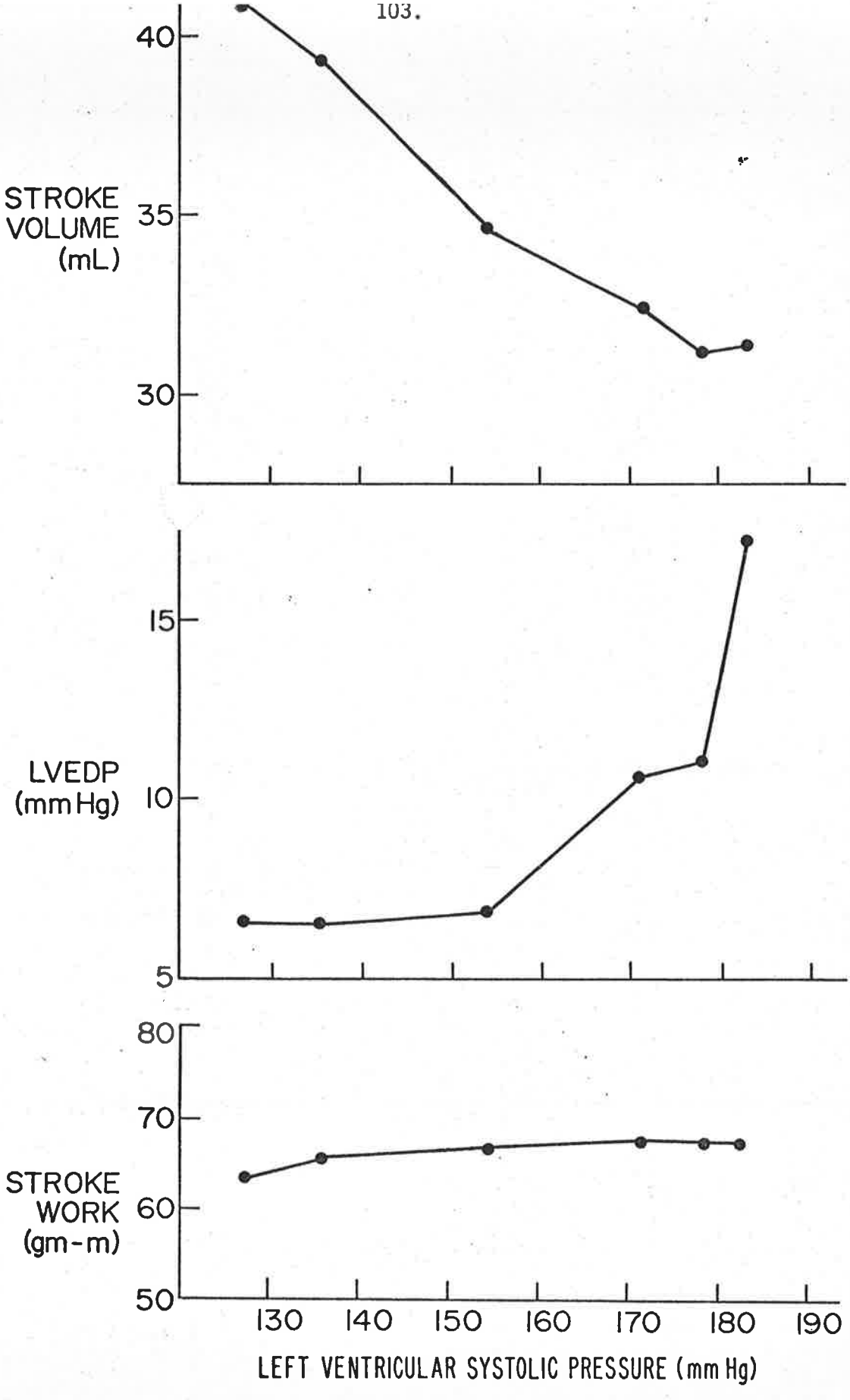


Figure 17. The haemodynamic response of a normal dog to a bolus of 400 micrograms of phenylephrine injected into the left atrium, at the arrow.

Figure 18. Changes in stroke volume, left ventricular end-diastolic pressure and stroke work following phenylephrine injection.


40
35
30
STROKE VOLUME (mL)
15
10
5
LVEDP (mm Hg)
80
70
60
50
STROKE WORK (gm-m)
130
140
150
160
170
180
190
LEFT VENTRICULAR SYSTOLIC PRESSURE (mm Hg)

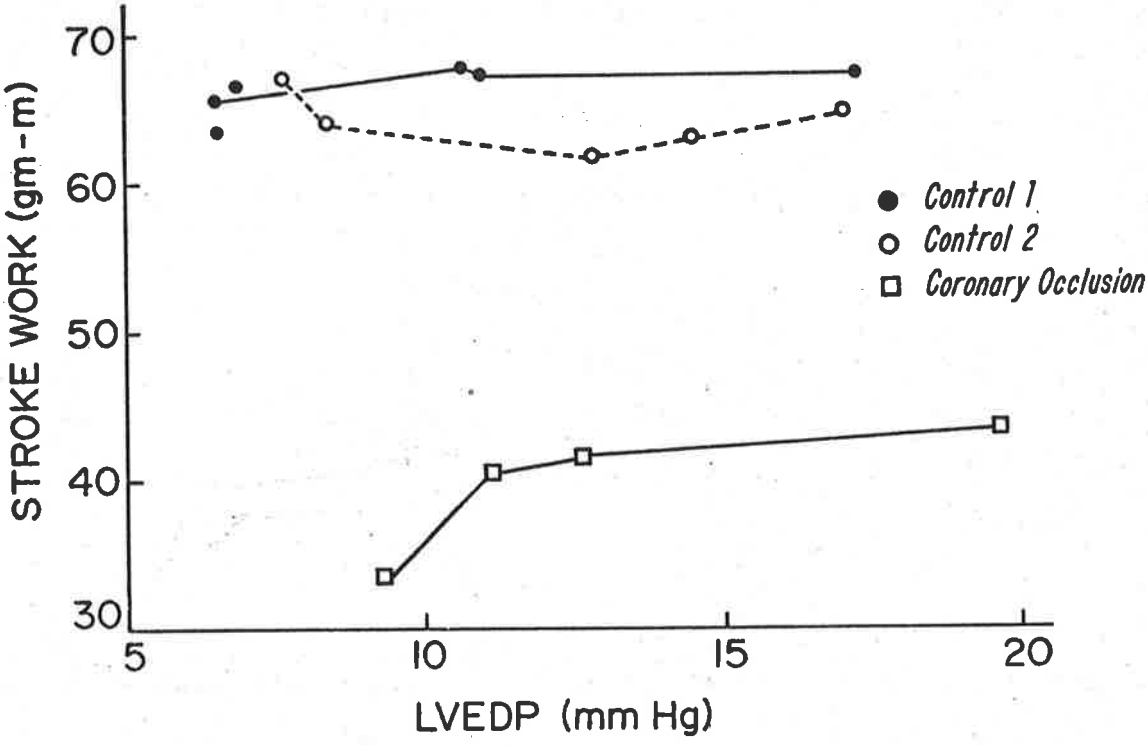


Figure 19. Ventricular function curves generated by a phenylephrine bolus before (control 1, control 2) and one hour after occlusion of the circumflex coronary artery.

from the same animal, as illustrated in Figure 18. In all three curves stroke work remained fairly constant in spite of the rise in left ventricular end-diastolic pressure, indicating that stroke volume decreased as a function of increasing aortic pressure.

In 17 normal dogs, one to three ventricular function curves were obtained. Figure 20 illustrates variations in mean stroke work (expressed as a percentage of control) as a function of increasing left ventricular end-diastolic pressure in these 17 dogs*. The initial (or control) and terminal points on the graph represent the mean of the stroke work and left ventricular end-diastolic pressure values at the beginning and end of each individual curve. The intermediate points are the mean values ±SEM of stroke work values read from the curves at 2.5 mm Hg increments of left ventricular end-diastolic pressure. Mean stroke work at the highest left ventricular end-diastolic pressure was not significantly increased above the control value. Although the curves in certain dogs sloped slightly upwards and, in others, downwards, the mean stroke work curve was essentially horizontal.

Figure 21 illustrates the mean stroke work values of eight ventricular function curves obtained in four dogs by stepwise increases in blood pressure produced by constant infusion of increasing dosages

* For table of values see Appendix.

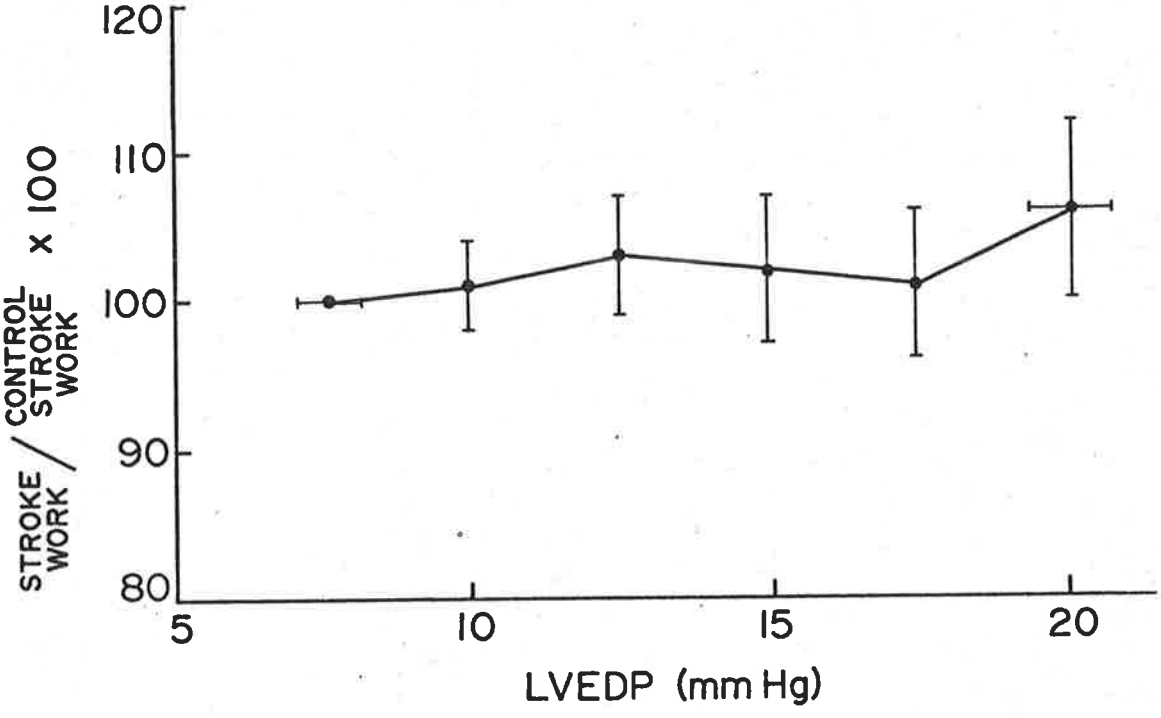


Figure 20. Stroke work response as a function of increasing left ventricular end-diastolic pressure in 17 dogs following a bolus injection of phenylephrine.

Each value represents mean ± SEM.

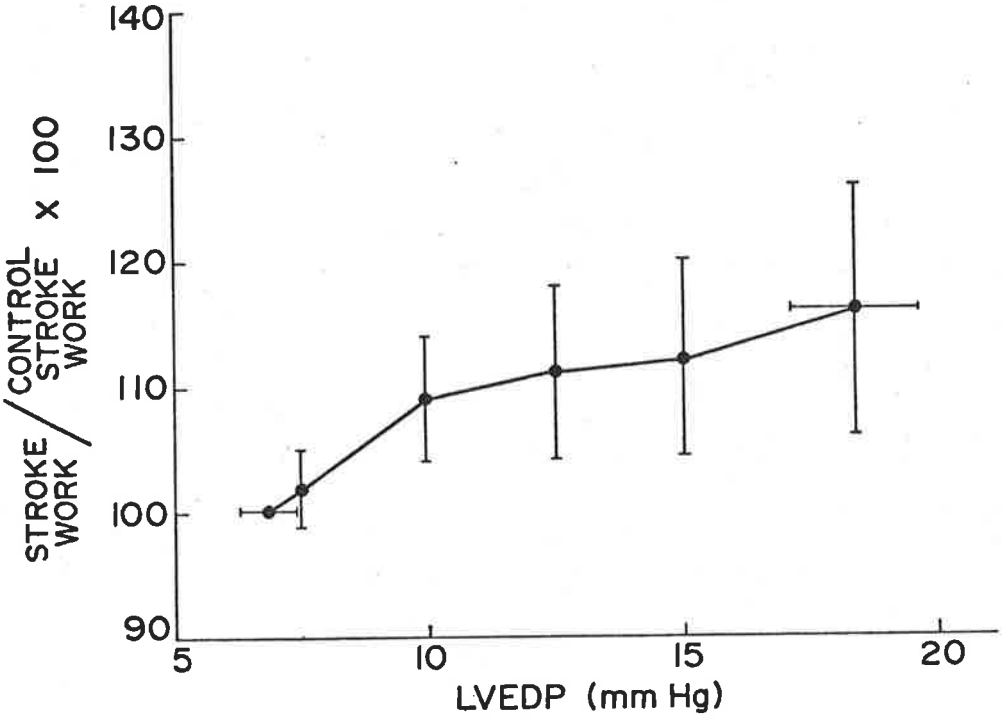


Figure 21. Stroke work response as a function of increasing left ventricular end-diastolic pressure in 4 dogs following phenylephrine infusion.

Each value represents mean ± SEM.

of phenylephrine (2-5 µg per kg per minute)*. Measurements were made during stable haemodynamic conditions. Although there is a slight upward slope to the curve, stroke work did not increase significantly above control with increasing left ventricular end-diastolic pressure. Thus stroke work responses to increases in aortic pressure produced by constant infusions and by bolus injections of phenylephrine were comparable. The bolus injection technique was chosen for the remainder of the study since it allowed a smaller total dosage of phenylephrine to be used and more frequent estimations of function to be performed. Following administration of propranolol the pressure-generated ventricular function curves were displaced downwards with respect to control curves. The gradient was either the same as or less than the control curves. Propranolol did not ever produce a more positive gradient. Figure 22 shows an example of the downward displacement produced by propranolol. Also shown in Figure 22 is upward displacement of the curve produced by norepinephrine infusion (0.4 µgm/kg/min).

The variability of two or more consecutive ventricular function curves was determined in 11 dogs. In a given dog, control left ventricular end-diastolic pressure values differed by an average of 15±2% (SEM) and control stroke work values differed by an average of 8±2%. At the highest common left ventricular end-diastolic

* For table of values see Appendix.

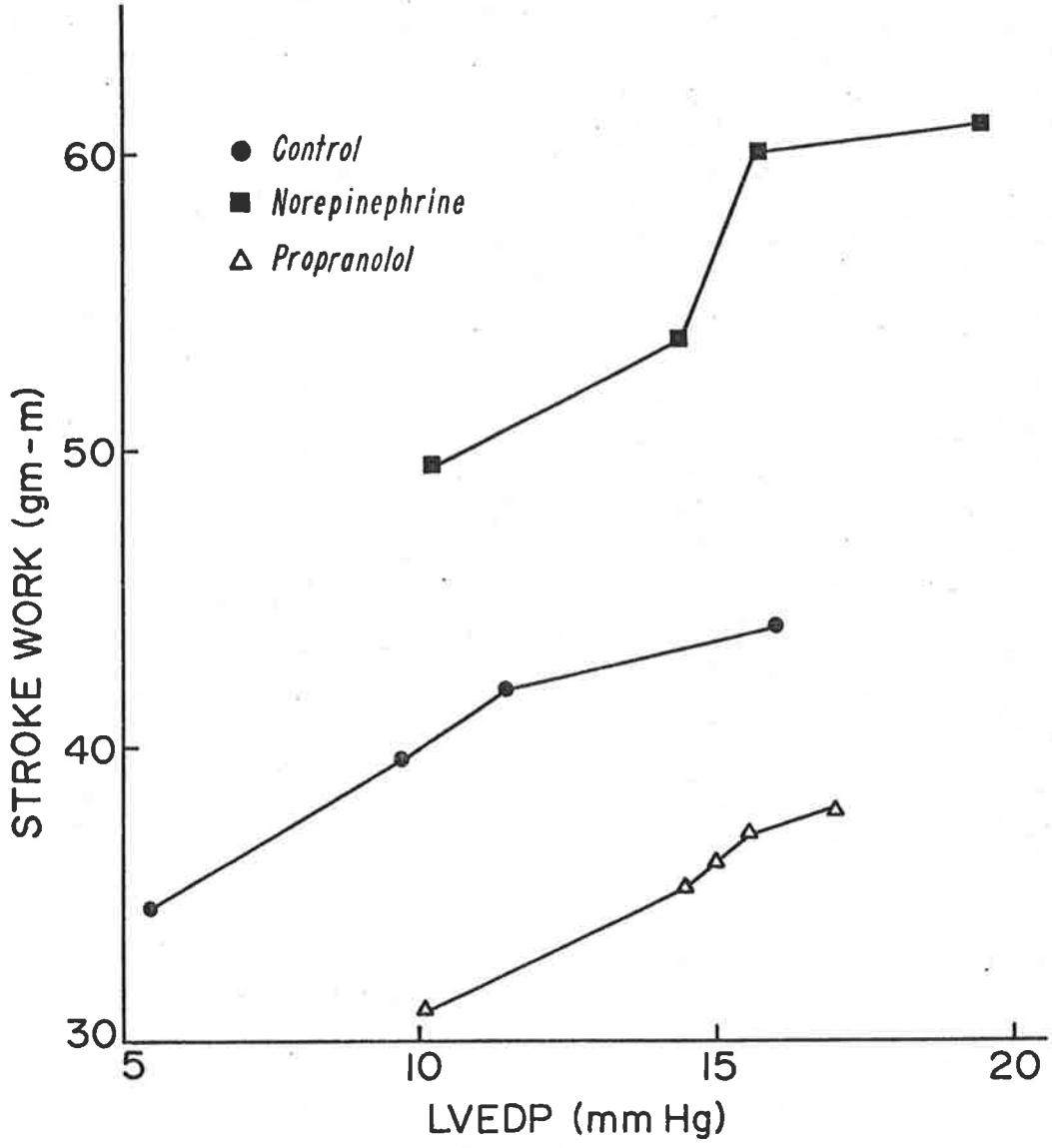


Figure 22. Ventricular function curves produced by phenylephrine bolus injections before (circles) and after (open triangles) administration of propranolol. The upper curve (closed boxes) was obtained by injecting a bolus of phenylephrine during a continuous infusion of norepinephrine.

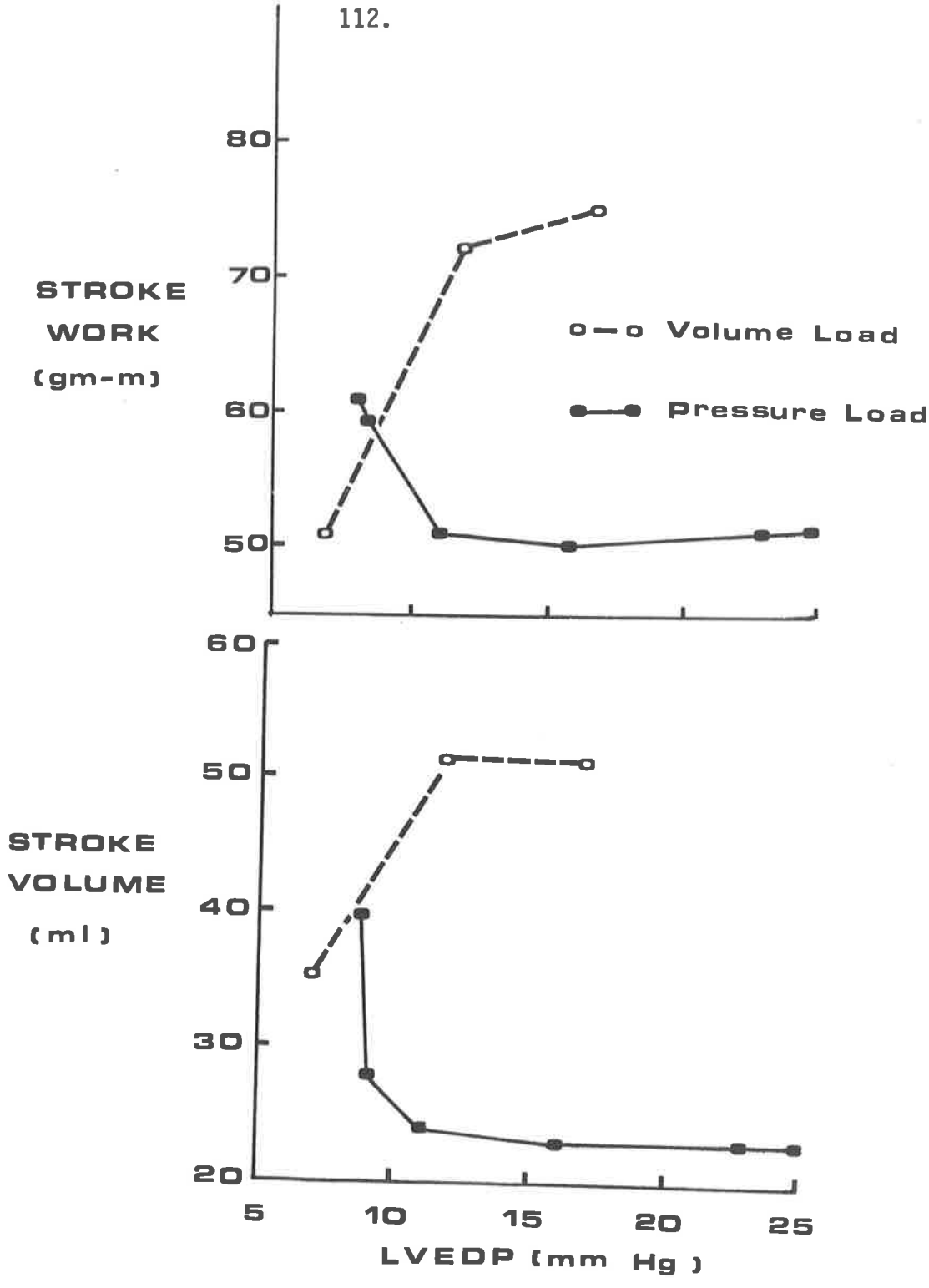
pressure, the stroke work values differed by an average of 7±2%. A second group of comparisons was made between curves obtained on different days. Curves from five dogs on two or three different days were compared. Control left ventricular end-diastolic pressure values varied by an average of 15±5% and control stroke work values varied by 11±1%. At the highest common left ventricular end-diastolic pressure, stroke work values varied by an average of 15±4%.

The stroke work response to volume loading utilising rapid infusions of Ringer's Lactate solution into the left atrium was measured in five of the seventeen dogs. These volume-generated ventricular function curves were upsloping with marked increases in stroke volume and a 69% mean increase in stroke work over control ($P<0.01$). Figure 23 shows ventricular function curves obtained by pressure and volume loading in the same animal. The difference between the upward sloping volume-generated curve and the somewhat downward sloping pressure-generated curve is readily apparent.

(B) CORONARY OCCLUSION

Figure 19 illustrates a typical example of the effect of a 60 minute coronary occlusion on the pressure-generated function curve. The occlusion decreased control stroke work and increased left ventricular end-diastolic pressure, indicating depressed ventricular function. Stroke work however showed no further change as aortic pressure increased. Thus there was not a greater separation of

Figure 23. The response of stroke work (upper panel) and stroke volume (lower panel) as a function of left ventricular end-diastolic pressure following pressure loading (closed circles) and volume loading (open circles).


STROKE
WORK
(gm-m)
80
70
60
50
o—o Volume Load
Pressure Load
STROKE
VOLUME
(ml)
60
50
40
30
20
5
10
15
20
25
LVEDP (mm Hg)

pre-occlusion and post-occlusion stroke work values at the highest left ventricular end-diastolic pressure. Coronary occlusion was carried out and ventricular function studied in 14 dogs. Two dogs developed ventricular fibrillation following coronary occlusion and were excluded from the study. Two others developed intermittent sinus tachycardia following the occlusion. A combined plot of ventricular function curves obtained before and after occlusion in the remaining 10 dogs is shown in Figure 24*. Following occlusion, mean stroke work was decreased by 37%, but this decrease was not accentuated at high left ventricular end-diastolic pressure.

Figure 25 illustrates the mean values for the 10 occluded dogs of all haemodynamic measurements taken during control conditions and at the peak of the pressure response, before and after the one hour occlusion*. All parameters were changed significantly by the coronary occlusion with the exception of peak dp/dt and left ventricular end-diastolic pressure after the phenylephrine administration. Coronary occlusion reduced stroke volume by 28%, systolic left ventricular pressure by 10 to 12%, and stroke work by 37%. Haemodynamic changes produced by coronary occlusion were not magnified by pressure loading.

The "pressure function curve" is a plot of systolic left ventricular pressure against left ventricular end-diastolic pressure during

* For table of values see Appendix.

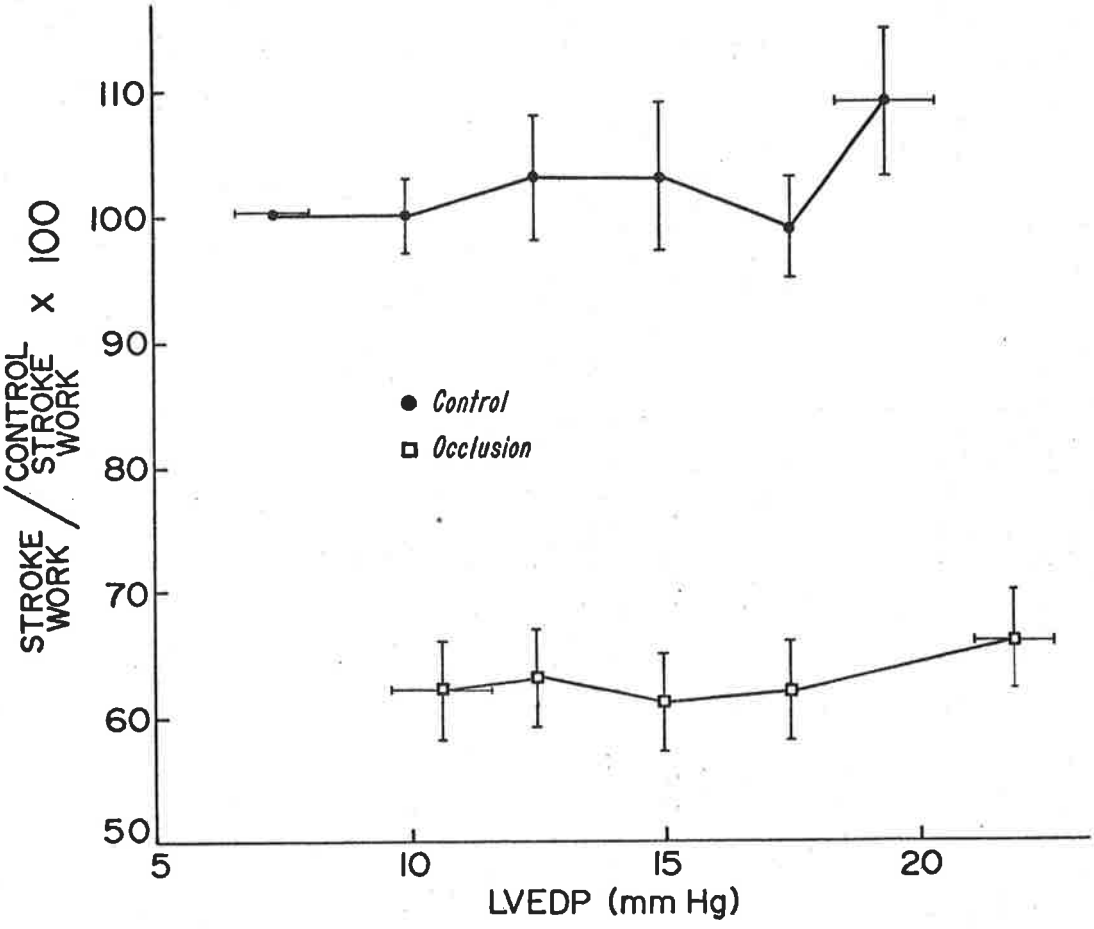
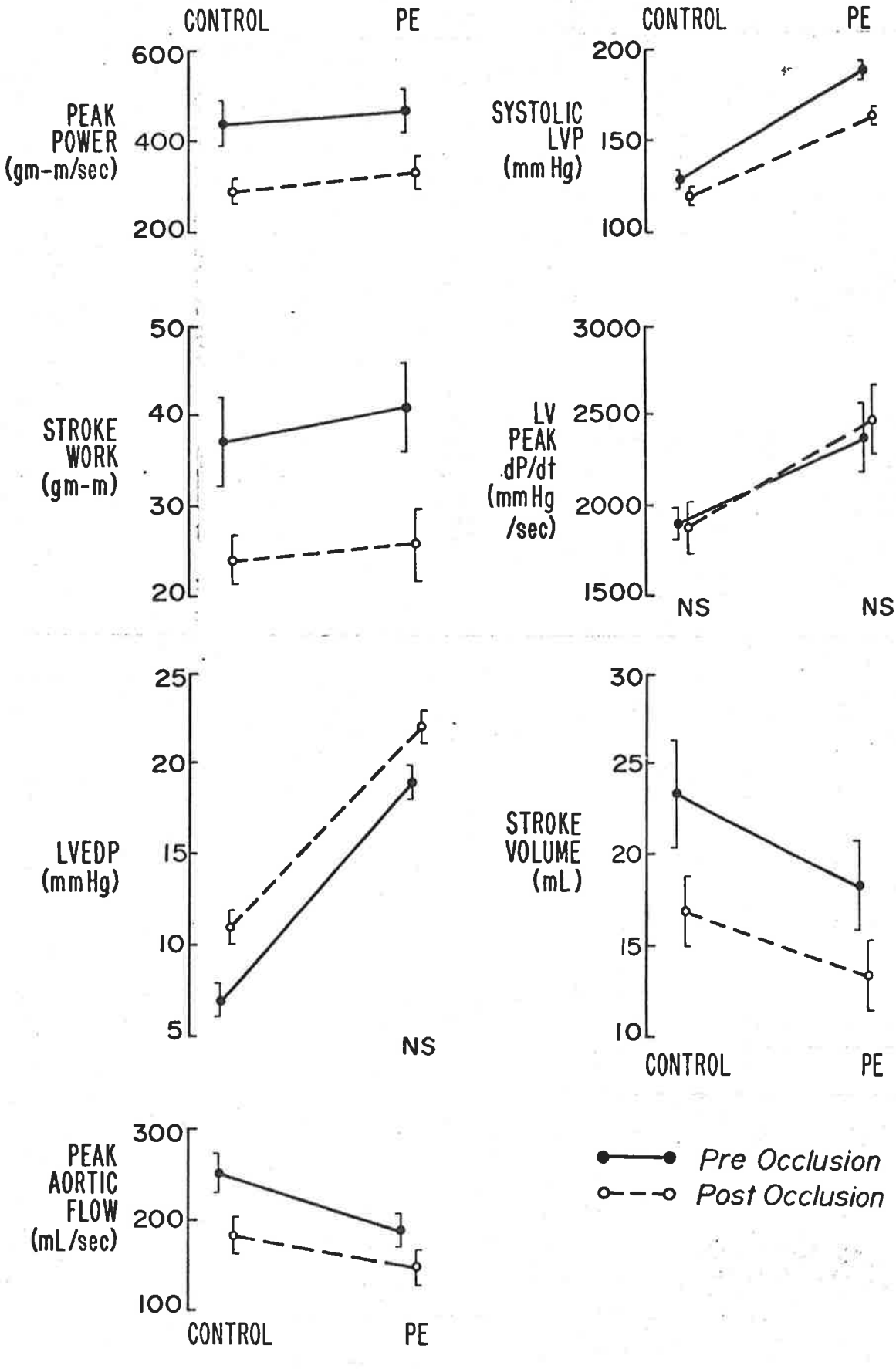


Figure 24. Ventricular function curves produced in 10 dogs by phenylephrine bolus injection before and one hour after occlusion of the circumflex coronary artery. The values given represent mean ± SEM and were obtained using the same method as for Figure 20.

Figure 25. Haemodynamic parameters before and one hour after coronary occlusion. The values given are the mean ± SEM for ten dogs. The left hand points are values measured before phenylephrine administration and the right hand points are values at the peak of the phenylephrine pressor response. The pre-occlusion and post-occlusion values of all parameters were significantly different at the one per cent level except where indicated (N.S.).


CONTROL
PE
PEAK POWER (gm-m/sec)
600
400
200
SYSTOLIC LVP (mm Hg)
200
150
100
STROKE WORK (gm-m)
50
40
30
20
LV PEAK dP/dt (mm Hg /sec)
3000
2500
2000
1500
NS
NS
LVEDP (mm Hg)
25
20
15
10
5
NS
STROKE VOLUME (mL)
30
25
20
15
10
CONTROL
PE
PEAK AORTIC FLOW (mL/sec)
300
200
100
CONTROL
PE
Pre Occlusion
Post Occlusion

aortic pressure loading and has been recommended to detect impairment in ventricular function produced by myocardial infarction without the necessity of measuring aortic blood flow (Hood et al., 1969). Figure 26 shows pressure function curves obtained before and after coronary occlusion from the same 10 dogs used for Figure 24. Within a physiological range of left ventricular end-diastolic pressures, aortic pressure loading did not produce greater separation of the pre-occlusion and post-occlusion systolic left ventricular pressure values. Pressure function curves provided a clear separation between the control and post-occlusion states but the decrease in systolic left ventricular pressure produced by the coronary occlusion (mean = 22%) was less than the stroke work decrease (mean = 37%).

(C) REVASCULARISATION

Effect on Mortality

Altogether 18 dogs were given coronary occlusions. Two developed ventricular fibrillation and one (no. 13) was put to death four hours after occlusion. The remaining 15 were followed for up to a week (Table 5). Of the nine control animals six died within a week, whereas of the six revascularised dogs only one died within the week.

In no case at autopsy was any significant extracardiac lesion found and death was assumed to have resulted from acute arrhythmia or cardiac failure.

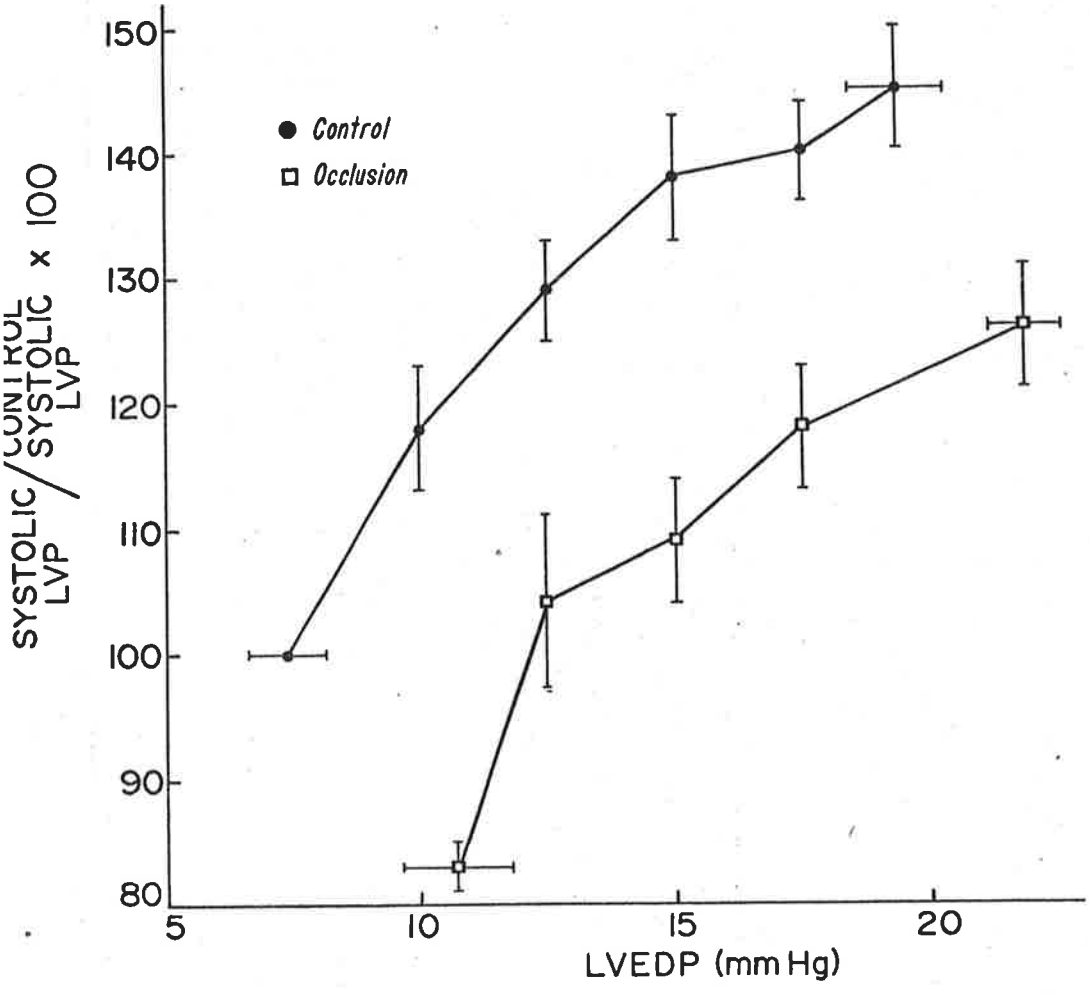


Figure 26. "Pressure function curves" - systolic left ventricular pressure vs left ventricular end-diastolic pressure, generated by aortic pressure loading before and after coronary occlusion in ten dogs. The values given represent mean ± SEM and were obtained using the same method as for Figure 20.

TABLE 5

EFFECT OF REVASCULARISATION AFTER ONE HOUR OF OCCLUSION

DOG NO.	TWO HOUR CURVE	FOUR HOUR CURVE	LATE CURVE	INFARCT AS % OF L.V.	SURVIVAL
PERMANENT OCCLUSION (CONTROL) GROUP					
1	No recovery	Not done	Partial recovery	-	Lived
2	No recovery	Partial recovery	No recovery	36	Lived
3	No recovery	No recovery	-	29.3	Died
4	No recovery	Partial recovery	-	14.2	Died
5	Partial recovery	No recovery	-	30	Died
6	No recovery	No recovery	-	-*	Died
7†	-	-	-	34.5	Died
8†	-	-	-	38.1	Lived
9†	-	-	-	22.9	Died
Mean				29.3±3.1%**	6 died out of 9 (67%)††
REVASCULARISED GROUP					
10	No recovery	No recovery	-	17.8	Died
11	No recovery	Full recovery	Full recovery	0.4	Lived
12	No recovery	Partial recovery	Full recovery	9.2	Lived
13	Partial recovery	Full recovery	-	-	Sacrificed
14	No recovery	No recovery	Full recovery	8.8	Lived
15	No recovery	Partial recovery	Full recovery	11.6	Lived
16†	-	-	-	6.3	Lived
Mean				9.0±2.3%**	1 died out of 6 (17%)††

* Died within hours of infarct. ** $P < 0.005$.

† No function studies done. †† $P = 0.06$.

Effect on Infarct Size

The infarct sizes are shown in Table 5. The estimates of infarct sizes by weight and volume differed by an average of only 2.4%. In most animals both measurements were obtained and the mean value used. The mean infarct size in the revascularised group: 9.0±2.3% of the left ventricle, was less than one third of that in the control group: 29.1±3.2% ($P<0.005$). In the control group the infarcts were either transmural or involved two-thirds or more of the thickness of the left ventricular wall (Figure 27). In the revascularised group the infarcts were mainly subendocardial and involved half or less of the thickness of the left ventricular wall.

Although the posterior papillary muscle was frequently involved in the infarct, at angiography no animal showed significant mitral insufficiency and only two showed a trace of mitral insufficiency.

Effect on Ventricular Function

Examination of the ventricular function curves obtained at two and four hours and at one week after coronary occlusion revealed several different response patterns. Depression of function and failure to recover is illustrated by dog 3 from the control (permanent occlusion) group. Coronary occlusion produced a profound depression of the ventricular function curve recorded at one hour with no recovery at two or four hours (Fig. 28). The dog died before a late study could be done and at autopsy was found to have an infarct of 29%

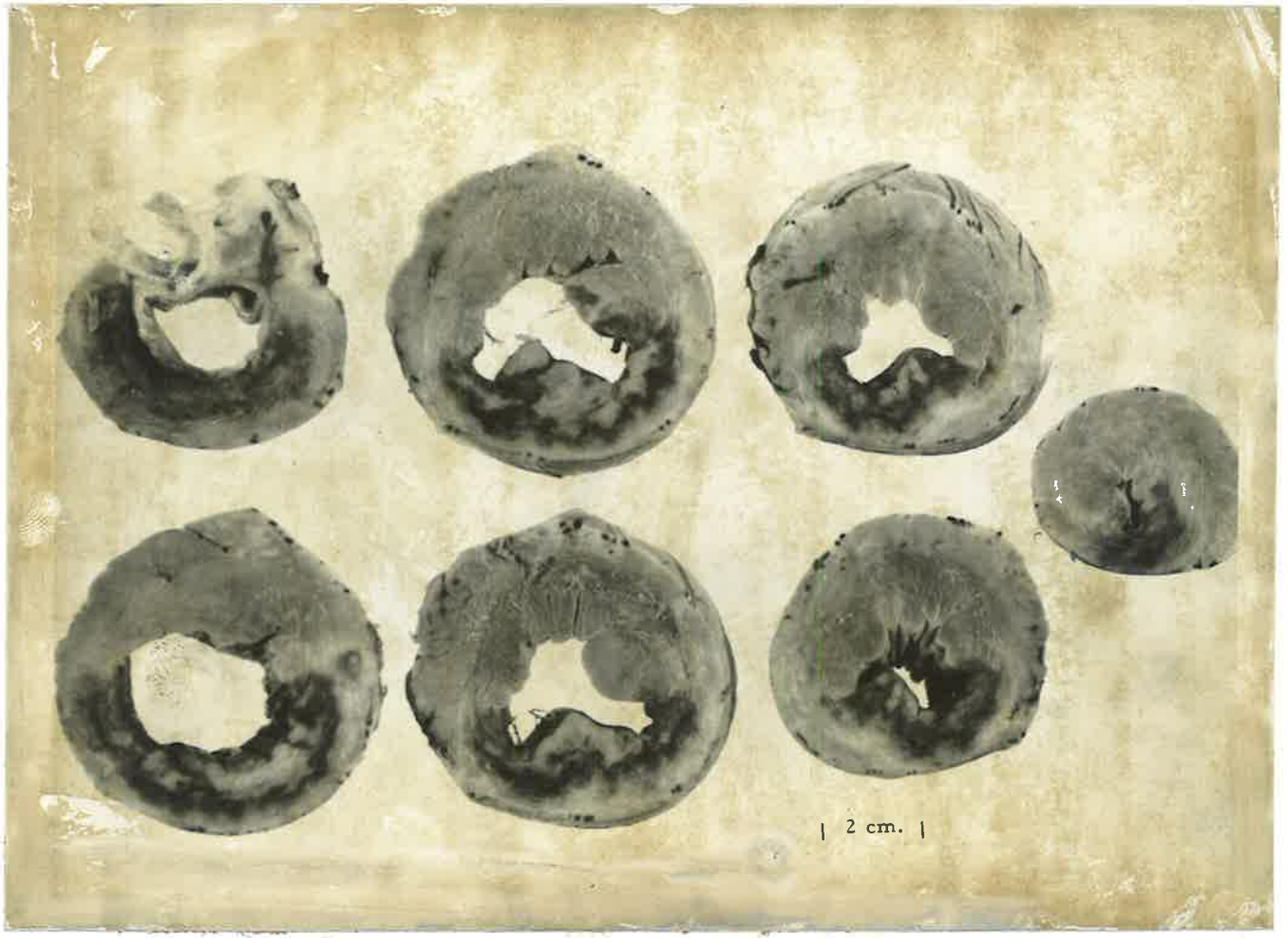
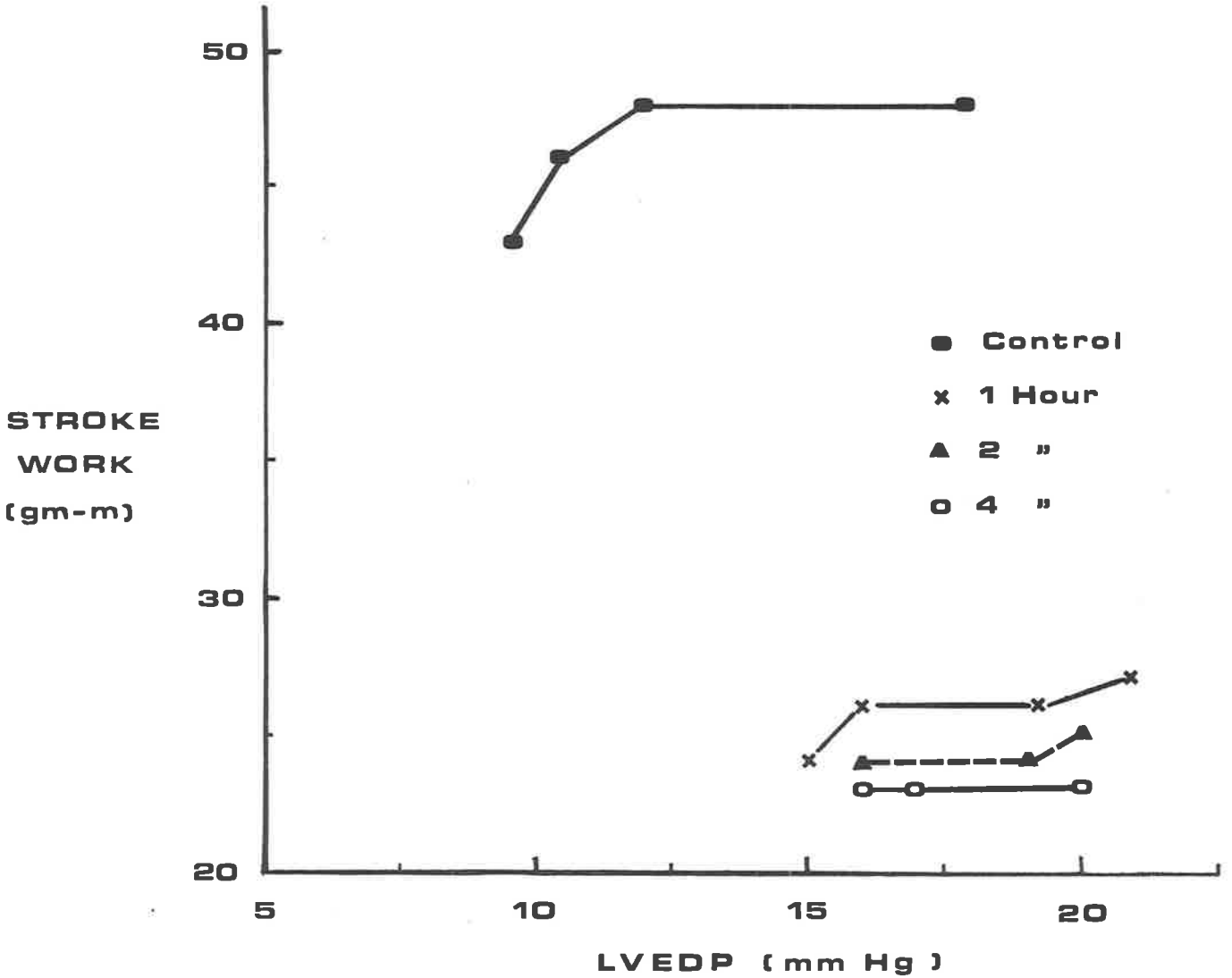


Figure 27. Serial sections of the left ventricle in a dog from the control group showing a large posterior infarct.

Figure 28. Ventricular function curves obtained before and one, two and four hours after the beginning of coronary occlusion.


50
40
30
20
STROKE
WORK
(gm-m)
Control
1 Hour
2 "
4 "
5
10
15
20
LVEDP (mm Hg)

of the left ventricle. On the other hand depressed ventricular function following coronary occlusion which had almost returned to normal by four hours is illustrated by dog 11 from the revascularised group (Fig. 29). This dog survived for re-study at one week, at which time ventricular function had returned to pre-occlusion levels. Pathologically the ventricle had an infarct of less than 1% of the left ventricle, confined to the posterior papillary muscle.

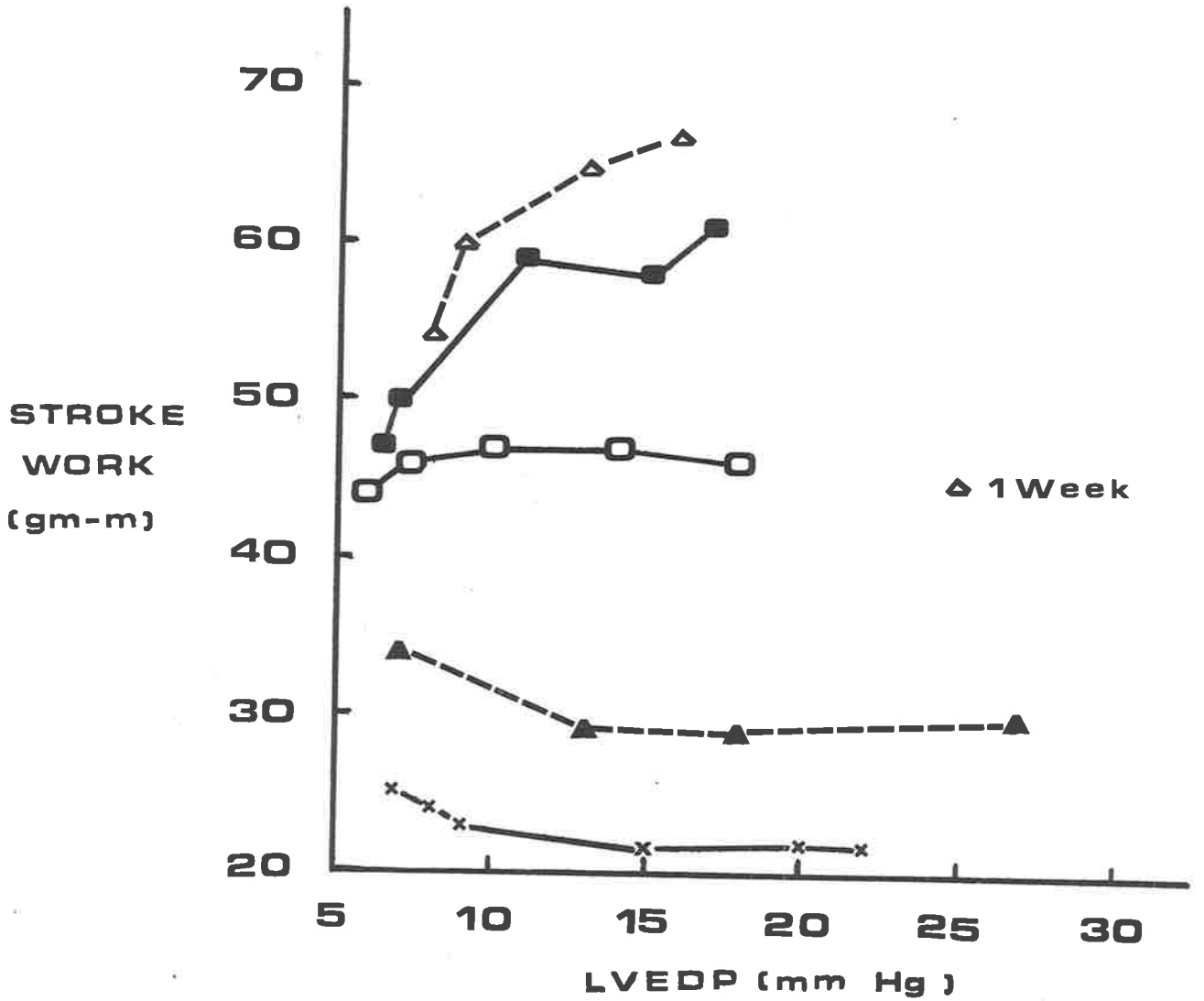
To facilitate tabular comparison of the two groups, recovery of depressed ventricular function was categorised as follows by inspection of the function curves generated at two and at four hours after occlusion:

1. Full recovery: curve back to control levels.
2. Partial recovery: recovery of approximately 50% of stroke work depression produced by coronary occlusion.
3. No recovery: no difference from curve recorded one hour after occlusion.

On this basis the functional effects following occlusion and revascularisation are summarised in Table 5. Ventricular function studies were done in 12 of 16 dogs surviving coronary occlusion. In dogs nos. 7, 8, 9 and 16 no function measurements were obtained. These animals were used only for estimation of infarct size.

The two-hour curves were obtained two hours after the occlusion began, i.e. one hour after release of the occlusion in the revascularised group. Similarly the four-hour curves were obtained four hours after

Figure 29. Ventricular function curves obtained before and one, two and four hours after and one week after coronary occlusion. The symbols used are the same as for Figure 28.


STROKE
WORK
(gm-m)
70
60
50
40
30
20
5
10
15
20
25
30
LVEDP (mm Hg)
1 Week

the occlusion began, i.e. three hours after release of the occlusion in the revascularised group. In either group the two-hour curves did not differ significantly from the curves obtained during coronary occlusion. In the five control dogs with four-hour curves, three of the four-hour curves showed no recovery and the other two showed partial recovery. In the six revascularised dogs at four hours, two showed no recovery, two showed partial recovery and two showed full recovery. These results do not indicate any statistically significant difference (chi-square test) between the ventricular function of control and revascularised groups at four hours in this small number of animals.

Only two of the six control animals survived for re-study at one week. One showed partial recovery of function and the other no recovery. One revascularised dog (no. 13) had abnormal electrocardiographic ST-segment changes compatible with pericarditis when first studied. This dog was sacrificed immediately after the four hour curve to look for and exclude any previous infarction. Of the five revascularised animals remaining, one died and four survived for re-study at one week, at which time all showed full recovery of ventricular function.

The comparison of ventricular function between the control and revascularised groups can be summarised as follows:

Two hours after coronary occlusion

Control Group:	Ventricular function showed no significant change from level one hour after occlusion.	
Revascularised Group:	As above.	

Four hours after coronary occlusion

Control Group:	No recovery	3 dogs
	Partial recovery	2 dogs
	Total	5 dogs
Revascularised Group:	No recovery	2 dogs
	Partial recovery	2 dogs
	Full recovery	2 dogs
	Total	6 dogs

One week after coronary occlusion

Control Group:	No recovery	1 dog
	Partial recovery	1 dog
	Total survivors	2 dogs (out of 6 followed for one week)
Revascularised Group:	Full recovery	4 dogs
	Total survivors	4 dogs (out of 5 followed for one week)

CHAPTER 9

DISCUSSION

(A) PRESSURE-GENERATED VENTRICULAR FUNCTION CURVES

This study clearly indicates that in the intact unanaesthetised animal if heart rate is held constant the normal response to an acute increase in aortic pressure is an increase in left ventricular end-diastolic pressure and a decrease in stroke volume. Although in some animals, as aortic pressure increased, stroke work also increased slightly, and in others it decreased, the average response for the group showed no significant change in stroke work. Thus the ventricular function curves produced by increasing aortic pressure in the present study were essentially horizontal. This response resulted from either a bolus injection or a constant infusion of phenylephrine. The shape of these pressure-generated ventricular function curves differs from volume-generated curves obtained in unanaesthetised open-chested dogs which have a steep initial slope (Sarnoff and Berglund, 1954). The steep initial segment of these curves is obtained at abnormally low filling pressures achieved by bleeding the animal into a reservoir. Ventricular function curves obtained in normal human subjects during infusions of dextran are

surprisingly flat and lack an initial steep segment (Sanghvi et al., 1972). Ventricular function curves produced by volume infusion in the present study were clearly upsloping with a small but significant mean increase in stroke work of 69% from the beginning to the end of the curves.

Imperial and associates (1961) reported a decrease in stroke volume in response to increased outflow resistance in canine heart-lung preparations. They found that peak aortic flow and stroke volume were inversely related to outflow resistance. Stroke work was not significantly changed by moderate increases in resistance but was reduced by greater increases in aortic resistance. Similarly Monroe and French (1961) utilising an isolated heart preparation observed that stroke volume decreased as ejection pressure increased. The results of the present study differ from those reported by Sonnenblick and Downing (1963) who used a cat heart preparation to examine the response of stroke volume and stroke work to increases in aortic blood pressure. In this preparation stroke work consistently increased and stroke volume remained constant in response to increases in mean aortic pressure up to 150 mm Hg. However, as the heart was paced at a constant rate, stroke volume was controlled by the pump in the circuit and, therefore, could not decrease in any one curve. Nevertheless if the aortic pressure was "raised beyond a certain level generally more than 150 mm Hg" a decrease in stroke volume at any left ventricular end-diastolic pressure was usually observed.

Ross and Braunwald (1964) used a constant infusion of angiotensin to increase aortic pressure in order to study left ventricular function in patients with varying degrees of heart disease. In patients with minimal disease, the stroke work vs left ventricular end-diastolic pressure curves sloped steeply upward. Flat or downward sloping curves in the patients with more severe disease were interpreted as demonstrating impaired ventricular function. Cardiac index, however, increased in five of the six patients with upsloping curves and heart rate did not show a reflex decrease despite the increase in aortic pressure. The positive inotropic and chronotropic effects of angiotensin (Koch-Weser, 1964; Fowler and Holmes, 1964) must account for the observed increase in cardiac index and absence of reflex slowing of the heart and would in turn explain the upward slope of the ventricular function curves.

Several possible explanations for the flat ventricular function curves have been considered. It may be hypothesised that reflex inhibition of resting sympathetic tone due to baroreceptor stimulation as blood pressure increased would tend to depress contractility and thus lower the terminal part of the curve. If such an effect occurred, then sympathetic blockade would be expected to reveal the normal upsloping curve. Ventricular function curves obtained after beta-receptor blockade with propranolol, however, had the same or lesser slopes compared with control curves. In addition, resting sinus rate in the awake animals used in this study was

approximately 80 beats/min, indicating minimal resting sympathetic tone. Norepinephrine infusion to maintain a more constant level of sympathetic stimulation before and during the curve, resulted in an upward displacement of the curve with no significant change in the slope.

A second possible explanation is that increasing myocardial ischaemia as aortic pressure increased may have resulted in a failure of stroke work to increase. Coronary blood flow, however, increased progressively, i.e. two to three times control value, as aortic pressure increased. Thus it is improbable that myocardial ischaemia could account for the shape of the curves.

Thirdly, it is unlikely that the flat curves represent an unsteady haemodynamic state prior to autoregulatory increases in contractility since similar curves were obtained during steady state periods produced by constant infusions of phenylephrine.

Finally, increasing amounts of mitral insufficiency with increasing aortic pressure might be expected to depress the curves. There was, however, no significant mitral insufficiency as determined by left ventricular cineangiograms either before or after myocardial infarction. Furthermore, occlusion of the circumflex coronary artery would be expected to enhance any tendency for mitral insufficiency and thus should produce a greater depression of stroke work at increased pressure. This was not the case in the present studies since the curves before and after infarction

were comparable in shape with no greater separation at the maximum left ventricular end-diastolic pressure.

(B) DRUGS USED

1. Phenylephrine

Phenylephrine hydrochloride (Neo-synephrine HCL), 1-isomer of 3-hydroxyphenylethanol-methylamine is a pressor amine with a similar action to noradrenalin but with a lesser inotropic effect and a longer duration of action. Parenteral administration produces marked peripheral vasoconstriction, increased arterial pressure and bradycardia. In a study of 15 sympathomimetic amines Goldberg et al. (1953) concluded that phenylephrine and methoxamine produced the least effect on myocardial contractility.

In the present study where phenylephrine was given as a bolus into the left atrium it might be expected that the drug would very rapidly reach the myocardium via the coronary circulation and that any positive inotropic effect might be seen in the several beats before any peripheral vasoconstriction occurred. During the period immediately following administration of the drug and before the rise in aortic pressure began, no positive inotropic effect as evidenced by a change in the left ventricular dp/dt, left ventricular end-diastolic pressure or peak aortic flow could be seen.

When given as described, phenylephrine produced no arrhythmias or disturbing effects on the awake animals and was considered a suitable drug for achieving the rapid increase in aortic pressure with little direct effect on the heart.

2. Lidocaine (Xylocaine)

Lidocaine has a weak myocardial depressant effect which becomes significant only at high dosage (Hoffman and Bigger, 1971). At the dosage levels used in this study (1-2 mg/kg), lidocaine has a negligible negative inotropic effect (Schumacher et al., 1968; Harrison et al., 1963).

No change was observed in any haemodynamic measurement in response to the administration of lidocaine 2 mg/kg IV before or after coronary occlusion. The half length of lidocaine in plasma is 22 minutes. No ventricular function curves were obtained less than 20 minutes after the last dose of lidocaine.

Hence it is highly unlikely that lidocaine used as described could have influenced ventricular function measurements in this study.

(C) CORONARY OCCLUSION

In the present study occlusion effected significant changes in all haemodynamic parameters measured except peak left ventricular dp/dt. Stroke work demonstrated a greater change than any other parameter. This observation complements the finding that in patients

following acute myocardial infarction stroke work is the best single haemodynamic predictor of mortality rate (Scheidt et al., 1970).

The "pressure-function curve" derived from systolic left ventricular pressure and left ventricular end-diastolic pressure is less sensitive to changes in ventricular function brought about by acute myocardial infarction than is the stroke-work vs left ventricular end-diastolic pressure curve.

In the dogs which were re-studied one week after coronary occlusion, despite the presence of a myocardial infarct averaging 8% of the left ventricle, control haemodynamic measurements had returned to pre-occlusion levels and increases in aortic pressure did not reveal abnormal function. Clearly these measures of overall ventricular function are not sensitive enough to detect these small degrees of regional damage to the ventricle.

In summary the induced increase in aortic pressure did not accentuate the depression of stroke work or other haemodynamic measurements after acute or chronic infarction. This finding contrasts with that of the first study in which volume loading using the right heart bypass technique did help to detect impaired ventricular function.

(D) REVASCULARISATION

Release of the coronary occlusion after one hour to allow re-perfusion of the ischaemic area resulted in a significantly

smaller infarct than that produced by a permanent coronary occlusion. Thus after one hour of ischaemia there exist in the ischaemic zone, areas of myocardium which are not yet irreversibly damaged. Continuation of ischaemia will cause this muscle to die; re-perfusion will result in its survival.

This finding differs from that of Jennings et al. (1960) in a study in which the circumflex coronary artery was clamped for varying periods of time in anaesthetised open-chested dogs. It was concluded that the infarcts resulting from sixty minutes occlusion "were about the same size and distribution" as those found after permanent occlusion. However, this study was concerned only with changes in the posterior papillary muscle and overall infarct size was not accurately measured.

In a study on anaesthetised, open-chested dogs Ginks used an epicardial mapping technique to predict probable infarct size which would result from a standard coronary occlusion (Ginks et al., 1972). In control animals with permanent coronary occlusion, infarct size averaged 68.8% of the predicted value whereas in dogs in which the occlusion was released after three hours the infarct averaged only 10.2% of that predicted. This study suggests that even under conditions of anaesthesia viable myocardium still survives after three hours of ischaemia.

Cox et al. (1968) were able to identify by histochemical staining an ischaemic but structurally intact area surrounding a myocardial infarction in the dog. This injured zone reached its

maximum at 18 hours following coronary occlusion and subsequently regressed until 24 hours,after which it remained relatively constant. Salvage of some of this ischaemic zone before it progresses to infarction must explain the beneficial effect of revascularisation. The longer revascularisation is delayed the greater is the amount of ischaemic muscle which progresses to infarction. Restoration of flow, no matter how complete, cannot resurrect dead muscle.

The difference between the percentage mortality of the control group (67%) and the revascularised group (17%) just failed to reach statistical significance at the 5% level in the small number of animals involved. However, the trends are suggestive and larger numbers might have shown a significant difference. The mean infarct size in those dogs dying within one week of infarction was 26.7±3.3% of the left ventricle. This was more than double the mean infarct size in the survivors: 12.1±5.0% ($P<0.05$).

The mortality rate and the functional differences between the two groups one week after coronary occlusion were suggestive of benefit from revascularisation. However, there was no significant difference between the ventricular function of control and revascularised animals two and four hours after the onset of occlusion. This suggests that restoration of flow to muscle in the contracting ventricle does not result in an immediate return to normal function in that area. Maximum recovery of function may not occur for many hours or even days. In clinical practice, successful surgical

revascularisation of an acute myocardial infarction would not be expected to reverse the cardiac failure immediately. Thus if balloon counterpulsation had been necessary before surgery was performed, this support would still be required in the early post-operative period.

A study such as this which compares coronary occlusions in two groups of dogs has the problem of variations in coronary arterial distribution in different animals resulting in a wide range of infarct sizes and functional depression within each group. When the variable buffering effects of the sympathetic neurohumoral responses are added, considerable overlap between the ventricular function of control and experimental groups is to be expected.

In summary, after one hour of coronary occlusion, those dogs which were revascularised developed much smaller myocardial infarcts than dogs which were not revascularised. The effects of revascularisation on ventricular function and survival were not clear cut, but the revascularised dogs appeared to have a greater chance of survival with better ventricular function than the controls.

PART C

CONCLUSIONS

CHAPTER 10

CONCLUSIONS AND CLINICAL APPLICATIONS

In chapters five and nine the conclusions drawn from the experimental findings have been presented. In this chapter these conclusions will be summarised and their clinical applications discussed.

(A) REVASCULARISATION OF THE CHRONICALLY ISCHAEMIC MYOCARDIUM

In the animal model of chronic myocardial ischaemia used in the first study, revascularisation produced only a small improvement in ventricular function. In order to clearly demonstrate this functional improvement it was necessary to apply to the ventricle a stress which increased myocardial oxygen consumption. In order to evaluate the effect of a coronary bypass graft in patients it would seem desirable to use a test which involves the application of a stress to the heart. This requirement is satisfied by both treadmill exercise testing and supine exercise during cardiac catheterisation. Alternatively, angiographic examination of the regional behaviour of akinetic or hypokinetic segments of ventricular wall before and after revascularisation should be more useful than measurements of the function of the ventricle as a whole.

Although there was only a small number of dogs with complete measurements of coronary blood flow, and functional change, the

results suggested that a high ratio of graft flow to collateral flow was most commonly associated with an improvement in ventricular function. In other words revascularising an area of myocardium with an already abundant collateral blood supply is unlikely to produce any improvement in the function of that area and the initial flow in the graft may be low.

After the experimental bypass grafts had been functioning for an hour or more, there was an increase in the reactive hyperaemic response, an increase in graft flow and a decrease in collateral flow. These observations were highly suggestive of closure of coronary collateral vessels produced by the abolition of the pressure gradient across them. This effect has been described previously by Khouri and Gregg (1971).

As might be expected, in several animals occluding the graft after the collateral vessels had closed produced a greater effect on ventricular function than when the collaterals were open. This phenomenon shown by the ventricle of increasing dependence on graft flow was therefore called the "graft dependence effect". This effect would help to explain the clinical observation that following thrombosis of a bypass graft ventricular function is usually poorer than before bypass surgery (Rees et al., 1971). In practice graft dependence is made even more absolute by the tendency following bypass grafting for subtotal occlusions of the coronary artery

proximal to the graft to progress to total occlusion (Kakos et al., 1972; Aldridge and Trimble, 1971).

(B) VENTRICULAR FUNCTION AND THE EFFECT OF ACUTE CORONARY OCCLUSION

The study carried out in awake dogs demonstrated clearly that when heart rate is held constant, the normal response in the intact animal to a sudden rise in aortic pressure produced by peripheral vasoconstriction is a rise in left ventricular end-diastolic pressure and a fall in stroke volume. Stroke work however being a product of pressure and volume remains relatively constant as the rise in aortic pressure is offset by an equivalent fall in stroke volume.

The application of an increased afterload to the ventricle by peripheral vasoconstriction does not accentuate the depression of stroke work or other haemodynamic measurements after acute or chronic infarction. This negative finding suggests that administration of phenylephrine or other pure vasoconstrictors has no place as a clinical stress test in ischaemic heart disease.

Acute coronary occlusion in awake dogs produced significant changes in stroke work, stroke volume, peak left ventricular power, left ventricular end-diastolic pressure, peak aortic flow and systolic left ventricular pressure. Of all these parameters stroke work demonstrated the greatest change. Thus in monitoring patients following acute myocardial infarction left ventricular stroke work measurement should be useful in assessing severity and in gauging the response to therapy.

(C) REVASCULARISATION FOLLOWING ACUTE MYOCARDIAL INFARCTION

Dogs in which an acute coronary occlusion was released after one hour sustained smaller infarcts than dogs with permanent coronary occlusions. Undoubtedly if the time before release of the occlusion were made greater and greater, recovery of function would be less and less. The time of occlusion after which ischaemic damage becomes irreversible was not investigated in this study and must form the subject of a further investigation.

The findings suggest that in situations in which very prompt revascularisation is possible following coronary occlusion, e.g. coronary occlusion occurring on the cardiac catheterisation table, good recovery of myocardial viability and function should be expected after surgery. More than three hours are required for the return of coronary flow to restore myocardial function. Thus even after successful revascularisation surgery a period of circulatory support such as that provided by the intra-aortic balloon counterpulsator would be desirable before the ventricle could be expected to perform optimally.

Improvement in overall ventricular function following myocardial revascularisation is probably small in most cases and may be absent altogether. Three other beneficial effects of revascularisation, namely long term relief of angina, a reduced re-infarction rate and a reduced mortality rate from coronary artery disease,

are the remaining criteria by which the ultimate value of coronary bypass surgery must be assessed.

APPENDIX

MYOCARDIAL ISCHAEMIA STUDY

ANIMAL NO. 8289 DUKE

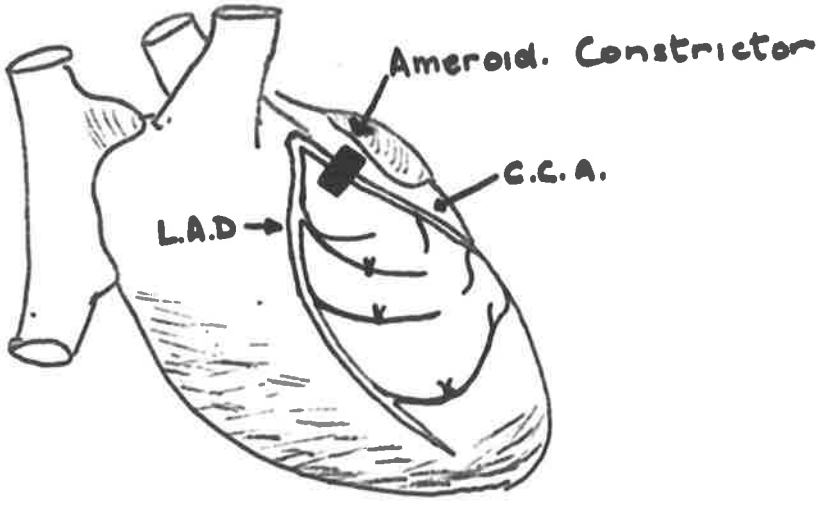
WEIGHT 40lb

AMEROID OPERATION

DATE 20/9/71

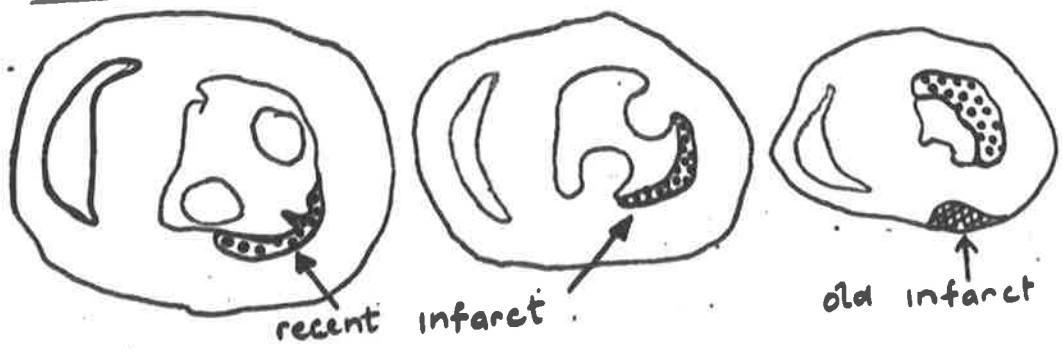
AMEROID SIZE 2·5 m.m.

REMARKS 3 L.A.D. branches tied as shown.



VENTRICULAR FUNCTION STUDY 6/10/61.

AUTOPSY



EFFECT OF OPENING GRAFT UPON L.V.E.D.P.

DOG	LOW STRESS				HIGH STRESS				PROPRANOLOL			
	Closed		Open		Closed		Open		Closed		Open	
	LVEDP	AoP	LVEDP	AoP	LVEDP	AoP	LVEDP	AoP	LVEDP	AoP	LVEDP	AoP
GROUP A												
1	18	66	15	97	29	107	18	111	-	-	-	-
2	19	86	7	80	31	126	18	128	-	-	-	-
3	8	99	6	95	39	151	31	161	-	-	-	-
4	9	128	4	125	17	200	12	190	30	141	15	152
5	10	102	4	96	28	117	8	116	24	63	9	74
6	10	114	10	117	34	172	27	172	30	136	24	148
Mean	12	99	8	102	30	146	19	146	28	113	16	125
SE	2.0	8.8	1.7	6.7	3.0		3.6	13.3	2	25.2	4.3	25.4
P			<0.05				<0.01					
GROUP B												
7	8	115	9	122	16	148	15	148	-	-	-	-
8	5	113	6	111	12	145	10	136	-	-	-	-
9	6	72	7	65	15	123	12	120	40	102	13	96
10	3	111	3	107	11	162	11	165	18	124	8	126
11	7	104	6	100	12	133	12	130	26	145	13	148
12	6	109	8	110	11	130	12	136	11	131	10	125
13	10	63	10	66	29	103	29	105	40	118	38	110
Mean	6	97	7	96	15	135	14	134	27	124	16	121
SE	0.8		0.87		2.4		2.5		5.8		5.5	
P					N.S.							

PRESSURE-GENERATED VENTRICULAR FUNCTION CURVES IN 17 DOGS.

DOG NO.	LVEDP*	S.W.†	LVEDP	S.W. % contr	LVEDP	S.W. % contr	LVEDP	S.W. % contr	LVEDP	S.W.	LVEDP	S.W.	S.W. % contr
1	6.5	63.2	10	106	12.5	106	15	106	17.5	106	17.2	67.1	106
3	9.6	43.1	"	104	"	112	"	110	"	110	18	47.8	111
4	10	16.9	"	100	"	106	"	89	"	82	25.5	15.7	93
5	7.9	52	"	92	"	85	"	90	"	100	19.8	55.7	107
6	7.1	44.6	"	96	"	92	"	77	"	85	23.6	34.1	76
10	6.3	35.6	"	125	"	137	"	148	"	-	15.4	46.1	150
11	4.0	38	"	92	"	94	"	88	"	89	16	33.6	88
12	5.0	35.7	"	87	"	98	"	99	"	99	23	38.1	107
13	9.8	17.7	"	98	"	87	"	82	"	86	19	15.5	88
14	10.3	42.9	"	100	"	110	"	112	"	109	21.2	52.0	121
15	3.7	24.3	"	98	"	102	"	105	"	108	19	29.7	122
17	5.5	34.5	"	116	"	123	"	126	"	128	17.5	44	128
18	10	36.3	"	100	"	104	"	108	"	113	20.2	39.8	109
19	9.2	67.4	"	97	"	89	"	81	"	78	26.5	48.7	72
20	8.0	17.4	"	86	"	87	"	99	"	110	23.2	18.4	106
21	8.5	22.8	"	92	"	84	"	78	"	73	19.8	15.9	70
22	8.4	50.7	"	120	"	136	"	138	"	142	18.4	73.6	145
MEAN	7.6	100%	"	100.5	"	103.1	"	102.1	"	101.1	20.2	-	105.8
Std. Error	0.5	-	"	2.7	"	4.0	"	5.0	"	4.6	0.8	-	5.6
P Value	Vs peak <0.001	-		Vs cont N.S.				N.S.		N.S.	Vs cont <0.001		N.S.

* LVEDP in mmHg

† S.W. in gm-m.

VENTRICULAR FUNCTION CURVES GENERATED BY PHENYLEPHRINE INFUSION IN 4 DOGS.

DOG NO.	CURVE	LVEDP*	S.W.†	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W.	S.W. % cont
I 1.	1	7.0	50.5	7.5	103	10.0	117	12.5	123	15	-	17.5	-	20	-	12.5	61.9	123
	2	5.7	48.5	"	117	"	134	"	142	"	147	"	153	"	157	24.4	80.2	165
I 2.	1	5.0	52.5			"	107	"	109	"	111	"	114	"	119	20.0	62.6	119
I 3.	1	9.1	32.0			"	97	"	89	"	83	"	77	"	71	19.5	22.7	71
	2	4.2	28.5	"	91	"	86	"	81	"	87	"	86	"	82	20.0	23.4	82
I 4.	1	7.9	60.7			"	115	"	115	"	121	"	-	"	-	16.4	77.1	127
	2	7.8	71.3			"	106	"	113	"	116	"	118	"	119	19.6	84.6	119
	3	7.8	75.1			"	107	"	112	"	120	"	-	"	-	14.7	90.3	120
	MEAN	6.8				"	109	"	111	"	112	"	110	"	110	18.4		116
	SE	0.6				"	5	"	7	"	8	"	13	"	15	1.3		10
P VALUE																		N.S.

* LVEDP in mmHg † S.W. in gm-m

PRESSURE-GENERATED VENTRICULAR FUNCTION CURVES IN 10 DOGS BEFORE AND AFTER CORONARY OCCLUSION.

	DOG NO.	LVEDP*	S.W.† % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont	LVEDP	S.W. % cont
BEFORE OCCLUSION	1	6.5	100	10	106	12.5	106	15	106	17.5	106	17.2	106		
	3	9.6	"	"	104	"	112	"	110	"	110	18.0	111		
	4	10.0	"	"	100	"	106	"	89	"	82	25.5	93		
	5	7.9	"	"	92	"	85	"	90	"	100	19.8	107		
	10	6.3	"	"	125	"	137	"	148	"	-	15.4	150		
	11	4.0	"	"	92	"	94	"	88	"	89	16.0	88		
	12	5.0	"	"	87	"	98	"	99	"	99	23.0	107		
	13	9.8	"	"	98	"	87	"	82	"	86	19.0	88		
	14	10.3	"	"	100	"	110	"	112	"	109	21.2	121		
	15	3.7	"	"	98	"	102	"	105	"	108	19.0	122		
MEAN ± SE		7.3 ± 0.8			100.2 ± 3.3		103.7 ± 4.7		102.9 ± 6		93.8 ± 3.6	19.4 ± 1.0	109.3 ± 5.0		
P VALUE												control vs peak	c. vs peak N.S.		
1 HOUR AFTER OCCLUSION	1	5.8	53			12.5	64	15	66	17.5	67	19.6	69		
	3	15.2	55			"	-	"	55	"	60	21.3	63		
	4	12.0	62			"	63	"	68	"	68	19.5	72		
	5	12.5	58			"	58	"	58	"	57	25.5	65		
	10	9.0	82			"	87	"	80	"	80	21.0	82		
	11	7.0	69			"	57	"	56	"	56	22.0	55		
	12	10.0	49			"	50	"	53	"	56	23.0	64		
	13	13.2	39			"	-	"	36	"	40	19.3	47		
	14	13.6	80			"	-	"	80	"	81	25.8	86		
	15	9.0	74			"	64	"	53	"	55	21.4	60		
MEAN ± SE		10.7 ±0.96	62.1 ± 4.4				63.3 ± 4.6		60.5 ± 4.2		62.0 ± 3.9	21.8 ± 0.7	66.3 ± 3.7		
P VALUE		cont vs 1 hr	<0.001				<0.001		<0.001	-	<0.001	N.S.	N.S.	(c vs 1hr)	

* LVEDP in mmHg † S.W. in gm-m. # P=<0.001

HAEMODYNAMIC PARAMETERS BEFORE AND ONE HOUR AFTER OCCLUSION.

	CONTROL							AFTER PHENYLEPHRINE						
Dog No.	Stroke Volume	Peak Flow	Peak L.V.P.	LVEDP	Peak Power	Stroke Work	Peak dp/dt	Stroke Volume	Peak Flow	Peak L.V.P.	LVEDP	Peak Power	Stroke Work	Peak dp/dt
Before Occlusion														
1	41	395	127	8.5	673	53.2	1798	31.5	287	183	17.2	693	57.1	-
3	25	256	147	9.6	504	43.1	2780	24	218	182	17.4	528	51.2	3000
4	11	119	128	10	205	16.9	1320	7	76	194	25.5	196	15.7	1590
5	30.1	280	141	7.9	528	52	1510	27.2	251	178	19.8	599	55.7	1630
10	22.1	256	121	4.5	412	30.1	2330	19.1	220	200	15.4	579	46.1	3350
11	26.0	250	121	4.0	406	38.0	1820	15.0	158	183	16.0	388	33.6	2240
12	25.9	302	125	4.0	513	35.7	2080	18.5	209	193	23	549	48.1	2560
13	13.2	162	115	9.8	251	17.7	1770	9.7	101	171	19	231	15.5	2430
14	26	268	163	14	579	50.4	2250	21	226	210	21.2	620	52.0	2680
15	16	180	120	3.7	292	24.3	1680	13.1	137	195	19	352	29.7	2130
Mean ± S.E.M.	23.6± 2.8	240.8 (24.7)	130.8 (4.7)	7.4 (1.1)	436.3 (47.8)	37.1 (4.8)	1930 (136)	18.6 (2.4)	188.3 (21)	188.9 (3.7)	19.3 (1.0)	473.5 (54.1)	40.5 (5.4)	2401 (194)
After Occlusion 1	27.2	299	105	5.8	415	33.7	1670	23.4	245	162	19.6	533	43.5	-
3	15	160	139	15.2	291	23.6	2250	14	142	168	21.3	316	27.3	2630
4	8	92	115	12	140	10.5	1320	6	67	165	19.5	148	12.1	1590
5	21.5	216	122	12.5	345	30.1	1580	17	169	176	25.5	397	33.7	3320
10	20.5	227	110	9	333	25.3	3260	20.1	233	164	24.4	509	36.6	3510
11	20	209	108	7	303	26.1	1590	11	127	170	22	288	20.8	1960
12	13.8	174	126	10	298	17.5	1960	14.3	168	143	20	337	23	1900
13	6.8	93.9	94.0	13.2	117	6.81	1560	5.1	77.9	141	19.3	147	8.4	2370
14	22	232	133	13.6	407	42.9	2150	17	173	193	25.8	433	37.0	2680
15	12	146	124	9	238	18.0	1680	7.3	95.1	174	21.4	223	14.7	2240
Mean ± S.E.M.	16.7± 2.1	184.9 (20.5)	118 (4.3)	10.7 (1.0)	288.7 (31.5)	23.5 (3.4)	1912 (174)	13.5 (1.9)	149.7 (19.1)	165.6 (4.8)	21.9 (0.8)	333.1 (43.2)	25.7 (3.8)	2467 (214)
P value	<0.001	<0.001	<0.01	<0.01	<0.001	<0.001	NS	<0.01	<0.01	<0.001	NS	<0.001	<0.001	NS
Percentage Change	29	25	10	45	34	37		27	22	12	13	30	37	

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