

SURGERY FOR CORONARY
ARTERY DISEASE

EDINBURGH CLINICAL EXPERIENCE
AND EXPERIMENTAL STUDIES

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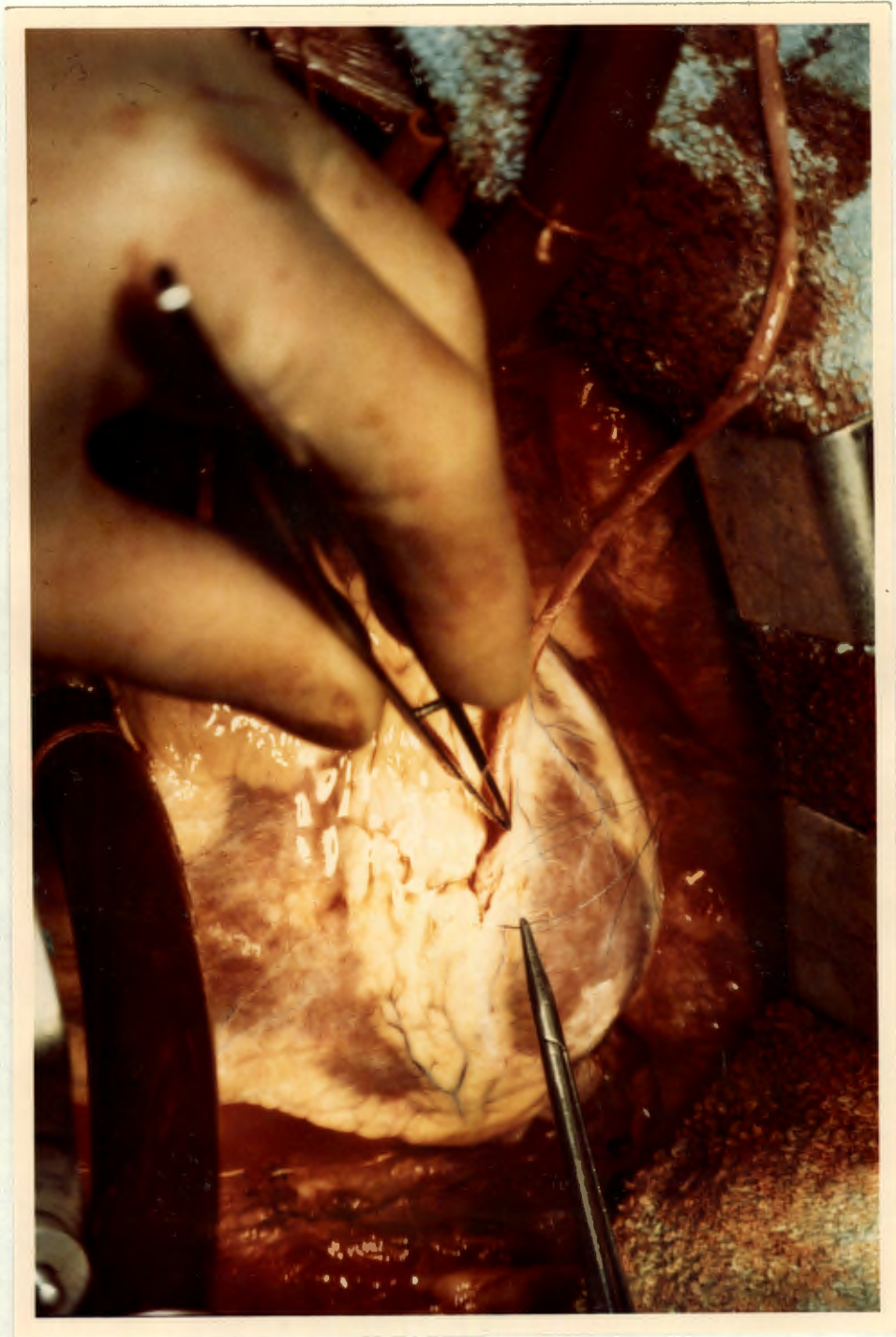
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SECTION 1
INTRODUCTION

INTRODUCTION

Surgical intervention for coronary artery disease has been practised for many years. Initial procedures had little success, although experimental justification for their use was often claimed.

During the past decade there has been unprecedented growth in the practice of aorto-coronary bypass grafting. This has had undoubted clinical success, at least in the treatment of angina. Relatively little experimental work underlies this practice.

There remains considerable uncertainty about the role of coronary surgery particularly with regard to indications and long term results. There is also scope for refinement of techniques to allow of optimal benefit from surgical intervention.

The role of coronary surgery will undoubtedly become clearer with accumulating clinical experience. Refinement of surgical techniques requires more careful appraisal of the operative procedure of aorto-coronary bypass grafting and understanding of myocardial perfusion in the presence of coronary obstruction.

For this purpose experimental studies provide a means of making observations which are not possible in clinical practice. The principles illustrated by such experimental studies require to be applied with caution to clinical practice, as artificial conditions in an acute animal experiment may not truly simulate the naturally occurring spectrum of disease in the human. However, with this reservation in mind, it is instructive to look at experimental studies from the point of view of the coronary surgeon, who, in spite of the complexity and variability of the disease, has a relatively limited choice of operative manoeuvres at his disposal. It is to aid optimal application of these manoeuvres that this study has been undertaken.

PERSONAL EXPERIENCE OF CORONARY SURGERY

During 1966 and 1967 as a Surgical Resident in Bridgeport, Connecticut I assisted Drs Berry, Marash and Shea at a number of operations intended to improve myocardial blood flow in patients with angina, and personally performed three of these operations. The surgery consisted of internal mammary artery implantation combined with omentopexy and pericardial abrasion. During this period I was present during a very early attempt at direct coronary surgery by gas endarterectomy performed by Sawyer at Kings County Hospital, New York. These experiences highlighted for me the surgical problems and shortcomings in this common disease.

It was therefore with considerable interest and pleasure that I was associated with Mr (now Professor) N M A Rogers in 1971 at Wentworth Hospital, Durban, when he introduced aorto-coronary bypass grafting in that Unit with the first operation on 18th March 1971 (a single graft to the anterior descending artery in a 41 year old man with severe angina of nine months duration). On 14th November 1971, under his guidance, I performed my first aorto-coronary bypass graft operation (graft to right and anterior descending arteries in a 48 year old man with crescendo angina).

During 1972 and 1973 as Senior Registrar to Mr J K Ross and Mr D N Ross at the National Heart Hospital, London, I undertook 40 such operations, and assisted with many more. My interest in this surgery continued in Glasgow in 1974 and 1975, and since January 1976 as Senior Lecturer in Cardiac Surgery at the University of Edinburgh it has been a major clinical commitment.

No "academic" pursuit in surgery can carry authority without a clear basis in practical, clinical experience. For this reason my personal experience of coronary surgery in Edinburgh during 1976 and 1977

is reviewed in this thesis. The major portion of the thesis however, is devoted to the experimental assessment of the effects of coronary arterial obstruction on myocardial perfusion, and the influence of factors of surgical relevance, such as heart rate, rhythm, perfusion pressure and left ventricular cavity pressure, as well as observations on the severity of obstructive lesions resulting in myocardial underperfusion and possible aids to the surgeon in deciding the need for, or adequacy of, bypass grafting in clinical context. This experimental study has been undertaken during 1977 and 1978 in the Department of Clinical Surgery of the University of Edinburgh.

ASPECTS OF WORK DONE PERSONALLY

The surgical series of patients undergoing coronary surgery in Edinburgh during 1976 and 1977 (Section 3a) is entirely a personal series. Coronary surgery then, and in the period since, in Edinburgh has been almost entirely done by me. The surgical service provided serves not only the Edinburgh area, but also the Outer Isles; the Inverness and Dundee areas, and the Border areas - most of the North and East of Scotland. The work load continues to increase and is limited only by operating facilities and personal time. In 1978, over 100 patients had coronary surgery and the clinical place of this form of surgery would appear well established and set for expansion in Scotland.

The ideas and development underlying the animal experimental study are entirely a personal responsibility; the animal model is an original idea. All the work of performing the animal surgery (which included obtaining donor blood; setting up and running cardiopulmonary bypass for each experiment; anaesthetising the animals, monitoring the pressures and flow rates; making the grid and the angiograms; and blocking the myocardium) has been personally performed for each experiment.

All illustrations have been personally drawn and all calculations of perfusion levels for the regional mapping have been personally done using an Olivetti 100 computer. Most of the Versatec print-outs have been run off the PDP 12 computer personally. All operations or angiograms are of patients personally treated during the past 3 years.

The concept of using thermography was an original idea, although it has been used in a limited way before. The development of this technique in isolated hearts and finally in an operating theatre has been a personal undertaking.

ASPECTS OF WORK DONE BY OTHERS

The obtaining and preparation of tracer microspheres has been done by Dr R Riemersma of the Department of Medicine. The weighing of myocardial samples and counting of radioactivity in the Walloch counter has been done by Mr Ian Ansell of the Department of Clinical Surgery. The programming of the PDP 12 computer for making the regional myocardial perfusion maps has been done by Dr Keith Boardman of the Department of Medical Physics and Medical Engineering.

SECTION 2

BACKGROUND TO THESIS

THE DEVELOPMENT OF SURGERY FOR CORONARY ARTERY OBSTRUCTION

Francois-Frank, a Professor of Physiology in Paris, suggested in 1899 that division of cervical sympathetic nerves might help relieve angina pectoris (Sabiston, 1978). This suggestion was put into practice by Jonnesco in 1916 (Jonnesco, 1920; Vansant and Muller, 1960). This initial operation - historic in this field - demonstrates several problems common to many procedures for angina:- the diagnosis was probably wrong; the physiological background was unsound; and the patient improved!

Jonnesco's operation was modified to resect only sensory sympathetics and 100 patients treated in this way were available for review in 1925 (Vansant and Muller, 1960). In 1927 it was observed that only symptomatic relief was offered (Cutler, 1927) and that results varied - not unlike some recent comments on current techniques of aorto-coronary bypass surgery ("Coronary Artery Surgery at the Crossroads" - Editorial, The New England Journal of Medicine, September 22, 1977). Experimental evidence was forthcoming to show that sympathectomy did reduce mortality and infarct size following coronary occlusion (Cox and Robertson, 1936; Ochsner and De Bakey, 1937) and this form of surgery was advocated up to the late 1930's (Miller, 1977).

Attempts to interrupt sympathetic nerves in the pre-aortic cardiac plexus at thoracotomy, and division of the posterior roots of the upper four thoracic spinal nerves were tried but abandoned in the 1930's (Vansant and Muller, 1960).

Total thyroidectomy was tried for control of angina, but the mortality rate, resultant myxoedema, and frequent tetany, did not justify the technique, which was abandoned in the early 1940's (Miller, 1977).

Ligation of both internal mammary arteries in the belief that this

would distend collateral vessels to the coronary tree and improve coronary flow is difficult to accept as a serious suggestion. Nevertheless, a series of 41 patients treated by this questionable procedure was reported as recently as 1956 (De Marchi et al, 1956) and a series of 100 patients treated in this way was reported in 1957 (Glover et al, 1957). Again, experimental justification for such surgery was reported by some (Glover et al, 1957) and refuted by others (Vansant and Muller 1959 and 1960).

Direct attempts to improve blood supply to myocardium began with the creation of epicardial and pericardial abrasions to provoke adhesion formation with the expectation that these adhesions would carry blood from non-coronary sources to myocardium (Beck, 1935). A variety of chemical and physical irritants were subsequently used to achieve adhesion formation.

Many attempts were made to improve the non-coronary blood source by wrapping omentum, skeletal muscle flaps, or lung around the heart; and other ingenious attempts were described in experimental animals (Vansant and Muller, 1960). Clinical improvement was claimed for each operation, but these procedures fell into disrepute with the advent of newer procedures.

Wearn et al (1933) postulated that in the presence of coronary obstruction blood could gain access to perfuse myocardium from heart chambers via thebesian veins. Experimental stenosis of the coronary sinus was shown to confer some protection from the effects of acute coronary artery occlusion in dogs (Gross and Blum, 1935; Gregg and Dewald, 1938). Beck and Mako (1941) concluded that the procedure was not justified clinically; however it was applied extensively and there are many reports of relief of angina from this form of surgery (Beck, 1935; Beck et al 1951; Beck and Leighninger, 1955; Selman, 1955).

A further development of the Beck procedure was the two-stage operation

(Beck II) in which partial coronary sinus occlusion was followed a few weeks later by an arteriolisation procedure using a vein graft to the coronary sinus (Beck, 1957).

In 1946 Vineberg introduced the procedure of implanting the internal mammary artery into the myocardium (Vineberg 1946, 1949, 1952). Continued patency with demonstrable communication with coronary vessels could be shown with this procedure and very satisfactory clinical results with 90% of patients having complete or near-complete relief of angina are reported (Vineberg and Walker, 1957).

A number of other ingenious procedures have been proposed; some have been tried experimentally; a few have been used clinically. The subject is well reviewed by Vansant and Muller (1960) and this review provides fascinating reading. It is apparent from the literature that:

- 1) sound physiological backgrounds were claimed for many procedures;
- 2) no convincing evidence of significantly increased myocardial perfusion was produced for any procedure (Miller, 1977). This partly reflected the problems of measuring regional perfusion; satisfactory techniques were not then available;
- 3) no coronary angiographic evidence was available to confirm the clinical diagnosis; still less to allow rational application of surgery;
- 4) satisfactory clinical results were obtained in spite of the above problems. This resulted in a measure of scepticism for myocardial revascularisation surgery, which although justified, has perhaps resulted in unfortunate polarisation of viewpoints (McIntosh and Garcia, 1978). It is further apparent that a degree of caution and humility on the part of the current generation of coronary surgeons would not be misplaced!

The first direct surgical procedures on the coronary arteries consisted of coronary endarterectomy (Bailey et al 1957; Longmire et al,

1958). This procedure alone did not achieve consistent results, especially when attempted on the left coronary tree. Inability to totally remove atheromatous cores, and frequent re-occlusion due to local thrombosis made the procedure unacceptable, although it is now frequently combined with aorto-coronary bypass grafting (See Section 3) (Miller, 1977).

The first reported aorto-coronary bypass graft using saphenous vein was performed by Sabiston in 1962 (Sabiston 1974 and 1978) but the patient died shortly after. Garret et al (1973) reported a 7 year follow-up of an aorto-coronary bypass graft performed in 1964. Favaloro et al (1970) from the Cleveland Clinic, and Johnson et al (1969) from Milwaukee were the first groups to describe results of aorto-coronary bypass grafting in large numbers. The rapid increase of this form of surgery in the United States is illustrated by the estimate that over 100,000 such operations had been performed in the USA by 1974; 30,000 to 40,000 in 1974; 54,000 in 1975; 60,000 in 1976, and possibly 80,000 to 100,000 in 1977 (McIntosh and Garcia, 1978).

There is now widespread acceptance that this form of surgery provides good symptomatic relief from angina in 70-80% of patients (Sabiston, 1978; McIntosh and Garcia, 1978; Miller, 1977). In spite of the large number of patients who have had such surgery the effect on natural history is unclear, although evidence of improved longevity in operated groups is accumulating (Spencer and Isom, 1978; Sheldon, 1977; De Bakey and Lawrie, 1978; Jones et al 1978).

The details of current practice are now fairly well established (Miller, 1977) and operative technique as followed in Edinburgh is representative of that followed in many major centres, and is described in Section 3.

ANATOMY OF THE CORONARY VESSELS

The anatomy of coronary vessels in all mammals appears to be basically similar (Grant and Regnier, 1926). Coronary anatomy in human hearts has been extensively studied (Schlesinger, 1938; Blumgart et al, 1940; Barold et al, 1956; James and Burch, 1958; May, 1960; James, 1961; Fulton, 1965; Farrer-Brown, 1977).

It is, however, the coronary arteriographic demonstration of the coronary anatomy (and pathology) which is of interest to the clinical coronary surgeon. The arteriographic appearances of the commonest variety of human coronary anatomy - the dominant right system - are shown in Section 3b.

Demonstration of the coronary arteries and their pathology in humans was first attempted radiologically by non-selective techniques, with a bolus of radio-opaque medium being injected into the ascending aorta by a trans-sternal injection (Radner, 1945; Hoyos and Del Campo, 1948) with poor results and obvious hazard. Retrograde arterial catheterisation with injection into the ascending aorta was less hazardous (Jonsson, 1948; Helmsworth et al, 1950; Dr Guglielmo and Guttadauro, 1952; Paulin, 1964) but coronary opacification was generally poor. Attempts to improve coronary filling during injection of contrast medium by inducing bradycardia (Lehman et al, 1959) or occlusion of the ascending aorta (Dotter and Frische, 1958) carried considerable risk.

Selective coronary angiography was developed and refined in the early 1960's - Mason Sones being probably the outstanding pioneer (Sones and Shiley, 1952; Rickets and Abrams, 1962; Gensini, 1963). The Sones technique (using a brachial artery cut-down) and the Judkins technique (Judkins, 1968), (using a percutaneous femoral artery puncture) are now well established (Austen et al, 1975) and carry very little hazard.

The anatomy of the dog's coronary arteries has been well described (Pianetto, 1939; Blair, 1961). The dog has a left dominant system, as shown in Figure 4.8. This type of system (the circumflex supplying posterior left ventricle as the posterior descending artery) is present in about 10% of human and pig hearts. The canine coronary anatomy is particularly favourable for showing the left ventricle together with its entire arterial supply on a single-plane angiogram (a factor which influenced the choice of experimental animal in this study). The dog has a very large septal artery which arises close to the left coronary ostium and supplies much of the septum - it is shown in Figure 4.8.

The major coronary arteries, shown well by angiography, and familiar to the coronary surgeon, run on or near the surface of the heart. They give rise to penetrating branches which supply the myocardium. These vessels are of two types - "branching" vessels which divide in tree-like fashion to supply the whole thickness of the myocardial wall; and "straight" vessels which penetrate, with few branches, to supply papillary muscles and trabeculae on the endocardial surface (Farrer-Brown, 1977).

The branching arterioles contain muscle cells capable of altering the lumen, and give rise to capillaries which run alongside myocardial fibres. Not all capillaries are functional at once; precapillary sphincters can close off the lumen (Provenza and Scherlis, 1959a and 1959b; Farrer-Brown, 1977).

Venous channels join up to form the great cardiac vein anteriorly and the coronary sinus posteriorly. There is a deeper venous circulation which drains into atria and ventricles via thebesian veins. A system of myocardial sinusoids is also described, which communicates with arterioles, capillaries and heart cavities (Christensen and Campeti, 1959; Gregg, 1950; James and Burch, 1958) and form an anatomical basis for explaining the rationale of the Vineberg operation for ischaemic heart disease

(Vineberg 1949 and 1952).

Collateral vessels in the coronary circulation have been well described (Fulton, 1965; Schaper, 1971). They are present in normal hearts and can be demonstrated in the newborn (Farrer-Brown, 1977). They are relatively large and superficial in the normal dog heart, about 40 μ in diameter, and are demonstrable by injection-and-clearing studies (Schaper, 1971). It is well known that collateral vessels develop in response to experimental major coronary occlusion and naturally occurring occlusion, and that this collateral development is accompanied by a rise in peripheral coronary pressure beyond the occlusion (Gregg, 1950; Fulton, 1965; Schaper, 1971).

PHYSIOLOGY OF MYOCARDIAL PERFUSION

Current understanding of myocardial perfusion is derived from a considerable volume of work undertaken throughout this century (Gregg and Fisher 1963; Gorlin 1974 and 1960; Rowe 1969; Berne 1964; Braunwald 1971; Resnekov 1977).

The comparatively recent advent of surgery for coronary artery disease has added impetus to this work (Holman 1977; Hottenrott et al 1974; Kleinman and Wechsler 1978).

In order to understand the evolution of this work it is necessary to consider the available methods for investigation of myocardial perfusion physiology.

Langendorff in 1895 and Porter in 1896 described isolated, perfused heart preparations which allowed measurement of coronary arterial inflow and coronary sinus drainage (Porter 1896). Further studies became possible once heart-lung preparations were developed (Knowlton and Starling 1912; Anrep 1936). An artificial lung was used in a perfusion circuit for studying myocardial perfusion by Evans et al in 1934, and many developments of this technique followed (Gregg and Fisher 1963).

The naturally perfused heart of the anaesthetised open-chest dog was studied by Wiggers (1936) and this type of experimental model has since provided considerable insight into the physiology of myocardial perfusion. Measurement of myocardial perfusion has been made by direct application of flow probes to the coronary arteries (Gregg and Fisher 1963) or by measurement of nitrous oxide washout (Bing 1960) or washout of indicators from myocardium (Salisbury et al 1962; Kirk and Honig 1964; Bassingthwaighe et al 1968; Herd et al 1962; Love et al 1965). All these techniques however measure flow per unit weight of

myocardium and do not relate flow to anatomical region. It is well recognised that myocardial perfusion abnormalities may only become apparent during stress (Holman 1978; Friersinger 1977) and it is therefore helpful to use the more recent technique of tracer microspheres for assessment of myocardial blood flow in the presence of coronary disease. This technique, developed by Rudolph and Heyman (1967) has been validated by many workers (Domenech et al 1969; Buckberg et al 1971) and is now the technique widely used (Kleinman and Wechsler 1978; Hoffman 1978). The details of the technique, which has been used in the experimental study described in this thesis are described in detail in Section 4c.

Coronary flow varies considerably in response to myocardial oxygen demand. At rest in man the usual value for left ventricular flow given is 0.7 to 0.9 ml/Gm/minute (Gregg and Fisher 1963; Gorlin 1974). Up to five fold increases in resting flow for the dog have been recorded experimentally (Gorlin 1974). Gorlin points out the difficulty in calculating vascular resistance for coronary flow because of systolic impedance of flow by muscle contraction.

The phasic nature of coronary flow is well described (Gregg and Fisher 1963) and is shown in Section 5e (Figure 5e-7). Left ventricular blood flow is largely diastolic because of the compressive effect on intramyocardial vessels due to myocardial contraction. Thus diastolic pressure (perfusion pressure) and heart rate (diastolic perfusion time) are crucial factors determining the ability of the coronary tree to deliver an adequate volume of blood to meet the needs for myocardial oxygen consumption.

The coronary flow rate to the myocardium, while being dependant on adequate diastolic pressure and duration of diastole, is regulated by coronary arteriolar resistance. Changes in coronary arteriolar

vasomotor tone can vary coronary flow up to five times resting level (Gorlin 1974). It is at the level of the coronary arterioles that coronary vascular resistance is regulated. Only with severe coronary obstructive disease does large coronary vessel resistance become a factor influencing myocardial perfusion.

The most potent stimulus for coronary vasodilatation is myocardial hypoxia (Gregg 1950). Approximately 70% of the oxygen in the coronary arterial blood is extracted in its course through the coronary bed (Gorlin 1974) and the normal desaturation of coronary sinus blood (30% saturation) is well known to the cardiac surgeon. It is clear therefore that any increased demand for myocardial work requires prompt change in myocardial perfusion rate which is effected by lowering of vasomotor tone by coronary arteriolar vasodilatation. Because myocardial metabolism is normally aerobic any requirement for increased myocardial work (eg: exercise, tachycardia, sudden increase in systolic blood pressure) is immediately met by increased coronary flow. The precise nature of the vasodilating stimulus is unclear - local metabolites are commonly implicated (Milnor 1974).

By comparison, changes in vasomotor tone effected by autonomic nervous stimuli or circulating catecholamines are far less important (Milnor 1974). Drugs can profoundly alter vasomotor tone and papaverine, dipyridamole and adenosine have been used for this purpose experimentally (Schaper 1971; Schaper et al 1975; Downey et al 1975).

PATHOLOGY OF CORONARY ARTERY OBSTRUCTION

Coronary artery atheroma is the usual cause of coronary artery obstruction (Vlodaver and Edwards 1971; Eliot and Edwards 1974; Farrer-Brown 1977). Although coronary ostial obstruction in syphilis, coronary arterial inflammatory disease, and coronary arterial dissection as part of aortic dissection, spasm or coronary embolus (Eliot and Edwards 1974) or congenital abnormalities (Wheatley et al 1975) can occasionally be responsible for myocardial ischaemia it is advanced obstructive coronary atherosclerosis (or atheroma) which is familiar to every coronary surgeon, and it is this disease which is illustrated in Section 3b, and the exclusive reason for the surgery reviewed in Section 3a.

The process probably begins in the intima but later affects all layers of the artery. The lesions are commonly not circumferential (see Section 3b) and angiographically require views in at least two planes for assessment.

The bifurcations of arteries are particularly likely to be affected - the bifurcation of distal right artery and origin of diagonal branches of anterior descending artery are commonly encountered examples (see Figures 3-14 and 3-15).

Pathologically, the lesions consist of accumulations of lipid-filled macrophages in the intima, around which fibrous tissue reaction develops. This fibrous tissue, encapsulating the lesion, intrudes on the lumen. Lipid material within the lesions, extruded from the macrophages crystallises and calcifies, and the lesions, as they enlarge involve intima, media and adventitia.

The lesions may be complicated by surface ulceration, surface thrombosis with total occlusion of the coronary arterial lumen, or haemorrhage within the lesion resulting in its enlargement and obstruction

of the lumen. The lesions are well illustrated by Farrer-Brown (1977).

The disease affects coronary vessels on the epicardium - the intramyocardial vessels being usually free from disease. The most commonly affected segment of artery is the distal right coronary artery (Figure 3-16 is a typical example). The lesions may be extremely localised - at least in their obstructive effects and angiographic appearance (as an example see Figures 3-10 and 3-11 - or may be diffuse and wide-spread with multiple areas of obstruction (see Figures 3-14, 3-15, and 3-16.).

The disease tends to affect the proximal portions of the epicardial coronary arteries predominantly (76% of anterior descending obstructions were in the proximal half; 17% in proximal and distal halves, and 7% in distal half only) - (Vlodaver and Edwards 1971).

The disparity between the angiographic appearance and the extent of disease assessed by palpation at surgery or examination at autopsy cannot be over-emphasised (Elliot and Edwards 1974). Angiography is essential in defining the disease in terms of its likely haemodynamic effects (see Sections 3b and 3c). Surgery is undertaken for coronary obstruction, not for coronary atheroma.

In a series of 313 angiographically studied patients (Diethrich et al 1967) 23% had significant involvement of only one major coronary artery, 40% had involvement of two vessels, 29% had involvement in 3 vessels. The distribution of disease in the Edinburgh series is given in Figure 3-3.

A review of the pathological changes in the myocardium as a consequence of coronary artery obstruction is given by Eliot and Edwards (1974). The surgeon encounters this in terms of left ventriculographic appearance, or as visible scar tissue at the time of surgery (Section 3).

SECTION 3a
EDINBURGH EXPERIENCE
OF
CORONARY SURGERY
1976 and 1977

1000000

PERSONAL EXPERIENCE IN EDINBURGH DURING 1976 and 1977

During 1976 and 1977 at the Royal Infirmary of Edinburgh aorto-coronary bypass grafting was undertaken on 189 patients. The sex distribution and age range of the patients is shown in Figure 3.1.

EDINBURGH CORONARY SURGERY 1976 - 77

189 patients. { 158 men (84%)
31 women (16%)

age	number
30 - 39	7 (4%)
40 - 49	63 (33%)
50 - 59	91 (48%)
60 - 69	28 (15%)

Figure 3.1

It is of interest and considerable socio-economic importance to note that the majority were well below retirement age - nearly half being in the 50 to 60 decade and a third in the 40 to 50 decade. No specific preference has been given to patients of any particular age group.

Chronic stable angina pectoris was the symptom for which surgery was undertaken in all except two, where unstable angina, refractory to medical management, was the indication.

EDINBURGH CORONARY SURGERY 1975 - 77

189 patients

Symptoms

chronic stable angina	187	(99%)
breathlessness with angina	55	(30%)
unstable angina	2	

Previous myocardial infarction

86 patients 45%

Risk factors

smoking	175	(93%)
elevated serum lipids	19	(10%)
hypertension	12	(6%)
diabetes mellitus	6	(3%)

Angina had usually been present for several years, and in some for a decade or more. Breathlessness accompanied angina in 30% of the patients - it did not indicate poor left ventricular function, in contrast to those patients whose predominant complaint was breathlessness, and in whom surgery was not recommended.

Angina was always managed initially by medical means, which included beta blockade in all, glyceryl trinitrate and frequently perhexilene. In some patients drugs were not tolerated and this made selection for surgery easier. In most the decision to investigate by coronary angiography with a view to surgery was made on a rather arbitrary basis of unsatisfactory response to medical therapy. Angina that was sufficiently frequent or severe as to interfere with work was the usual indication - this is clearly a subjective assessment and varied with the referring physician. Of those in whom coronary angiography was undertaken about

20% did not come to surgery - about half because no significant coronary pathology was demonstrated; and half because of a combination of extremely poor left ventricular function and diffuse, widespread coronary disease.

Previous myocardial infarction had occurred in 45% of the group - and often there had been multiple infarcts. It was practice not to investigate patients within 3 months of myocardial infarction and in 4 patients in whom infarction occurred between the time of angiography and surgery re-investigation was undertaken.

The only commonly encountered recognised risk factor was cigarette smoking in 93% of the group. Although preoperative evidence of hypertension was present in only 6% of the group it was a very common observation at surgery that marked hypertension was seen following induction and continuing into the post-operative phase for the first 24 hours. This clinical impression, so different from our experience with valve replacement surgery, is of interest and relevance to aetiological factors in coronary disease, and seems worthy of prospective study.

EDINBURGH CORONARY SURGERY 1976 - 77

189 patients

Coronary arteriography

significant disease in one vessel	:	34 (18%)
two vessels	:	75 (40%)
three vessels	:	76 (40%)
left main	:	4 (2%)

Left ventricular function

good	:	102 (54%)
moderately impaired	:	47 (25%)
poor	:	40 (21%)

Figure 3.3

Figure 3.3 shows the distribution of arteriographically assessed significant disease. The definition of 'significant disease' is difficult

and is a major concern of this thesis. However, for clinical purposes a lesion reducing lumen diameter by 50% or more was considered significant - although the more common finding of severe or total vessel obstruction with filling of the distal vessel from collaterals usually left little doubt in assessment. Significant disease was present in one major vessel (that is, anterior descending, circumflex or right) in 18%; in two vessels in 40% and in three vessels in 40%. Four patients had significant stenosis of the left main artery.

Left ventricular function was estimated by the appearances at left ventriculography and by measurement of the left ventricular end-diastolic pressure and ejection fraction. The group could be rather arbitrarily divided into those with good left ventricular function (54%) where there was no major hypokinetic segment, and ejection fraction was more than 50% and left ventricular end-diastolic pressure below 20 mm Hg prior to angiography; those with moderately impaired left ventricular function (25%) where there was localised hypokinesia or akinesia, ejection fraction between 30 and 50%, and left ventricular end-diastolic pressure exceeding 20 mm Hg prior to angiography; and those with poor left ventricular function (21%) where there was severe generalised hypokinesia, ejection fraction below 30% and left ventricular end-diastolic pressure exceeding 30 mm Hg prior to angiography. Nearly all patients were receiving beta blockers at the time of investigation. The difficulties of defining left ventricular function, and of estimating ejection fraction particularly with asynchronous or dyskinetic wall motion were well recognised.

Surgery was undertaken with cardio-pulmonary bypass, with moderate hypothermia (25 - 28°C) in the majority; about half the single grafts were inserted with the aid of normothermic bypass. Intermittent periods of aortic cross clamping were used to obtain a blood-free field as necessary. Most right grafts would be inserted with local control of the vessel

only: a number of anterior descending grafts were inserted in the same way. The left heart was vented by a cannula inserted into the left atrium in many patients; with progress of the experimental study the wisdom of avoiding the possibility of left ventricular distension became increasingly apparent, and latterly all patients had left heart venting via the left atrium.

EDINBURGH CORONARY SURGERY 1976-77

189 patients

Number of vessels grafted

one	:	53	(28%)
two	:	77	(41%)
three	:	53	(28%)
four	:	6	(3%)

Coronary endarterectomy 55 (29%)

Additional procedures

left ventricular aneurysm repair	:	13
aortic valve replacement	:	11
mitral valve replacement	:	7
open mitral valvotomy	:	1

Figure 3.4

Figure 3.4 shows the surgical procedures. The disparity between the number of vessels considered significantly diseased (Figure 3.3) and the number of grafts inserted reflects the fact that some vessels were considered at surgery to be too small or diseased to allow a graft to be inserted, or occasionally, that an angiographically visualised vessel could not be found because of its course within fat or myocardium.

Coronary endarterectomy was performed in 29%. Two thirds of these were on the distal right coronary artery or in the region of its

bifurcation. Blunt dissection and careful traction on the atheromatous core usually freed an otherwise totally occluded artery permitting insertion of a graft. There was a preference for inserting a graft beyond obvious disease into normal vessel, but where this was not feasible endarterectomy was undertaken. It was noted that the obtuse marginal branch of the circumflex artery was commonly located just below the surface of the myocardium and when opened in this situation was invariably free from disease and ideal for grafting.

Leg incisions for removal of veins were confined to the leg below the knee when possible. Varicosities caused serious difficulties in four patients - arm veins were used in three and internal mammary artery in one of these.

Left ventricular aneurysm resection or plication was undertaken in 13 of the patients in combination with coronary artery grafting. In this group it was uncommon to graft the anterior descending artery - it was usually occluded and often transgressed during repair of an antero-lateral aneurysm. Definition of the extent of the aneurysm was greatly aided by left ventricular vent suction, which produced marked indrawing of thin scar areas. When valve surgery was undertaken in combination with coronary surgery the major lesion was judged to be the coronary disease (a smaller group of patients having valve replacement with coronary grafting for coronary lesions discovered by chance at angiography during investigation of their valve disease is excluded - this is a rather arbitrary distinction at times, particularly when aortic stenosis and coronary disease co-exist). Valve surgery was performed using profound topical myocardial cooling by coronary flush with Dextrose-Saline-solution (1/5N saline) with 10 milli-equivalents of potassium chloride added to 500 ml of the solution - 500 to 1,000 ml coronary flush was used for profound

myocardial cooling following the achievement of moderate hypothermia by cardio-pulmonary bypass, and was supplemented with topical cold saline. Valve replacement was performed first and the coronary grafts were inserted into the coronary arteries next. Some or all of the proximal anastomoses were made with the heart reperfused, depending on the time taken for the procedure. One practical point of importance is the need for prior marking of the proposed site for coronary arteriotomy when this technique is used, as the bloodless coronary artery does not show up well and may be difficult to find, difficult to distinguish from coronary vein, and difficult to open with accuracy.

EDINBURGH CORONARY SURGERY 1976-77

189 patients

5 deaths at operation

all had poor left ventricular function
and three vessel disease

failure to maintain cardiac output due
to intra-operative myocardial infarction

3 post-operative deaths

one on 1st day (myocardial infarction at operation)

one on 4th day (myocardial infarction on 3rd day)

one on 4th day (sudden cerebrovascular accident)

total 8 hospital deaths (4.2%)

Figure 3.5

Figure 3.5 shows the immediate results of surgery. In the 189 patients there were 5 deaths at operation. All occurred in patients with poor left ventricular function and all with three-vessel disease. Intra-operative myocardial infarction was the presumed cause of failure to maintain cardiac output in spite of inotrope and intra-aortic balloon counterpulsation support. Post-mortem examination in all revealed patent

grafts and confirmed the diffuse nature of the coronary disease and the widespread old ischaemic damage to the left ventricle, although recent changes of infarction were not identified, presumably because sufficient time had not elapsed prior to death.

Three further deaths occurred in hospital - one due to infarction sustained at the time of operation, one due to infarction sustained on the third post-operative day, and one due to a sudden cerebrovascular accident on the fourth day of an uneventful post-operative recovery. This gives a hospital mortality rate for the group of 4.2%.

The diagnosis of intra-operative infarction is not always easy. Clear evidence of such infarction, manifested by a need for post-operative inotrope support, or the appearance of new Q waves on electrocardiograms, or greater than usual rise of the non-cardiac-specific enzymes which were routinely measured (Serum glutamate oxaloacetate transaminase - SGOT - and Lactate dehydrogenase - LDH) was present in 12 patients, who all made uneventful recoveries. Because of the difficulties in diagnosis of intra-operative infarction as well as the relevance to surgical techniques a prospective study of cardiac-specific enzyme release and technecium ^{99m} pyrophosphate scanning has been instituted.

EDINBURGH CORONARY SURGERY 1976 - 77

<u>Follow - up</u>	181 patients
	6 months to 2 1/2 yrs
Late death	5 (3%)
No improvement from pre-operative status	18 (10%)
Mild angina and/or continued medical therapy	28 (15%)
Symptom free without medical therapy	130 (72%)

Figure 3.6

The 181 survivors have so far been followed for between 6 months and 2 1/2 years (Figure 3.6). Late death is known to have occurred in five -

due to myocardial infarction in three, cerebrovascular accident in one and non-cardiovascular cause in one.

There has been no improvement in symptoms from pre-operative status in 10% of the group - these are back on medical therapy with angina.

15% still have mild angina or have required to re-start medical therapy, but claim definite improvement from their pre-operative status.

72% are symptom-free without medical therapy.

The period of follow-up is relatively short, and to date there are no studies on the functional improvement in these patients. However, the results are in keeping with those reported from major centres in North America and we would therefore expect continued satisfactory improvement in the majority of these patients for at least several years to come.

EDINBURGH CORONARY SURGERY 1976 - 77

<u>Re-investigation</u>		24 patients
20 symptomatic	:	7 all grafts patent 7 no grafts patent 6 at least one graft patent
4 asymptomatic	:	2/2 1/2 2/2 2/3 grafts patent
28 of 46 grafts shown to be patent		

Figure 3.7

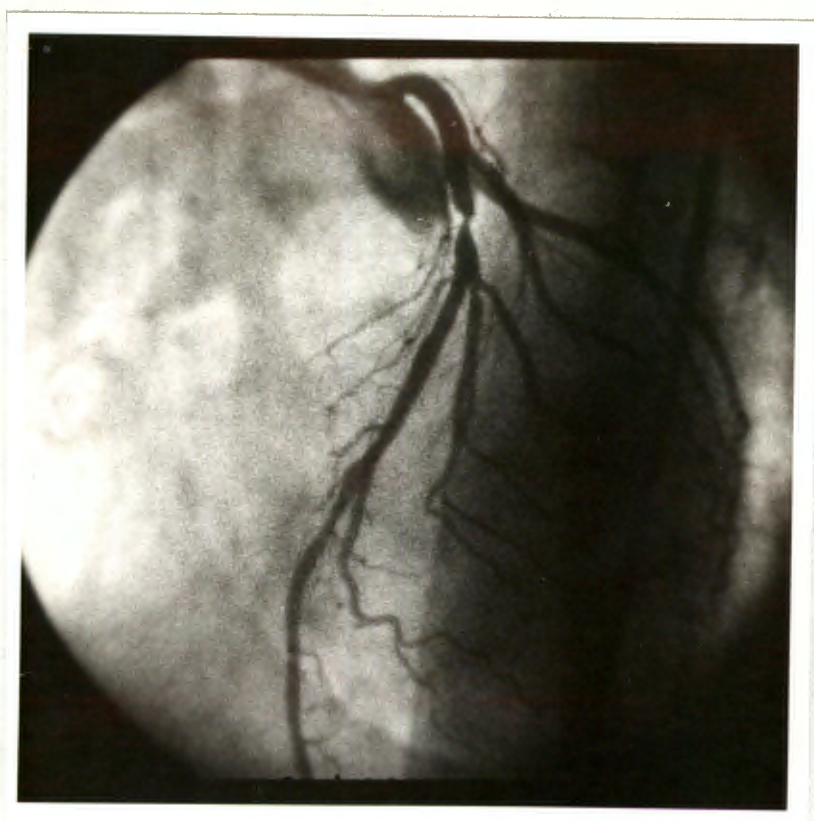
As shown in Figure 3.7 only 24 of these patients have been restudied by angiography - and the majority have been because of failure of symptomatic improvement. This unfavourable group is unlikely to be representative of the whole group as the symptom-free patients have not been studied. In this small group of 24 patients, 28 of the 46 grafts were shown to be patent - a patency rate of 60% between 6 months and 2½ years.

The early results with 72% of patients symptom free and off drug therapy at 6 to 30 months, and a further 15% improved are at least as good as reported American results. The oft-voiced criticism of American practice that too often medical therapy has not been adequately tried has certainly not applied to Edinburgh practice. Coronary surgery continues to be offered for those patients not satisfactorily managed by medical means. It is hoped that further refinements of surgical technique resulting from the experimental study reported in this thesis will further improve surgical results and aid in overall understanding of the role of this form of surgery.

SECTION 3b

CORONARY ARTERIOGRAPHY

EDINBURGH PRACTICE

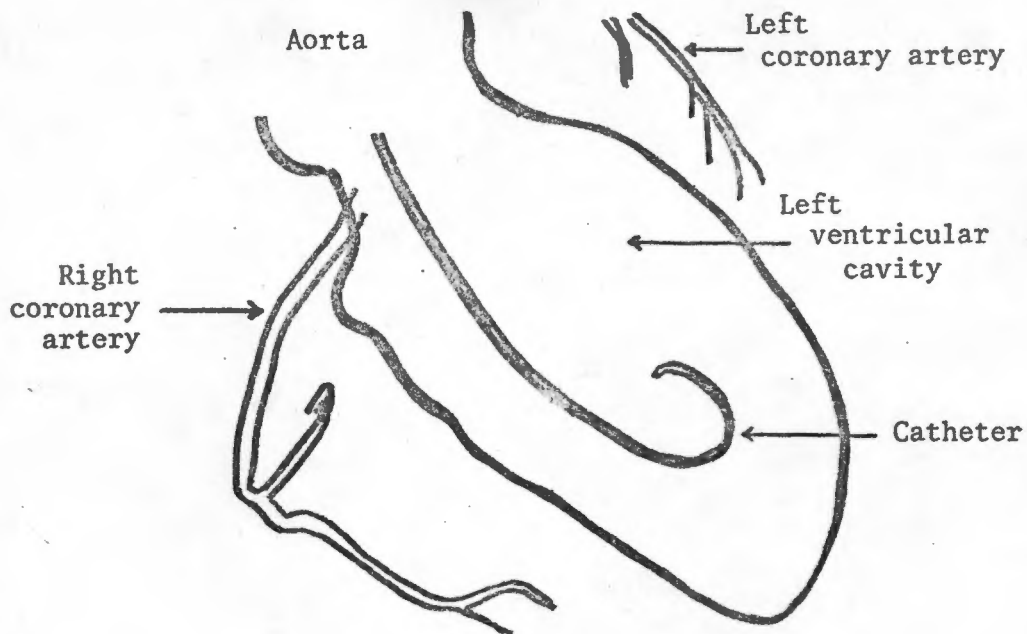


Selective Coronary Arteriography and Left Ventriculography

The Judkins technique of percutaneous femoral arterial puncture is used for selective coronary arteriography and left ventriculography (Judkins 1967 and 1968). Single plane angiograms are made using Compagnie Generale Radiologie equipment giving 35 mm cine angiograms.

Left ventricular morphology and function is demonstrated first by injection of 50 ml Urografin 76 at 12 ml per second into the left ventricle. If satisfactory left ventricular function is anticipated a right anterior oblique projection only is recorded; if localised dyskinesia or generally poor function is present an additional left anterior oblique projection is recorded to aid assessment.

Figure 3.8 shows a single cine-angiogram frame of a left ventriculogram at end-diastole. This, and the following five illustrations are all of a 41 year old man with increasingly severe angina of 9 months duration, initially with exercise only, later at rest as well as with exercise and emotion, up to 10 episodes daily being precipitated by brisk walking, one flight of stairs or moderate inclines, worse on cold days. Physical examination revealed no abnormal findings, blood pressure 130/80. Chest radiography and resting electrocardiogram were normal, but exercise electrocardiogram was positive for ischaemia. Response to beta-blockade had been poor. Figure 3.8 shows a normal-shaped left ventricular cavity. The opacification of the coronary arteries is inadequate for making a diagnosis of coronary disease, but it is helpful to note the presence of a right coronary artery. Occasionally the conal branch of the right coronary artery is selectively catheterised (it arises frequently as a separate branch from the aorta) and it has on occasion led to an incorrect diagnosis of obstruction of



LEFT VENTRICULAR ANGIOGRAM

RIGHT ANTERIOR OBLIQUE VIEW END-DIASTOLE

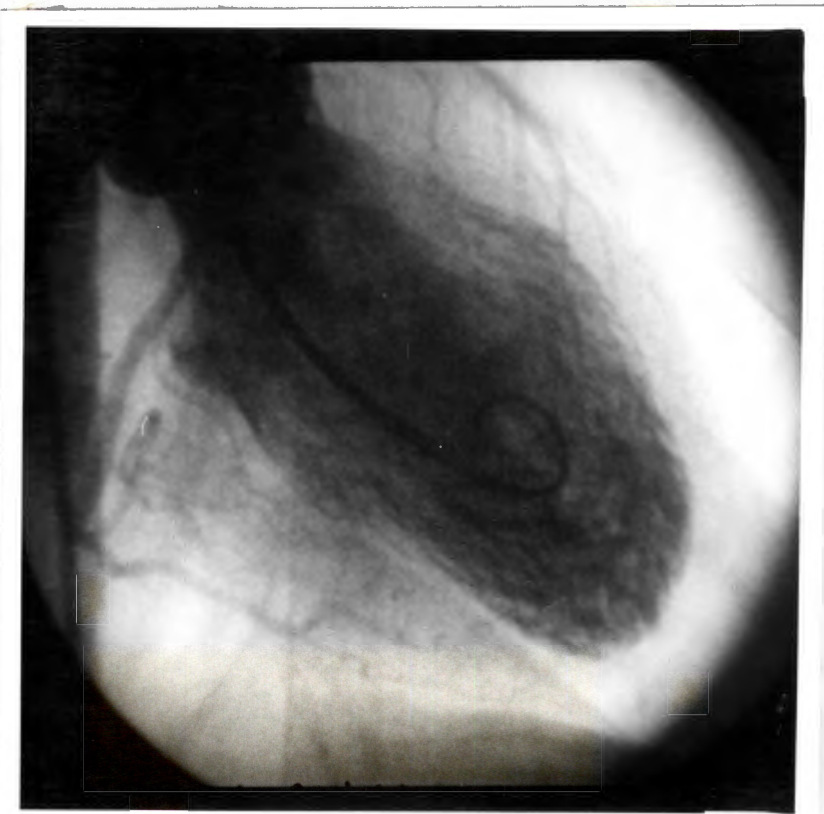
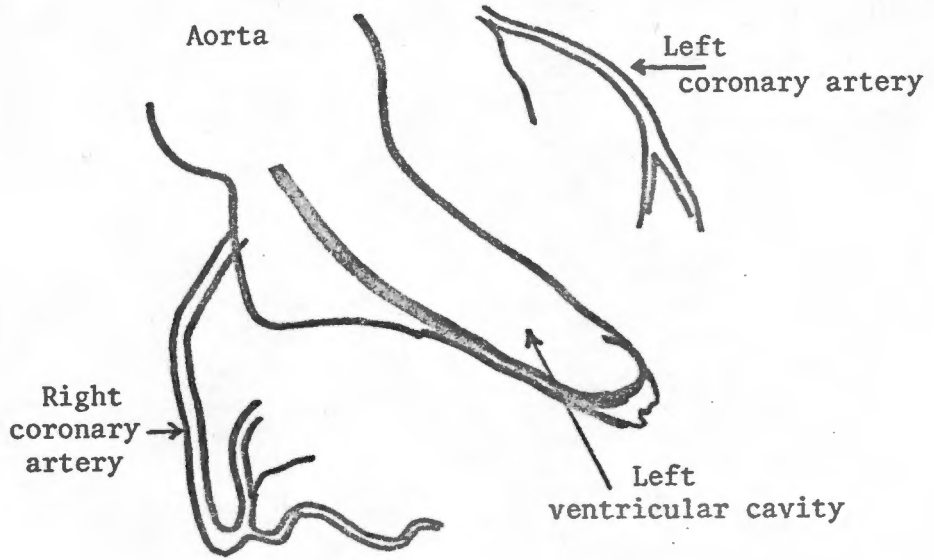


Figure 3-8



LEFT VENTRICULAR ANGIOGRAM

RIGHT ANTERIOR OBLIQUE VIEW END-SYSTOLE



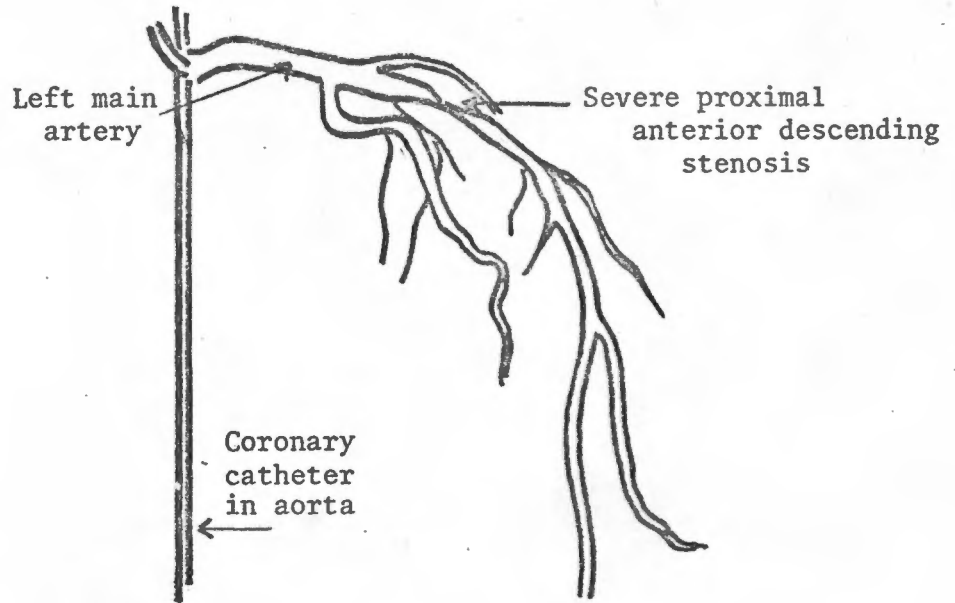
Figure 3-9

the main right coronary artery, a pitfall avoided by noting the presence of the right coronary artery on the ventriculogram.

Figure 3.9 shows a single cine-angiogram frame at end-systole. There is good contraction of the left ventricle, a small end-systolic volume, and all areas of the ventricular wall move well. This is a normal left ventriculogram. Further evidence of left ventricular function is obtained by measurement of left ventricular pressure and by calculation of ventricular volumes and ejection fraction (Greene et al 1967; Sandler and Dodge 1968; Kreulen et al 1975).

Figure 3.10 shows the selective left coronary arteriogram of the same patient in the right anterior oblique projection. The anterior descending artery has a severe stenosis (loss of about 90% of lumen diameter) situated in the proximal third of the artery just beyond the first septal branch. The septal vessels and the course toward the left ventricular apex help to identify the anterior descending artery. On the cine-angiogram this vessel moves less than its diagonal branches. The proximal portion of the anterior descending artery is often obscured by overlap of diagonal vessels, and has given most difficulty in assessment. The use of cranio-caudal views (Figure 3.15) has helped considerably in overcoming this difficulty, and has also allowed accurate assessment of the origin of the diagonal branches of the anterior descending artery.

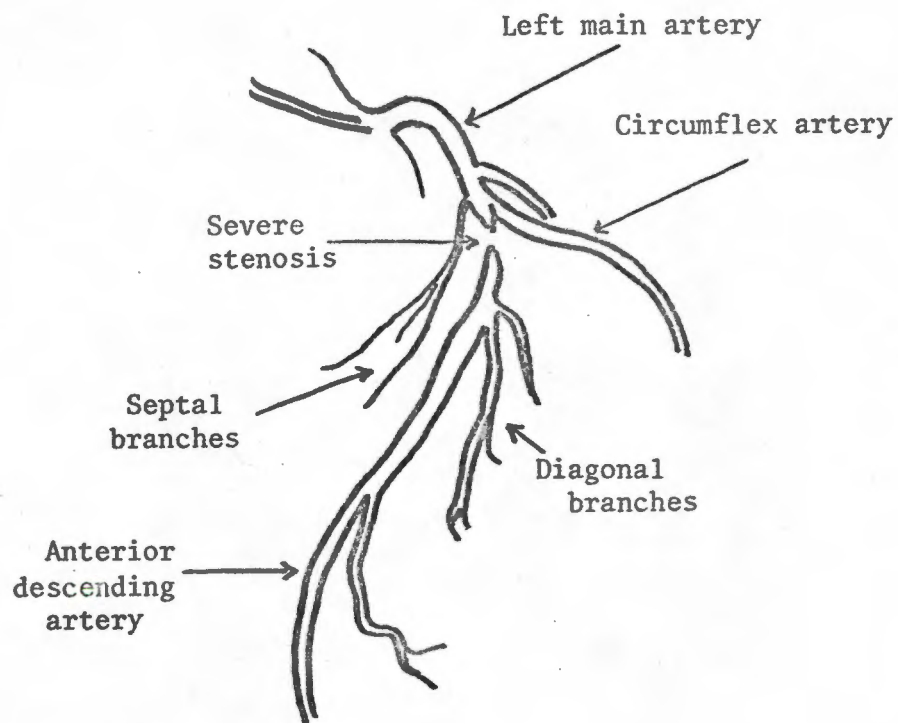
Figure 3.11 shows the selective left coronary arteriogram in the left anterior oblique projection. The severe, proximal anterior descending artery stenosis is well shown. In this view, however, this area of the anterior descending artery is "fore-shortened" and lesions here may be missed - (compare cranio-caudal view in Figure 3.15).



SELECTIVE LEFT CORONARY ARTERIOGRAM
RIGHT ANTERIOR OBLIQUE VIEW



Figure 3-10



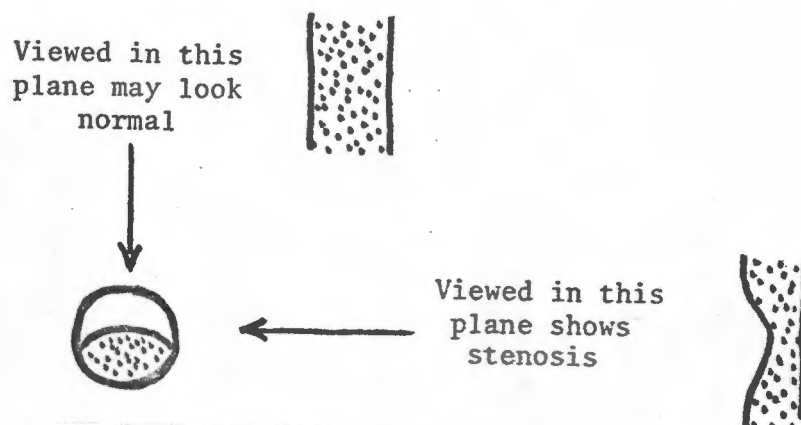
SELECTIVE LEFT CORONARY ARTERIOGRAM

LEFT ANTERIOR OBLIQUE VIEW



Figure 3-11

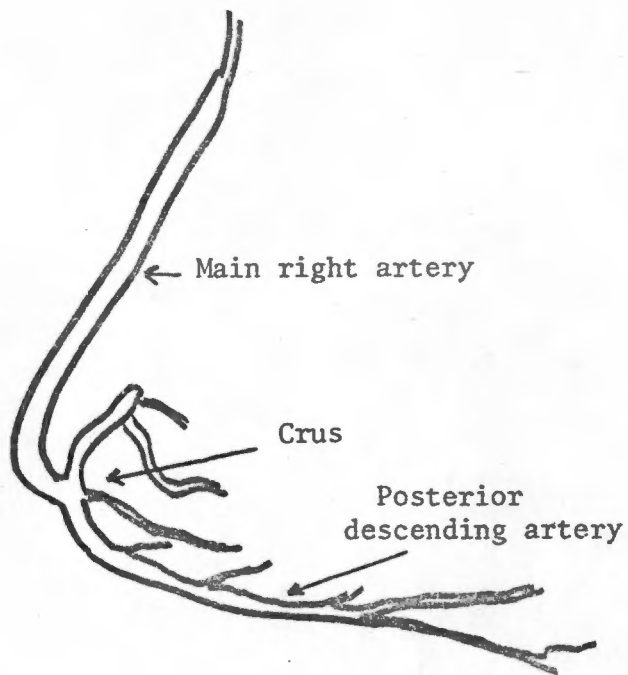
Two views of each coronary artery are always required - atheroma often produces crescentic obstruction which may not be apparent in one view.



The left coronary arteriogram is made after the left ventriculogram. 7 or 8 ml of Urografin 76 is usually sufficient by hand injection.

The selective right coronary arteriogram is then made using 4 or 5 ml of Urografin 76. Figure 3.12 shows the right coronary arteriogram in right anterior oblique projection. This vessel is judged to be normal - at least to have no significant areas of stenosis. Coronary surgical practice soon reinforces the knowledge that atheroma and stenosis are not synonymous. Apparently normal arteries on arteriography may be visibly and palpably diseased at surgery.

Figure 3.13 shows the right coronary artery in left anterior oblique projection. This is a good view as the vessel is clear of the diaphragm. Failure to clearly view the distal portion of the right coronary artery risks missing lesions just before or at the crus - the point where the right artery divides into posterior descending and left ventricular branches, and a frequent site for atheroma. Figure 3.13 illustrates the typical common "dominant" right coronary artery.



SELECTIVE RIGHT CORONARY ARTERIOGRAM
RIGHT ANTERIOR OBLIQUE VIEW

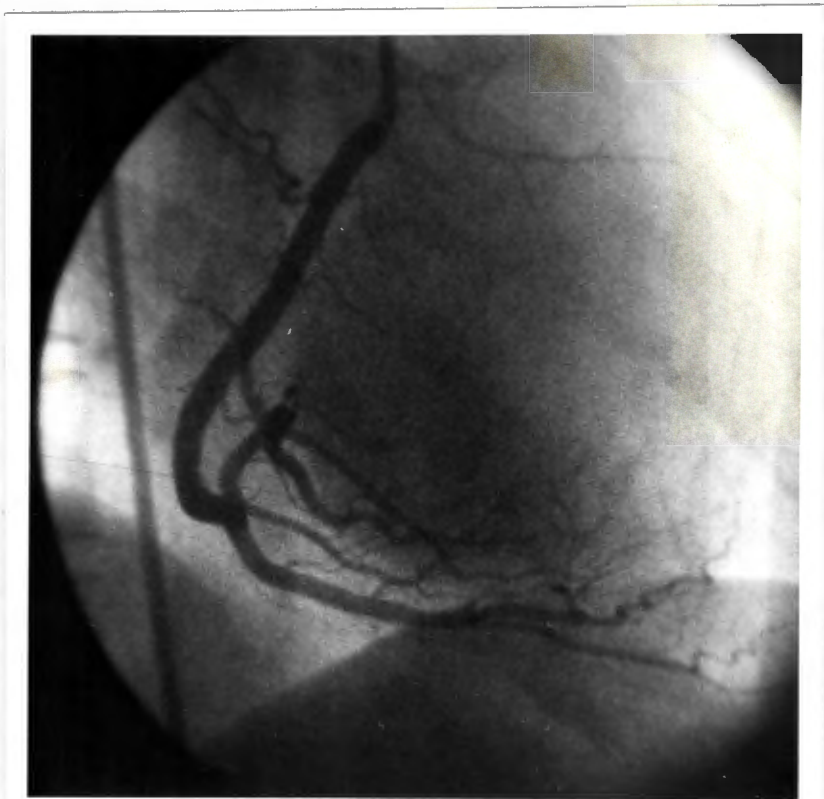
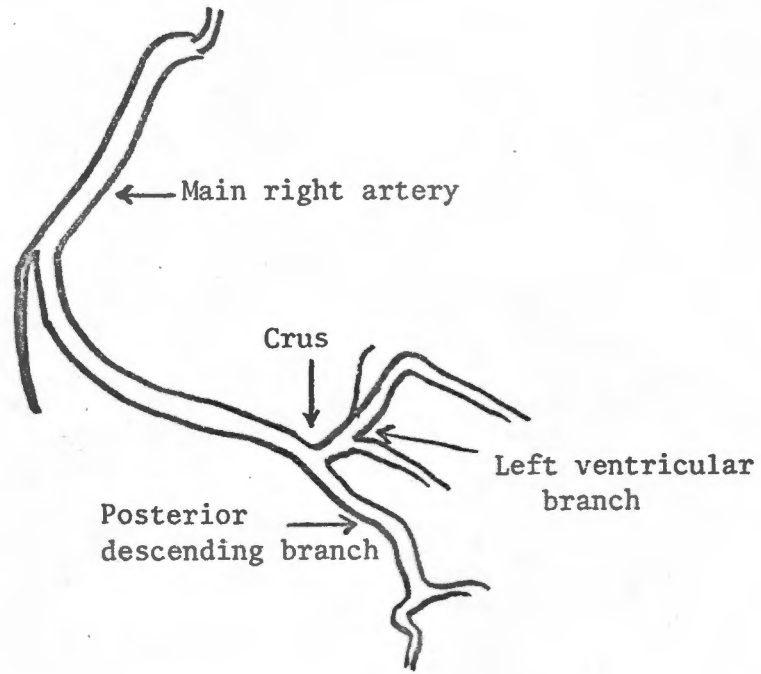


Figure 3-12



SELECTIVE RIGHT CORONARY ARTERIOGRAM
LEFT ANTERIOR OBLIQUE VIEW



Figure 3-13

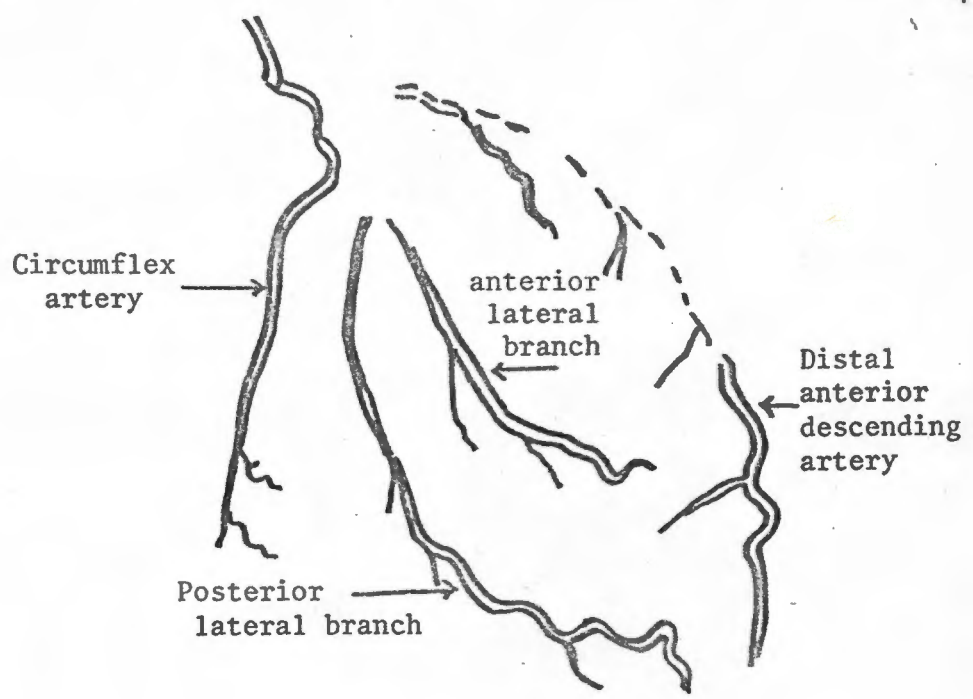
This patient, whose angiograms have been used for illustration, represents a relatively simple surgical prospect - little operative risk is likely and an excellent symptomatic result is to be expected (as was the case in this instance). An example of a less favourable surgical prospect is illustrated in Figures 3.14, 3.15 and 3.16. These arteriograms are of a 52 year old man with a 5 year history of angina on effort which gradually became more frequent and incapacitating, with poor response to beta-blockade.

Figure 3.14 shows the selective left coronary arteriogram, at a relatively late phase of filling, in the right anterior oblique view. The proximal anterior descending artery failed to show clearly - it becomes better defined distally. Two large, late-filling lateral branches of the circumflex artery are seen - in both filling was retrograde. The circumflex artery itself is relatively prominent, and is stenosed proximally. The diagonal branches overlap the anterior descending artery and are poorly shown.

Figure 3.15 shows the same left coronary artery in a cranio-caudal projection. The multiple stenoses in the left anterior descending artery are clearly shown. The left main artery and proximal anterior descending branch are particularly well shown in this view.

Figure 3.16 shows the right coronary artery of the same patient. There is severe disease with multiple stenoses in the main right artery - disease with moderate stenosis in the region of the crus, and faint filling of part of the anterior descending artery via collaterals.

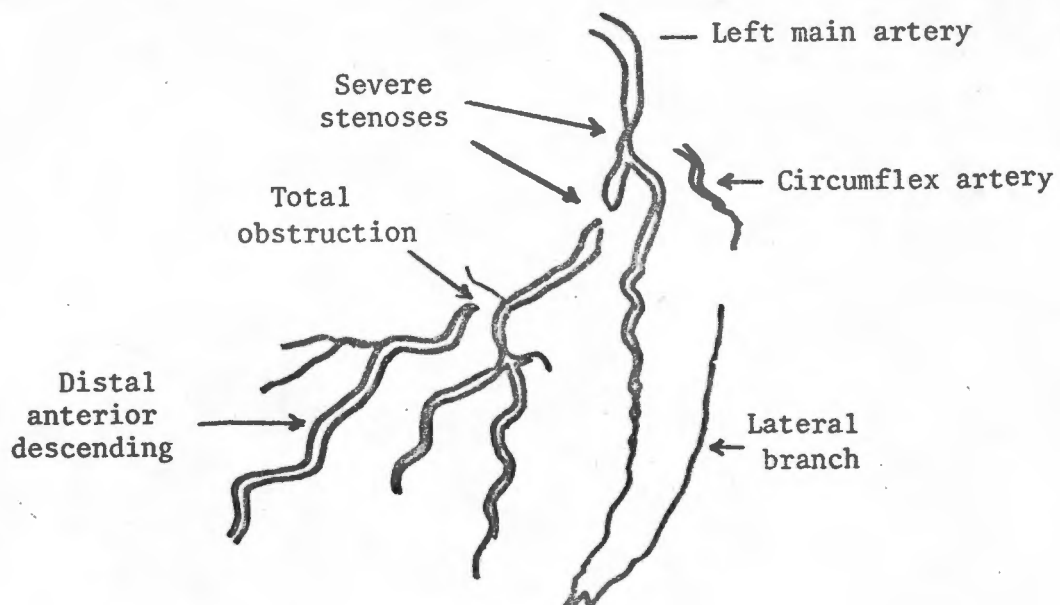
This man has been symptomatically cured by surgery which involved bypass



SELECTIVE LEFT CORONARY ARTERIOGRAM
RIGHT ANTERIOR OBLIQUE VIEW



Figure 3-14



SELECTIVE LEFT CORONARY ARTERIOGRAM

CRANIO-CAUDAL VIEW

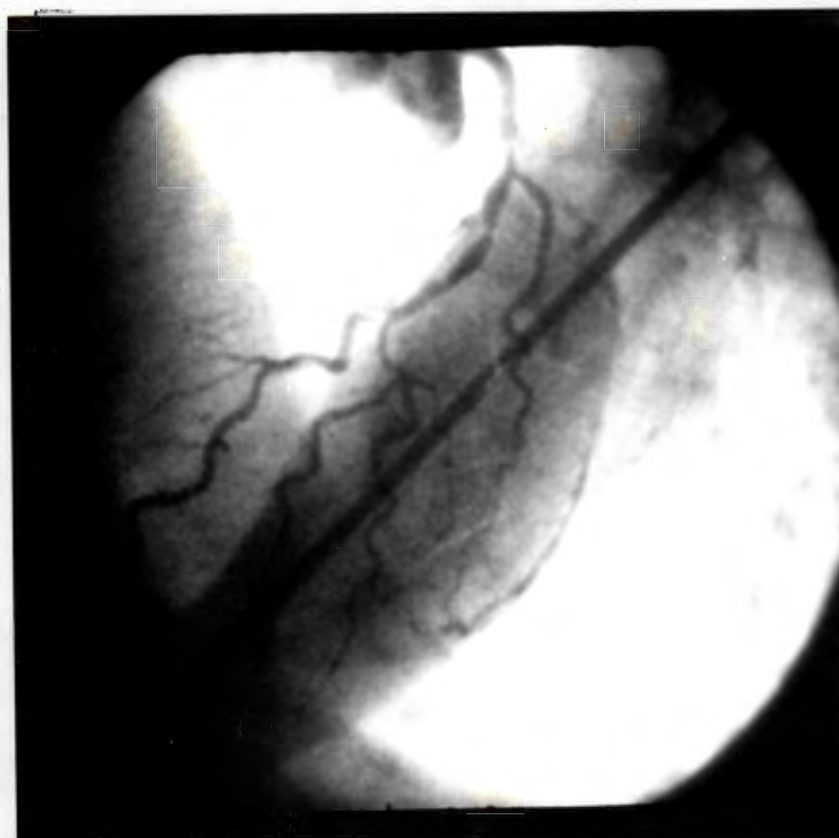
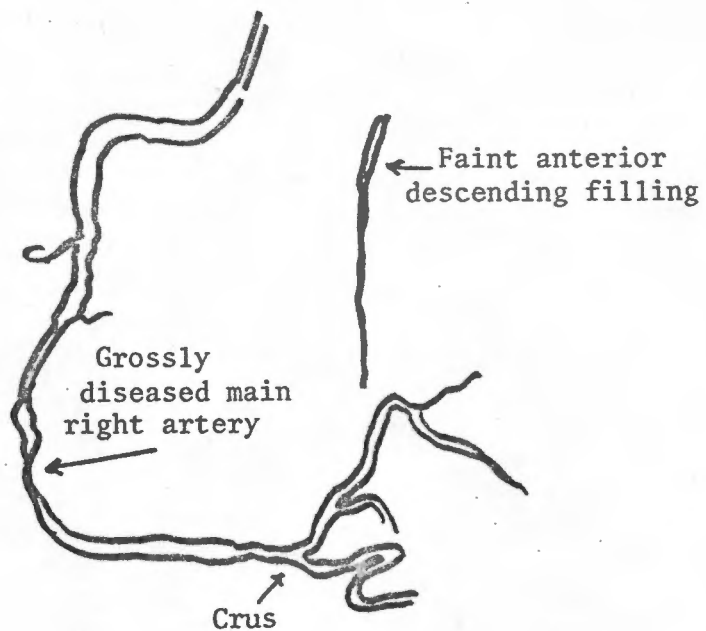


Figure 3-15



SELECTIVE RIGHT CORONARY ARTERIOGRAM

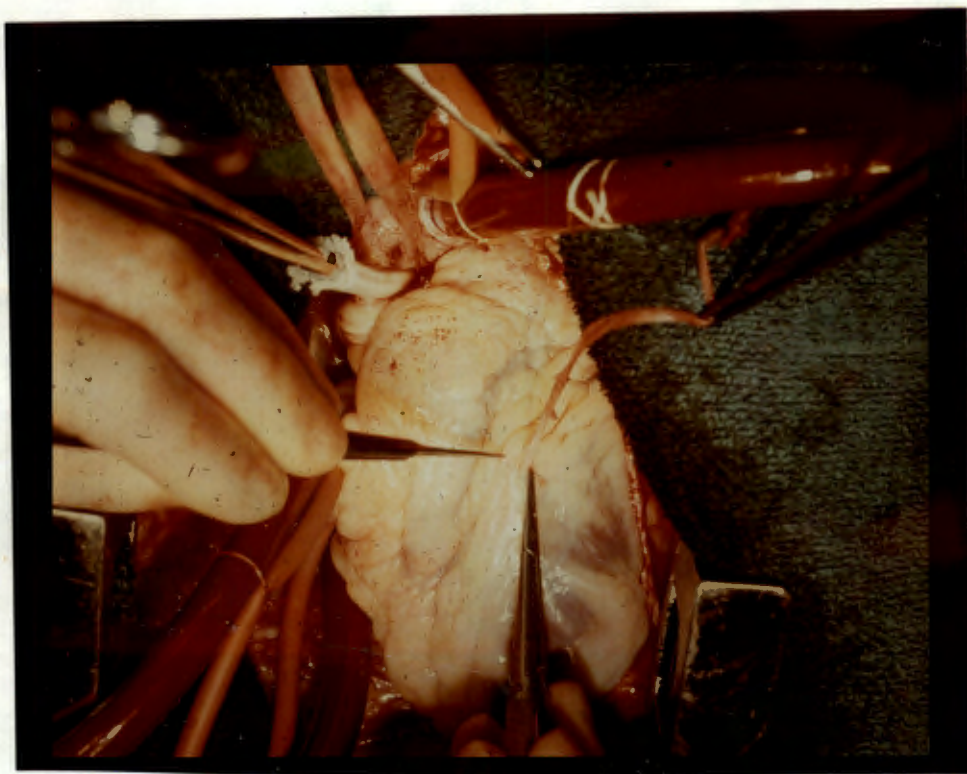
LEFT ANTERIOR OBLIQUE VIEW



Figure 3-16

grafting to five vessels - distal right (with endarterectomy), anterior lateral branch (with endarterectomy), posterior lateral branch (with endarterectomy), distal anterior descending artery, and diagonal branch of anterior descending artery (with endarterectomy). Satisfactory flow to each vessel was measured. This example is at the opposite end of the spectrum from the first example with regard to the disease in the arteries - it is not an attractive prospect and requires rapid surgery with effective means for myocardial protection.

SECTION 3c

CORONARY SURGERY
EDINBURGH PRACTICE

PREPARATION FOR SURGERY

Selection for coronary angiography, with a view to subsequent surgery is made by a cardiologist. The current indication is almost exclusively chronic stable angina, in keeping with usual practice in major North American centres (Miller 1977; McIntosh and Garcia 1978). The decision to undertake angiography in a patient with chronic stable angina is rather arbitrary and varies from one cardiologist to another. Unsatisfactory response to medical therapy leading to interference with work or leisure is the guide, but this is impossible to quantitate. Positive exercise electrocardiograms for ischaemia at relatively low work levels usually sway decisions toward investigation by coronary arteriography. The review of 1976 and 1977 Edinburgh practice in section 3a indicates what has appeared reasonable and satisfactory policy.

Blood grouping and testing for Australian antigen is done prior to admission. Full physical examination, chest radiography, electrocardiography and blood tests for blood count, urea and electrolytes, creatinine clearance and liver function tests are undertaken on admission for surgery. Specialised investigations may be required, such as angiography for peripheral vascular or cerebrovascular disease, but these investigations are not routinely done.

Most patients are admitted on beta blockade therapy; this is maintained until the evening before surgery. The policy of operating on fully beta blocked patients has not led to difficulties; indeed, the results of the animal study encourage this practice which is supported

by experimental and clinical experience from other centres (Shorthouse and Parker 1978; Hedley-Brown and Krause 1978; Buckley 1978). Liberal use of sublingual nitroglycerin is encouraged for any angina occurring in hospital.

Premedication

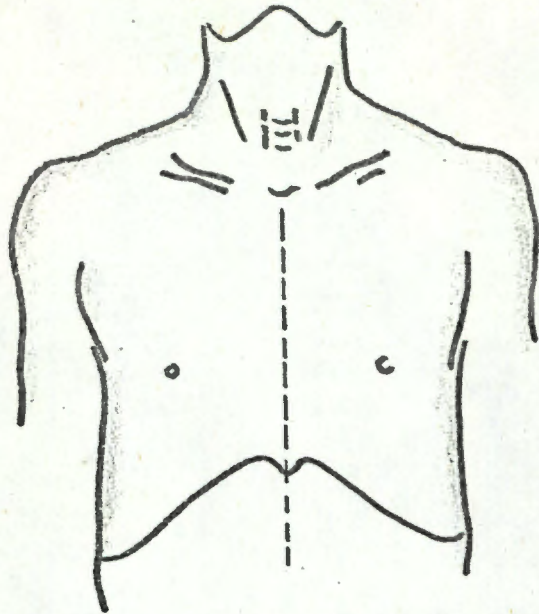
Atropine 0.3 mg and Omnopon 15-20 mg are given subcutaneously one hour before surgery.

Induction of Anaesthesia is undertaken with electrocardiographic monitoring.

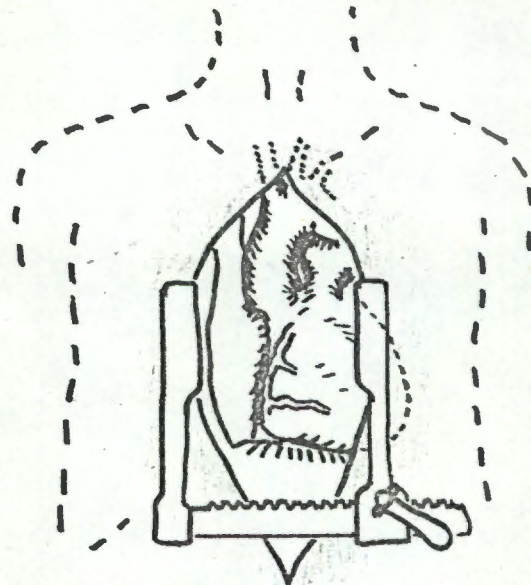
A sleep dose of Thiopentone (50 - 200 mg judged on effect) is given intravenously and 50% oxygen/50% nitrous oxide mixture is given by mask. Pancuronium (12 mg) is given intravenously, an endotracheal tube is inserted and 65% nitrous oxide/35% oxygen is given during operation. Supplements of omnopon are given as required. The aim is to maintain a slow heart rate, a mean blood pressure of about 90 mmHg, and full oxygenation. If the blood pressure rises excessively halothane is added for a period.

Monitoring

A radial artery cannula is placed percutaneously for continuous blood pressure recording and blood gas measurements. The electrocardiogram is continuously displayed and a urinary catheter is placed for measuring urinary output. Temperature probes are inserted in the nasopharynx and in the oesophagus.

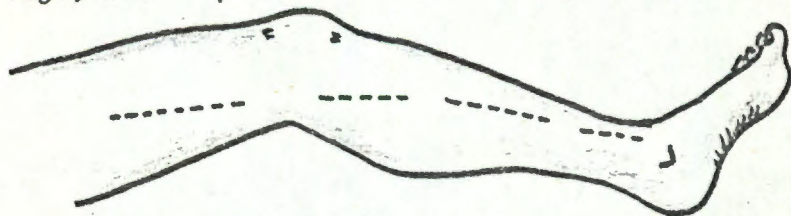


The chest is opened by vertical sternotomy.
Diathermy is used to ensure haemostasis.



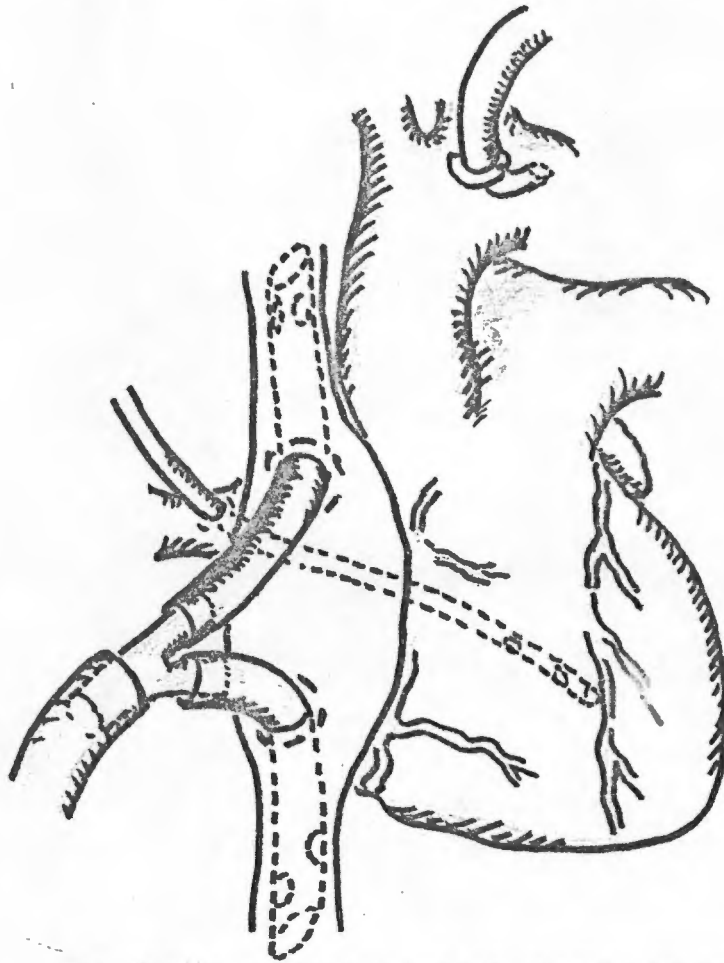
The sternum is spread sufficiently to allow cannulation
of aorta and cavae. The heart is not handled at this stage.

At the same time saphenous vein is removed from one or
both legs, with a preference for the leg below the knee.



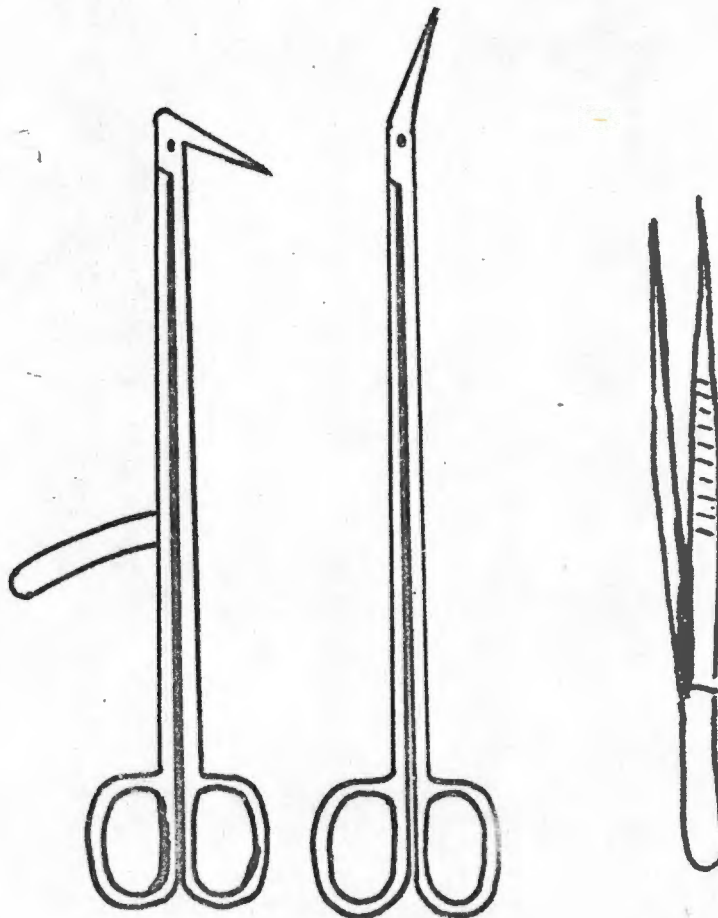
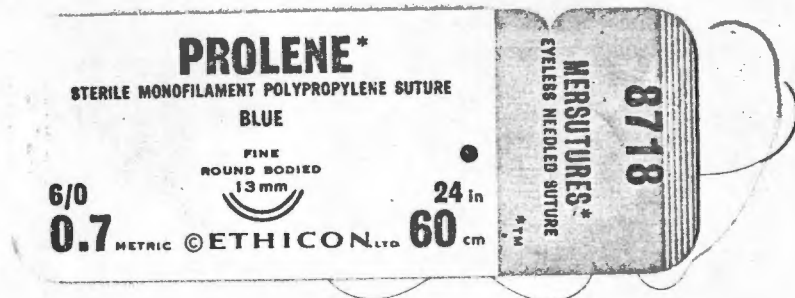
Undue handling of vein is avoided- branches are securely
ligated flush with the vein.

Following heparinisation (3 mg/Kg body weight) the aorta is cannulated just below the innominate artery using a Sarns Morris cannula. The venae cavae are cannulated via the right atrium. A USCI fluid-filled vent is inserted via the right superior pulmonary vein into the left atrium or left ventricle once bypass is established. Care is taken to avoid introducing air into the heart.

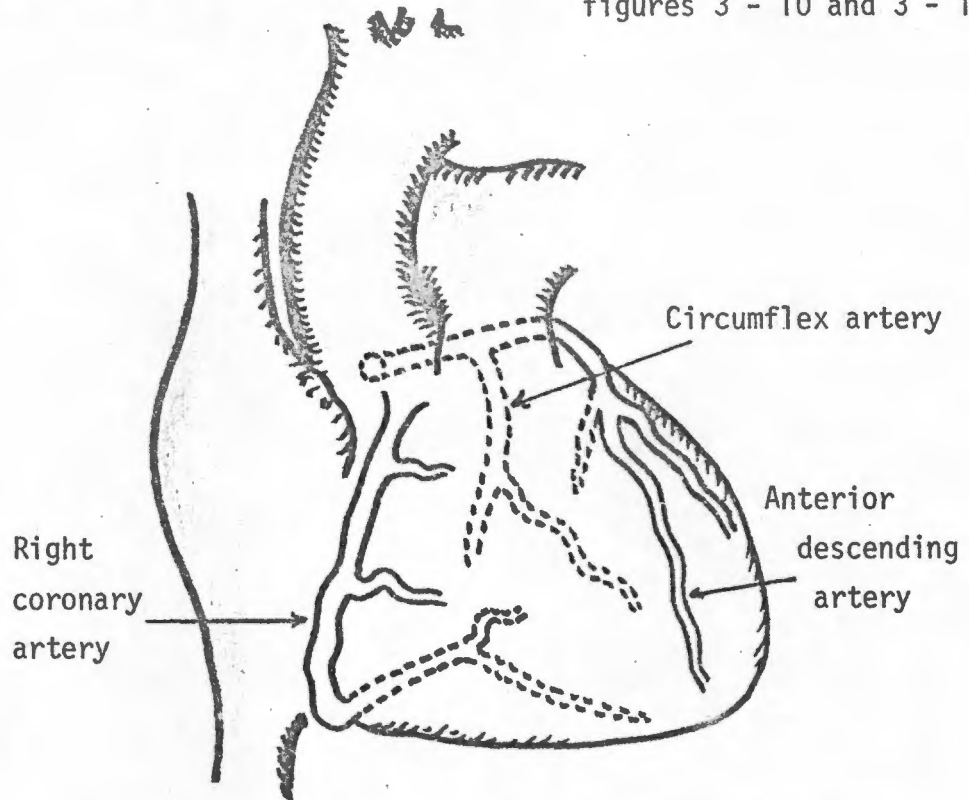


The Cardio-pulmonary bypass circuit is primed with Ringer lactate solution. A Harvey bubble oxygenator is used with a pump flow rate of 2.4L/sq. metre/minute. Ventilation is stopped. The left atrial vent is allowed to drain by gravity. The temperature is dropped to 28 - 30°C. A perfusion pressure in the aorta of about 70 - 90 mm Hg is maintained by increasing pump flow rate if necessary.

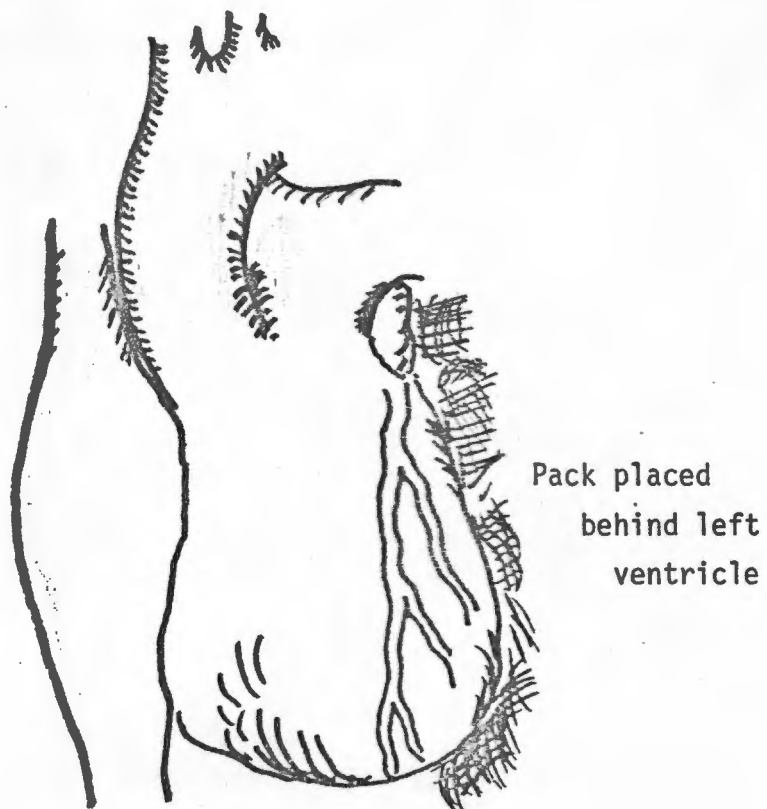
CORONARY SURGICAL INSTRUMENTS



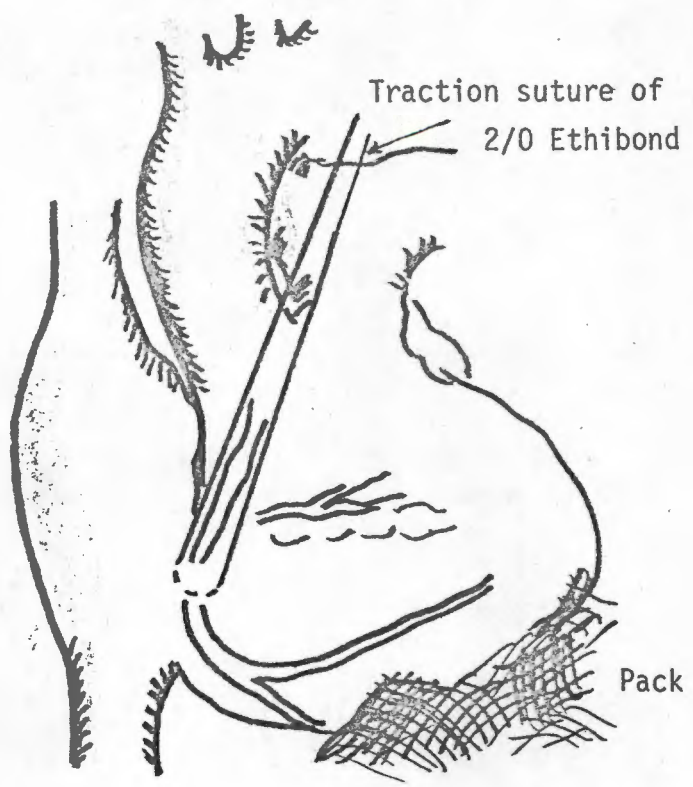
Accessible coronary vessels are shown here - compare with figures 3 - 10 and 3 - 12



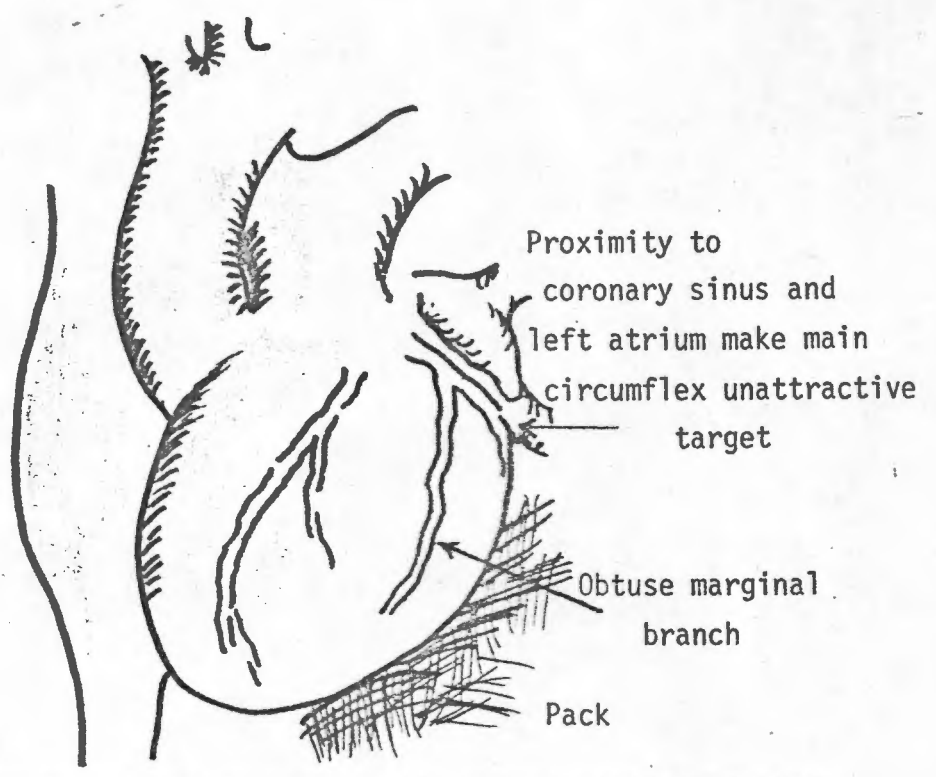
Although coronary disease can be palpated this is not synonymous with coronary obstruction. The angiographic evidence must be available in the operating room to guide surgery.



EXPOSURE OF ANTERIOR DESCENDING ARTERY AND ITS DIAGONAL BRANCHES



EXPOSURE OF THE DISTAL RIGHT ARTERY, THE CRUS, AND THE POSTERIOR DESCENDING ARTERY. OPERATING TABLE ROTATED TO THE LEFT.



EXPOSURE OF CIRCUMFLEX ARTERY AND ITS OBTUSE MARGINAL BRANCH - THE USUAL SITE FOR GRAFTING TO CIRCUMFLEX TERRITORY. OPERATING TABLE ROTATED TO RIGHT.

Site for grafting is selected



The artery, undisturbed in its bed, is stroked with a No 15 scalpel blade

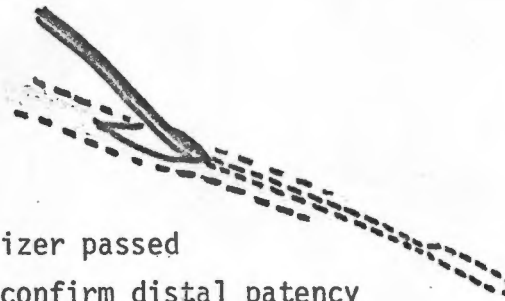


Spurt of arterial blood indicates that lumen is entered

Arteriotomy extended to 5 - 6 mm using Potts scissors



Aorta cross-clamped to control blood; saline irrigation used to clear site of blood



Flexible sizer passed gently to confirm distal patency

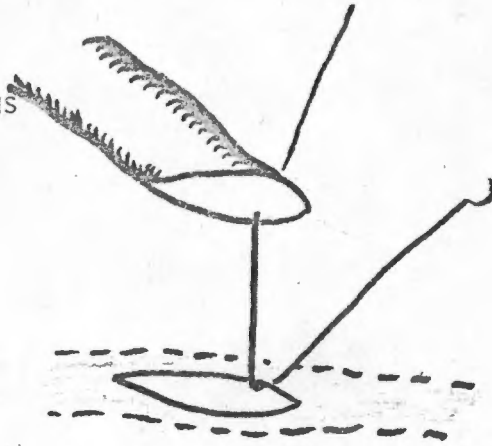


Stay sutures (4/0 Ethibond) may be used to open out arteriotomy

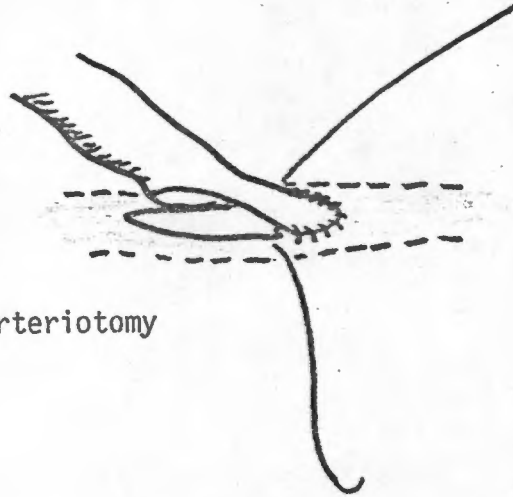


Reversed saphenous vein is prepared by removing excess adventitia near tip and bevelling end, which is further cut back to correspond with arteriotomy size.

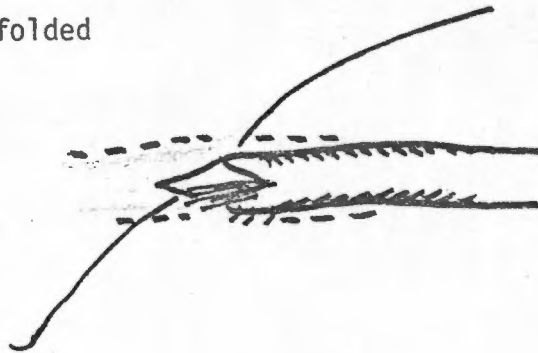
6/0 or 7/0 Prolene
is used for continuous
suture beginning
away from the ends
of the coronary
arteriotomy



Fine bites are
taken of vein and
artery to avoid
bunching up tissue,
particularly at distal
and proximal ends of arteriotomy



The vein conduit is folded
back to expose the
proximal end of
the arteriotomy
for precise suturing



The completed suture is pulled tight with gentle traction-

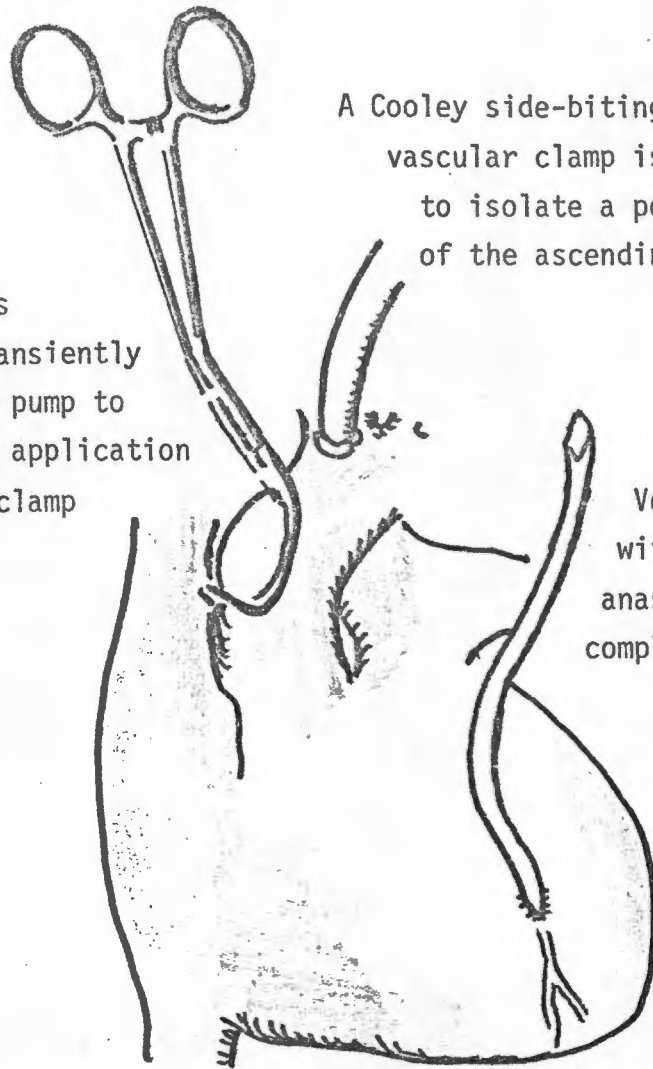


loose loops being pulled through with a blunt hook if
necessary, and the suture ends are tied securely.

Perfusion pressure is dropped transiently by slowing pump to allow easy application of Cooley clamp

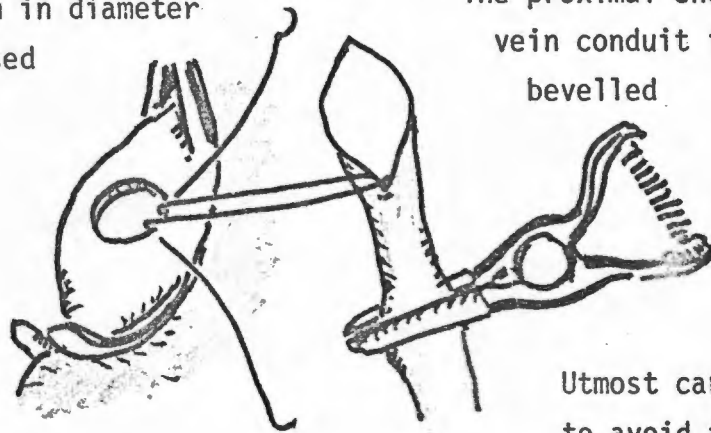
A Cooley side-biting vascular clamp is used to isolate a portion of the ascending aorta

Vein conduit with distal anastomosis completed

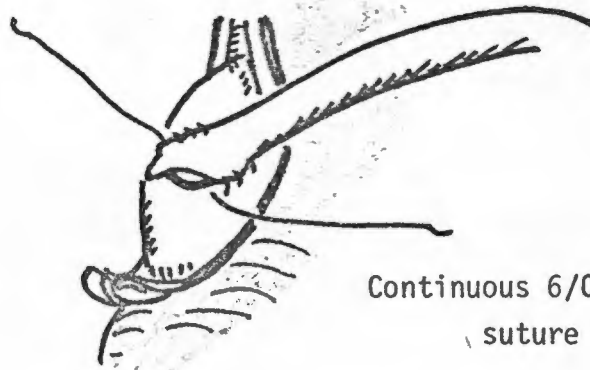


A disc of aorta 5 - 8 mm in diameter is excised with a No 11 blade

The proximal end of the vein conduit is bevelled

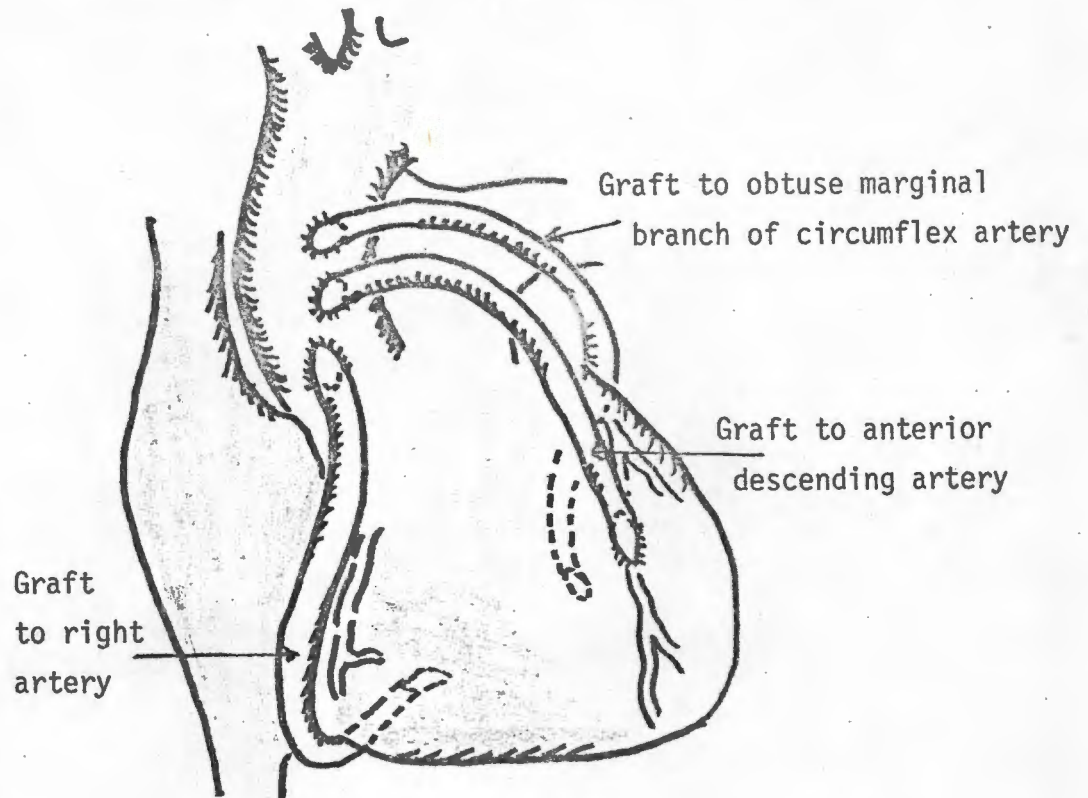


Utmost care is taken to avoid twisting vein

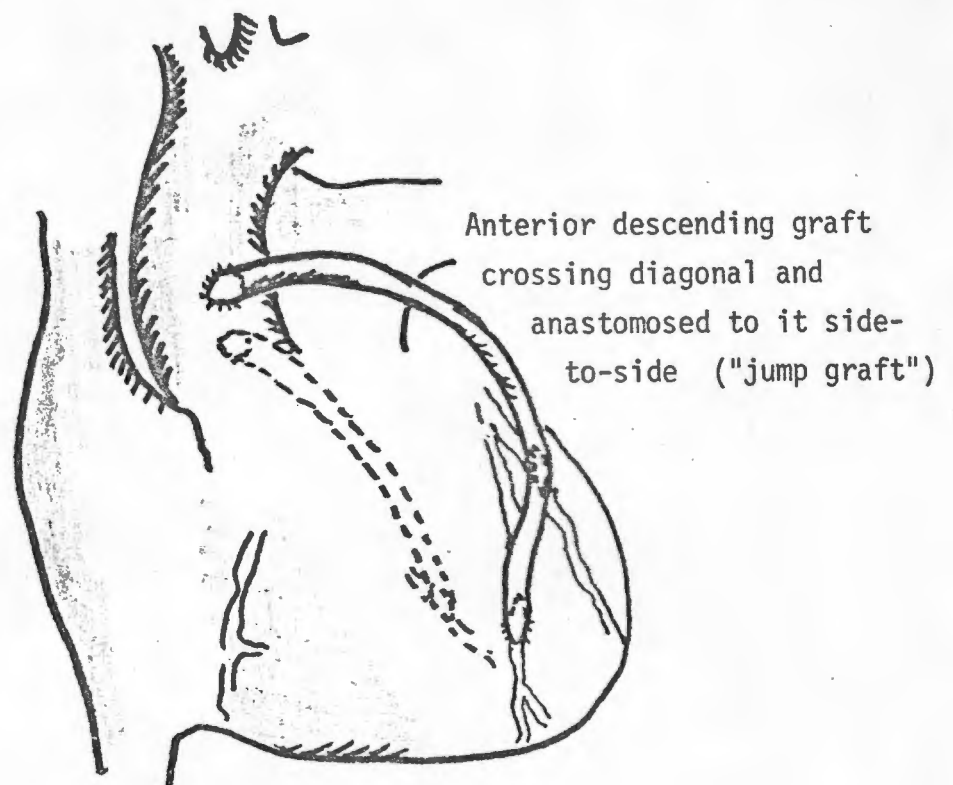


Continuous 6/0 Prolene suture

THE USUAL POSITIONING OF VEIN GRAFTS

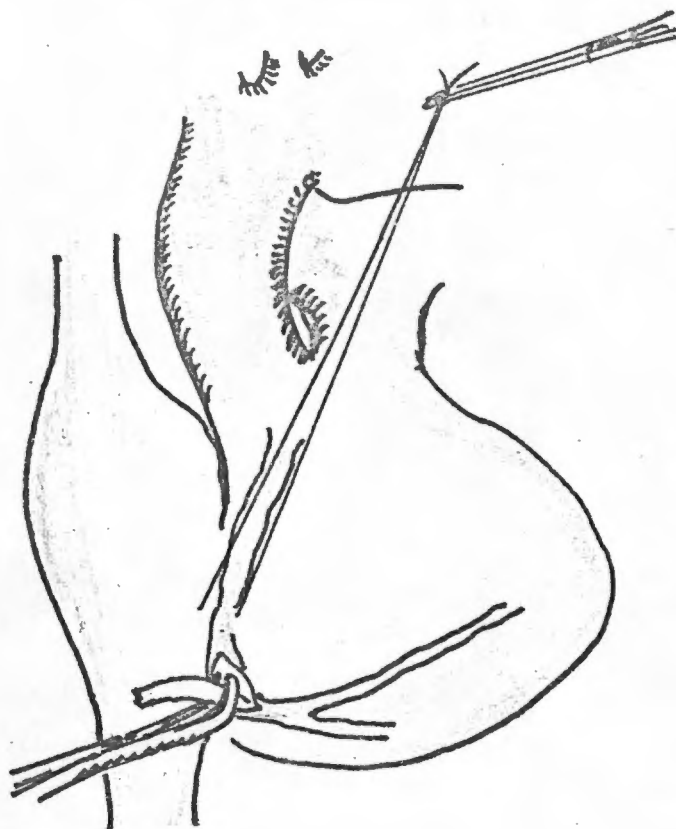


Care is required to avoid undue tension (too short) or kinking (too long). Grafts are tacked to epicardium with 6/0 Prolene to fix them in optimal position.



An alternative route for a circumflex or obtuse marginal graft is via the transverse sinus to the posterior aspect of the ascending aorta

CORONARY ENDARTERECTOMY



ENDARTERECTOMY OF DISTAL RIGHT CORONARY

Traction is applied gently to the freed end of the core of atheroma. A Watson-Cheyne dissector helps in establishing a cleavage plane. The distal right artery usually endarterectomises well, often freeing the posterior descending and left ventricular branches. Any coronary artery may require endarterectomy. By choice the tendency is to graft beyond major disease, but this is not always feasible. Probing is avoided after endarterectomy because of the risk of raising an intimal flap.

Aortic cross-clamping periods are kept to a minimum - rarely exceeding 20 minutes for any one distal anastomosis; and avoided altogether if severe obstruction is present and pressure proximal to the arteriotomy will control blood loss.

Following re-warming and discontinuation of bypass care is taken to ensure that perfusion pressure remains above a mean of 70 mmHg - in practice inotrope support is rarely required.

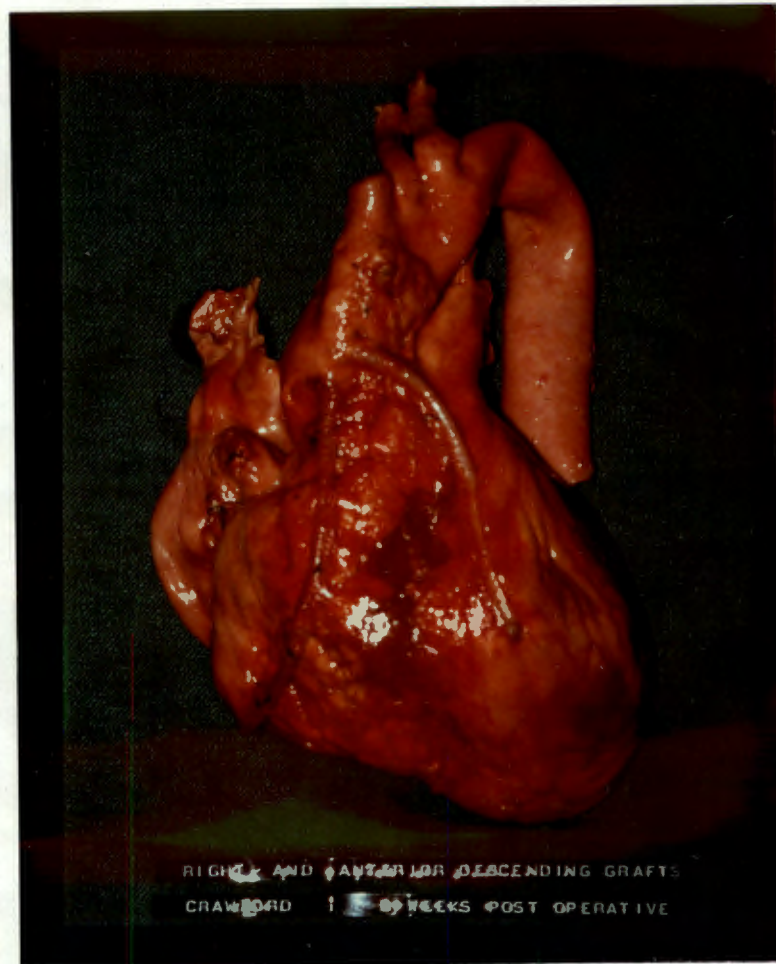
Pressure and flow measurements are made for each graft and protamine is given to neutralise heparin.

The pericardium is closed unless this appears to compress grafts. Tubes are placed for pericardial and mediastinal drainage and the sternum is repaired with wire: soft tissues with dexon or catgut and skin with nylon.

Post-operatively adequate sedation is maintained with omnopon. Ventilation is continued for several hours until anaesthesia has worn off. The routine observations for cardiopulmonary bypass surgery are made. Few complications have occurred (See Section 3a).

The opportunity for seeing coronary grafts in place in the human have been rare. Such an opportunity did present in a 52 year old man who died suddenly at 2 weeks of a rapidly progressive cerebro-vascular accident, after uneventful post-operative recovery from coronary surgery.

The autopsy specimen shows the heart from the front with the aortic arch displayed. Saphenous vein aorto-coronary bypass grafts to the anterior descending and distal right arteries can be seen to be well fixed to the epicardium in a layer of fibrin.



This shows, 2 weeks after surgery, the inside of the ascending aorta. The two aortic ostia for the aorto-coronary bypass grafts are readily identified by their suture lines. These surgically created openings can be compared with the natural left coronary ostium seen in the lower left of the picture.



SECTION 4a
NEED FOR EXPERIMENTAL STUDY

NEED FOR EXPERIMENTAL STUDY

The review of surgical procedures for myocardial ischaemia performed in the past (Section 2a) has indicated the large number of procedures which have been tried and abandoned. The lack of sound physiological basis for these procedures has been indicated.

A serious consequence of this is a justifiable scepticism on the part of many for any surgery for myocardial ischaemia, which still influences attitudes in the United Kingdom. Critics of such surgery are able to point to the dearth of experimental validation for the current forms of surgery for myocardial ischaemia.

While clinical results, particularly with long-term follow-up, and results of controlled trials of surgical or medical management will in time clarify the place of such surgery there are problems here. The number of patients carefully reviewed is remarkably small, a point forcibly made by McIntosh and Garcia (1978). Clinical trials are difficult to set up, particularly in North America. A criticism of such trials is that they may well compare medical therapy with surgery undertaken during the early phase of surgical experience - and this has happened in the European Trial (in which Edinburgh participates). Clearly, it would be of value to be confident that experimental confirmation of the efficacy of aorto-coronary bypass surgery is available.

A further reason for the need for an experimental study is the requirement for the surgeon, anaesthetist and cardiologist involved in management of patients with ischaemic heart disease to have a thorough understanding of the physiological effects of coronary obstruction, and the influence of the many factors which can be controlled in the operative and perioperative period. Perioperative infarction is a known hazard of coronary surgery (Miller 1977; McIntosh and Garcia 1978).

As will be shown in this thesis many factors can be varied during the perioperative period - and some of these factors, particularly perfusion pressure and heart rate, may influence regional myocardial perfusion.

Most of the considerable amount of reported work on myocardial perfusion relates to normal coronary vessels, or to artificial stenoses under otherwise "physiological" conditions. Indeed, considerable efforts are expended in obtaining basal or semi-basal conditions, and the closed-chest, conscious dog has been a useful model for many studies (Schaper 1971; Cobb et al 1974). However, the coronary surgeon is faced with rather unique conditions, having control of many fundamental cardiovascular parameters. It is to allow of wisdom in controlling these parameters for the benefit of the patients undergoing such surgery that an experimental study is required.

SECTION 4b
AIMS OF STUDY

AIMS OF THE STUDY

The experimental study which is reported in this thesis has the following aims:

1. To create an animal model which will simulate as closely as possible the clinical surgical setting of aorto-coronary bypass grafting for coronary artery obstruction. The model will allow correlation of angiographic appearance of coronary obstruction, local haemodynamic effects, and effects on regional myocardial perfusion.

It is recognised that acute stenosis in an experimental animal may differ from the chronic stenosis of clinical practice in the degree of collateral development. However, it seems unnecessary to create chronic stenosis, which requires prior surgery (Schaper 1971; Wiisten et al 1973; Scheel et al 1973) with its attendant hazards, to increase collateral flow as it has been shown that collateral flow is well developed in normal dogs (Schaper 1971; Wiisten et al 1973), and even with acute occlusion of the anterior descending artery in Beagles 31.5% of normal resting anterior descending flow is reported to continue from collateral vessels (Wiisten et al 1973). Moreover, collateral flow influences local haemodynamic effects of stenosis (Schaper 1971; Scheel et al 1973) and is thus allowed for in the model and is measured.

2. To use this model for testing the influence of factors which can be modified in the operative and perioperative period in clinical surgery on regional myocardial perfusion in the presence of coronary obstruction (Miller 1977, Stiler et al 1976).

Thus, the effect of coronary vasomotor tone, perfusion pressure, varied stenosis, heart rate, left ventricular cavity pressure and

ventricular fibrillation are assessed in terms of their influence on regional myocardial perfusion.

3. To assess the relationship of graft flow measurements and distal coronary pressure to the coronary obstruction, relating angiographic appearance and effects on regional myocardial perfusion to these measurements.

4. To seek methods of aiding or confirming the diagnosis of coronary obstruction, and confirming the adequacy of surgery at the time of operation.

5. To assess critically the surgical techniques in current use in Edinburgh and to assess the adequacy of aorto-coronary bypass grafting in correcting for coronary obstruction.

The study is specifically aimed at assessing manoeuvres relevant to coronary surgery and thus the main interest is in aspects of coronary blood (and hence oxygen) supply. It is important to bear in mind from the outset that myocardial ischaemia (as distinct from myocardial perfusion) is dependant on the balance between coronary blood supply and myocardial oxygen demand. This demand is influenced by many factors - rest, lowering of hypertensive blood pressure and beta-blockade being obvious examples of clinical and cardiological significance. The coronary surgeon naturally makes use of such knowledge, but his specific role is that of influencing coronary blood supply. Thus this study concentrates on aspects of myocardial perfusion as it is a "surgical" study about a "surgical" mode of treatment undertaken by a surgeon.

SECTION 4c
DESIGN OF ANIMAL MODEL

DESIGN OF ANIMAL MODEL

Although care is required in applying conclusions from acute canine experiments to naturally occurring human coronary disease recourse to an animal model was dictated by:

- 1) The nature of the currently available techniques for measuring regional myocardial perfusion.
- 2) The need for isolating readily definable factors and testing these over a range not possible in clinical practice under controlled conditions.
- 3) The ethical and practical restrictions of clinical practice.

The dog was chosen as the animal model for the following reasons:

- 1) Most of the reported experimental work on regional myocardial perfusion has been undertaken on dogs. As a result there is adequate available literature for comparison of results.
- 2) The size and anatomy of the dog heart and major vessels are suitable for simulation of clinical coronary surgery.
- 3) The usual dominant left coronary anatomy of the dog allows mapping of the left ventricular myocardium together with its total coronary supply in a single flat muscle mass.
- 4) Availability and reasonable cost made the dog a practical choice.

GENERAL PRINCIPLES OF THE ANIMAL MODEL

Simulation of clinical coronary surgery:

In order to provide conditions which simulated as closely as possible those of clinical coronary surgery (Miller et al 1977, see also Section 3b) the canine heart was exposed by vertical sternotomy; cardio-pulmonary bypass was used, and stenosis or occlusion was created in either proximal anterior descending or proximal circumflex arteries with insertion of a corrective bypass graft distal to the stenosis.

VARIATION OF FACTORS INFLUENCING REGIONAL MYOCARDIAL PERFUSION

- 1) Coronary vasomotor tone was influenced by giving papaverine to produce maximal vasodilatation (Schaper 1971; Downey et al 1975) in order to assess effects of coronary stenosis when coronary flow is maximal - analagous to exercise.
- 2) Coronary stenosis or occlusion was created by stenosing the artery around an accurately measured obturator and expressing the degree of stenosis in conventional fashion (McIntosh and Garcia 1978) as percentage loss of lumen diameter on the coronary arteriogram.
- 3) Perfusion pressure was regulated by controlling extracorporeal pump flow rate.
- 4) Heart rate was controlled by giving beta blockade (practolol) to slow heart rate, and by using a pacemaker to increase rate as desired.
- 5) Heart rhythm: Regular rhythm (usually sinus rhythm) was present for most experiments. Electrically induced ventricular fibrillation was present for some experiments.
- 6) Left ventricular cavity pressure was varied in some experiments by distending a balloon within the left ventricular cavity at known pressures.

For most experiments the left ventricular vent drained by gravity at zero pressure.

MEASUREMENT OF PRESSURE AND FLOW IN CORONARY VESSELS AND GRAFTS

- 1) Measurement of total coronary flow: Measurement of timed coronary sinus drainage was used to measure total coronary flow and to check on measurement obtained by other methods.
- 2) Measurement of coronary vessel or graft flow was obtained by use of electromagnetic flow probes. Special coronary configuration 2mm transducers were used.
- 3) Measurement of pressure: In order to measure the effect on pressure of a coronary stenosis a measurement of aortic pressure and distal coronary pressure is required (Figure 4-1). In practice this was readily achieved by using a single transducer attached to a side arm from the graft. Clamping the graft at the appropriate point allowed measurement of aortic or distal coronary pressure with the same transducer, thus avoiding errors due to transducer drift (Figure 4-2).

MEASUREMENT OF REGIONAL MYOCARDIAL PERFUSION

Regional myocardial perfusion was measured using the tracer microsphere method (Schaper 1971; Wagner et al 1969; Rudolph and Heymann 1967; Downey et al 1975; Bartrum et al 1974; Domenech et al 1969; Wiisten et al 1973; Flameng et al 1973; Utley et al 1974; Becker 1976; Becker et al 1973; Becker et al 1975). This technique is well established and has many applications. The usual experimental arrangement for using the technique is illustrated in Figure 4-3. Buckberg et al (1971) described the technique and the requirements for accuracy, which include:-

AORTA - CORONARY PRESSURE DROP / GRAFT FLOW RELATION

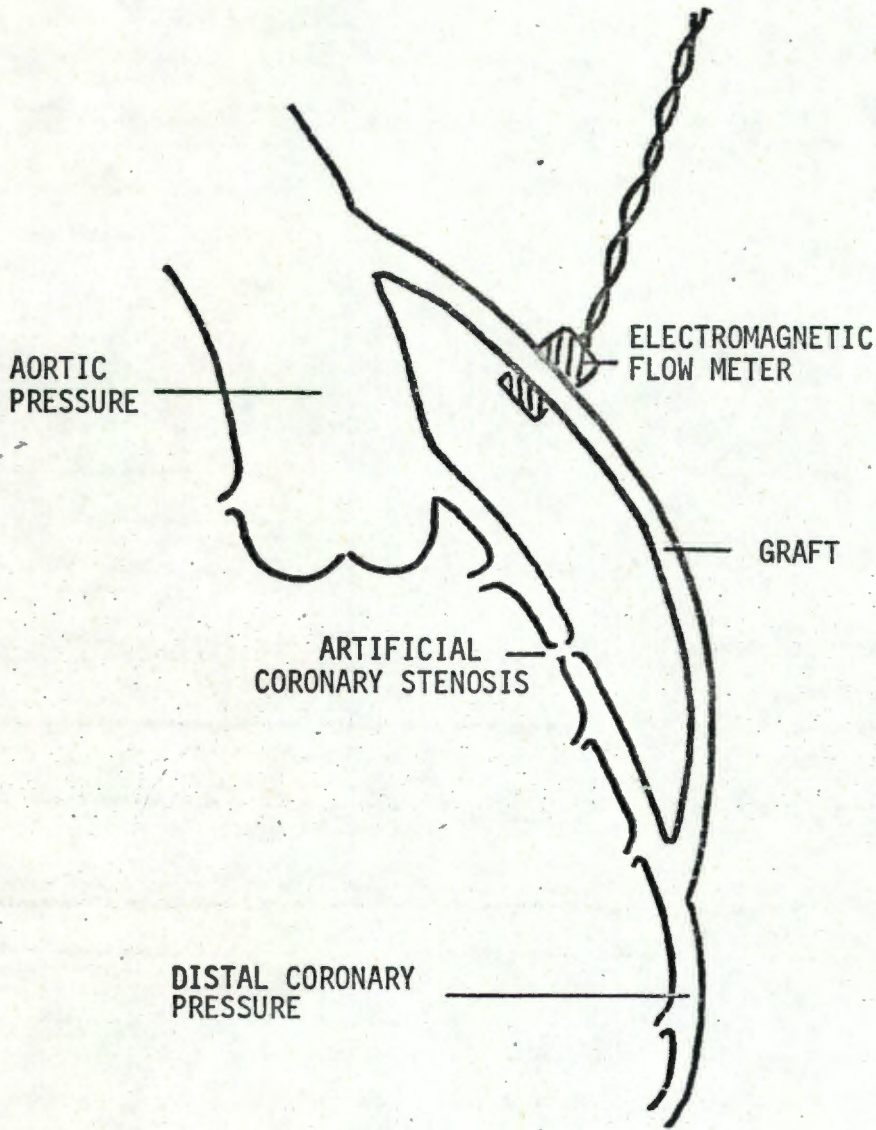


FIGURE 4-1

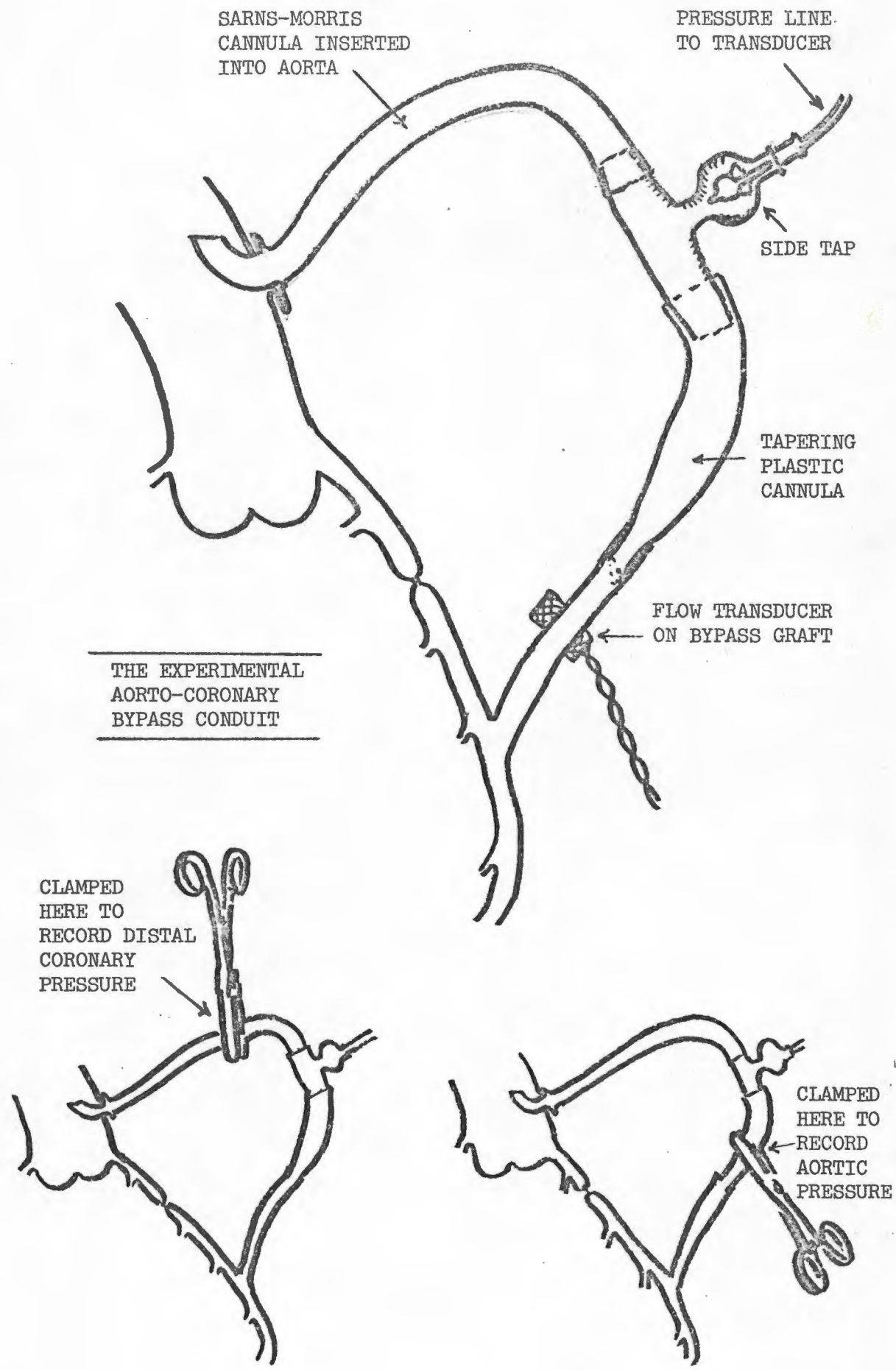


FIGURE 4-2

- 1) adequate mixing of microspheres at injection site
- 2) distribution after injection in proportion to regional blood flow
- 3) trapping of all microspheres in small vessels in first circulation
- 4) no disturbance of circulation

These workers further described the reference sample technique for quantitating regional flow in which constant rate withdrawal of blood is made during the transit of the microspheres. The flow (F_k) to, and the radioactivity (C_k) in one organ are measured, and since the method implies that the ratio of flow and radioactivity will be the same in all organs the flow (F_u) to any other organ can be determined by measuring its radioactivity (C_u) and calculating

$$F_u = \frac{F_k \times C_u}{C_k}$$

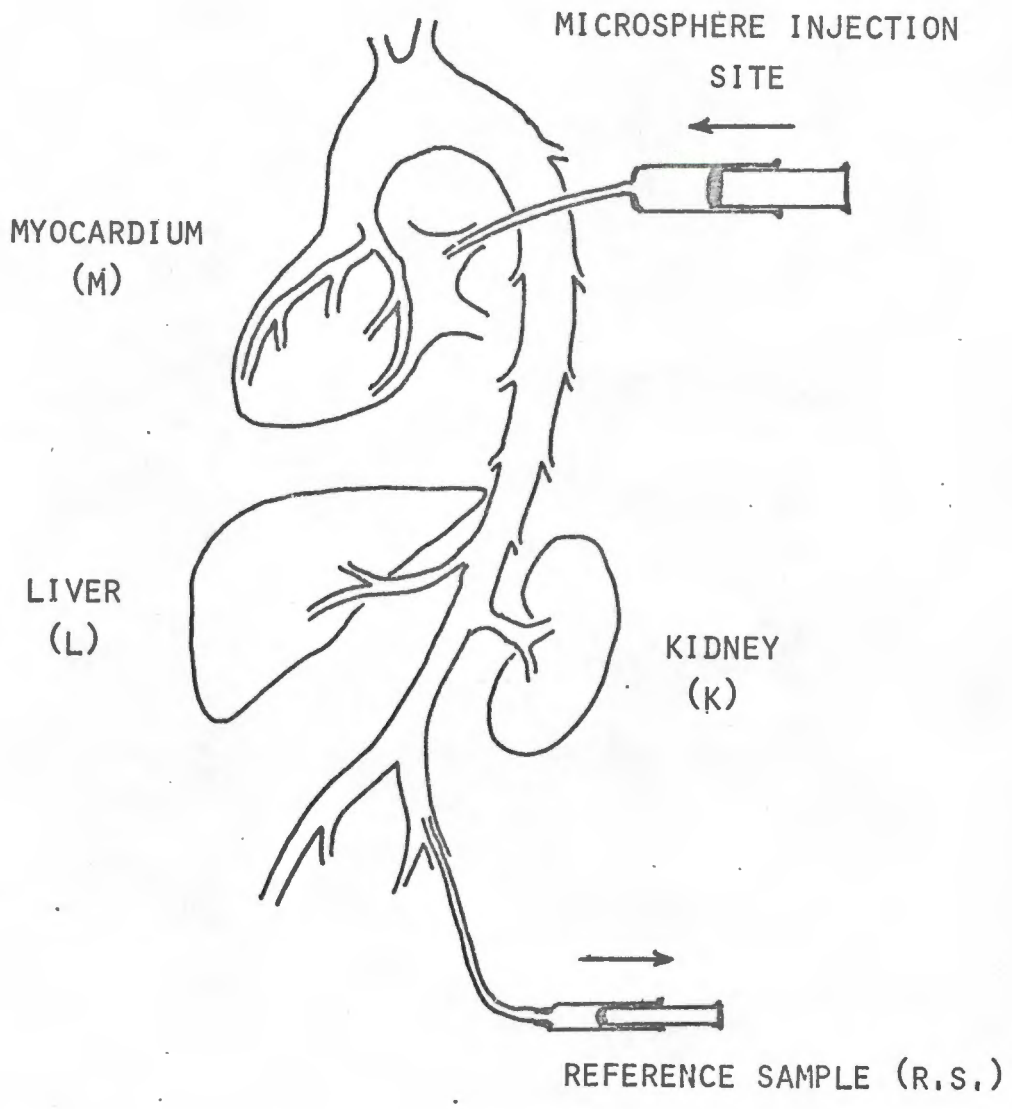
To avoid problems of measuring organ flow (F_k) a known volume of blood is withdrawn at constant rate during microsphere transit - the "end-organ" or reference sample (See Figure 4-3).

These workers further point out the need for an adequate number of microspheres (a minimum of 400) in the tissue to be assessed in order for the technique to be accurate.

The tracer microsphere method for measuring regional myocardial perfusion has been used with cardio pulmonary bypass (Hottenrott et al 1974; Kleinman and Wechsler 1978).

In order to simulate clinical coronary surgery and to increase the accuracy of the tracer microsphere method sufficiently to allow reliable mapping of left ventricular perfusion the usual method was modified (Figure 4-4). In order to divert the maximum possible number of microspheres into the coronary circulation the descending thoracic aorta was temporarily occluded just above the diaphragm for the period of microsphere

REGIONAL BLOOD FLOW MEASUREMENT
USING TRACER MICROSPHERES



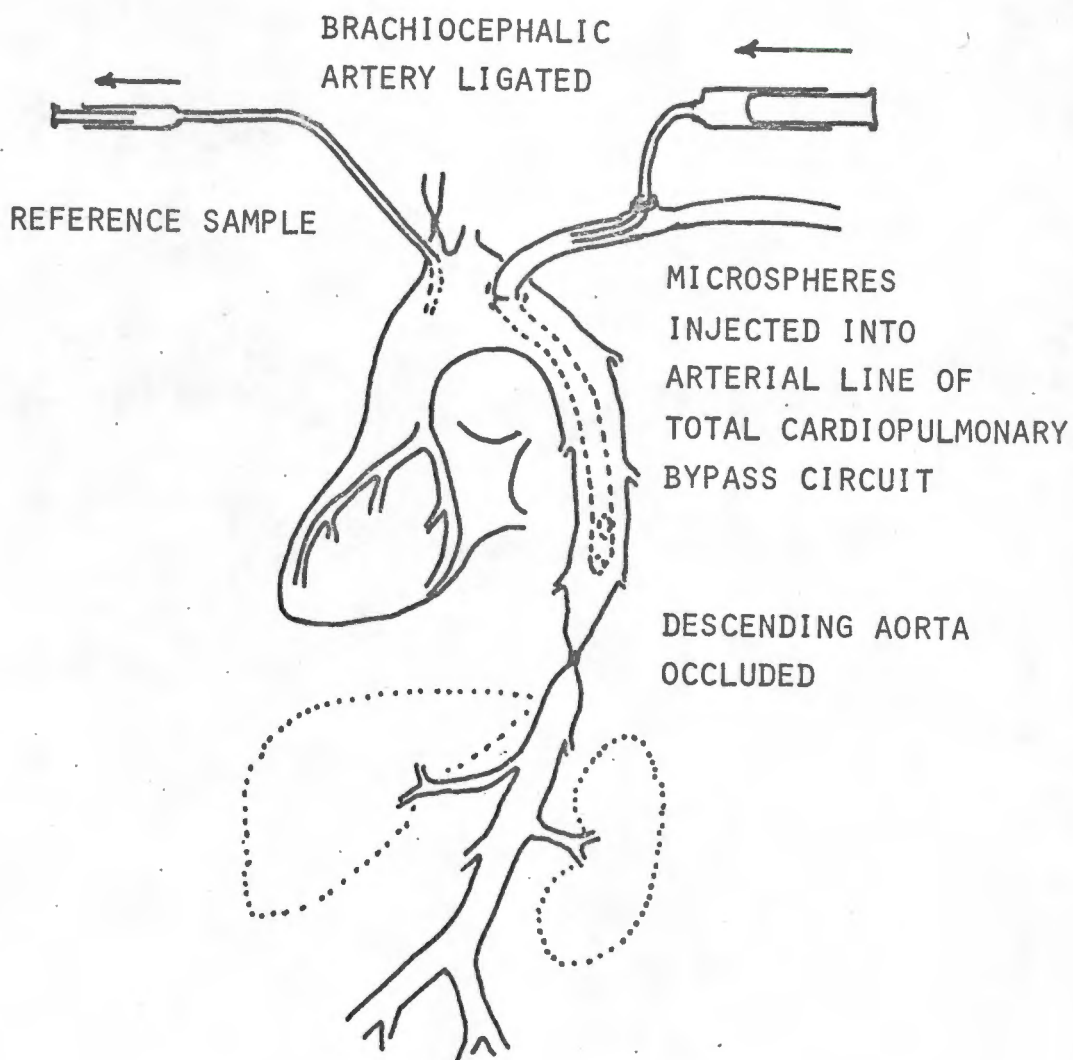
F = FLOW
C = RADIOACTIVITY

$$\frac{F_M}{C_M} = \frac{F_L}{C_L} = \frac{F_K}{C_K} = \frac{F_{RS}}{C_{RS}}$$

$$\therefore F_M = \frac{F_{RS} \times C_M}{C_{RS}}$$

FIGURE 4-3

CIRCULATORY MODIFICATIONS FOR STUDY
OF MYOCARDIAL PERFUSION USING
TRACER MICROSPHERES



HIGH PROPORTION OF SYSTEMIC ARTERIAL
BLOOD ENTERS CORONARY CIRCULATION

FIGURE 4-4

injection. Further reduction in aortic "run-off" was achieved by ligating the brachiocephalic trunk (a large vessel in the dog which supplies both common carotid arteries and right subclavian artery). The reference sample was withdrawn from the ascending aorta. Microspheres were injected into the arterial line of the cardiopulmonary bypass circuit via a plastic cannula with multiple side-perforations to ensure thorough mixing. The heart was vented to ensure that the aortic valve remained closed. The coronary arteries were then supplied by blood from the descending aortic cannula, well mixed with tracer microspheres. A large proportion of extra-corporeal pump output passed into the coronary tree.

METHOD

Dogs weighing between 18 and 30 Kg were used for the study. 40 dogs were used for the experimental study - 30 mongrels and 10 labradors. In addition, donor dogs were used for a source of blood and arterial grafts. These donor animals were usually experimental animals undergoing acute experimental procedures on the preceding day or two; they provided a convenient source of blood. When suitable donors were not available from this source, small dogs (8-10 Kg) were used - this was necessary on 8 occasions. Most of the blood volume was removed by cannulating a femoral artery and vein and infusing Ringers lactate during exsanguination of the anaesthetised donor.

Premedication and Anaesthesia:

Acepromazine maleate B.P.C. (0.25 mg/Kg) and atropine (0.4 mg) subcutaneously one hour before anaesthesia. General anaesthesia was induced with pentobarbitone sodium (30 mg/Kg body weight) intravenously. A cuffed endotracheal tube was inserted for positive pressure ventilation

with a Manley ventilator using an 80% nitrous oxide and 20% oxygen mixture. 60-120 mg boluses of pentobarbitone sodium were given intravenously as necessary to supplement anaesthesia.

Monitoring:

A femoral arterial cannula was placed for pressure monitoring using a Sanborn Pressure Transducer (Model 267BC) with a Sanborn 4 channel Recorder (Model 954A-100 Hewlett-Packard/Sanborn Division).

Electrocardiograph electrodes were inserted subcutaneously on each limb and the electrocardiogram was continuously displayed on the Sanborn Recorder.

Arterial blood gases were monitored from the femoral cannula to confirm adequate ventilation.

Arterial blood temperature was monitored.

Exposure:

The animal was positioned on its back with limbs extended. The chest and abdomen were shaved and prepared with tincture of iodine.

Vertical sternotomy was performed. Meticulous care was taken to secure haemostasis, and the sternal edges were waxed.

The pericardium was opened ventrally and the edges were sutured to the wound edges creating a supporting well for the heart.

Heparin (3 mg/kg body weight) was given intravenously.

Cannulation for Cardiopulmonary Bypass: Figure 4.5

Aortic cannula: An 18 FG arterio-venous catheter (U.S.C.I Bardicath) was inserted for 8 cms into the descending aorta via a purse-stringed stab incision in the aortic arch just beyond the brachiocephalic artery.

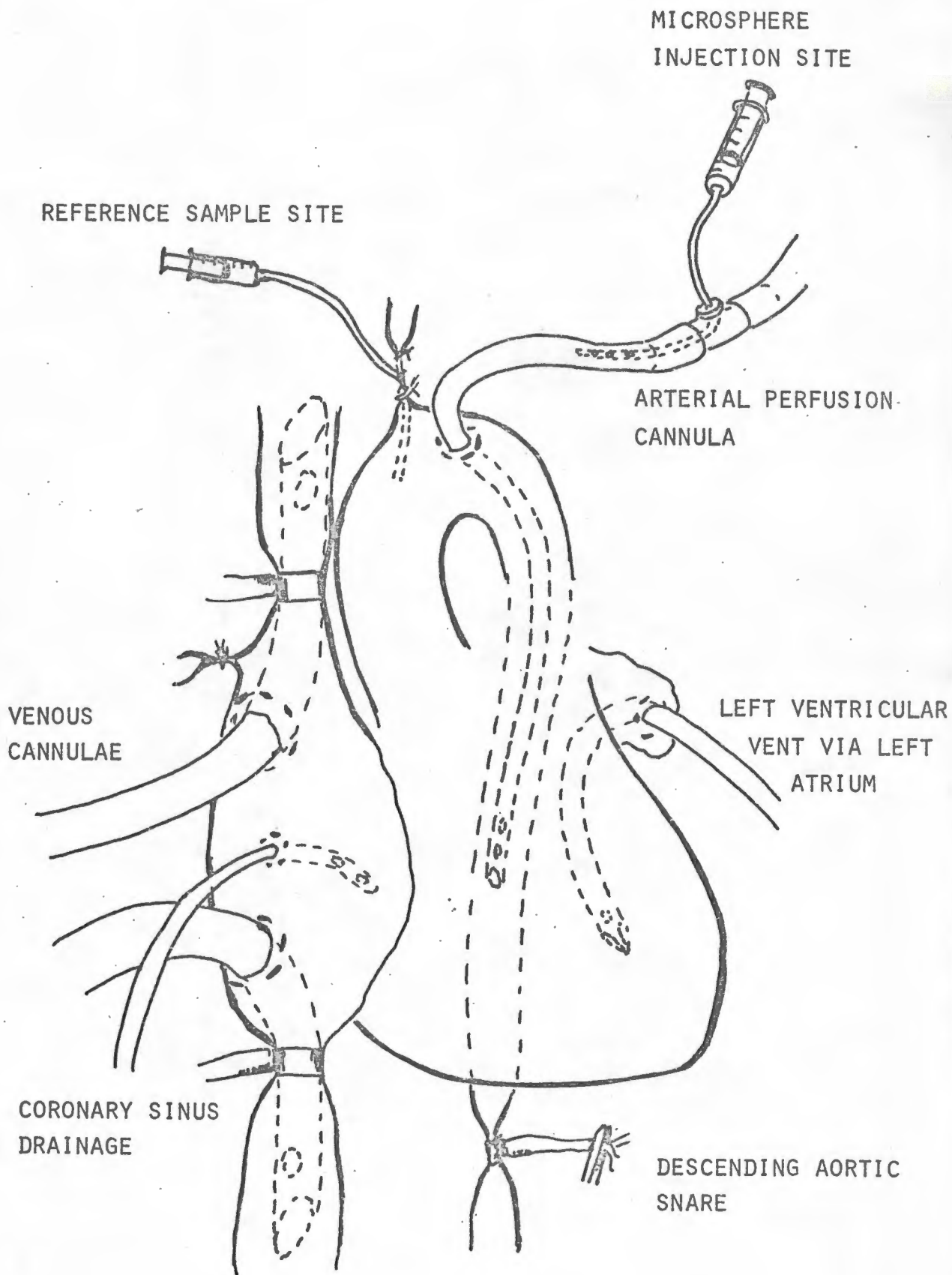


FIGURE 4-5

Venous Cannulae: Two 8 mm Cimid venous cannulae were inserted into the superior and inferior venae cavae respectively via separate purse-stringed stab incisions in the right atrium. Both cavae were taped for subsequent snaring.

Left ventricular vent: A soft tipped angled Polystan 5 mm venous cannula was inserted into the left ventricle via a purse-stringed stab incision in the left atrial appendage once cardiopulmonary bypass had been established.

The Cardio-Pulmonary Bypass Circuit

A Paediatric Harvey Disposable Bubble oxygenator (Model H-800 - William Harvey Research Corp. Santa Ana., California 92795) with a Sarns Roller pump was used for the extracorporeal oxygenator and pump. The circuit was primed with 1,500 ml of blood (haemoglobin 8-10 Gm/100 ml); to which was added 50 ml 8.4% NaHCO_3 ; 10 ml 10% CaCl_2 , 30 mg Heparin and 1 Gm of Cephalothin sodium.

The integral heat exchanger of the Harvey oxygenator was supplied with heated water from a Churchill pump to maintain arterial temperature at 37°C.

Gas supply to the oxygenator was oxygen 4 litres per minute and carbon dioxide 200 ml per minute. Pump flow rate was in the range of 800 to 2,400 ml/minute and was regulated to maintain desired arterial pressure (usually 100 mm Hg).

The left ventricular vent drained by gravity with zero pressure into the oxygenator; a cardiomy sucker with separate pump drained via a cardiomy reservoir to the oxygenator.

When necessary the prime was supplemented by adding further blood or Ringers lactate to maintain a safe operating level in the oxygenator.

Once cardiopulmonary bypass was established the ventilator was turned off; the main pulmonary artery was ligated (to obviate the possibility of pulmonary flow occurring, especially when coronary sinus blood was being collected). The descending aorta was taped distal to the aortic cannula tip for subsequent temporary snaring during microsphere injections. A reference sample catheter (Portex intracath) was inserted into the ascending aorta via the brachiocephalic artery which was then ligated round the catheter. The azygos vein was ligated to ensure accuracy when measuring coronary sinus drainage - see Figure 4-5.

The circumflex and anterior descending coronary arteries were then readily available for pressure and flow measurement, creation of artificial stenosis or occlusion, and insertion of a aorto-coronary bypass graft.

One artery with its territory of supply was selected as the "test" artery; the other acted as a control.

A period of aortic cross-clamping, which varied between 12 and 22 minutes was used for opening the selected artery for approximately 3 mm and sewing on a graft. The common carotid artery of the blood donor dog was ideal for this purpose. 7/0 Prolene continuous suture was used for the end-to-side anastomosis. The bypass graft vessel was then joined to a tapered ended U.S.C.I. Bardic arterial cannula which was joined via a metal connector with a side tap to a 6.5 mm Sarns Morris aortic cannula. This could readily be inserted into the ascending aorta via a purse-stringed stab incision, obviating the need for a proximal anastomosis, ensuring a rapid provision of an unrestricted source of aortic blood into the graft, and providing a simple means of measuring aortic and distal coronary pressure (see Figure 4.2) through the pressure line to a single Sanborn Pressure Transducer (Model 267 BC) and recorded on the 4-channel Sanborn recorder 954-A-100.

Artificial stenosis of the "test" artery was produced by tying a ligature of 4/0 ethiflex around the artery while an accurately measured

obturator was in the lumen, introduced through the arteriotomy prior to graft insertion.

Coronary sinus drainage was measured on bypass, with the pulmonary artery occluded by collecting right atrial blood from a 16 FG Fergusson venae caval catheter inserted through a purse-stringed stab incision in the right atrium. The caval tapes were snared and coronary sinus blood was collected and returned to the circulation via a cardiomy sucker. Once a stable flow rate had been established the filling of 100 ml measuring cylinders was timed with a stop-watch and the average time of 5 collections was used to calculate coronary sinus drainage. Once this measurement had been completed a caval snare was loosened and the coronary sinus cannula was clamped.

Coronary arterial flow was measured by means of a 2 mm Nycotron electromagnetic flow transducer with special configuration to reduce bulk and allow placement around a coronary vessel with minimal disturbance of the vessel. A Nycotron Blood Flow Meter 376 was used for flow measurement and a record of mean and phasic flow was made on the 4 channel Sanborn recorder 954 A-100.

For each experiment the defined factors influencing myocardial perfusion were held constant for ten minutes with the descending aorta snared to allow stabilisation prior to assessment of regional myocardial perfusion. These factors have been listed under General Principles of the Animal Model.

Regional myocardial perfusion was measured using radioactive microsphere (nominal diameter 15 μ - 3M Company or New England Nuclear) labelled with Co⁵⁷ or Ce¹⁴¹, Sn¹¹³, Sr⁸⁵, Sc⁴⁶ or Nb⁹⁵.

1.5 to 3.0 x 10⁶ spheres, suspended in 10% Dextran were sonicated in

a Dawe Sonicleaner type A for 5 minutes to disperse aggregating microspheres. Immediately before the injection microspheres were quickly drawn into a syringe containing Tween-80 (final concentration of Tween 80 less than 0.5%), mixed and injected into the arterial line of the extracorporeal circuit (Figure 4.5), via a plastic catheter with multiple side perforations, over a period of approximately 10 seconds. This catheter was then flushed with 5 ml of normal saline to ensure that no microspheres remained in the catheter.

A reference sample of blood was withdrawn from the ascending aorta (Figure 4.5) using a Harvard withdrawal pump at a rate of approximately 10 ml/minute. The collection began 10 seconds prior to injection of microspheres and lasted 2 minutes. The reference blood flow was calibrated by weighing and timing the collection accurately. The specific gravity of blood during bypass was found to be 1.03 g/ml.

Three or four different isotope-labelled microsphere injections were used to test different conditions in each animal.

At the end of the experiment the heart was excised. A coronary angiogram was made (Fulton 1965) by injecting Barium sulphate suspension (micropaque) to which 10% w/v crystalline gelatin had been added at 60 - 79°C. This resulted in a fine suspension which was fluid at 40°C and solidified at about 30°C within a few minutes. The micropaque/gelatin mixture was injected via coronary cannulas into the left coronary artery and the bypass graft at a pressure of 100 mmHg and a temperature of 38 - 40°C with the heart submerged in a water bath. Once coronary filling was complete the heart was immersed in iced water to allow solidification of the gelatin. Consistently good quality angiograms were obtained in this way.

The atria, major vessels and right ventricular myocardium were then trimmed from the heart. Excess barium sulphate was washed off. The left ventricle was then weighed.

An incision was made in the posterior aspect of the septum from

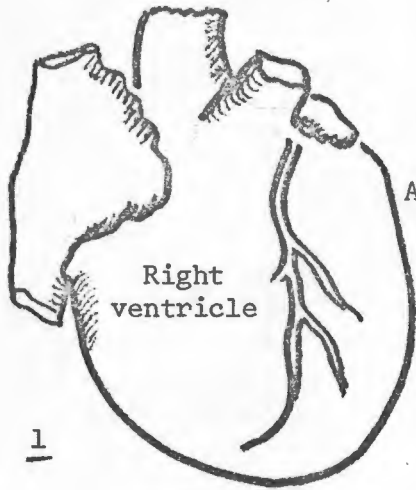
mitral annulus to apex. The aortic ring was divided and mitral valve and chordae were resected. This allowed the left ventricle to be opened out as a flat muscle block (Figure 4.6).

The left ventricular muscle mass was then fixed firmly with adhesive plastic sheet (Steridrape) to a perspex sheet with a reference grid consisting of two series of parallel metal wires spaced accurately at 1 cm intervals giving a grid measuring 8 x 12 cm containing 96 x 1 cm square subdivisions (Figure 4.7). Radiographs were then taken. The resultant coronary angiogram and the left ventricular myocardial outline were then related to the grid (Figure 4.8).

The myocardium was then cut into blocks which corresponded as closely as possible to the blocks of the grid. Each muscle block was divided into an endocardial and epicardial half; any fat or connective tissue or major coronary vessel was trimmed off and the muscle blocks were carefully and systematically placed in labelled, weighed counting tubes for reweighing to determine the myocardial weight.

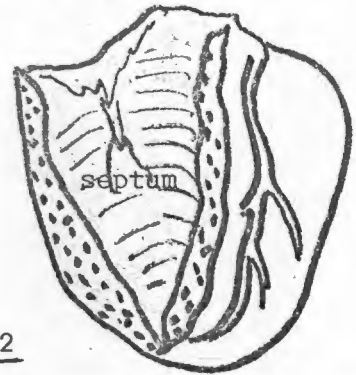
Radioactivity was determined with a two channel Wallach gamma counter and samples were counted for a fixed time until, on average, approximately 20,000 counts had been accumulated, usually 300 - 1000 seconds. The contribution of the 4 isotopes to the radioactivity in the different channels was determined in each experiment using the reference blood samples (which contained one isotope only) as the standard. After the crossover factors had been calculated the net counts of each isotope per biopsy were determined by solving four simultaneous equations. Myocardial blood flow for endocardial half and epicardial half biopsies was then calculated from the equation:-

$$\text{Myocardial blood flow} = \text{myocardial counts} \times \frac{\text{Reference blood flow}}{\text{Reference counts}}$$

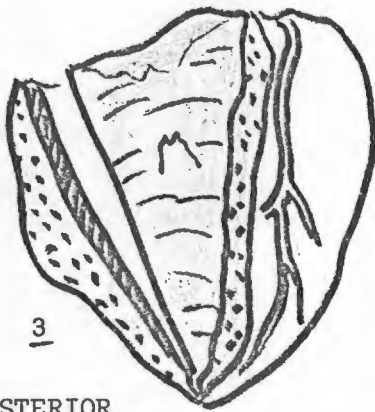


HEART EXCISED

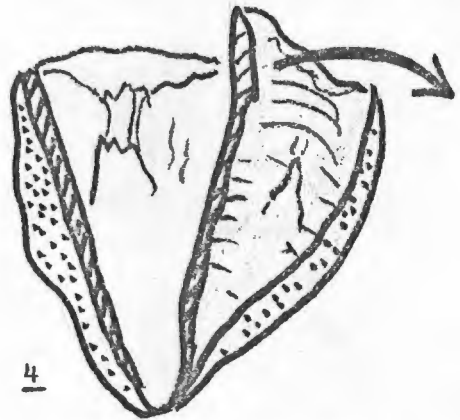
atria excised



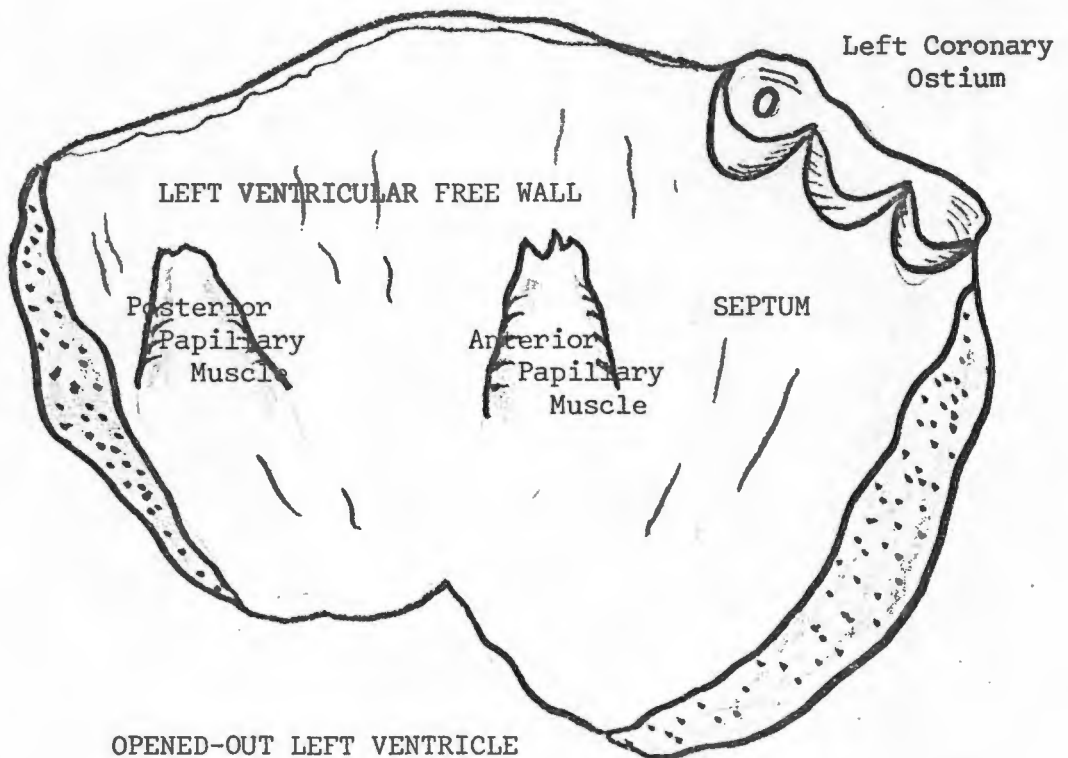
RIGHT VENTRICLE EXCISED



POSTERIOR ASPECT OF SEPTUM INCISED

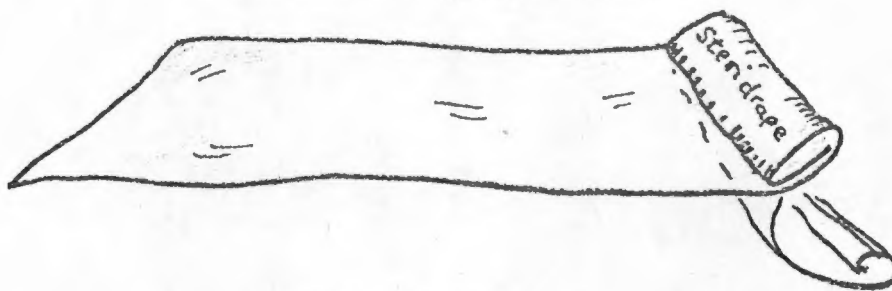


LEFT VENTRICLE OPENED

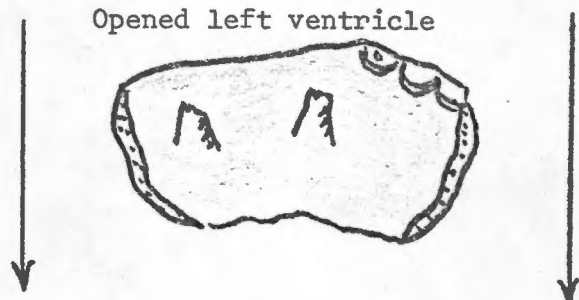


OPENED-OUT LEFT VENTRICLE

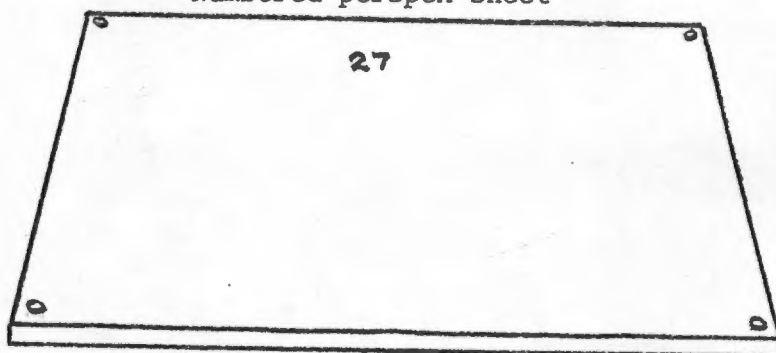
Adhesive plastic sheet used
to fix heart to perspex sheet



Opened left ventricle



Numbered perspex sheet



Wire grid on lower perspex sheet;
locating dowels fix upper sheet

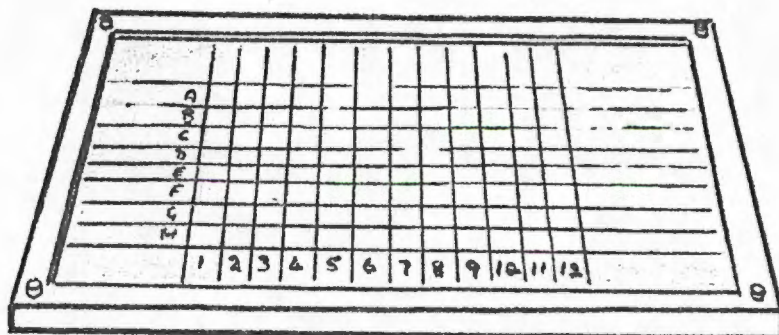
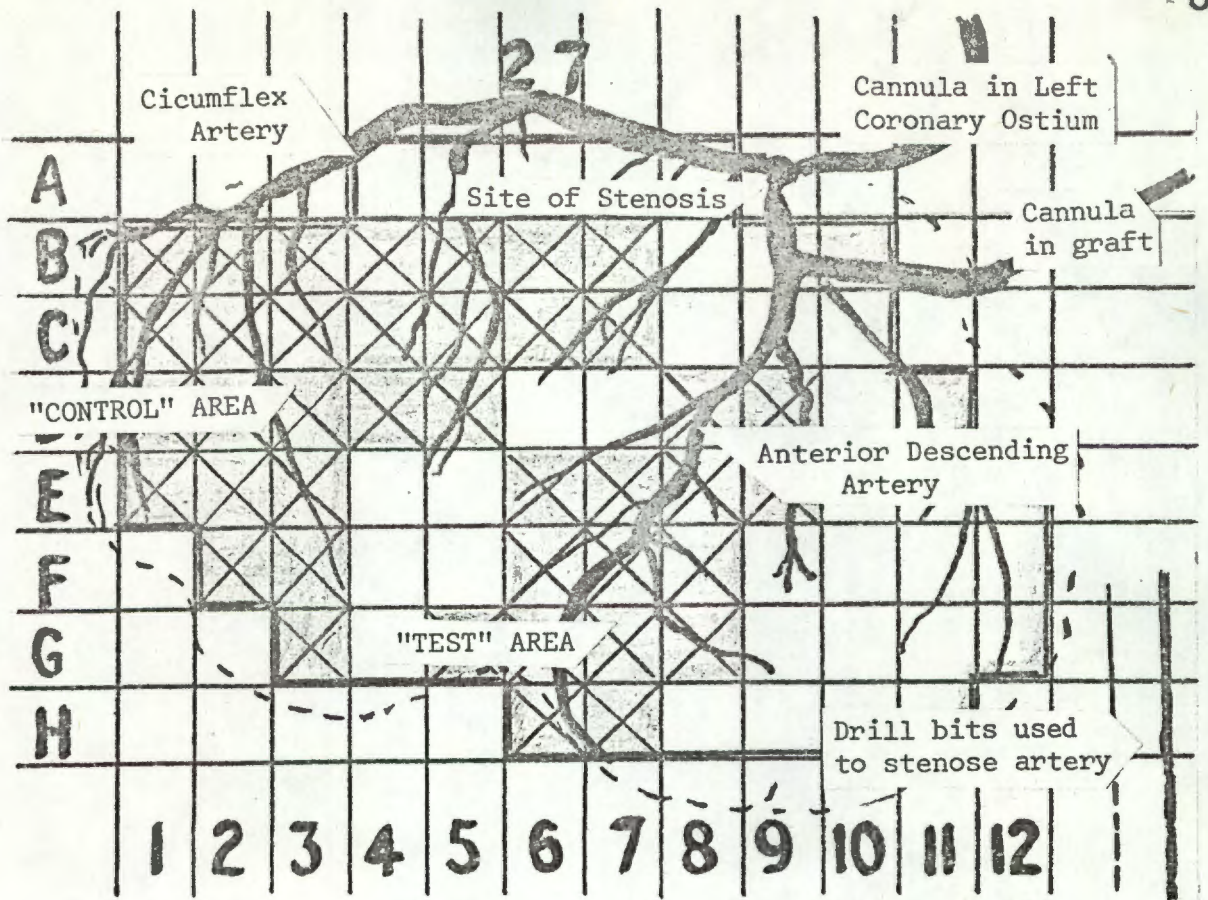


Figure 4 - 7



THESE BLOCKS USED FOR QUANTITATIVE ANALYSIS
SEE FIGURES 4-15 to 18 and 4 - 30 to 32

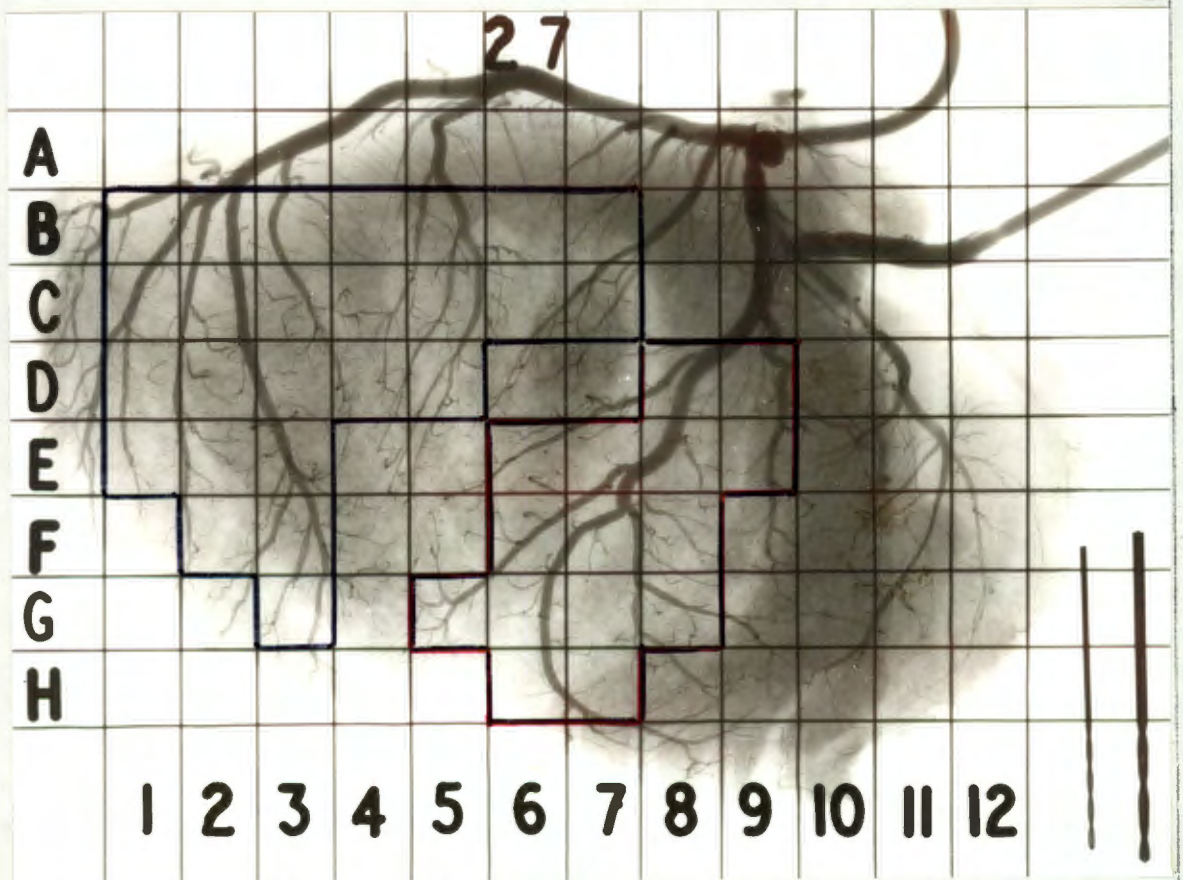


Figure 4 - 8

Data Analysis of Microsphere Studies

The analysis proceeded sequentially as:

- 1) Data entry from radio-isotope counter (Walloch) into DEC PDP12 computer consisting of
 - a) set of standards - 4 blood samples for each isotope.
 - b) two background measurements which were used for background correction on all samples.
 - c) two data sets, i.e. endocardium and epicardium. Each set was in the 12 x 8 array of the grid, with 192 tissue samples.
- 2) Weights of blood and tissue samples were fed in manually.
- 3) The first part of the analysis was to calculate the spill over factors for each isotope and energy window. The spill over coefficients were held as an $n \times n$ matrix where n was the number of isotopes in the study (Figure 4.21).
- 4) The spill over coefficients were used to solve the 192 sets of simultaneous equations, each set was of dimension n . The equations were solved using the method of Gauss elimination. In this study a Fortran subroutine, called GELG, was used, which is part of the IBM Scientific Subroutine Package (IBM, 1969).
- 5) The absolute flows for each tissue sample were computed from knowledge of the standards and the corrected counts and weights for each sample.
- 6) The last step in the analysis was the computation of the ratios of the endocardial to epicardial blood flows for each specimen pair.
- 7) The results of the processed data could be displayed in one of three ways:
 - a) An alpha-numeric line printer presentation of the data in matrix form.
 - b) By colour television (Boardman, 1976) in which a 12 x 8 matrix is displayed on the television screen. An eight level pseudo-colour scale is available in which flow rate intervals are linearly related to an arbitrarily assigned

colour scale. The display system is identical to that used in conventional gamma camera scintigraphy.

- c) A grey tone hard copy output is obtained by using a Versatec electrostatic printer/plotter. In this display the data are represented as a two dimensional array of pixels. The shading in each pixel can be set to one of eight levels, ranging from no shading at all (low blood flow) to uniform black (maximum blood flow). Intermediate blood flows are presented on a linear display scale.

In order to illustrate the method more fully the results of one experiment are shown in detail.

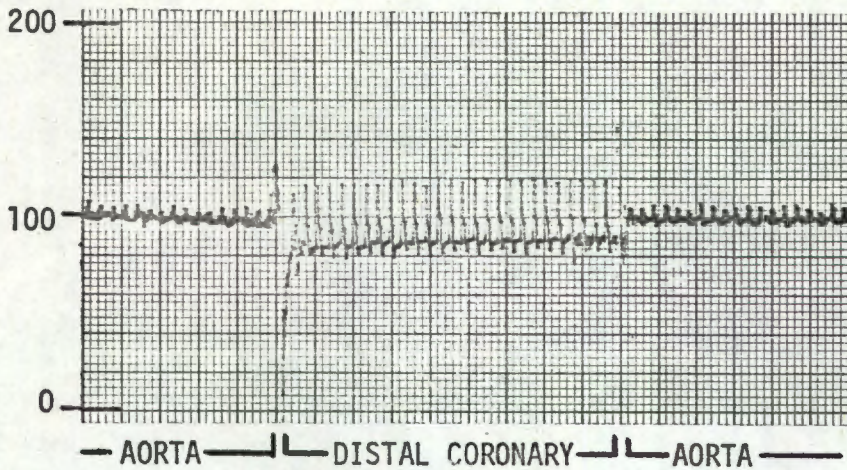
Experiment number 27 was undertaken to show the effects of varying degrees of stenosis of the anterior descending artery on myocardial perfusion.

Figure 4.8 shows the angiographic appearance of the left ventricle. The proximal anterior descending artery had been stenosed by placing two ligatures around the artery with the accurately measured drill bits seen on the angiogram placed within the lumen through the coronary arteriotomy (1.5 mm and 0.9 mm diameter). This created a stenosis of 45% or 70% as desired.

Figure 4.9 shows the pressure drop measured between the aorta and the distal coronary artery by the method illustrated in Figure 4.2, and also indicates the graft flow which was measured in the correcting bypass graft. This illustrates the consistently demonstrated finding of no pressure drop with no coronary stenosis; increasing pressure drop with more severe stenosis, until with total coronary occlusion the distal coronary pressure is about 20% of aortic pressure. Graft flow (here with maximal coronary vasodilatation achieved with papaverine) is low when no coronary stenosis is present and increases progressively with increasing coronary stenosis and increasing aorta-coronary pressure drop.

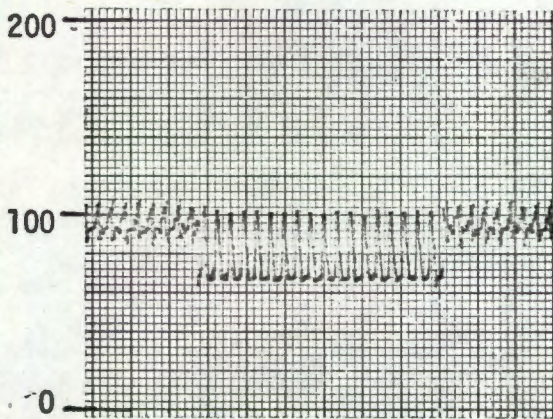
AORTA - CORONARY PRESSURE DROP / GRAFT FLOW RELATION

Pressure
(mm.Hg)



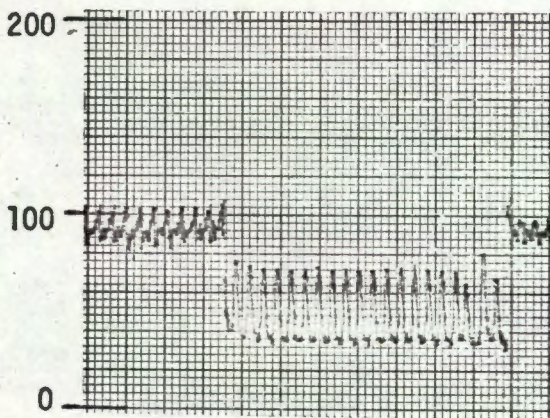
NORMAL
ANTERIOR DESCENDING
CORONARY ARTERY

GRAFT FLOW
20 ML/MIN



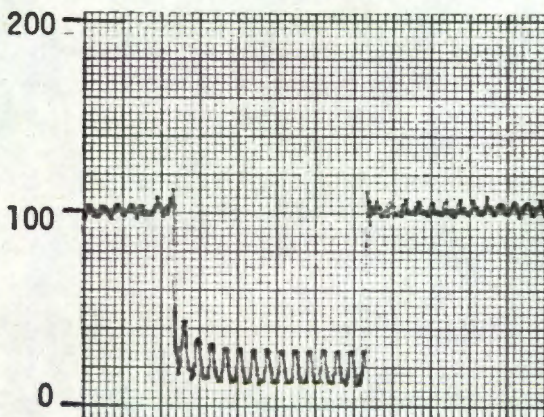
45% CORONARY STENOSIS

GRAFT FLOW
60 ML/MIN



70% CORONARY STENOSIS

GRAFT FLOW
95 ML/MIN



TOTAL CORONARY OCCLUSION

GRAFT FLOW
150 ML/MIN

FIGURE 4-9

Figures 4.10 to 4.21 inclusive show the computer print-out data in matrix form for dog 27.

Corrected counts for the endocardial halves of the myocardial blocks for each of the 4 isotopes used in the study are shown in Figures 4.10 and 4.11.

Corrected counts for the epicardial halves of the myocardial blocks for each of the 4 isotopes are shown in Figures 4.12 and 4.13.

Figure 4.14 shows the specimen weights. It will be noted that near the edge of the matrix some blocks were unrepresented eg. A1, A2, G1, H1. This was dependant on the size of the left ventricle, which would not necessarily always entirely cover the grid. This accounts for the shape of the maps (Figure 4.22).

Figures 4.15 and 4.16 show the absolute blood flow in ml/Gram of tissue/minute for each endocardial block.

Figures 4.17 and 4.18 show the blood flow for each epicardial block.

Figures 4.19 and 4.20 show the endocardial/epicardial flow ratios for each block of myocardium.

Figure 4.21 shows contribution or spill over factors for each standard used in the calculations.

Figure 4.22 shows the angiogram appearance of the left ventricle together with the grey tone hard copy output of the Versatec printer/plotter-- here showing the map of left ventricular perfusion in the presence of a 45% stenosis of the anterior descending artery, without coronary vasodilatation. The perfusion deficit in the region of the anterior descending arterial supply is discernable, and affects a relatively small area. This deficit is better seen in the endocardial map (4.22) but is just discernable in the epicardial map (Figure 4.23).

Figures 4.24 and 4.25 show respectively endocardial and epicardial blood flow maps at the same scaling factor with the same 45% stenosis of the anterior descending artery, but with maximum coronary vasodilatation induced by constant rate infusion of papaverine (1 mg per minute). Blood flow increases in all areas, but the jeopardised area remains relatively underperfused.

Figures 4.26 and 4.27 show respectively endocardial and epicardial blood flow maps at the same scaling factor, but with a 70% stenosis of the anterior descending artery, and maximum coronary vasodilatation. The greater perfusion deficit is obvious.

Figures 4.28 and 4.29 show respectively endocardial and epicardial blood flow maps at the same scaling factor, but with total occlusion of the anterior descending artery, and maximum coronary vasodilatation maintained. The perfusion deficit is maximal.

All other factors were kept at as near to constant levels as possible during this experiment.

Aortic pressure was kept at a mean of 100 mmHg by adjusting pump flow rate; heart rate was constant at 165-170/minute: sinus rhythm; left ventricular cavity pressure was zero. Pump flow rate was 1,900 ml/minute for the first injection (without papaverine) and was 4,050 ml/mixture for the remaining three injections (with papaverine). Haemoglobin level was 10.8 G.100 ml.

The flow maps give a clear and graphic picture of the effect of increasing coronary stenosis, but in order to quantitate the effect the data can be shown in numerical and graph form.

The blocks of myocardium clearly in the "control" territory are outlined in Figure 4.8. The blocks of myocardium clearly in the jeopardised "test" area are also outlined.

Using the numerical data presented in Figures 4.15, 4.16, 4.17 and 4.18 the mean flow for the sub-endocardial, and sub-epicardial halves of

the muscle blocks in the control and test areas can be computed. Using a programmed Olivetti 100 computer the mean, standard deviation and standard error of the mean were calculated for each control and test area under each condition for all experiments. Students' T-test was applied using a computer programme to estimate the significance of the difference between the means of control and test areas.

The numerical data computed in this way for experiment 27 are shown in Figures 4.30 and 4.31, and in graph form in Figure 4.32.

The difference between control and test results is highly significant in all cases ($p < 0.001$).

DJW (REV F) RUN ON 20- 9-78

IDENTIFICATION: DOG 27

ENDOCARDIUM CORRECTED COUNTS

	ENERGY 1 INJECTION 1											
	1	2	3	4	5	6	7	8	9	10	11	12
A	0	0	0	7619	9009	13153	8146	14645	172	0	0	0
B	15201	9000	7136	11798	14174	19374	18054	15796	8765	5163	0	0
C	23135	10107	14936	13388	12475	12940	12419	13169	13233	14319	0	0
D	18679	10646	15513	18655	10234	16207	14582	8102	14615	19632	11570	27
E	15149	8328	20546	13298	15594	12711	11435	12839	17820	16486	15697	15727
F	0	11909	15396	14146	10785	9679	8994	8513	15456	20243	18696	7839
G	0	0	8999	8928	15295	8405	14515	13875	21982	24026	26645	7925
H	0	7	0	0	35	5109	11846	15113	25947	18028	0	0

	ENERGY 2 INJECTION 2											
	1	2	3	4	5	6	7	8	9	10	11	12
A	0	405	39	9765	9653	12496	7347	15650	0	0	315	0
B	17125	8167	7350	15553	16416	17244	16845	21506	11247	6269	1003	7
C	23403	11241	19420	17663	15919	16015	15580	15399	16335	15569	0	6
D	18888	13688	22251	24281	12565	23492	18120	4022	13258	21578	13781	0
E	15742	8255	26395	17052	14388	7756	7533	5002	13202	19613	18625	17787
F	0	13625	19429	14717	6852	5668	4109	4018	13467	21782	22399	9014
G	0	0	11306	7017	8122	4594	6602	6139	14921	23755	27823	9263
H	1	0	16	0	0	11260	8115	12048	16919	20221	0	4

FIGURE 4-10

		INJECTION 3											
		ENERGY 3						INJECTION 4					
		1	2	3	4	5	6	7	8	9	10	11	12
A	0	0	0	0	13661	13716	16167	10441	22165	0	0	0	0
B	22404	14347	12548	18292	18292	21399	22128	22639	26681	15110	8854	0	9
C	30243	15309	26396	21338	21338	19255	20444	19781	25601	22975	22683	14	0
D	24634	16858	25794	29254	29254	15925	30676	25235	15009	25690	31884	26	0
E	19818	10726	27567	20697	20697	21425	21216	18096	18400	29003	28193	19672	0
F	0	18186	21515	20160	20160	15841	15868	13567	12537	24368	30466	31424	24227
G	0	0	12975	11456	19005	19005	14165	21602	20192	29198	34239	37837	12331
H	2	11	0	0	0	0	9221	18178	23383	34426	28420	0	12055
		INJECTION 4											
		ENERGY 4						INJECTION 4					
		1	2	3	4	5	6	7	8	9	10	11	12
A	0	0	0	3	3473	3856	4957	3293	6948	0	22	0	0
B	6886	3390	3076	5736	5736	6159	6585	6905	8501	4961	2968	0	0
C	9011	4524	7147	6049	6049	6068	6545	6928	5816	7465	7299	0	0
D	8025	4995	8101	8623	8623	4703	9063	6953	198	3162	9646	5806	0
E	6860	3491	8623	6259	6259	5261	619	1297	365	4807	8054	7999	6318
F	0	5291	6906	5591	5591	1374	249	237	161	3759	9291	9645	3848
G	0	0	4381	2290	2290	353	145	282	336	3259	10147	12634	4114
H	7	6	0	0	0	2	112	1750	3164	4705	8335	0	0

FIGURE 4-11

EPICARDIUM CORRECTED COUNTS

		INJECTION 1												INJECTION 2																									
		ENERGY 1						ENERGY 2						ENERGY 1						ENERGY 2																			
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12		
A	0	0	0	0	6890	6617	12390	7291	9785	16	0	0	0	A	0	0	0	0	0	0	0	0	0	0	0	0	A	0	0	0	0	0	0	0	0	0	0	0	0
B	13289	3707	7696	11527	10896	12624	7876	8826	8826	6581	4482	0	B	3864	7791	14805	9418	10174	10852	9293	7804	13245	12407	5402	0	B	13553	3864	7791	11068	10498	12737	7704	13245	10094	0	162	3	
C	14343	7837	14805	9418	10174	10852	9293	7804	10623	8051	9186	0	C	8929	12951	15340	9462	9507	13883	11694	7945	10623	7945	9340	0	C	16303	8929	12951	11068	9507	13883	11694	7945	10623	688	5402	0	
D	10793	8420	15668	10154	11882	7969	10116	6040	4345	8617	14343	0	D	9508	15340	14090	12702	12818	10921	12311	7007	4345	10879	13649	5	D	12713	9508	15340	12702	12818	10921	12311	7007	4345	10879	13649	5	
E	11903	6944	12556	8803	9565	8282	6000	5643	4141	9475	16246	0	E	9406	14090	10381	12191	10654	6778	4584	6403	4141	13472	13607	8838	E	15513	9406	14090	12191	10654	6778	4584	6403	4141	13472	13607	8838	
F	0	9677	8855	5964	5732	6490	6490	6211	6211	11989	13064	0	F	12575	10381	6894	6894	6721	3854	4706	7655	4081	14583	11876	7305	F	0	12575	10381	6894	6721	3854	4706	7655	4081	14583	11876	7305	
G	0	0	8982	9566	7454	4100	9689	6681	6681	10018	13815	0	G	0	12289	10864	10864	5166	2858	7474	6971	4798	17949	13493	9417	G	476	12289	10864	10864	5166	2858	7474	6971	4798	17949	13493	9417	
H	0	53	0	371	0	4415	8920	10880	10880	13353	11826	0	H	0	0	0	12	0	3168	5695	8769	8769	0	12405	0	H	0	0	0	12	0	3168	5695	8769	8769	0	12405	0	

FIGURE 4-12

		INJECTION 3															
		ENERGY 3						INJECTION 3									
		1	2	3	4	5	6	7	8	9	10	11	12				
A	B	C	D	E	F	G	H	A	B	C	D	E	F	G	H		
18522	15	0	7	11903	12607	13145	16231	8195	14347	10	0	1	0	0	0	2	2
21574	5719	11903	15995	17247	17191	17247	17191	9781	18495	13558	8752	0	0	0	0	2	2
15340	12871	19287	14356	14435	20240	14435	20240	15334	16337	15383	18051	0	0	0	0	2	2
20307	12735	21784	17013	19731	14931	19731	14931	18379	10906	18128	26469	16691	12561	12561	22248	11416	14038
0	11173	18557	15133	14547	13295	14547	13295	10126	10776	17066	24760	22248	12561	22248	21975	11416	14038
10	14956	13024	10065	12012	8488	12012	8488	9577	12202	21947	20399	21975	12561	21975	20399	11416	14038
0	11	14288	13878	10733	13878	10733	6864	16480	11857	17130	22648	25398	14038	25398	22648	14038	0
0	0	0	0	12	7477	12	7477	14810	20062	21314	18481	16	0	16	18481	0	0

		INJECTION 4															
		ENERGY 4						INJECTION 4									
		1	2	3	4	5	6	7	8	9	10	11	12				
A	B	C	D	E	F	G	H	A	B	C	D	E	F	G	H		
5475	0	0	3442	2847	3442	3337	3970	2556	4521	0	0	0	3	3	16	11	0
6714	1514	2847	4075	5255	4075	4594	5288	3343	6189	4482	2628	0	0	0	0	11	0
4927	3927	5255	3812	5939	4677	4067	6140	5423	3823	2241	3103	0	0	0	0	0	0
5635	3769	5939	4677	5601	4656	5635	4814	4757	316	419	4929	5238	4022	5238	4929	4022	0
13	3594	5601	4656	3681	2749	4273	626	170	207	476	4917	6372	4022	6372	4917	4022	0
0	4339	3681	3806	3977	3806	1529	139	121	118	459	5070	6886	3852	6886	5070	3852	0
10	0	3977	3806	5	3806	129	82	173	226	437	5232	8792	3852	8792	5232	5037	6
0	0	5	0	0	0	0	125	334	730	1084	4757	0	0	0	4757	6	0

FIGURE 4-13

ENDOCARDIUM SPECIMEN WEIGHTS

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.0000	0.0000	0.0000	0.5783	0.6301	0.7048	0.4466	0.9214	0.0000	0.0000	0.0000	0.0000	A
B	0.9184	0.6418	0.5999	0.7346	0.8979	0.8869	0.9468	0.9417	0.9039	0.5104	0.0000	0.0000	B
C	1.2574	0.6192	1.0696	0.8051	0.8345	0.9219	0.9292	1.2214	0.9280	1.1169	0.0000	0.0000	C
D	1.1192	0.6977	0.9498	0.9716	0.6232	1.1983	1.1483	0.7822	1.2684	1.4846	0.9805	0.0000	D
E	1.2236	0.4901	0.9723	0.7854	0.9593	1.0668	1.0479	0.9500	1.2880	1.1399	1.2346	0.9325	E
F	0.0000	0.7397	0.8312	0.7466	0.7480	0.7740	0.7881	0.5906	0.9201	1.3082	1.1865	0.5437	F
G	0.0000	0.0000	0.4796	0.4537	1.1205	0.6301	0.9444	0.8875	1.2908	1.4796	1.6325	0.4908	G
H	0.0000	0.0000	0.0000	0.0000	0.0000	0.4460	0.8688	0.9788	1.4388	1.2675	0.0000	0.0000	H

EPICARDIUM SPECIMEN WEIGHTS

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.0000	0.0000	0.0000	0.7007	0.7931	1.1278	0.6151	0.9692	0.0000	0.0000	0.0000	0.0000	A
B	1.2152	0.5032	0.8266	0.8477	1.0403	1.0307	0.5537	0.9107	1.0174	0.4990	0.0000	0.0000	B
C	1.3427	0.7764	1.0952	0.7463	0.9049	1.1619	0.8632	1.0601	1.0580	1.1412	0.0000	0.0000	C
D	1.0641	0.7344	1.1332	0.8529	1.1585	0.9075	1.3735	0.9344	1.1689	1.6626	1.0539	0.0000	D
E	1.1096	0.6318	1.0867	0.8412	0.8723	1.0874	1.0337	0.8736	1.1963	1.4148	1.1723	0.6329	E
F	0.0000	0.7558	0.7530	0.5738	0.7943	0.7677	0.9388	0.7580	1.3545	1.1895	1.2431	0.6805	F
G	0.0000	0.0000	0.6969	0.6421	0.9499	0.5373	1.0199	0.7256	1.0842	1.2172	1.5133	0.8694	G
H	0.0000	0.0000	0.0000	0.0000	0.0000	0.4799	0.9014	1.1251	1.2053	1.0511	0.0000	0.0000	H

FIGURE 4-14

BLOCKS SELECTED FROM ANGIOGRAM AS "CONTROL" AND "TEST" ARE OUTLINED FOR QUANTITATIVE ANALYSIS
 SEE FIGURES 4 - 8 and 4 - 30 to 32

ENDOCARDIUM BLOOD FLOW (ML/G/MIN)

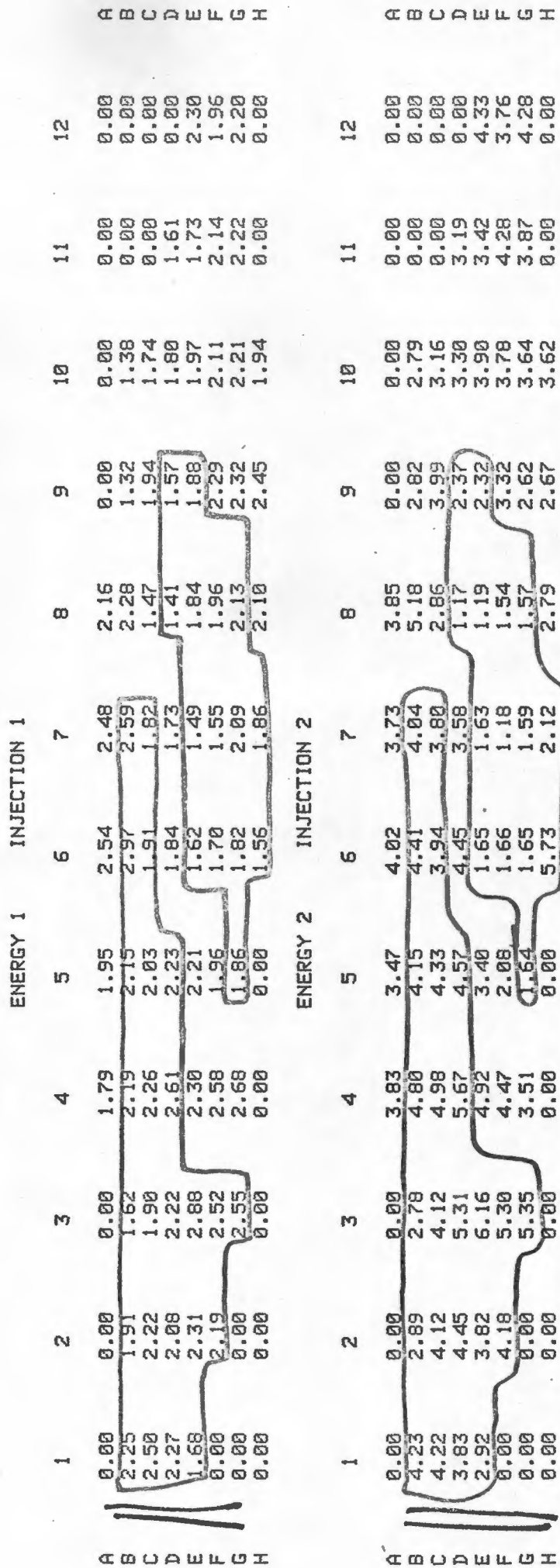


FIGURE 4-15

ENDOCARDIUM BLOOD FLOW

"CONTROL" AND "TEST" AREAS OUTLINED

ENERGY 3 INJECTION 3

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	4.12	3.80	4.00	4.08	4.20	0.00	0.00	0.00	0.00	A
B	4.26	3.90	3.65	4.35	4.16	4.35	4.17	4.98	2.92	3.03	0.00	0.00	B
C	4.20	4.31	4.31	4.63	4.03	3.87	3.72	4.98	4.32	3.54	0.00	0.00	C
D	3.84	4.22	4.74	5.25	4.46	4.47	3.83	3.66	4.32	3.75	0.00	0.00	D
E	2.83	3.82	4.95	4.60	3.90	3.47	3.01	3.35	3.53	4.32	3.50	4.53	E
F	0.00	4.29	4.52	4.71	3.70	3.58	3.00	3.38	3.93	4.06	3.90	3.96	F
G	0.00	0.00	4.72	4.41	2.96	3.92	3.99	3.70	4.62	4.04	4.62	4.29	G
H	0.00	0.00	0.00	0.00	0.00	3.61	3.65	4.17	4.18	3.91	0.00	0.00	H

ENERGY 4 INJECTION 4

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	3.63	3.70	4.25	4.45	4.55	0.00	0.00	0.00	0.00	A
B	4.53	3.19	3.10	4.71	4.14	4.48	4.40	5.45	3.31	3.51	0.00	0.00	B
C	4.33	4.41	4.03	4.54	4.39	4.29	4.50	2.88	4.86	3.95	0.00	0.00	C
D	4.33	4.32	5.15	5.36	4.56	4.57	3.66	0.15	1.51	3.92	3.58	0.00	D
E	3.39	4.30	5.36	4.81	3.31	0.35	0.75	0.23	1.88	4.27	3.91	4.09	E
F	0.00	4.32	5.02	4.52	1.11	0.19	0.18	0.16	2.47	4.29	4.91	4.27	F
G	0.00	0.00	5.52	3.05	0.19	0.14	0.18	0.23	1.52	4.14	4.67	5.06	G
H	0.00	0.00	0.00	0.00	0.00	0.15	1.22	1.95	1.97	3.97	0.00	0.00	H

FIGURE 4-16

"CONTROL" AND "TEST" AREAS OUTLINED

EPICARDIUM BLOOD FLOW (ML/GMIN)

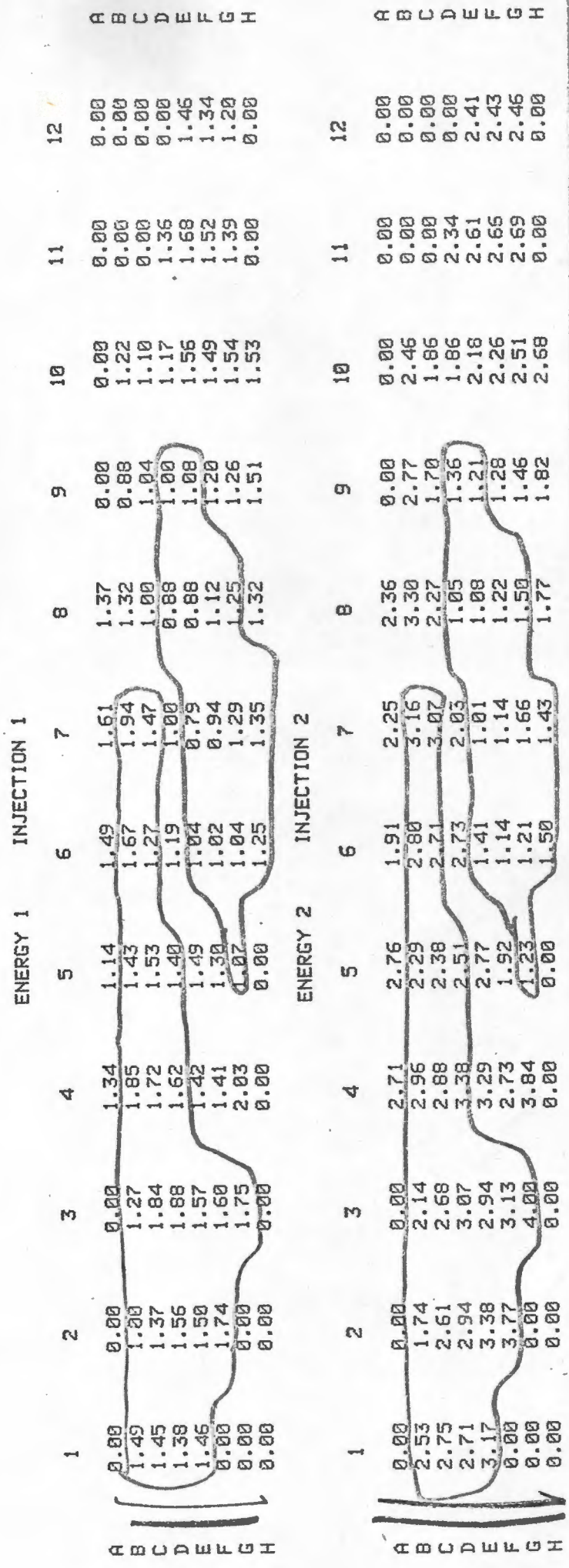


FIGURE 4-17

EPICARDIUM BLOOD FLOW

"CONTROL" AND "TEST" AREAS OUTLINED

ENERGY 3 INJECTION 3

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	3.14	2.89	2.51	2.32	2.58	0.00	0.00	0.00	0.00	A
B	2.66	1.98	2.51	3.29	2.89	2.91	3.08	3.54	2.33	3.06	0.00	0.00	B
C	2.60	2.89	3.07	3.36	2.78	3.04	3.10	2.69	2.54	2.76	0.00	0.00	C
D	2.52	3.03	3.35	3.48	2.97	2.87	2.34	2.04	2.71	2.78	2.76	0.00	D
E	3.19	3.09	2.98	3.14	2.91	2.13	1.71	2.15	2.49	3.05	3.31	2.63	E
F	0.00	3.45	3.02	3.06	2.64	1.93	1.78	2.81	2.83	2.99	3.08	2.93	F
G	0.00	0.00	3.58	3.77	1.97	2.23	2.82	2.85	2.76	3.25	2.93	2.82	G
H	0.00	0.00	0.00	0.00	0.00	2.72	2.87	3.11	3.09	3.07	0.00	0.00	H

ENERGY 4 INJECTION 4

	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	2.97	2.54	2.13	2.51	2.82	0.00	0.00	0.00	0.00	A
B	2.72	1.82	2.08	2.90	2.67	3.10	3.65	4.10	2.66	3.18	0.00	0.00	B
C	3.02	3.05	2.90	3.08	2.71	3.19	3.79	2.18	1.28	1.64	0.00	0.00	C
D	2.80	3.10	3.16	3.31	2.94	3.20	2.09	0.20	0.22	1.79	3.00	0.00	D
E	3.07	3.44	3.11	3.34	2.96	0.35	0.10	0.14	0.24	2.10	3.28	2.92	E
F	0.00	3.47	2.95	2.89	1.24	0.11	0.08	0.09	0.20	2.57	3.34	3.42	F
G	0.00	0.00	3.45	3.58	0.08	0.09	0.10	0.19	0.24	2.60	3.51	3.50	G
H	0.00	0.00	0.00	0.00	0.00	0.16	0.22	0.39	0.54	2.73	0.00	0.00	H

FIGURE 4-18

RATIOS OF ENDOCARDIUM / EPICARDIUM BLOOD FLOWS

	ENERGY 1 INJECTION 1												
	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	1.34	1.71	1.70	1.54	1.57	0.00	0.00	0.00	0.00	A
B	1.51	1.90	1.28	1.18	1.51	1.76	1.34	1.73	1.50	1.13	0.00	0.00	B
C	1.72	1.62	1.03	1.32	1.33	1.50	1.24	1.46	1.87	1.59	0.00	0.00	C
D	1.65	1.33	1.18	1.61	1.60	1.54	1.72	1.60	1.56	1.53	1.18	0.00	D
E	1.15	1.55	1.83	1.62	1.48	1.56	1.88	2.09	1.75	1.26	1.03	1.57	E
F	0.00	1.26	1.58	1.82	1.51	1.67	1.65	1.76	1.90	1.41	1.41	1.47	F
G	0.00	0.00	1.46	1.32	1.74	1.75	1.62	1.70	1.84	1.43	1.59	1.82	G
H	0.00	0.00	0.00	0.00	0.00	1.25	1.38	1.60	1.63	1.26	0.00	0.00	H

	ENERGY 2 INJECTION 2												
	1	2	3	4	5	6	7	8	9	10	11	12	
A	0.00	0.00	0.00	1.41	1.26	2.11	1.66	1.63	0.00	0.00	0.00	0.00	A
B	1.67	1.66	1.30	1.62	1.81	1.57	1.28	1.57	1.02	1.13	0.00	0.00	B
C	1.53	1.58	1.54	1.73	1.82	1.45	1.24	1.26	2.34	1.70	0.00	0.00	C
D	1.41	1.52	1.73	1.68	1.82	1.63	1.76	1.11	1.74	1.77	1.36	0.00	D
E	0.92	1.13	2.09	1.50	1.23	1.17	1.62	1.11	1.91	1.79	1.31	1.80	E
F	0.00	1.11	1.70	1.64	1.08	1.46	1.04	1.26	2.59	1.67	1.61	1.54	F
G	0.00	0.00	1.34	0.91	1.33	1.37	0.95	1.05	1.80	1.45	1.44	1.74	G
H	0.00	0.00	0.00	0.00	0.00	3.82	1.48	1.58	1.46	1.35	0.00	0.00	H

FIGURE 4-19

		INJECTION 3																				
		ENERGY 3				INJECTION 3																
		1	2	3	4	5	6	7	8	9	10	11	12	A	B	C	D	E	F	G	H	
A	0.00	0.00	0.00	0.00	1.31	1.31	1.59	1.75	1.63	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B	1.60	1.97	1.45	1.32	1.44	1.50	1.50	1.35	1.41	1.25	0.99	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
C	1.50	1.49	1.40	1.38	1.45	1.27	1.20	1.20	1.36	1.70	1.28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
D	1.53	1.39	1.41	1.51	1.50	1.56	1.64	1.64	1.64	1.31	1.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
E	0.89	1.24	1.66	1.46	1.34	1.63	1.76	1.76	1.57	1.58	1.41	1.18	1.72	1.72	1.72	1.72	1.72	1.72	1.72	1.72	1.72	1.72
F	0.00	1.24	1.50	1.54	1.40	1.85	1.69	1.69	1.32	1.63	1.36	1.50	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35
G	0.00	0.00	1.32	1.17	1.50	1.76	1.42	1.42	1.39	1.43	1.24	1.38	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.52	1.52
H	0.00	0.00	0.00	0.00	0.00	1.33	1.27	1.27	1.34	1.35	1.28	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

		INJECTION 4																				
		ENERGY 4				INJECTION 4																
		1	2	3	4	5	6	7	8	9	10	11	12	A	B	C	D	E	F	G	H	
A	0.00	0.00	0.00	0.00	1.22	2.00	2.00	1.77	1.62	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
B	1.66	1.76	1.49	1.62	1.62	1.45	1.21	1.21	1.33	1.25	1.10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
C	1.43	1.44	1.39	1.47	1.62	1.34	1.19	1.19	1.32	3.80	2.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
D	1.55	1.40	1.63	1.62	1.55	1.43	1.75	1.75	0.75	6.95	2.19	1.19	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
E	1.10	1.25	1.72	1.44	1.12	1.01	7.53	7.53	1.62	7.82	2.03	1.19	1.40	1.40	1.40	1.40	1.40	1.40	1.40	1.40	1.40	1.40
F	0.00	1.25	1.70	1.56	0.90	1.78	2.33	2.33	1.74	12.05	1.67	1.47	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25
G	0.00	0.00	1.60	0.85	2.32	1.51	1.75	1.75	1.21	6.26	1.60	1.33	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45	1.45
H	0.00	0.00	0.00	0.00	0.00	0.97	5.44	5.44	4.98	3.64	1.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

FIGURE 4-20

TOTAL ENDOCARDIUM WEIGHT	67.8670 G
TOTAL EPICARDIUM WEIGHT	70.8244 G
TOTAL HEART WEIGHT	138.6916 G

MEAN FLOWS COMPUTED FROM 74 SPECIMEN PAIRS:

ENDOCARDIUM FLOW (ENERGY 1) IS	2.05 ML/G/MIN
ENDOCARDIUM FLOW (ENERGY 2) IS	3.52 ML/G/MIN
ENDOCARDIUM FLOW (ENERGY 3) IS	4.01 ML/G/MIN
ENDOCARDIUM FLOW (ENERGY 4) IS	3.33 ML/G/MIN
EPICARDIUM FLOW (ENERGY 1) IS	1.36 ML/G/MIN
EPICARDIUM FLOW (ENERGY 2) IS	2.32 ML/G/MIN
EPICARDIUM FLOW (ENERGY 3) IS	2.82 ML/G/MIN
EPICARDIUM FLOW (ENERGY 4) IS	2.18 ML/G/MIN

CONTRIBUTION FACTORS FOR STANDARD 1

1.0000	0.0092	0.0019	0.0019
--------	--------	--------	--------

CONTRIBUTION FACTORS FOR STANDARD 2

0.3744	1.0000	0.0530	0.0010
--------	--------	--------	--------

CONTRIBUTION FACTORS FOR STANDARD 3

0.4961	0.2031	1.0000	0.0003
--------	--------	--------	--------

CONTRIBUTION FACTORS FOR STANDARD 4

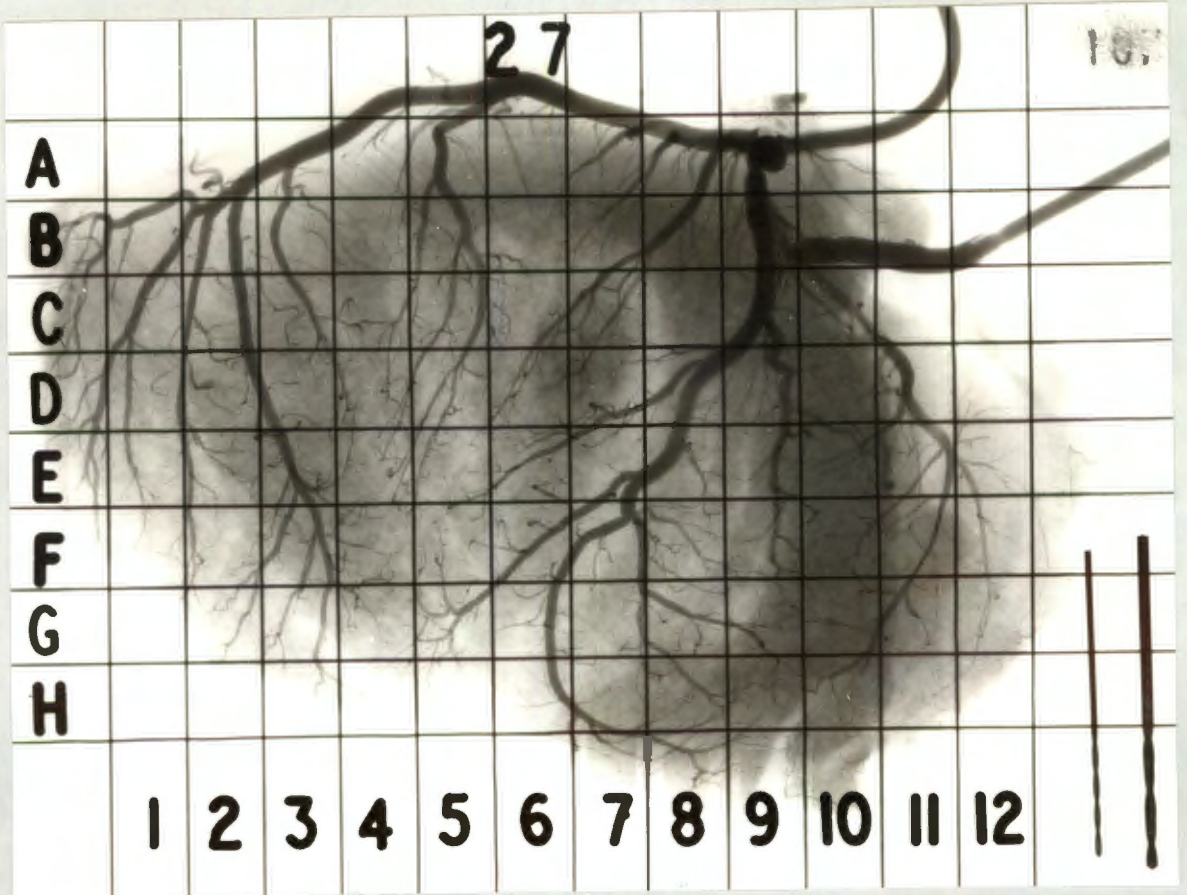
0.4039	0.5030	0.6389	1.0000
--------	--------	--------	--------

R.B.F.FACTOR FOR ENERGY 1: 0.136082E-03

R.B.F.FACTOR FOR ENERGY 2: 0.226810E-03

R.B.F.FACTOR FOR ENERGY 3: 0.174509E-03

R.B.F.FACTOR FOR ENERGY 4: 0.603847E-03



DOG 27 **45% STENOSIS** **NOT VASODILATED**
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 6.16

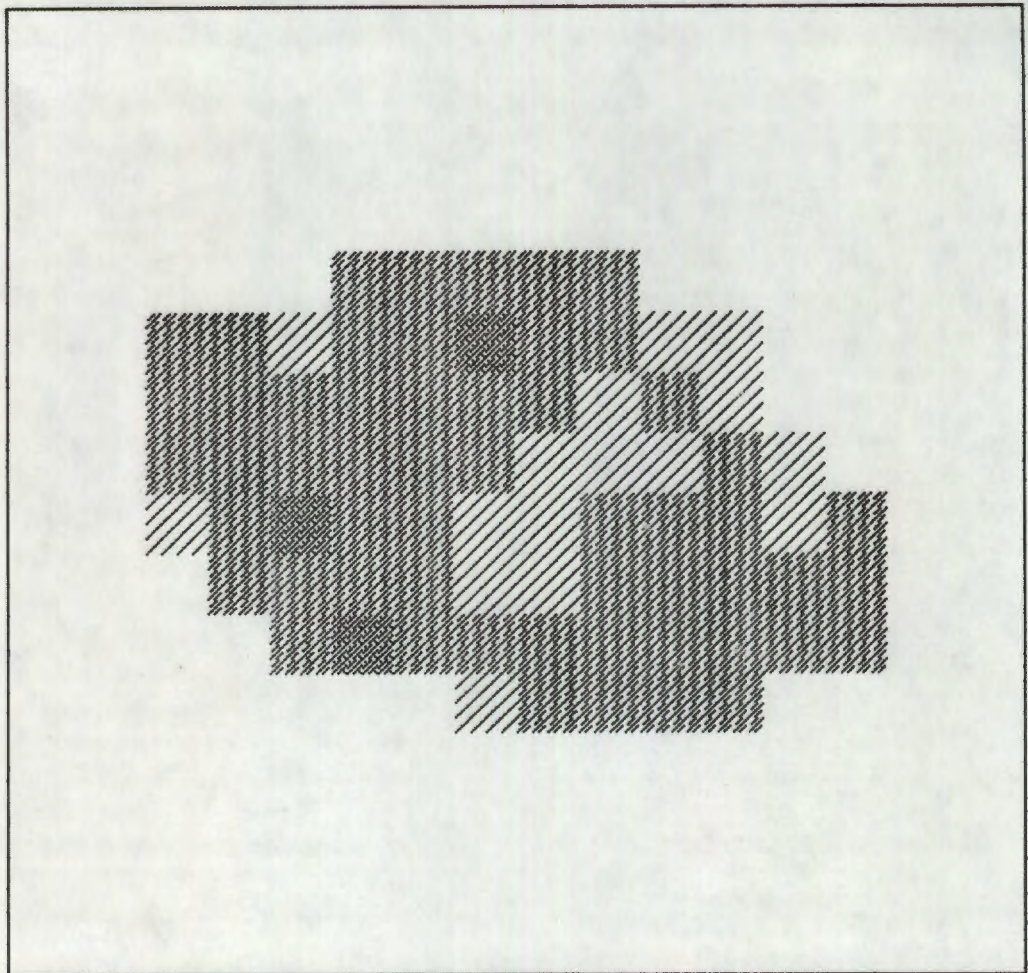
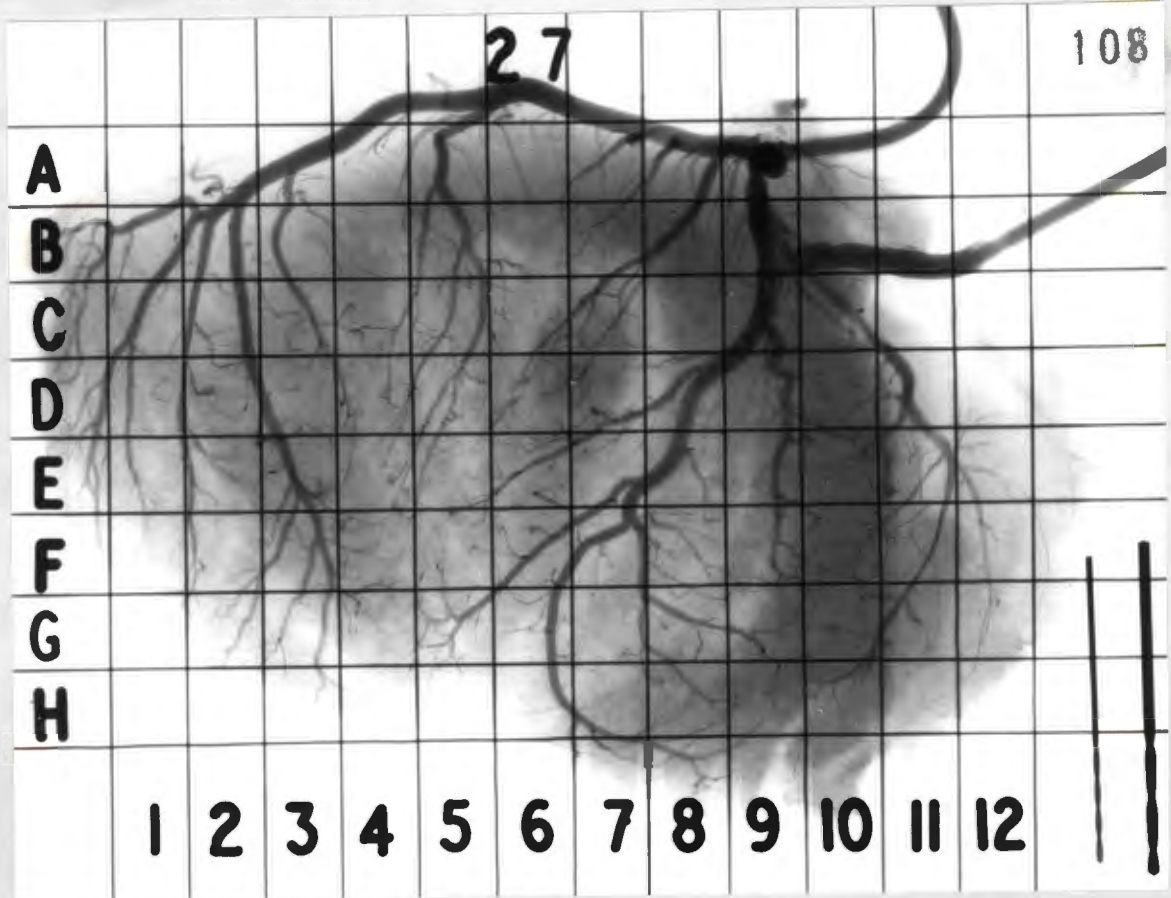


FIGURE 4-22



45% STENOSIS NOT VASODILATED
 EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 6.16

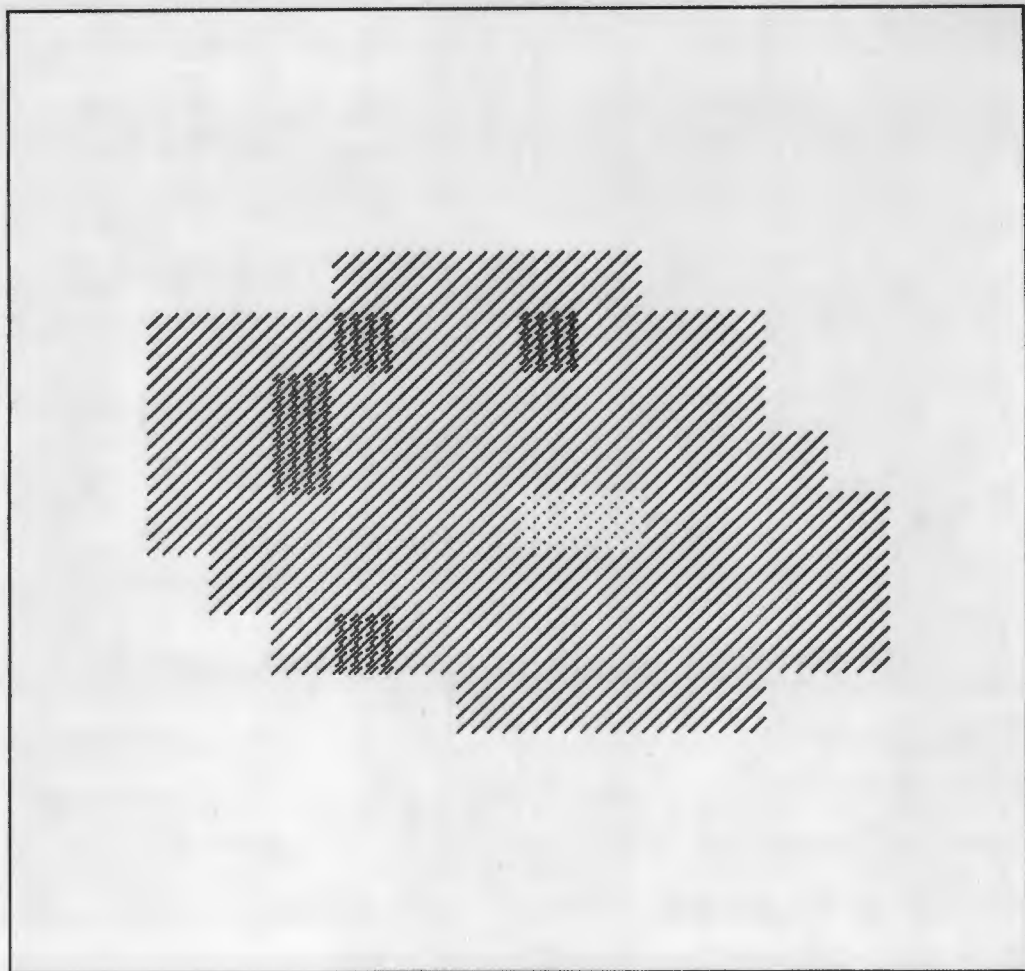
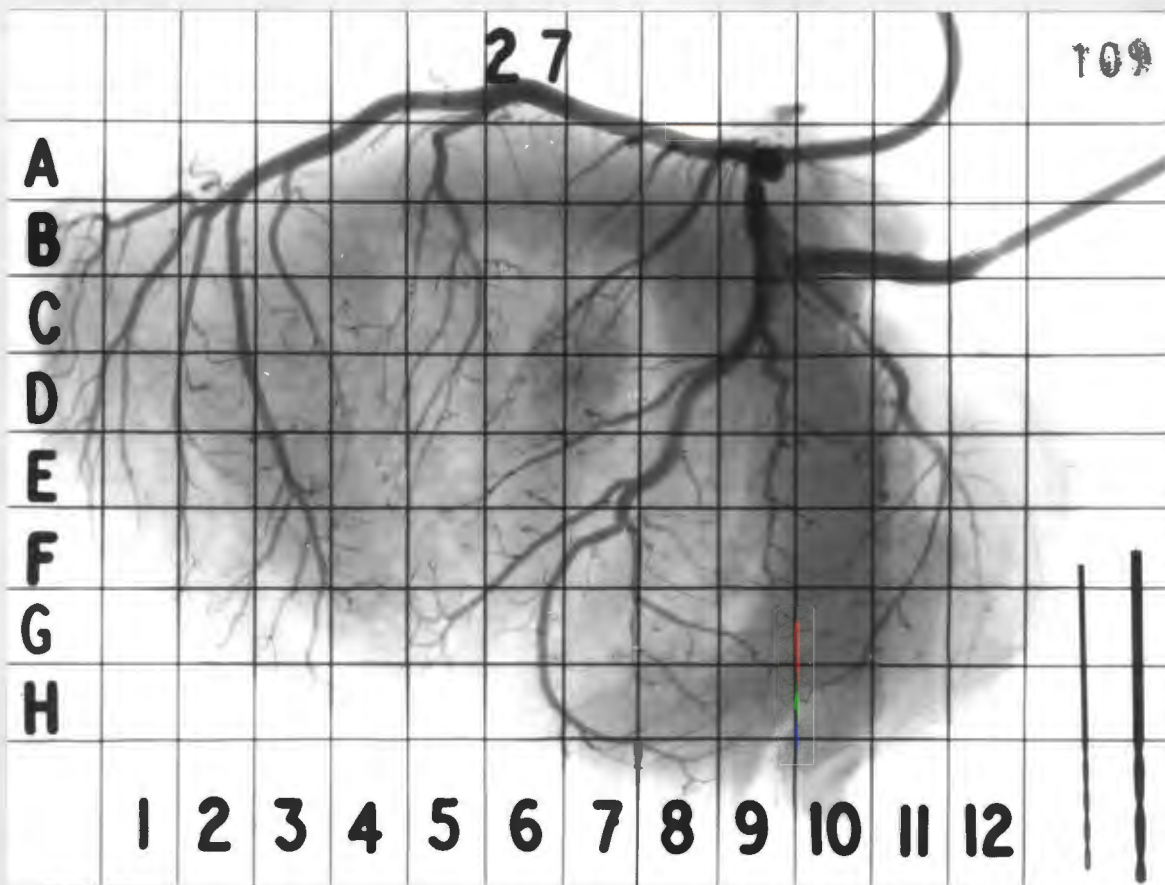


FIGURE 4-23



45% STENOSIS

VASODILATED

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 6.16

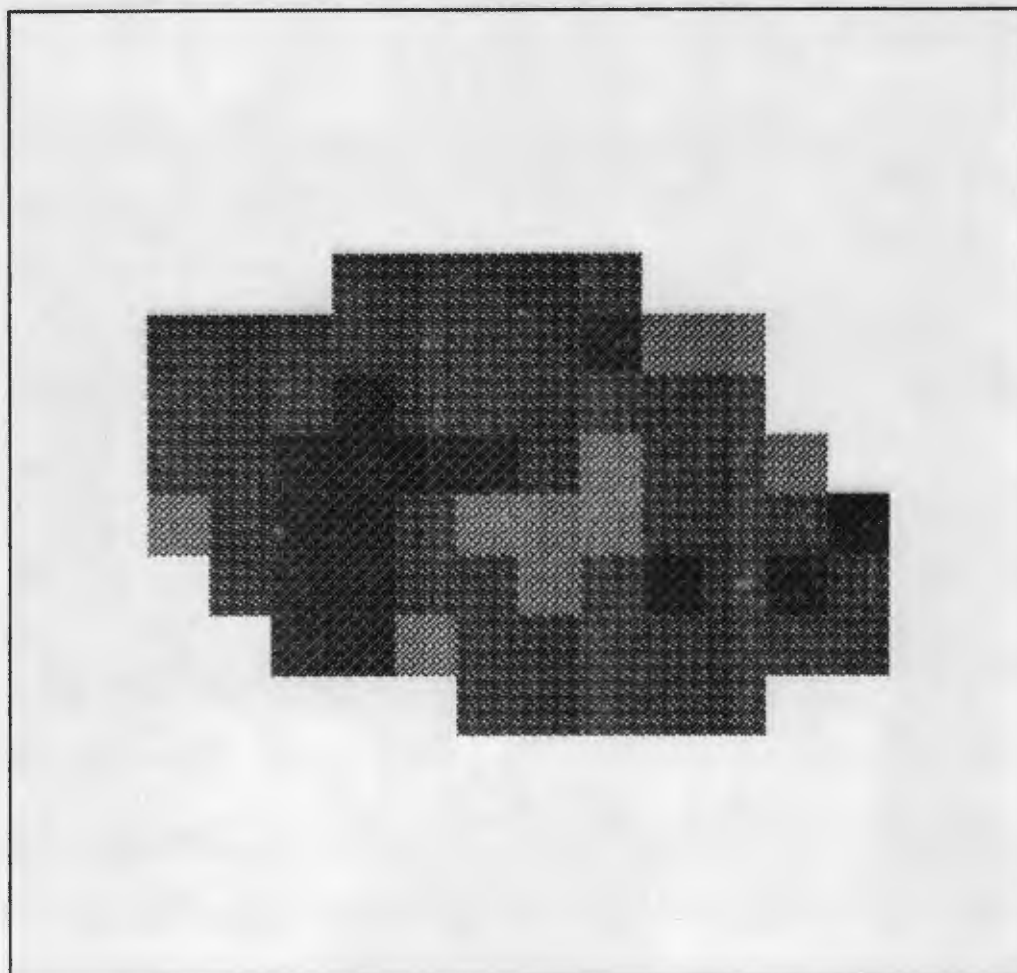
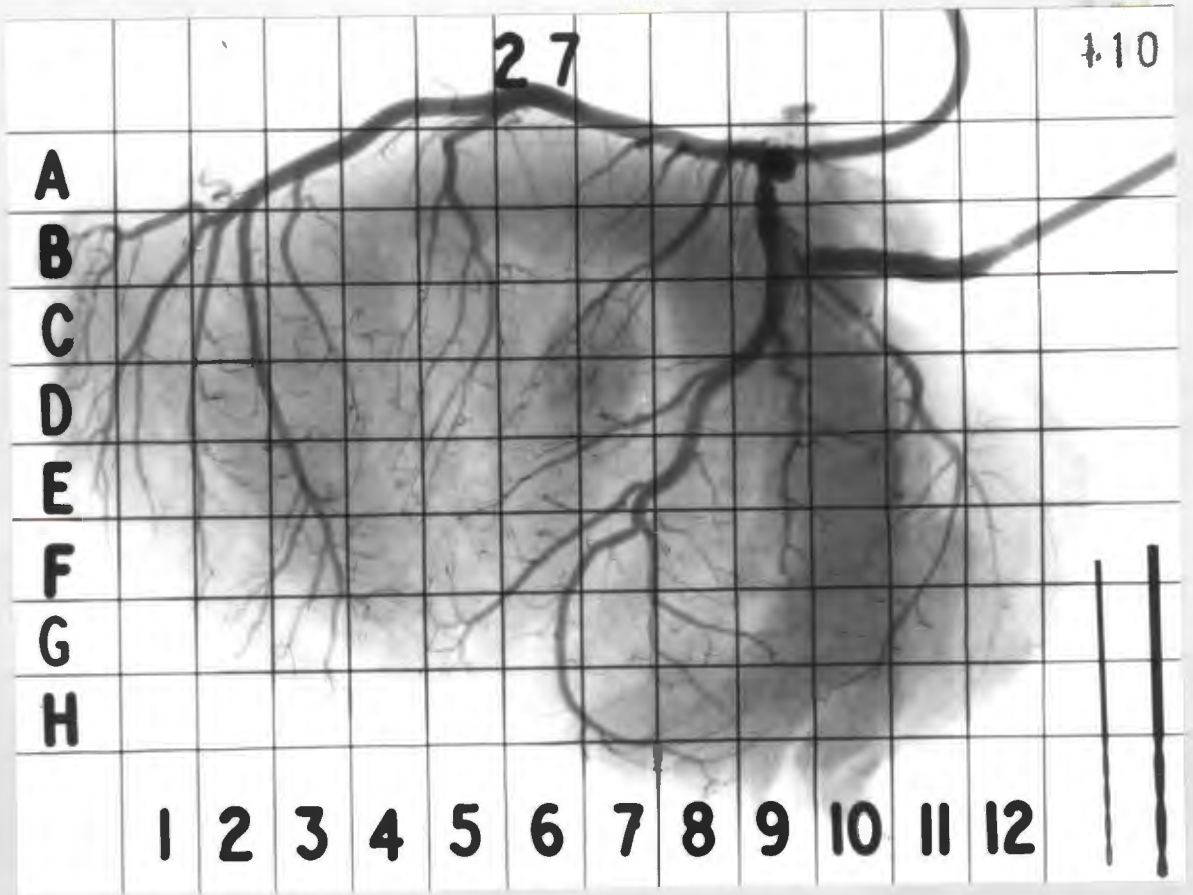


FIGURE 4-24



45% STENOSIS **VASODILATED**
 EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 6.16

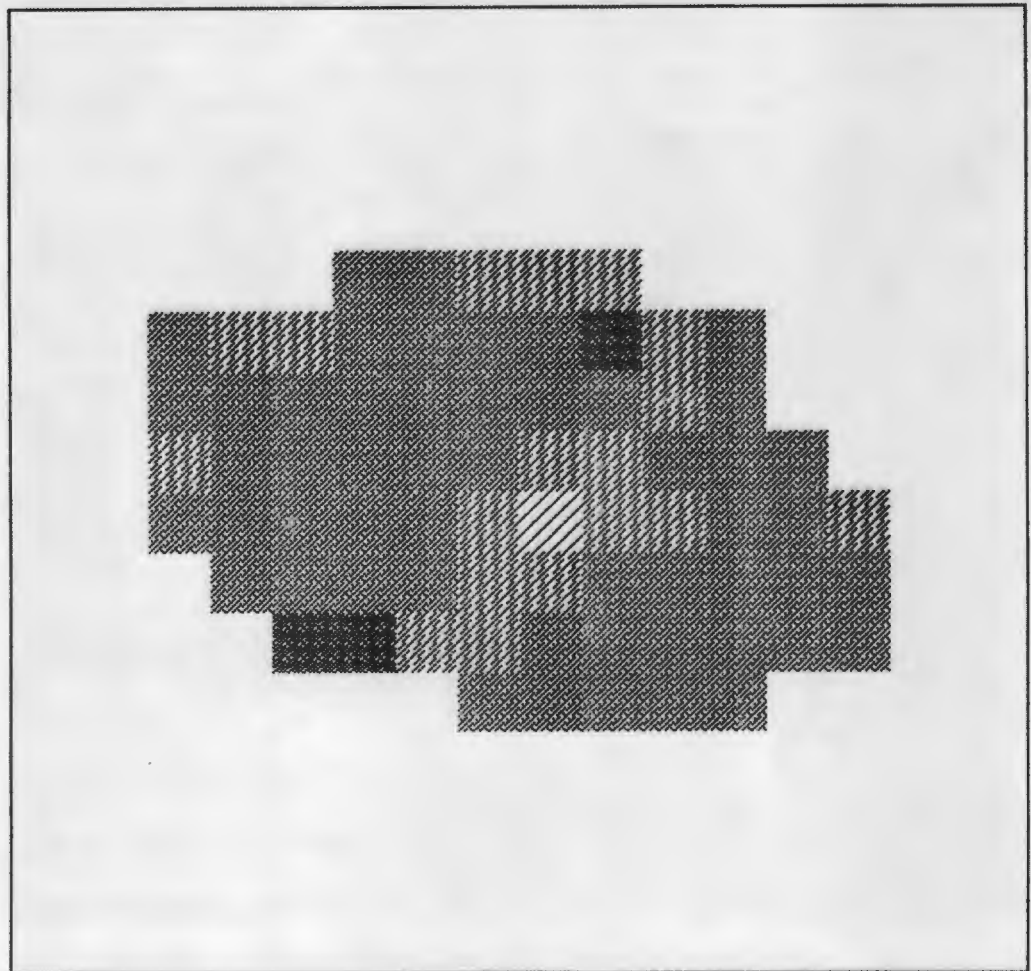
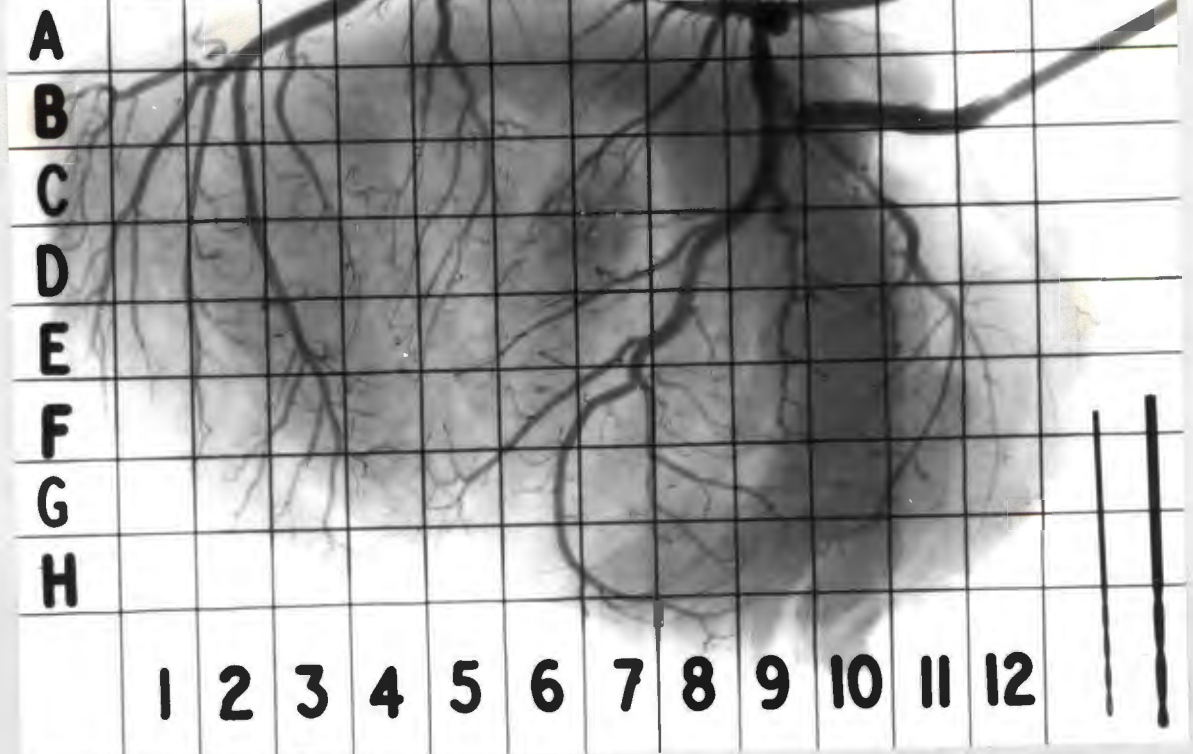


FIGURE 4-25

27

f11



70% STENOSIS

VASODILATED

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 6.16

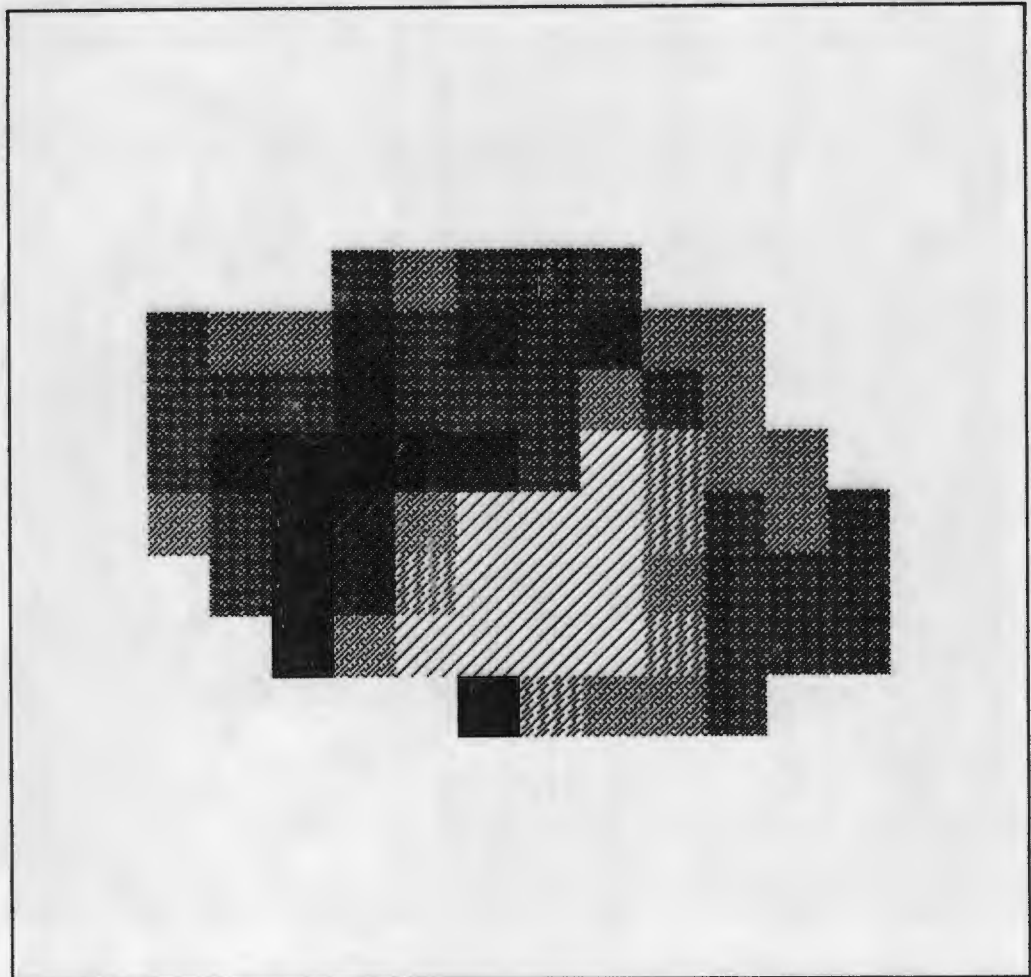
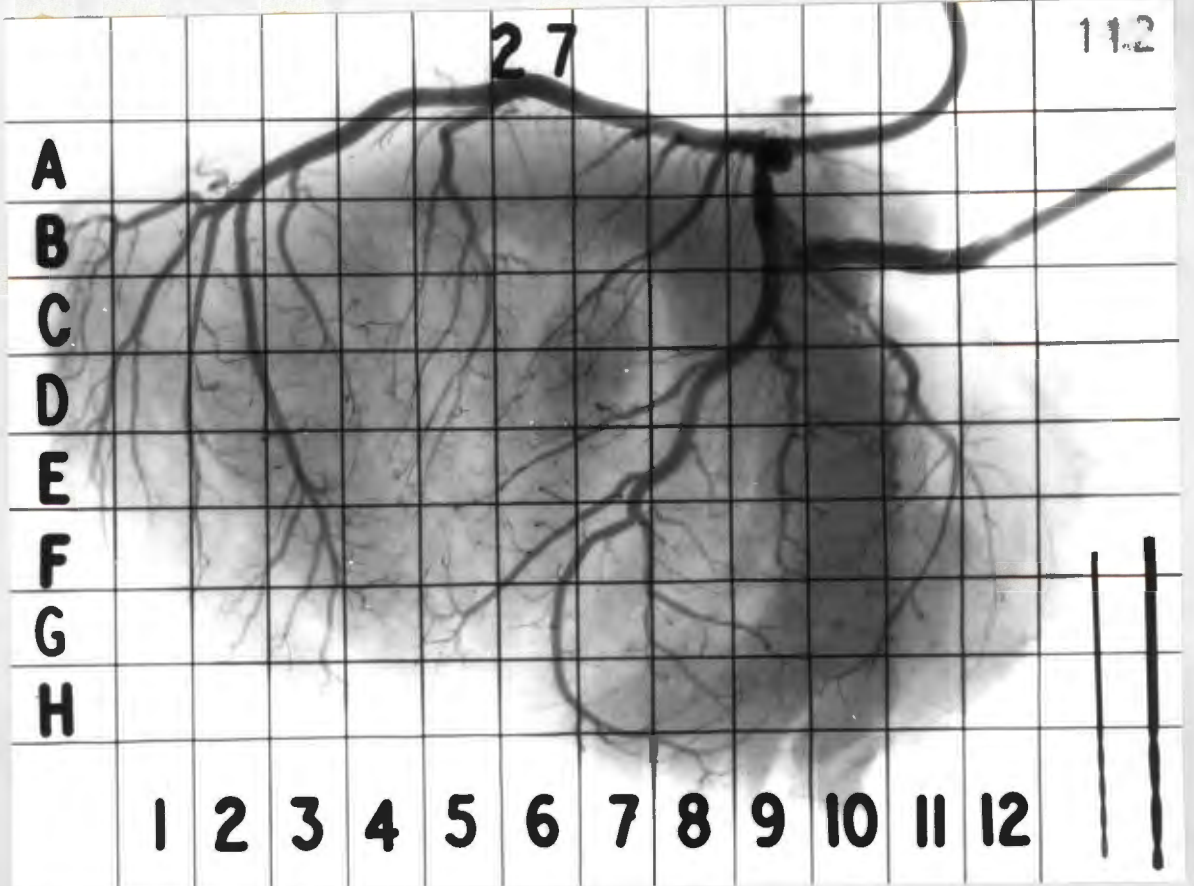


FIGURE 4 - 26



70% STENOSIS **VASODILATED**
EPICARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 6.16

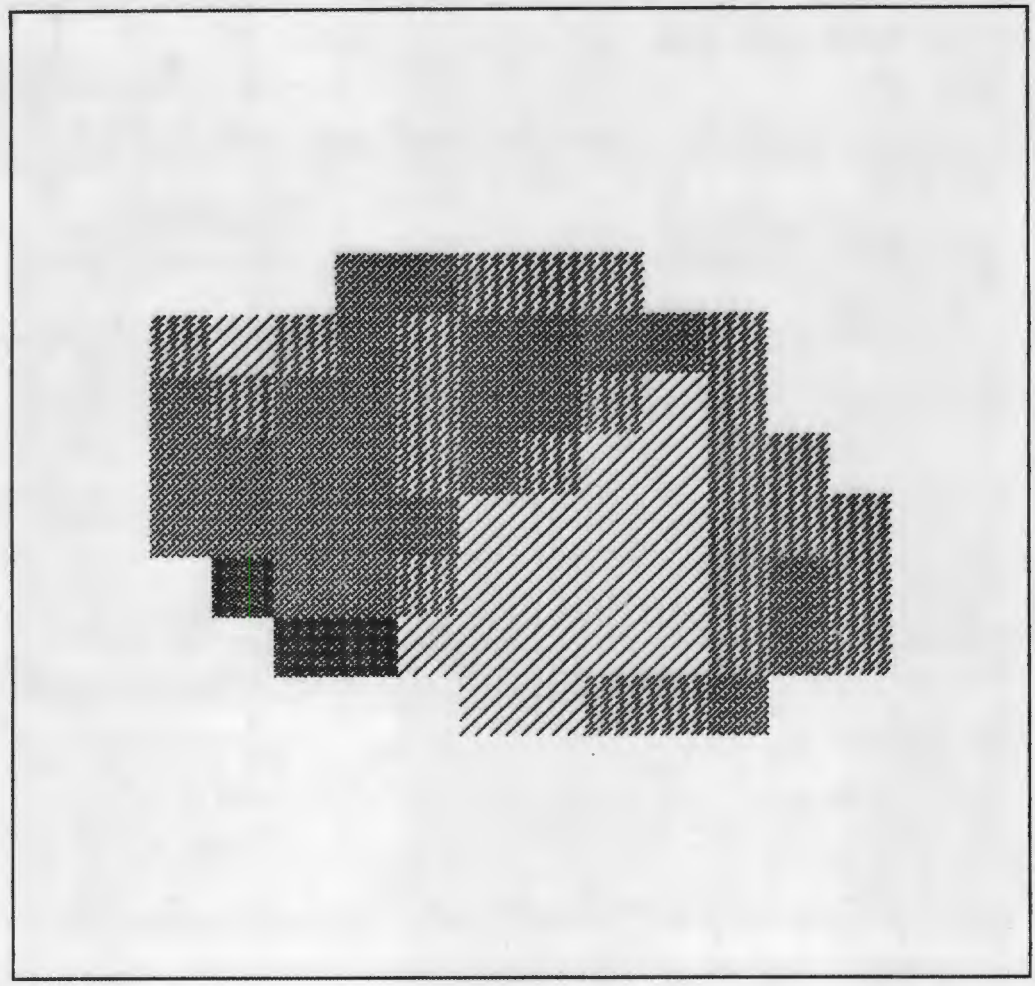
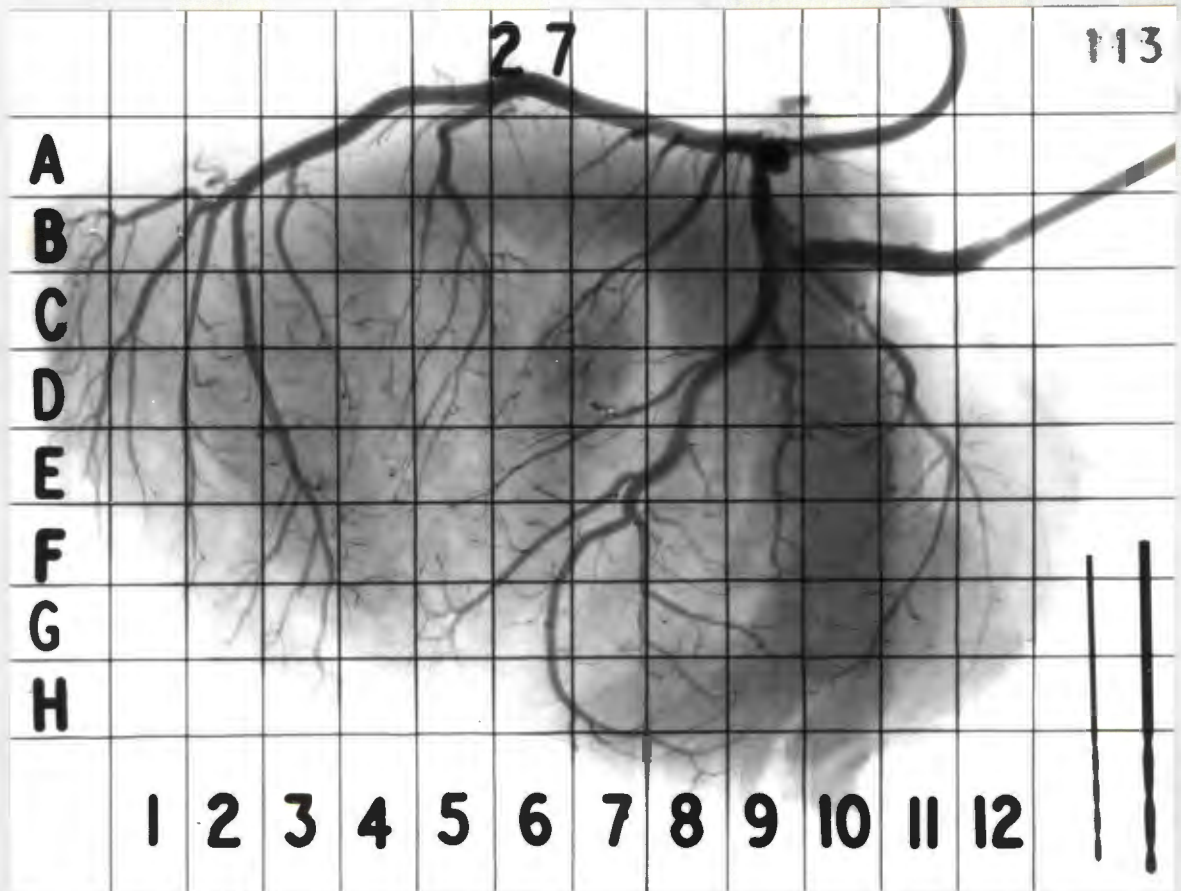


FIGURE 4-27



DOG 27 TOTAL OCCLUSION VASODILATED
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4. SCALED TO 6.16

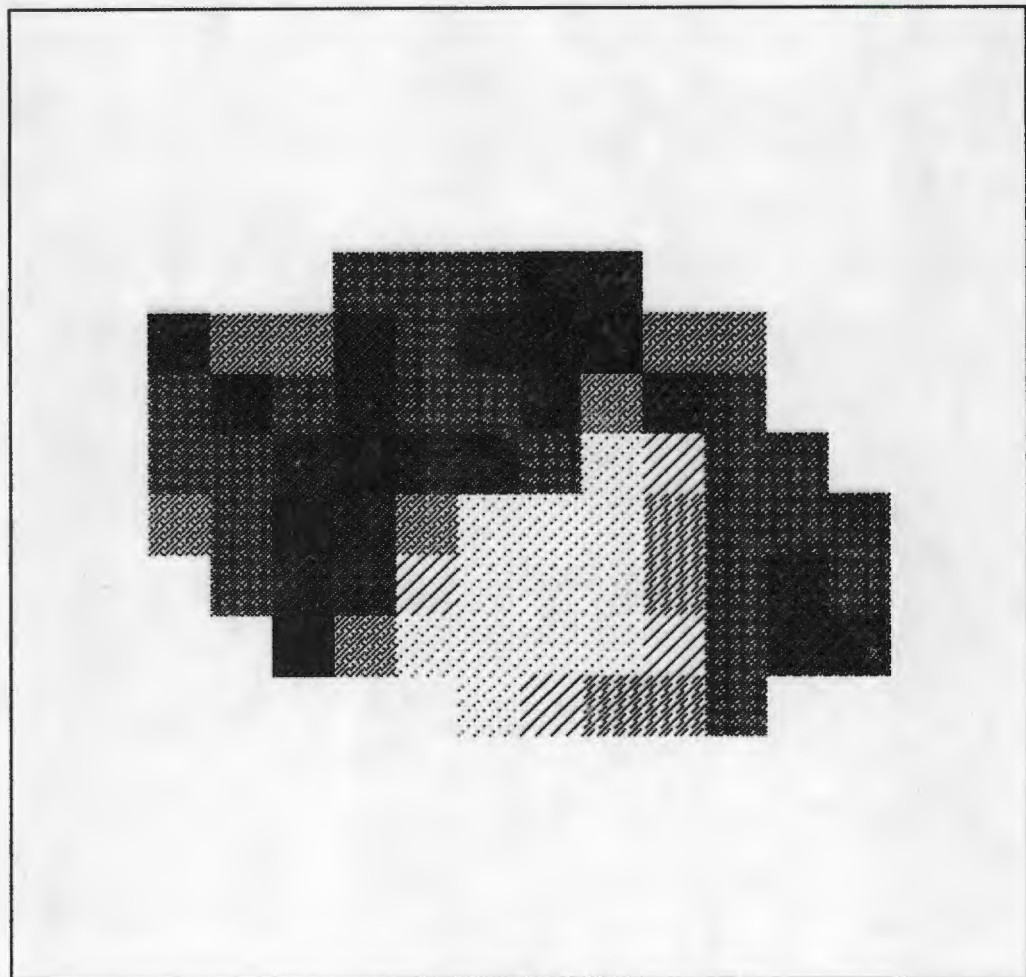
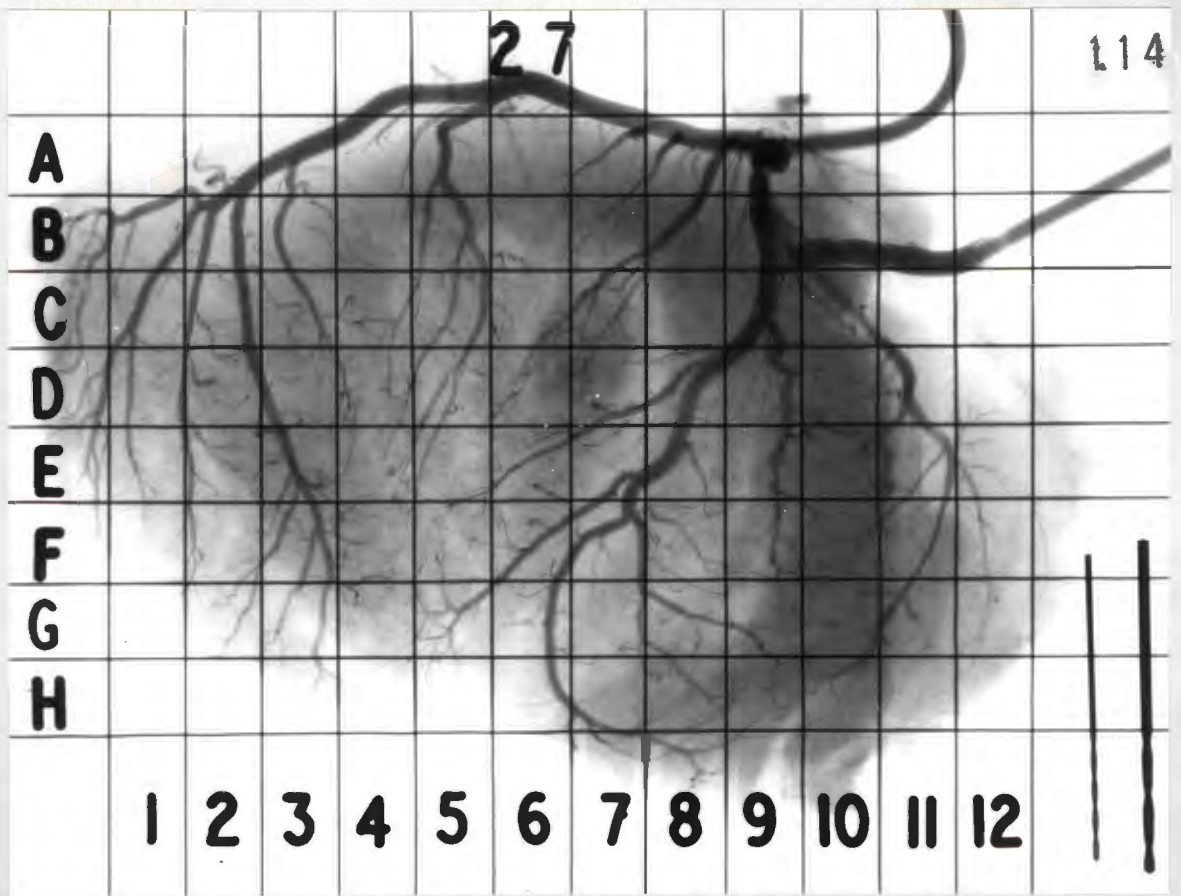


FIGURE 4-28



TOTAL OCCLUSION **VASODILATED**
 EPICARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 6.16

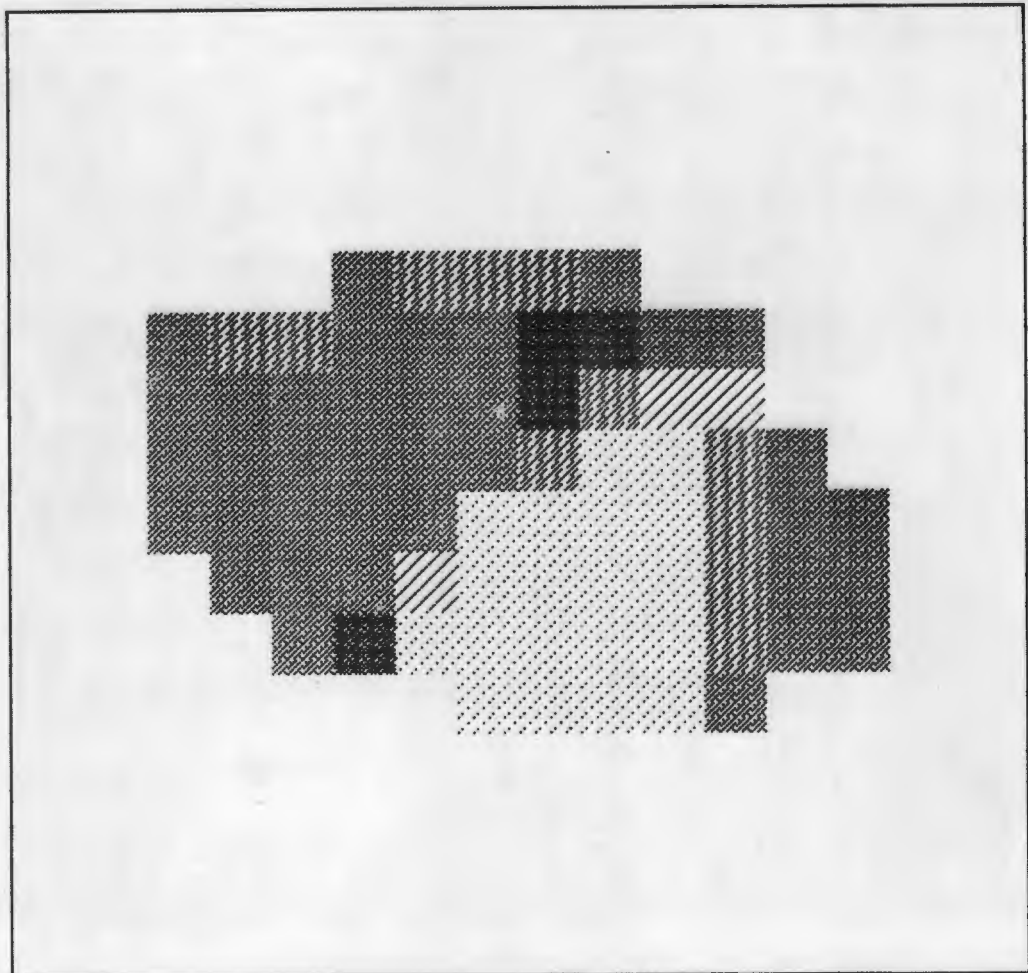


FIGURE 4-29

EXPERIMENT 27

MYOCARDIAL BLOOD FLOW

ENDOCARDIAL HALF

(ml/Gm/min)

	45% L.A.D. stenosis		No vasodilatation	
	Control	n = 25	Test	n = 15
Mean	2.23		1.76	
S.D.	0.34		0.22	
S.E.M.	0.07		0.06	
<hr/>				
	45% L.A.D. stenosis		Coronary vasodilatation	
	Control		Test	
Mean	4.22		3.54	
S.D.	0.48		0.35	
S.E.M.	0.10		0.09	
<hr/>				
	70% L.A.D. stenosis		Coronary vasodilatation	
	Control		Test	
Mean	4.33		1.93	
S.D.	0.83		1.11	
S.E.M.	0.17		0.29	
<hr/>				
	Total L.A.D. occlusion		Coronary vasodilatation	
	Control		Test	
Mean	4.43		0.50	
S.D.	0.60		0.57	
S.E.M.	0.12		0.15	

L.A.D. : Left anterior descending artery
 S.D. : Standard deviation
 S.E.M. : Standard Error of the Mean

Figure 4.30

EXPERIMENT 27

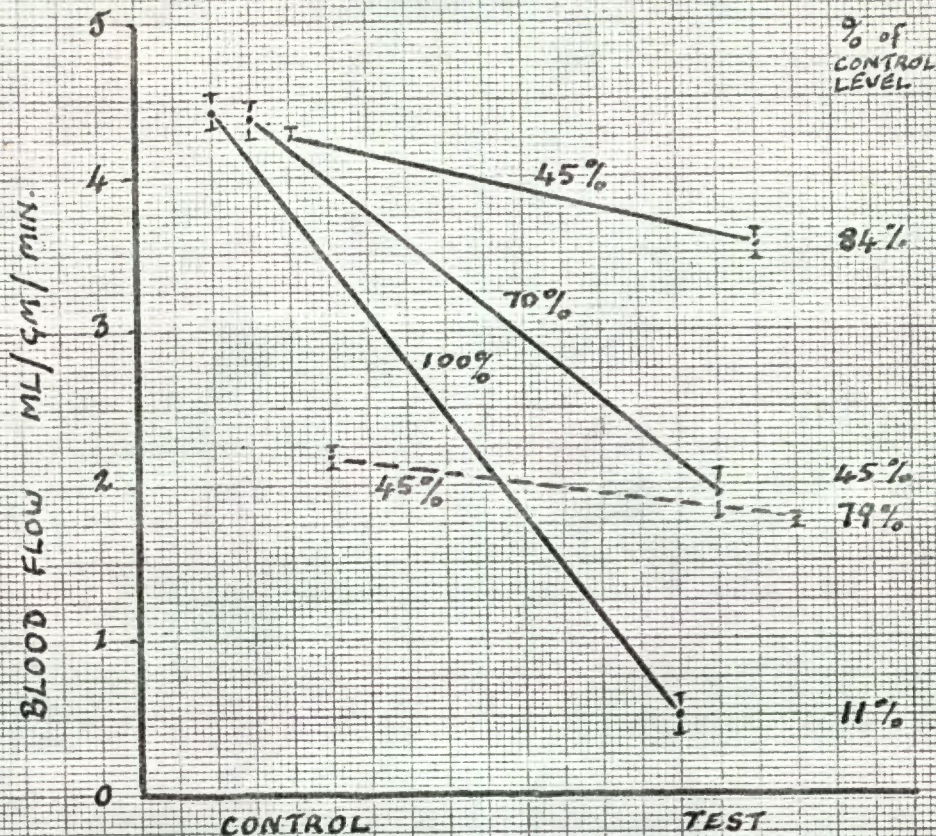
MYOCARDIAL BLOOD FLOW

EPICARDIAL HALF

(ml/Gm/min)

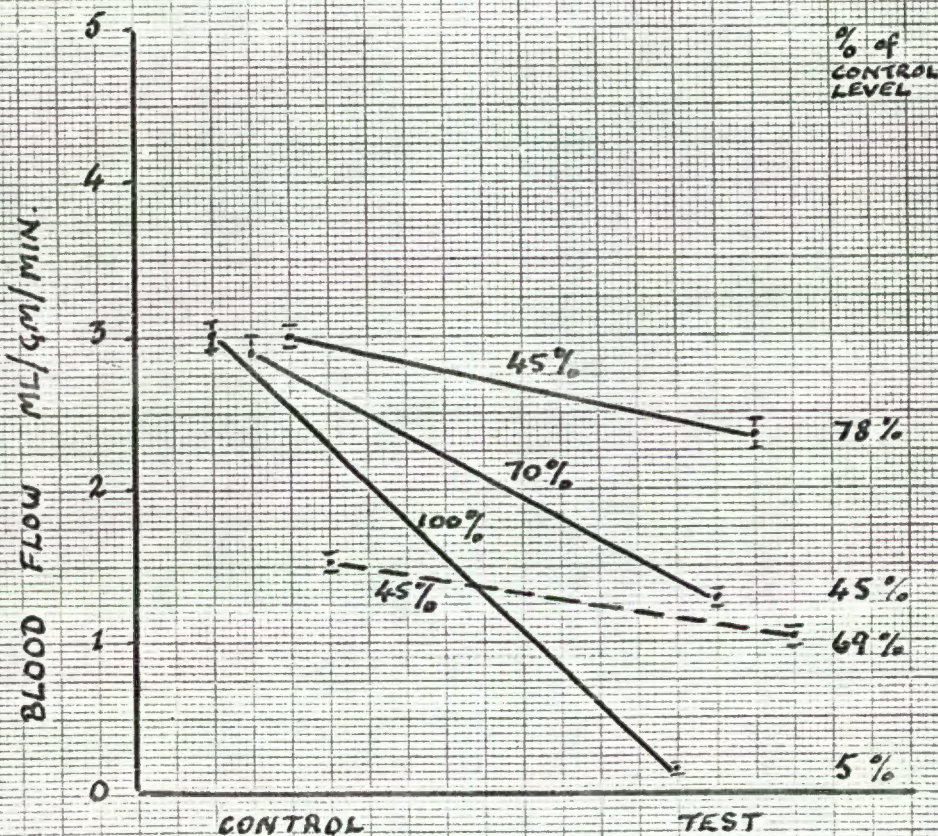
	L.A.D. stenosis	No vasodilatation
45%	Control n = 25	Test n = 15
Mean	1.55	1.07
S.D.	0.22	1.16
S.E.M.	0.04	0.04
45%	L.A.D. stenosis	Coronary vasodilatation
	Control	Test
Mean	3.00	2.35
S.D.	0.35	0.42
S.E.M.	0.07	0.11
79%	L.A.D. stenosis	Coronary vasodilatation
	Control	Test
Mean	2.87	1.28
S.D.	0.49	0.19
S.E.M.	0.10	0.05
Total	L.A.D. stenosis	Coronary vasodilatation
	Control	Test
Mean	3.02	0.16
S.D.	0.43	0.08
S.E.M.	0.09	0.02

Figure 4.31



MEAN FLOW FOR SUB-ENDOCARDIAL MUSCLE
(± STANDARD ERROR OF MEAN)

EXPERIMENT 27



MEAN FLOW FOR SUB-EPICARDIAL MUSCLE
(± STANDARD ERROR OF MEAN)

FIGURE 4-32

VALIDATION OF TECHNIQUE

Although the use of the tracer microsphere technique as described here has been documented by many workers (Domenech et al 1969, Hottenrott et al 1974, Kleinman and Wechsler 1978) it seemed desirable to confirm the accuracy of the technique in the model in the Edinburgh laboratory.

The following assessments were made:-

- 1) Coronary sinus blood was collected during the injection of the tracer microspheres into the arterial line for the duration of the withdrawal period in 4 dogs - both with and without coronary vasodilatation in order to assess whether any microspheres were passing through the coronary bed. In each case no detectable radioactivity was present in coronary sinus blood, confirming complete trapping of the microspheres in their passage through the coronary tree (Buckberg 1971).
- 2) The withdrawal line was coiled and placed in front of a scintillation counter during withdrawal of blood during the transit of the microspheres in 4 dogs. This confirmed clearly that most of the radioactivity had passed by 45 seconds, and all had passed by 90 seconds - well within the withdrawal period used in the experiments.
- 3) In one dog a total occlusion of the circumflex artery was produced and a perfusion map was produced - this is shown in Figure 4-33. This occlusion was then released and the anterior descending artery was occluded - the perfusion map produced under these circumstances is shown in Figure 4-34. Finally the anterior descending artery occlusion was released and a third perfusion map was produced and is shown in Figure 4-35. It can be seen that the perfusion deficits match the anatomically jeopardised areas accurately, and the uniform

- perfusion in Figure 4-35 corresponds to a normal coronary tree.
- 4) Using the method of Sestier et al (1975) a simultaneous injection of four differently labelled tracer microspheres was given to four dogs with ligation of either the anterior descending or circumflex arteries. The resultant perfusion maps for each individual isotope should of course be identical. An example of one such dog with an occluded anterior descending artery is shown in Figures 4-36, 4-37, 4-38 and 4-39. It can be seen that there is remarkable similarity in the perfusion maps for each isotope, and the calculated flow rates to the anterior descending territory and circumflex territory was not significantly different for any isotope.

PROGRAM: DJW (REV F)

DOG 32
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.50

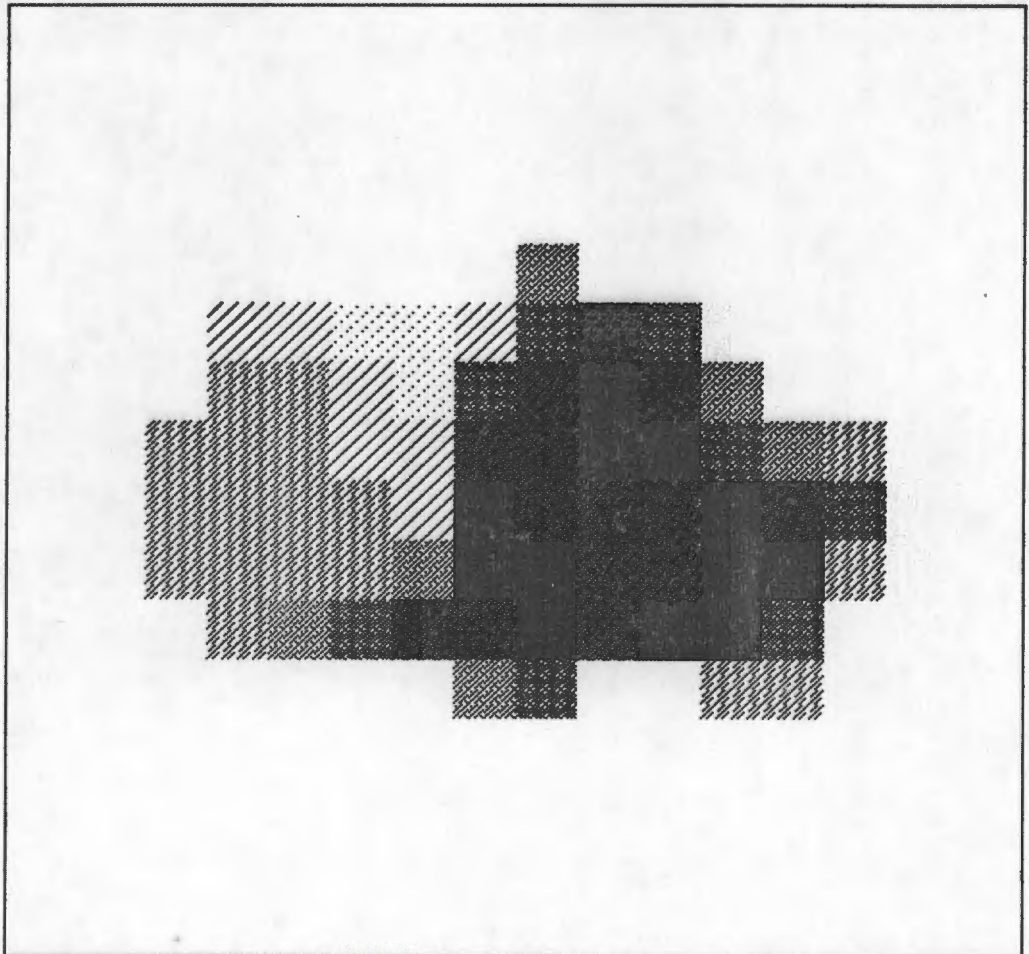


Figure 4-33.

PROGRAM: DJW (REV F)

DOG 32
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 2.50

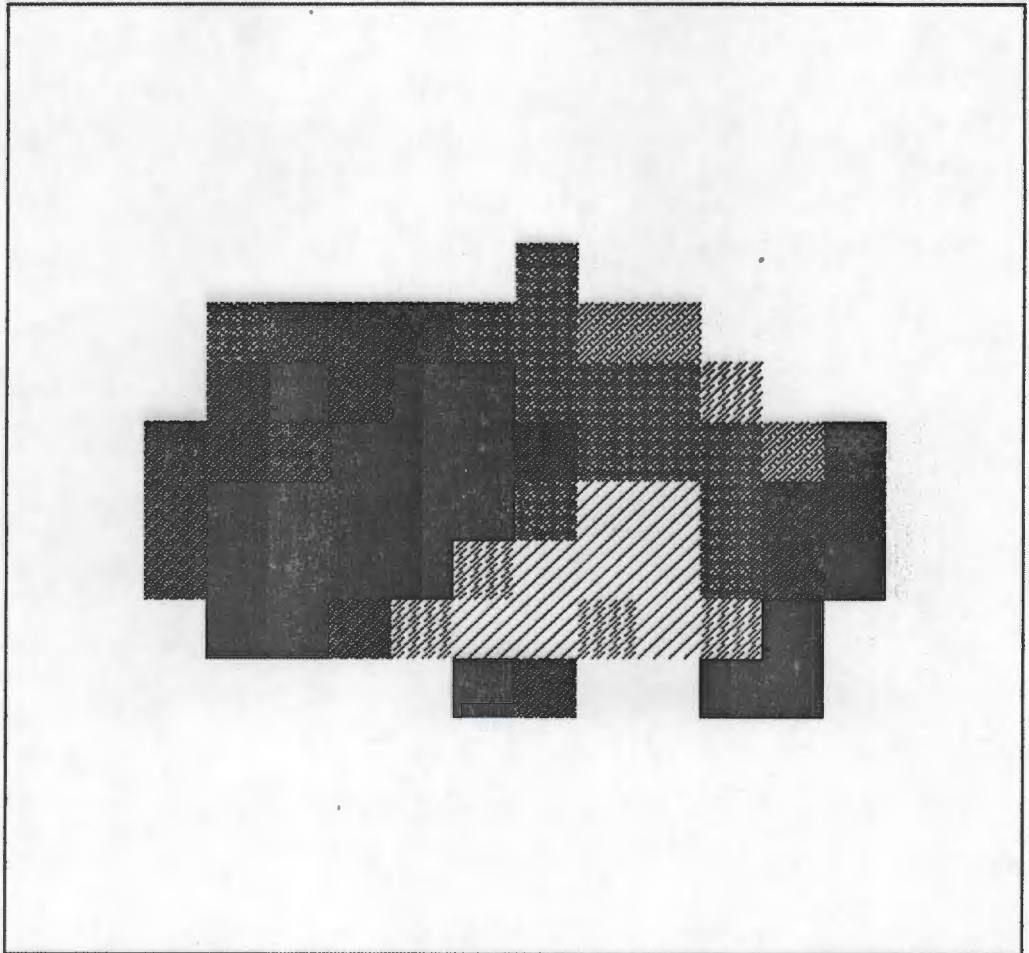


Figure 4-34

PROGRAM: DJW (REV F)

DOG 32
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4. SCALED TO 2.50

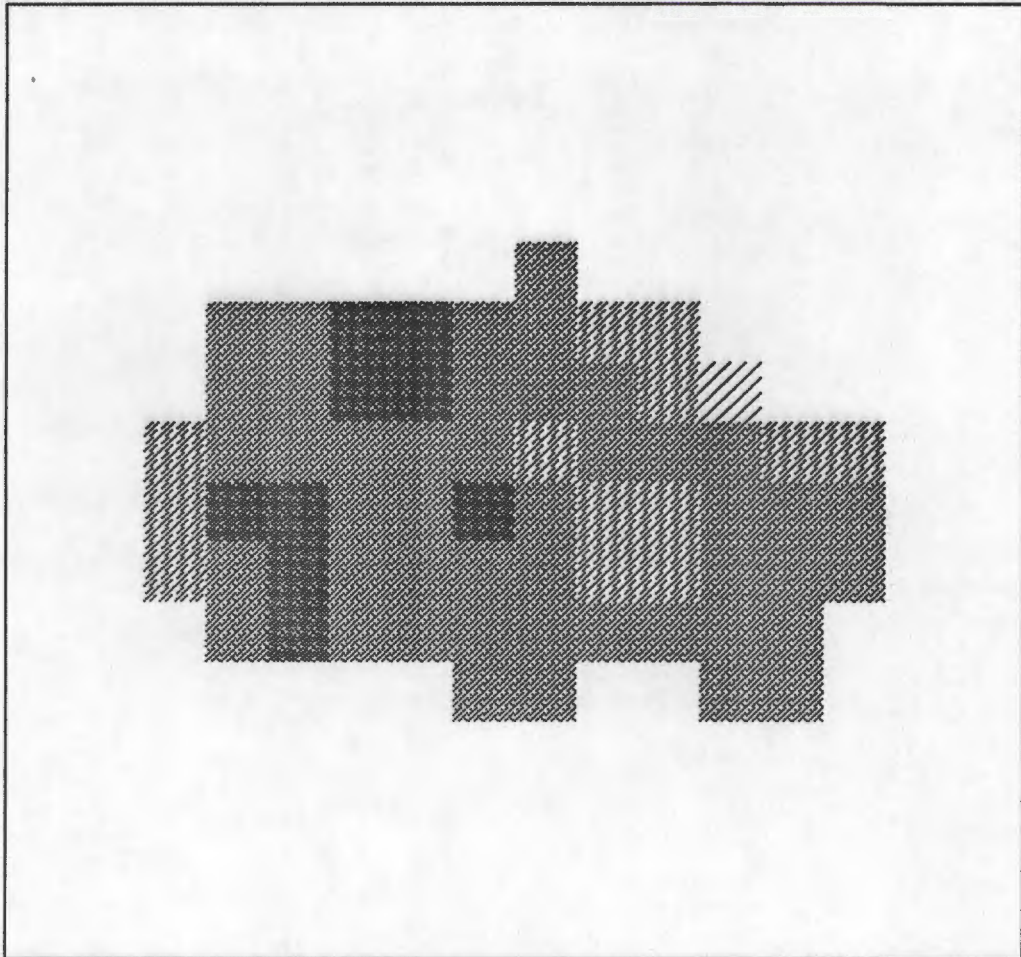


Figure 4-35

PROGRAM: DJW (REV F)

DOG 51
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1. SCALED TO 2.30

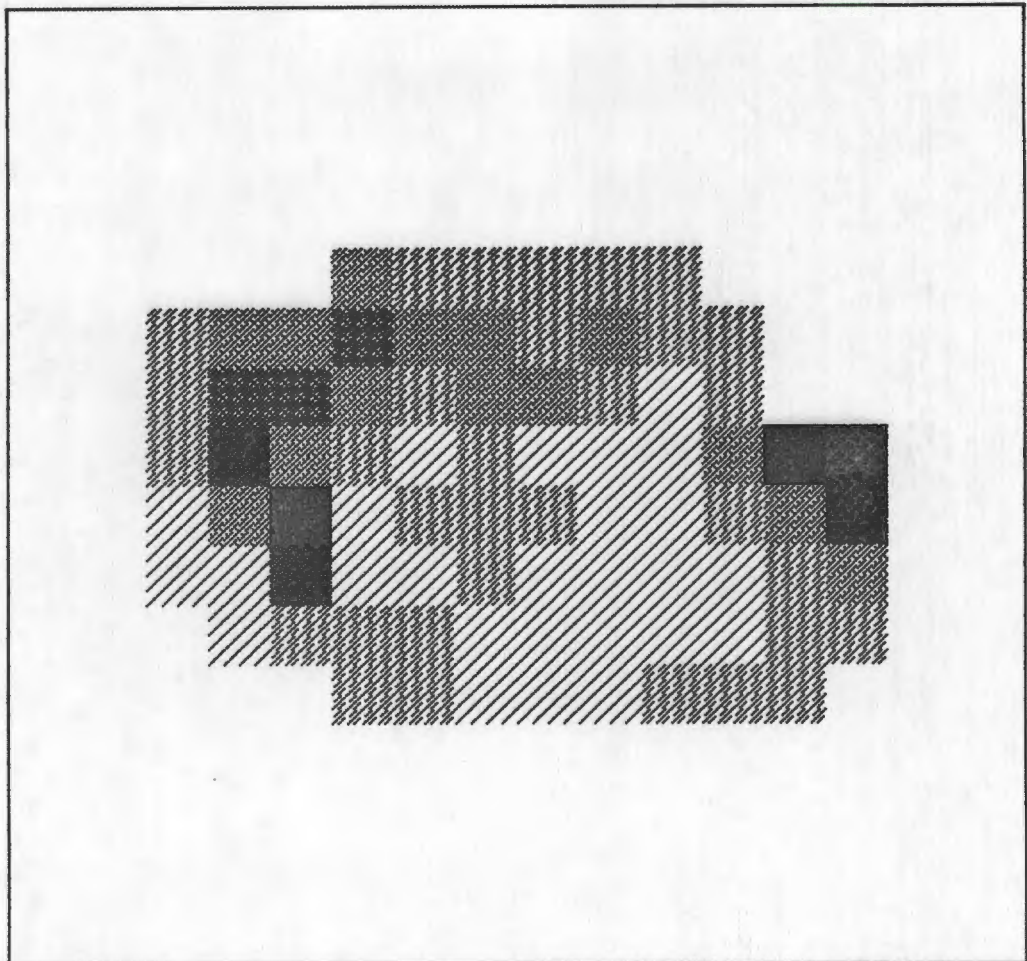


Figure 4-36

PROGRAM: DJW (REV F)

DOG 51
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 2.30

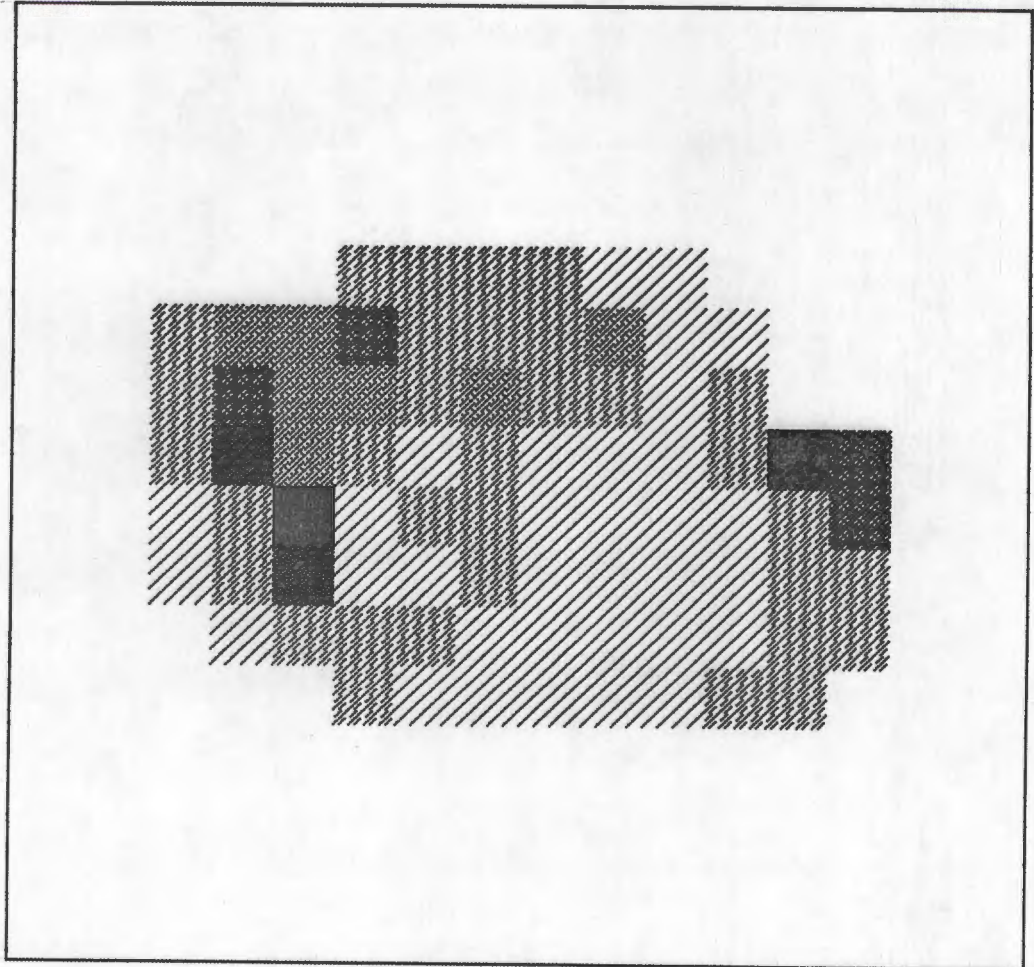


Figure 4-37

PROGRAM: DJW (REV F)

DOG 51
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3. SCALED TO 2.30

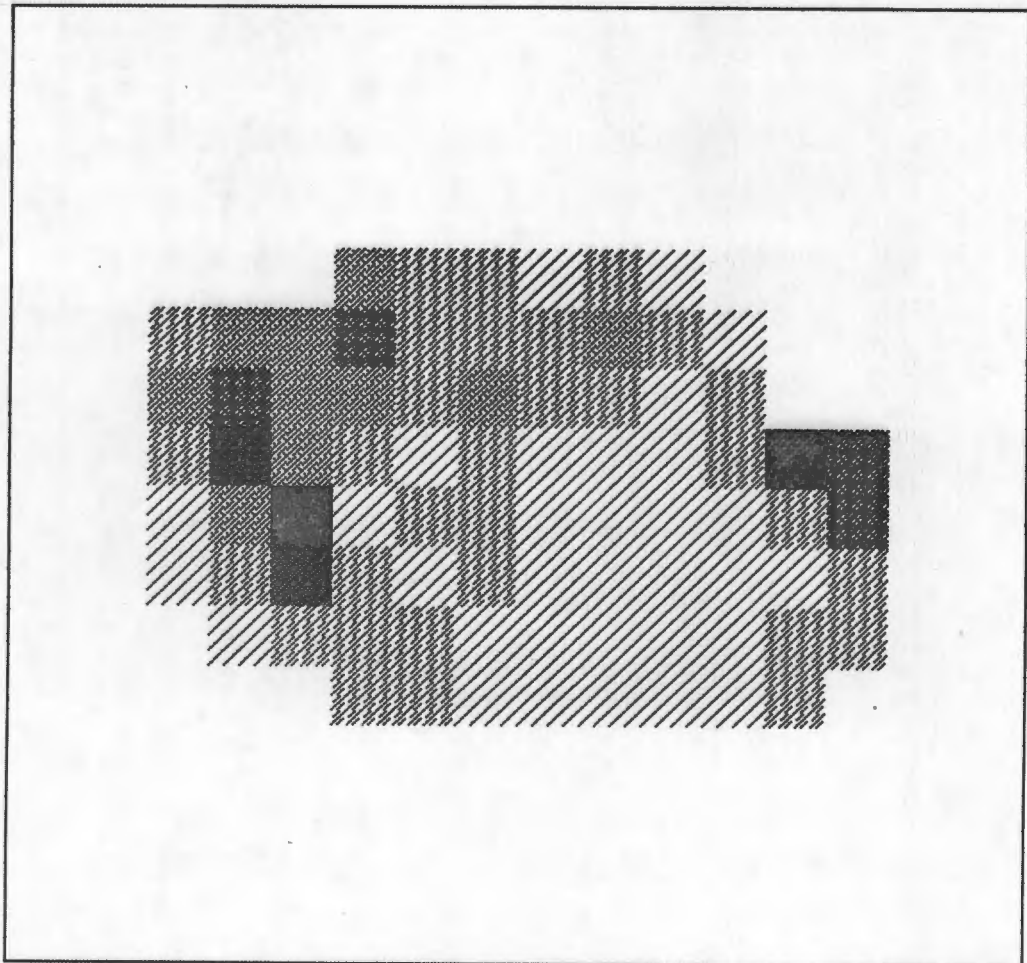


Figure 4-38

PROGRAM: DJW (REV F)

DOG 51
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4. SCALED TO 2.30

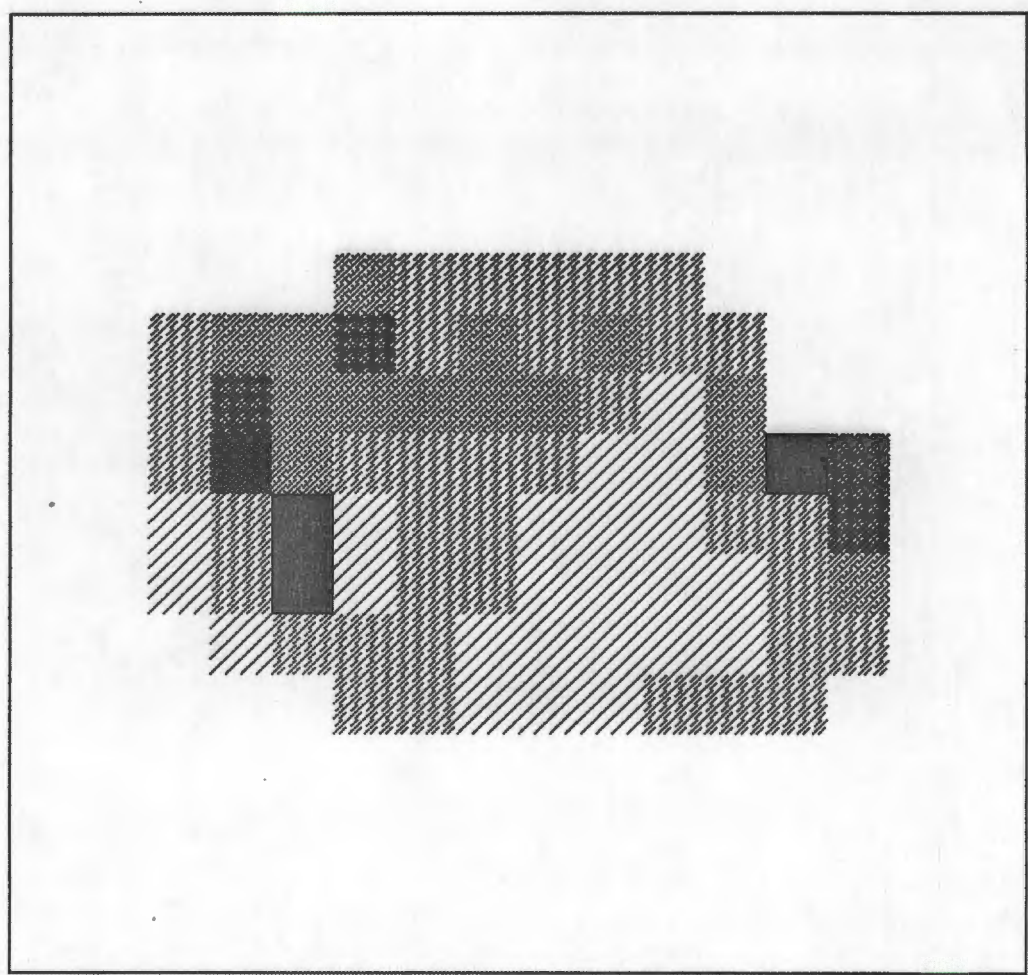
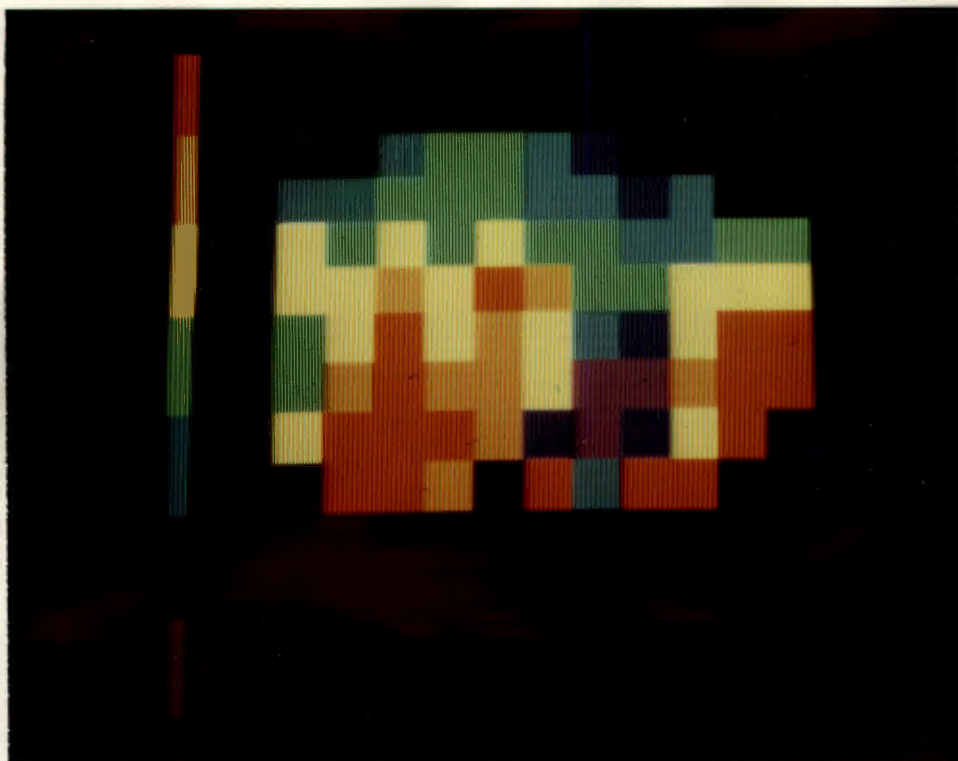
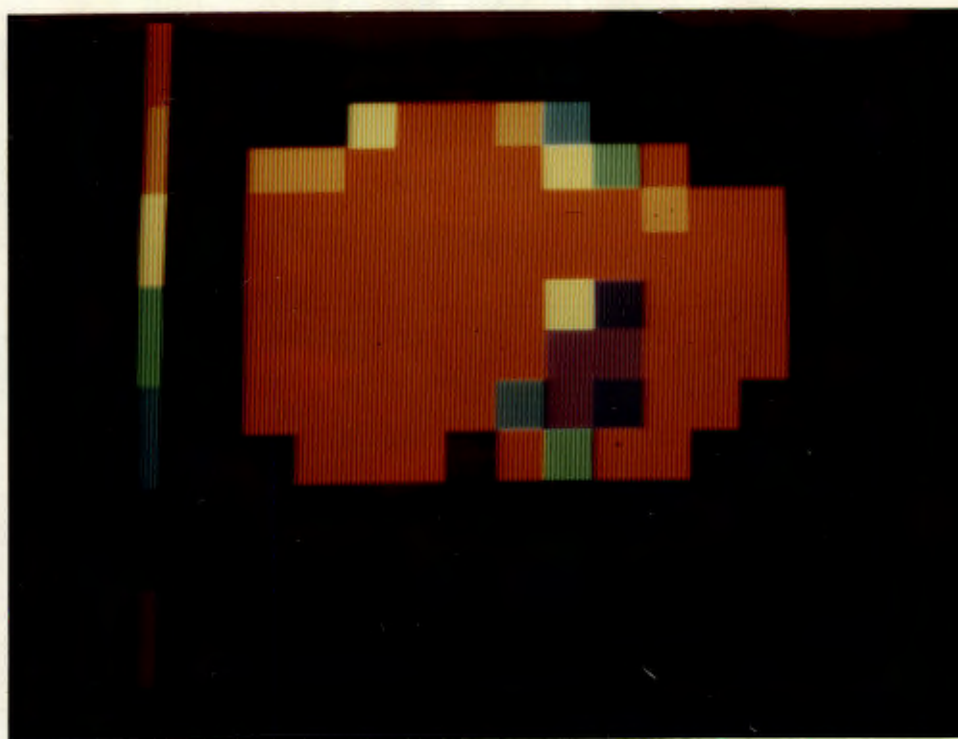


Figure 4-39

COLOUR TELEVISION DISPLAY
OF MYOCARDIAL PERFUSION MAPS

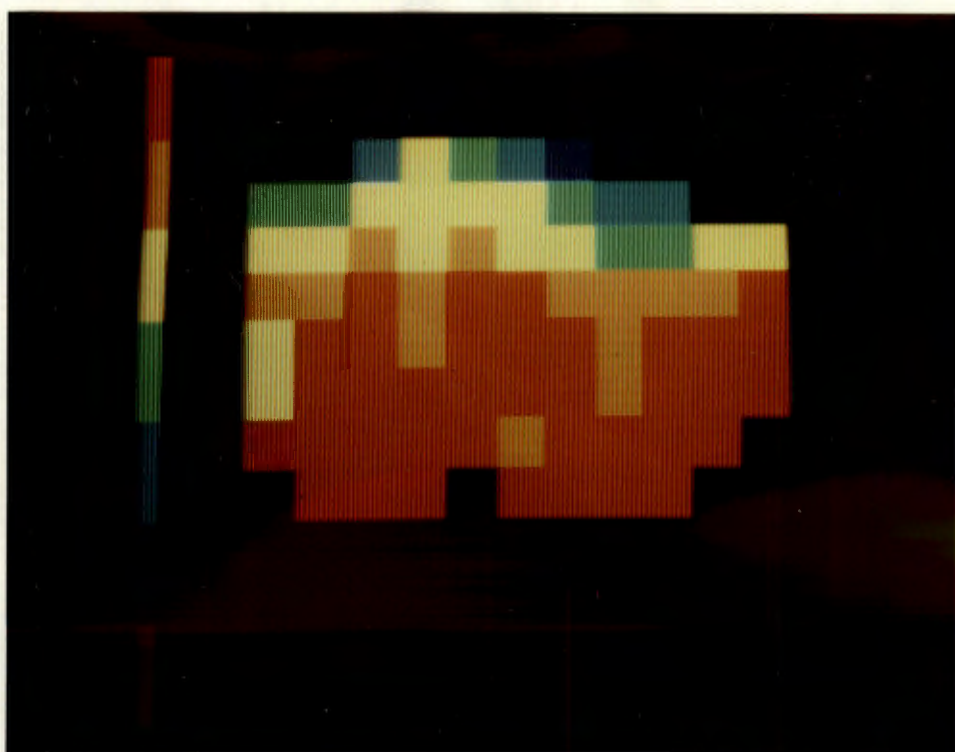


Dog 11 75% stenosis of anterior descending artery
"Resting" vasomotor tone



Dog 11 Same stenosis, but with coronary vasodilatation

COLOUR TELEVISION DISPLAY
OF MYOCARDIAL PERFUSION MAPS



Dog 11 The effect of opening an aorto-coronary
bypass graft.

See figures 5b - 1
 5b - 4
 5b - 5
 and
 5h - 1

for coronary arteriogram of Dog 11 and corresponding
myocardial perfusion maps in grey tone display.

NUMBERS OF ANIMALS USED IN STUDY

A total of 50 dogs were used for the experimental study. This excludes blood donor dogs, as dogs sacrificed after acute experiments in another department were made available for this purpose.

Validation of Tracer microsphere technique		5
Myocardial perfusion with normal coronaries (20)	}	31
with vasodilatation (5)		
Effect of vasomotor tone (14)		
Effect of varied stenoses (28)		
Effect of bypass graft (14)	}	6
Effect of perfusion pressure		
Effect of heart rate		5
Effect of LV cavity pressure (4)	}	6
Effect of ventricular fibrillation (3)		
		<hr/> 50

There was frequently opportunity for assessing more than one effect in a single dog. For example, with varied stenoses the effect of vasomotor tone or bypass grafting, or normal perfusion was often assessed in one dog using 4 isotopes, thus reducing the overall number of dogs required.

SECTION 5a
MYOCARDIAL PERFUSION
NORMAL CORONARY TREE
BEATING, NON - WORKING, VENTED HEART
CARDIO - PULMONARY BYPASS

MYOCARDIAL PERFUSION WITH CARDIOPULMONARY
BYPASS AND NORMAL CORONARY TREE

BEATING, VENTED, NON-WORKING HEART

NO VASODILATATION

PERFUSION PRESSURE MEAN 100 mmHg

HEART RATE 110 - 130/minute

In 15 dogs myocardial perfusion was assessed on cardiopulmonary bypass with a normal coronary tree, with "resting" coronary vasomotor tone (no papaverine; no previous aortic cross-clamping; normal acid-base balance). The hearts were beating in sinus rhythm with rates ranging from 110 to 130/minute. Aortic perfusion pressure was held as closely as possible to a mean of 100 mmHg by controlling extracorporeal pump rate. Left ventricular intra-cavitary pressure was zero. In one dog (No 16) three separate assessments were made at different times.

Using the tracer microsphere method as described in Section 4c myocardial blood flow for left ventricular muscle was calculated. The results showed a fairly wide variation and are shown on the next page:

Blood Flow for Total Left Ventricular Myocardium:

Mean: 1.11 ml/Gm/minute
Range: 0.28 - 2.32 ml/Gm/minute
Standard deviation 0.64
n = 17

**Blood Flow for Endocardial Half of Left Ventricular
Myocardium:**

Mean: 1.16 ml/Gm/minute
Range: 0.27 - 2.48 ml/Gm/minute
Standard deviation 0.67
n = 17

**Blood Flow for Epicardial Half of Left Ventricular
Myocardium:**

Mean: 1.05 ml/Gm/minute
Range: 0.29 - 2.36 ml/Gm/minute
Standard deviation 0.65
n = 17

Endocardial/Epicardial Flow Ratio

Mean: 1.27
Range: 0.71 to 1.78
Standard deviation 0.32
n = 17

In 20 dogs the distribution of blood flow to the left ventricular myocardium was assessed with a normal coronary tree. In each the left ventricle was beating in sinus rhythm, was not working, and was vented with zero intra-cavity pressure, with total cardio-pulmonary bypass. Heart rate varied from 110 to 140/minute; perfusion pressure was adjusted to 100 mmHg by varying extracorporeal pump rate as necessary. In 5 of the dogs papaverine (1 mg/minute) was added to the blood in the extracorporeal circuit to induce coronary vasodilatation. In one dog (Number 16) three such assessments were made at different times with a normal coronary tree.

The results were shown qualitatively by means of blood flow mapping as described in Section 4c.

Figures 5a.1 to 5a.6 inclusive show the appearances for Dog 16. Figures 5a.2 and 5a.5 show endocardial-half and epicardial half perfusion respectively in a state of coronary vasodilatation. It can be seen that perfusion is relatively uniform throughout the left ventricular myocardium. This appearance was typical of that for each dog tested with a normal coronary tree.

For a quantitative assessment of the results the numerical values for blood flow (ml/min/Gm) were computed for each block within the area of supply of the circumflex artery and for each block in the area of supply of the anterior descending artery (the "control" and "test" areas as illustrated in Figure 4.8). In each case the mean blood flow, standard deviation, and standard error of the mean was calculated for the two areas. These values for Dog 16 are shown in Figures 5a.1 to 5a.6. A Student's "t" test for paired comparison was applied in each case. There was no significant difference between the mean flows in the circumflex area and the anterior descending area in 18 of the 20 experiments ($p > 0.1$). In 2 dogs the difference

was statistically significant ($p < 0.05$) but as can be seen from Figure 5a.7 this difference was never great. Figure 5a.7 shows in graph form the values for myocardial blood flow over a range of coronary vasomotor tone for endocardial half and epicardial half for circumflex and anterior descending territory for all the dogs assessed.

Figure 5a.8 shows the ratio of blood flow for endocardial half of myocardium to blood flow for epicardial half of myocardium. The ratio for these 20 dogs varied from 0.7 to 1.7 and was independent of absolute endocardial flow for these beating, non-working hearts with zero left ventricular cavity pressure.

REGIONAL MYOCARDIAL PERFUSION

NORMAL CORONARY TREE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.73	0.73
S.D.	0.10	0.12
S.E.M.	0.02	0.03

PROGRAM: DJW (REV F)

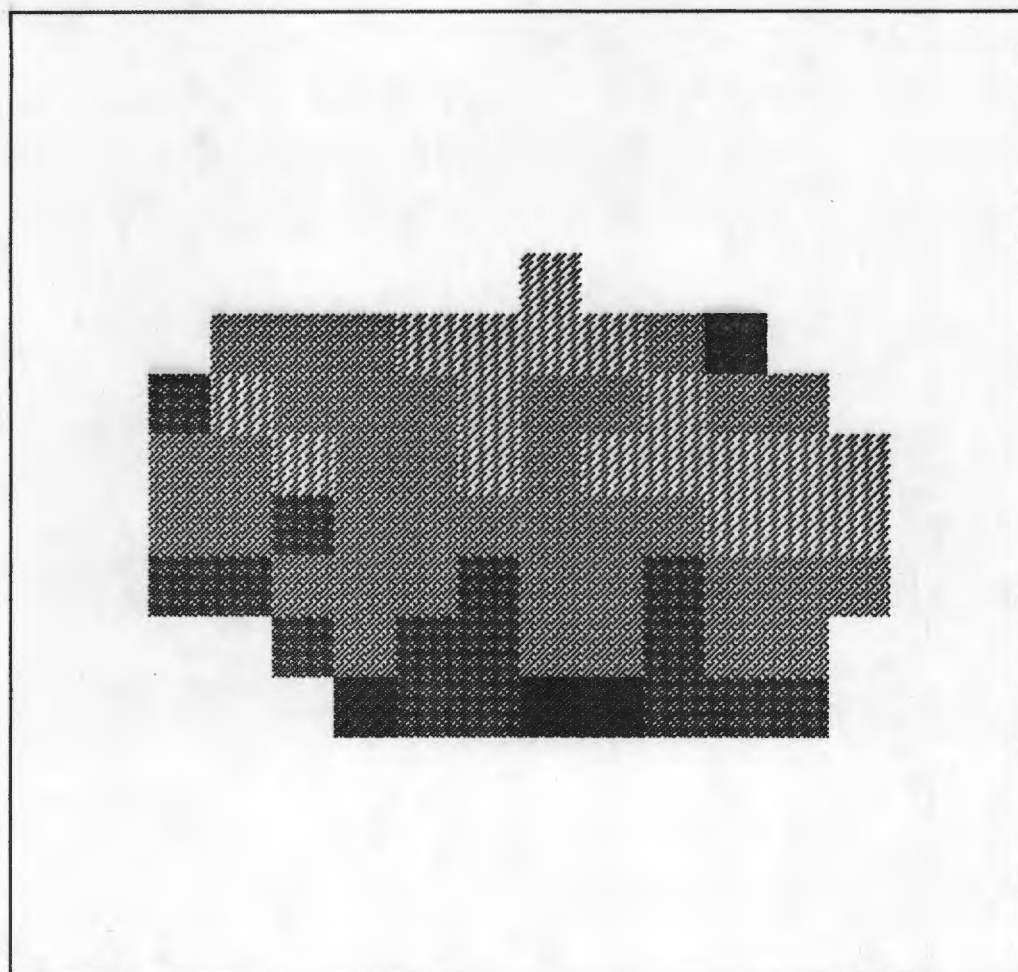
DOG 16
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 1.50

Figure 5a.1

REGIONAL MYOCARDIAL PERFUSION

NORMAL CORONARY TREE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.22	1.46
S.D.	0.22	0.25
S.E.M.	0.05	0.06

PROGRAM: DJW (REV F)

DOG 16

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 1.50

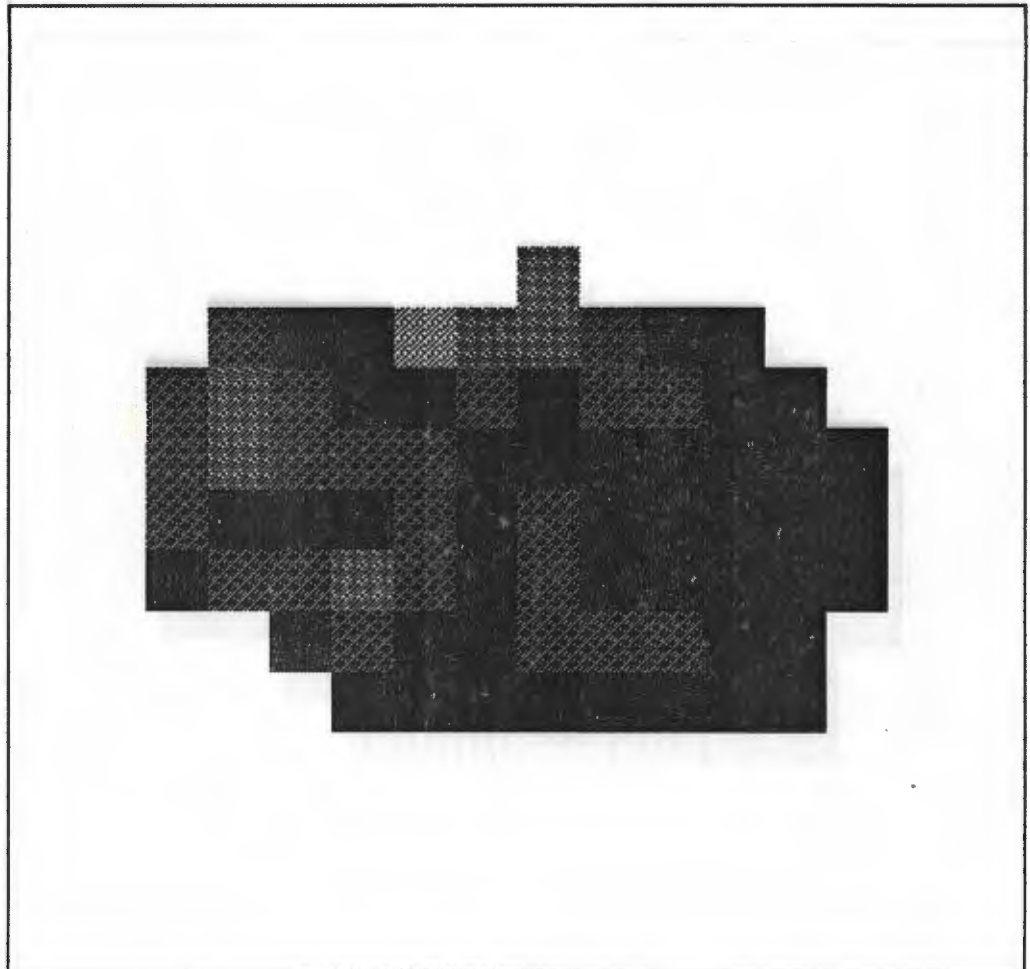


Figure 5a.2

REGIONAL MYOCARDIAL PERFUSION

NORMAL CORONARY TREE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.89	0.89
S.D.	0.20	0.11
S.E.M.	0.04	0.03

PROGRAM: DJW (REV F)

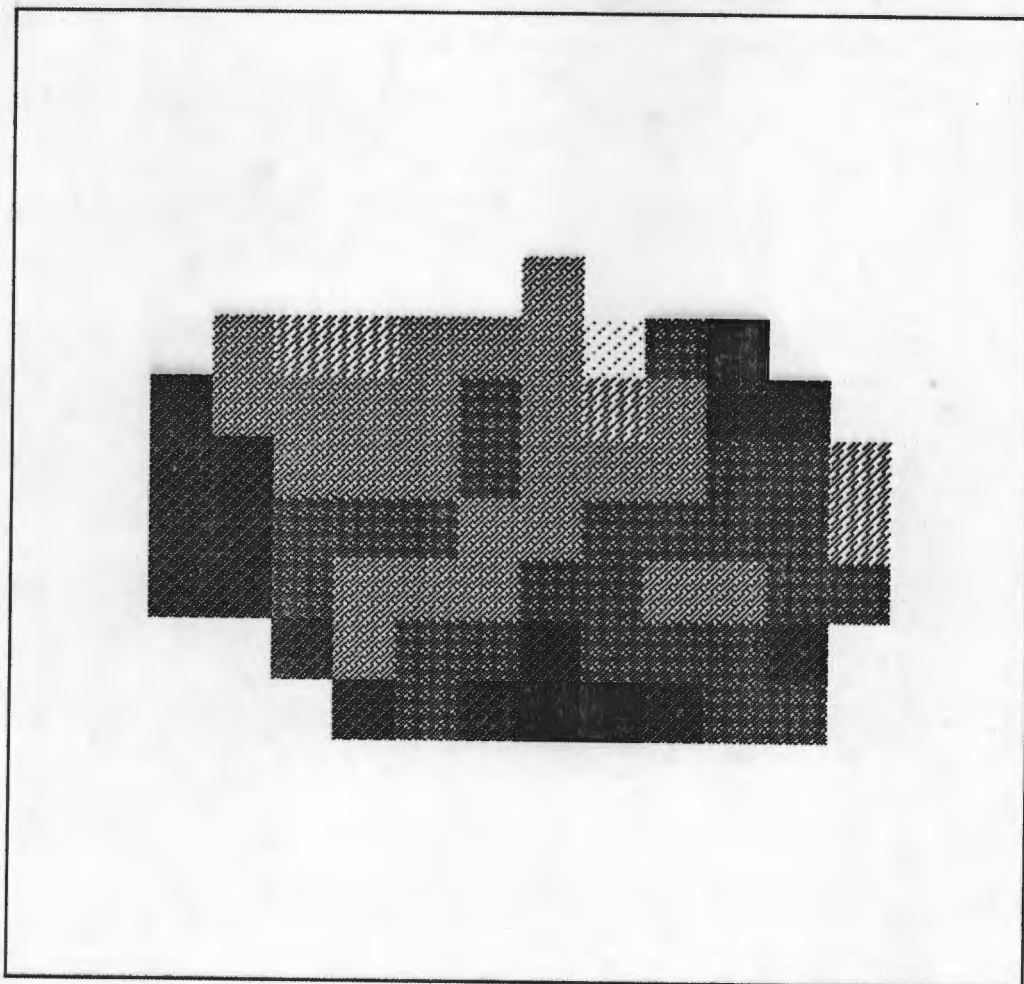
DOG 16
EPICARDIUM BLOOD FLOWS FOR ENERGY 1. SCALED TO 1.50

Figure 5a.4

REGIONAL MYOCARDIAL PERFUSION

NORMAL CORONARY TREE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.21	1.39
S.D.	0.36	0.29
S.E.M.	0.07	0.07

PROGRAM: DJW (REV F)

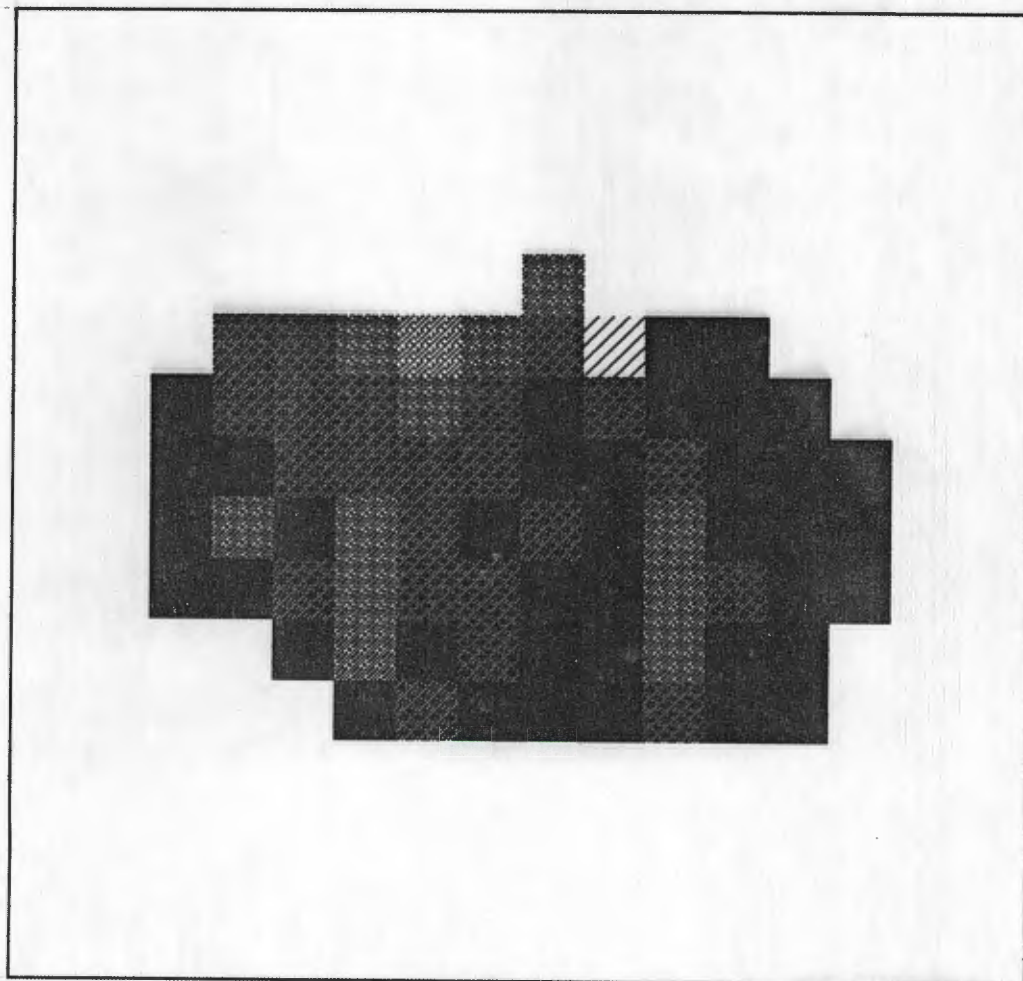
DOG 16
EPICARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 1.50

Figure 5a.5

REGIONAL MYOCARDIAL PERFUSION

NORMAL CORONARY TREE



	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.69	0.61
S.D.	0.18	0.08
S.E.M.	0.04	0.02

PROGRAM: DJW (REV F)

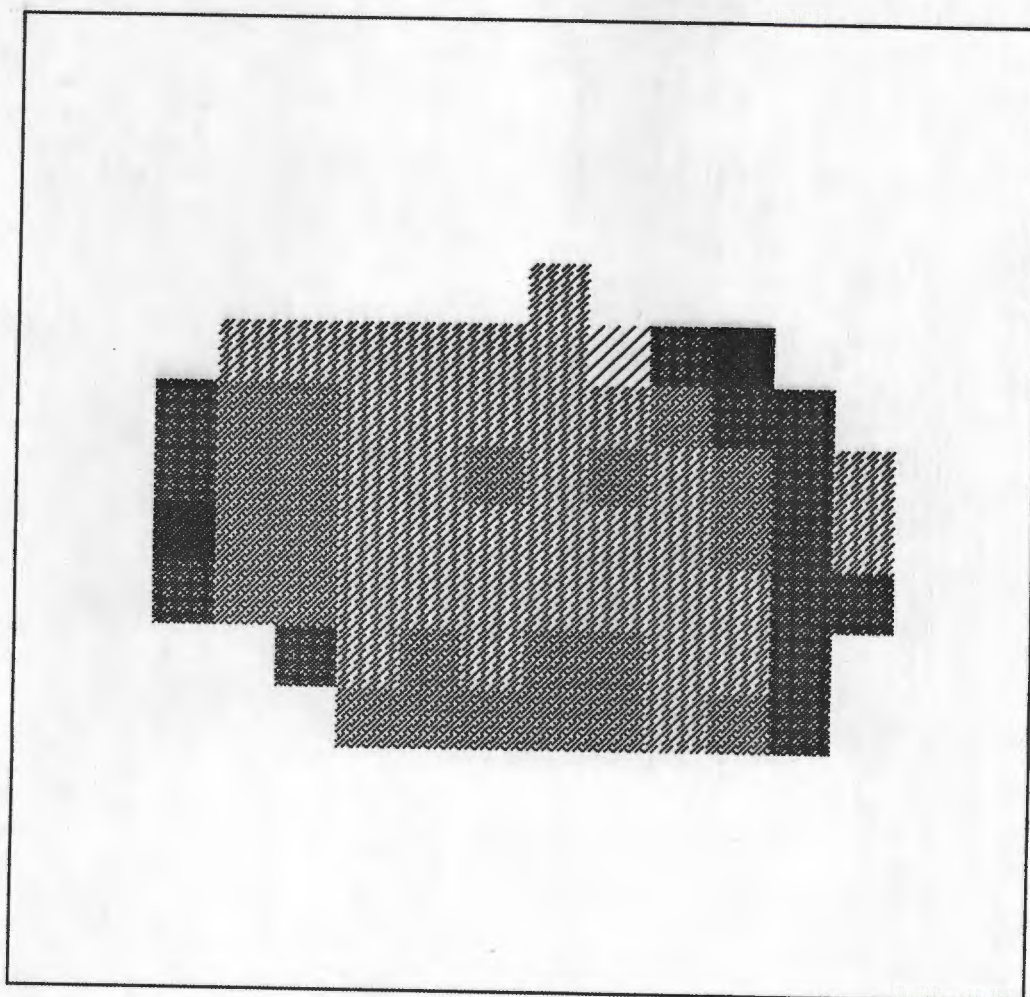
DOG 16
EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 1.50

Figure 5a.6

MYOCARDIAL BLOOD FLOW

RATIO OF ENDOCARDIAL HALF
TO EPICARDIAL HALF

BEATING, NON-WORKING HEART
ZERO LEFT VENTRICULAR CAVITY PRESSURE

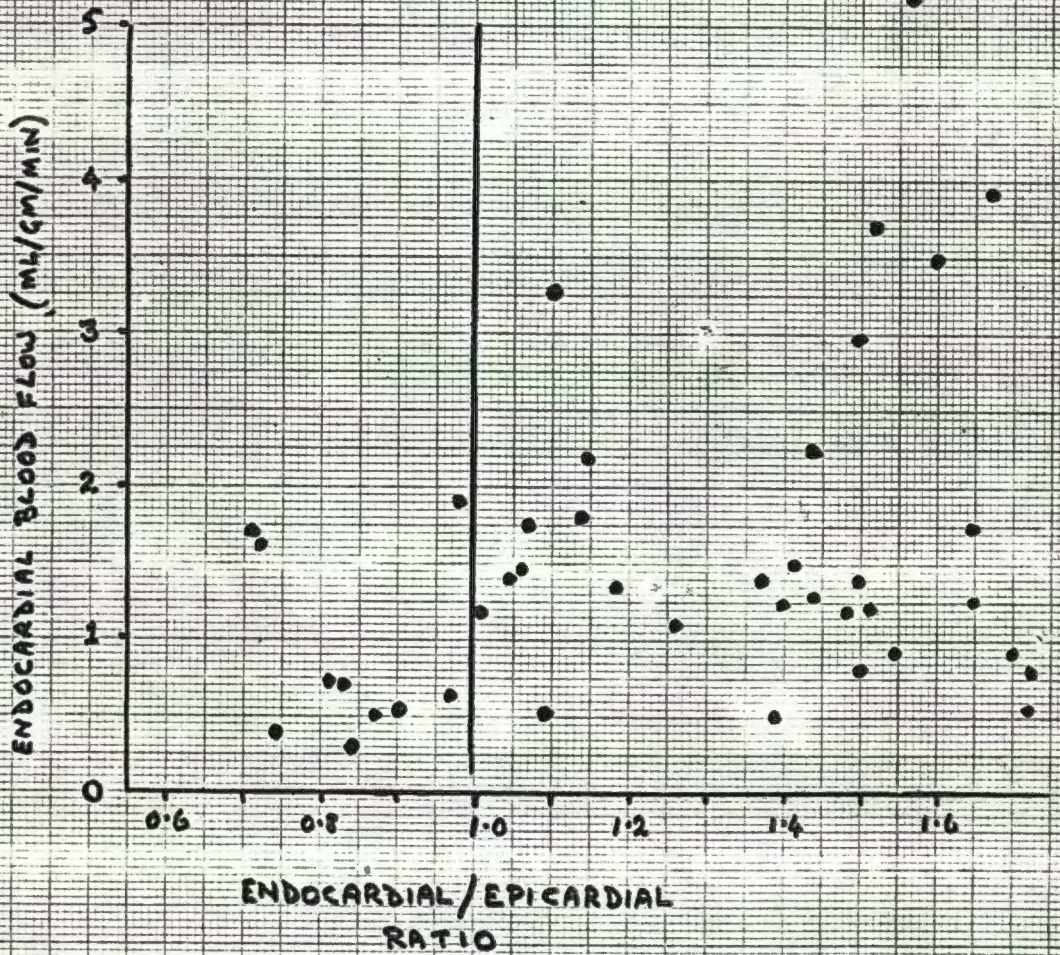


Figure 5a-8

DISCUSSION

Domenech et al (1969) pointed out that the tracer microsphere method, as used here, is the best available technique for experiment assessment of regional myocardial blood flow, having the advantage of measuring flow to specific regions which can be related to anatomical landmarks or angiographic appearances as described in Section 4c. This overcomes the fundamental problem of other techniques such as nitrous oxide washout (Eckenhoff et al 1948; Bing, 1960), washout of indicators from myocardium (Salisbury et al 1962; Kirk and Honig 1964) or from coronary arteries (Bassingthwaighte et al 1968; Herd et al 1962), or rubidium clearance techniques (Love et al 1965; Love 1964) which measure flow per unit weight of myocardium without relating it to anatomical area. The tracer microsphere method was well described for assessment of blood flow to all regions of the body by Rudolph and Heymann (1967), and Domenech et al (1969) validated the technique for assessment of regional myocardial flow. The requirements for accuracy of the method have been observed in this study (Section 4c) as defined by Buckberg et al 1971. Many workers have used the technique for regional myocardial blood flow assessment (Schaper 1971; Downey et al 1975) and the technique has been used in combination with cardiopulmonary bypass (Hottenrott et al 1974; Kleinman and Wechsler 1978). Downey et al (1975) showed that coronary flow is uniformly distributed across the left ventricular wall with maximal vasodilatation as it is in a normally functioning canine heart (Griggs and Nakamura 1968; Buckberg et al 1972; Cobb et al 1974), but, of greater relevance to this aspect of the study, they showed similar flows to different areas of the left ventricular free wall and septum, suggesting that overall blood flow distribution to left ventricular myocardium is

uniform. Similar findings are reported by Kleinman and Wechsler (1978).

Sestier et al (1975) used a similar animal model and showed with the tracer microsphere technique a variation in flow between adjacent regions. It is of interest that their muscle blocks averaged 600 mg (similar to this study - see Figure 4.14). The flows varied in a similar manner to those observed in this study (S.D. 0.17) - compare Figures 5a.1 to 5a.6.

This study shows that for the animal model described - beating, vented, non-working heart perfused at constant pressure on cardiopulmonary bypass, the distribution of blood is uniform over the whole of the left ventricle. There is no significant difference in measured flow to myocardium in the circumflex territory and to the anterior descending territory. This information is a necessary basis for assessing the effects of experimental stenosis in a major coronary artery. The study further illustrates the difficulty of ensuring "basal" conditions for measuring myocardial perfusion. Figure 5a-7 indicates the wide range of values for myocardial blood flow that were measured. The five highest values in the circumflex area for endocardial and epicardial flow were obtained with papaverine-induced vasodilatation. It is clear that these levels vary considerably and that some of the "non-dilated" levels are almost in the "vasodilated" range. This suggests that a degree of coronary vasodilatation is present in this model and that true "semi-basal" or "basal" conditions, not surprisingly, are not present (Gregg and Bedynek 1978; Khowi et al 1971). However, it will be noted that the left ventricular perfusion remains uniform whatever the state of vasodilatation. This model therefore, by having a "test" and "control" area of myocardium exposed to identical haemodynamic influences overcomes the difficulties of obtaining basal conditions.

The wide variation of endocardial/epicardial flow ratio was not dependant on the state of vasomotor tone, and the range of observed values was much greater than that reported for canine hearts not on cardiopulmonary bypass (Downey et al 1975; Buckberg et al 1972). It is of interest to note, however, that the variation (Figure 5a-8) suggests that on cardiopulmonary bypass with a non-working, vented heart the subendocardial regions are usually better perfused than in a working heart. Kleinman and Wechsler (1978) showed a similar wide variation in mean ratio of endocardial to epicardial flow after 30 minutes in the empty, beating heart on cardiopulmonary bypass.

SECTION 5b
EFFECT OF
CORONARY VASOMOTOR TONE

EFFECTS OF CORONARY VASOMOTOR TONE

It is well recognised that coronary vasomotor tone is a major determinant of myocardial perfusion (Gregg and Fisher 1963). The normally working heart with normal coronary tree regulates its blood supply over a wide range of perfusion pressure to maintain an appropriate balance between oxygen supply (via the coronary blood stream) and oxygen consumption (by the working myocardium) - so-called "autoregulation".

It is also known that in the presence of coronary obstruction areas of myocardium thereby jeopardised may be normally perfused at low levels of oxygen demand (and hence high coronary vasomotor tone and low coronary blood flow). However, increased demand for oxygen with increasing myocardial work may not in this case be matched by an appropriate increase in coronary flow in the jeopardised area and relative myocardial ischaemia results. Regional myocardial perfusion abnormalities are known to be frequently evident only during stress or exercise (Holman 1978; Friesinger 1977). The imbalance between myocardial oxygen requirement and coronary blood flow delivery becomes evident as angina during periods of increased oxygen demand when part of the coronary tree is unable to handle an appropriate increase in coronary flow because of fixed obstructing lesions in large coronary arteries.

In order to investigate this phenomenon in the animal model coronary vasodilatation was induced by giving papaverine (1 mg/minute) into the cardio-pulmonary bypass circuit and allowing stabilisation for 10 minutes prior to tracer microsphere injection. Papaverine was chosen because it is most commonly used for this purpose in clinical practice, and has been used in experimental studies (Downey et al 1975; Schaper 1971).

The effect of papaverine on the general systemic vascular resistance meant that cardiopulmonary bypass flow rate required to be increased during administration of papaverine to maintain a constant aortic perfusion pressure of 100 mmHg.

Examples of the effect of coronary vasomotor tone are illustrated for Dogs 11, 7, 6, 14 and 12. Each example has a severe stenosis of the anterior descending coronary artery.

Figure 5b-1 shows the angiographic appearance of Dog 11, with a 75% stenosis of the anterior descending artery (see in block B8 of the grid).

Figure 5b-2 shows the 40% pressure drop recorded across the 75% stenosis in the anterior descending artery with "resting" vasomotor tone (1.62 ml/Gm left ventricular myocardium/minute). This is a relatively high level of coronary flow - but "resting" in the sense of not having papaverine induced vasodilatation. This has been discussed in the discussion in Section 5a.

Figure 5b-3 shows that coronary vasodilatation induced with papaverine has increased myocardial blood flow by 204% to 3.3 ml/Gm left ventricular myocardium/minute. The pressure drop across the 75% stenosis has increased slightly to 50% and there is increased distal coronary pulse pressure.

Figure 5b-4 shows the regional myocardial perfusion map with "resting" vasomotor tone - a fairly well marked perfusion deficit is seen in the distribution of the anterior descending artery.

Figure 5b-5 shows the regional myocardial perfusion map with coronary vasodilatation in the same dog - the perfusion deficit is markedly accentuated.

Dog 11

75% STENOSIS OF ANTERIOR DESCENDING ARTERY

AORTO-CORONARY BYPASS GRAFT INSERTED 1 CM
DISTAL TO STENOSIS

EFFECT OF THIS GRAFT IN CORRECTING PERFUSION
DEFICIT IS SHOWN IN FIGURE 5h - 1

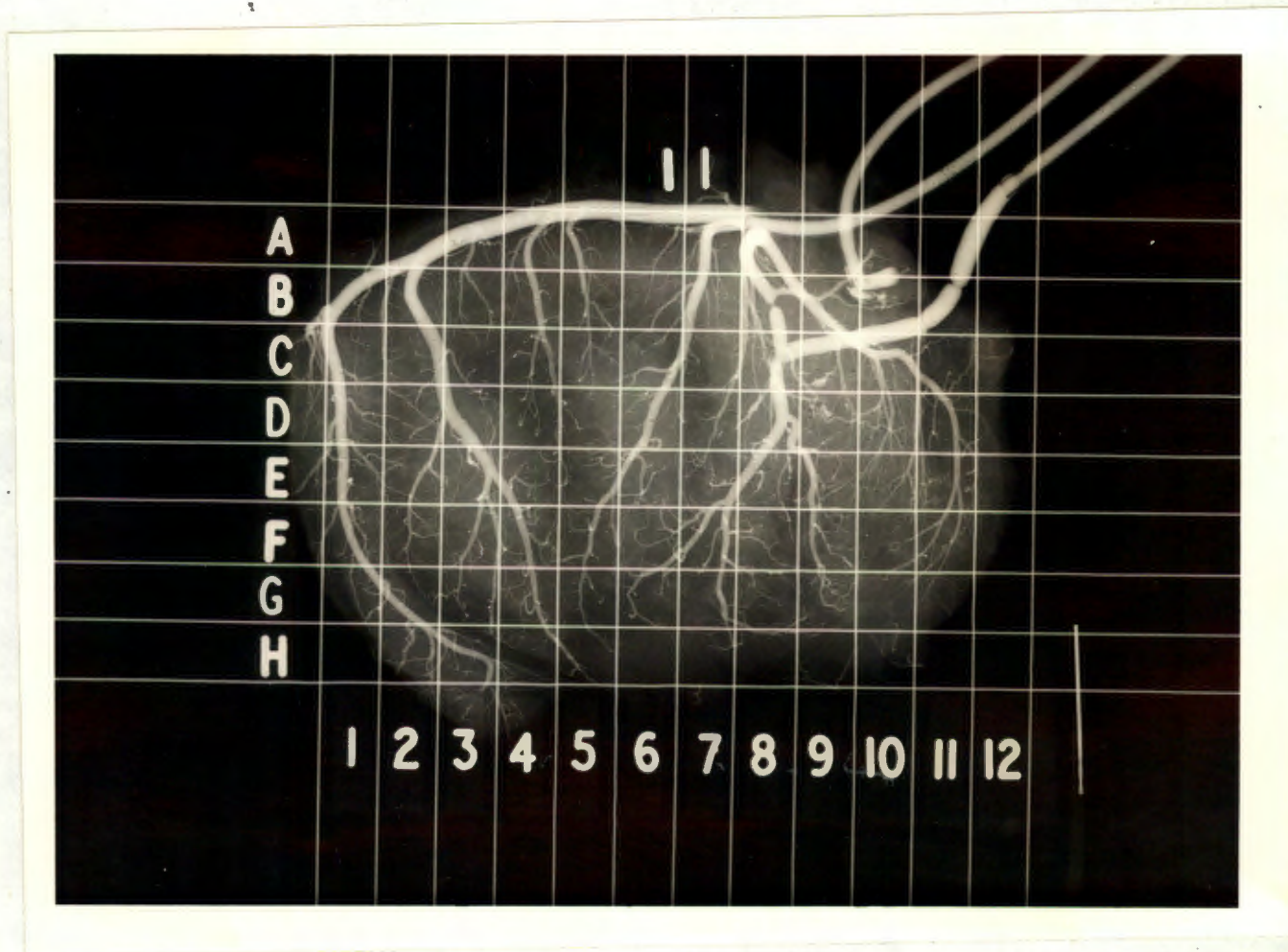


Figure 5b - 1

DOG 11

75% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 75% STENOSIS (mean 60 mmHg). A PRESSURE DROP OF 40% IS PRESENT.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURE 5b-4.

TOTAL HEART BLOOD FLOW : 200 ml/min (CORONARY SINUS DRAINAGE)

LEFT VENTRICULAR BLOOD FLOW : 201 ml/min
(TRACER MICROSPHERE METHOD)

TOTAL HEART WEIGHT : 169 Gm

LEFT VENTRICULAR WEIGHT : 124 Gm

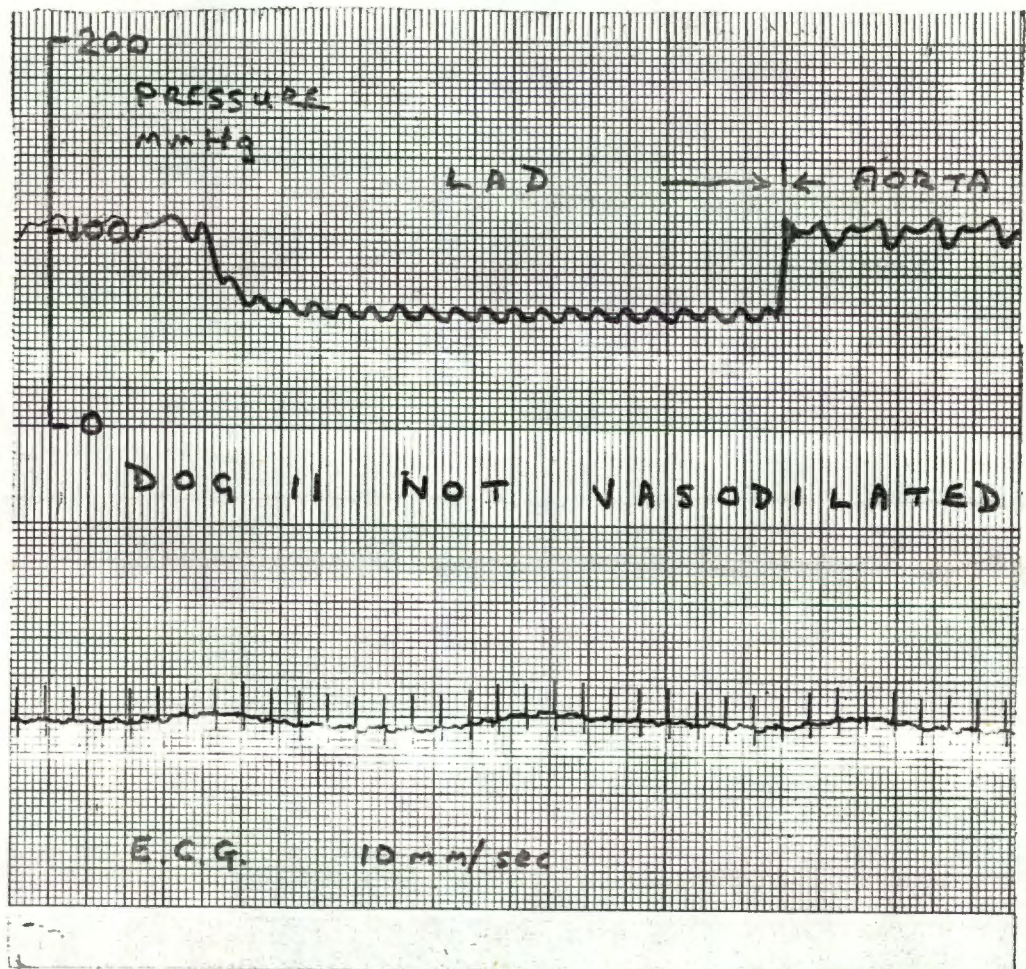


Figure 5b-2

DOG 11

75% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION INDUCED WITH PAPAVERINE
(1 mg/minute)

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 75% STENOSIS (mean 50 mmHg). A PRESSURE DROP OF 50% IS PRESENT: DISTAL CORONARY PULSE PRESSURE IS INCREASED.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURE 5b-5

TOTAL HEART BLOOD FLOW : 425 ml/min (CORONARY SINUS DRAINAGE)

LEFT VENTRICULAR BLOOD FLOW: 410 ml/min

(TRACER MICROSPHERE METHOD)

TOTAL HEART WEIGHT 169 Gm

LEFT VENTRICULAR WEIGHT 124 Gm

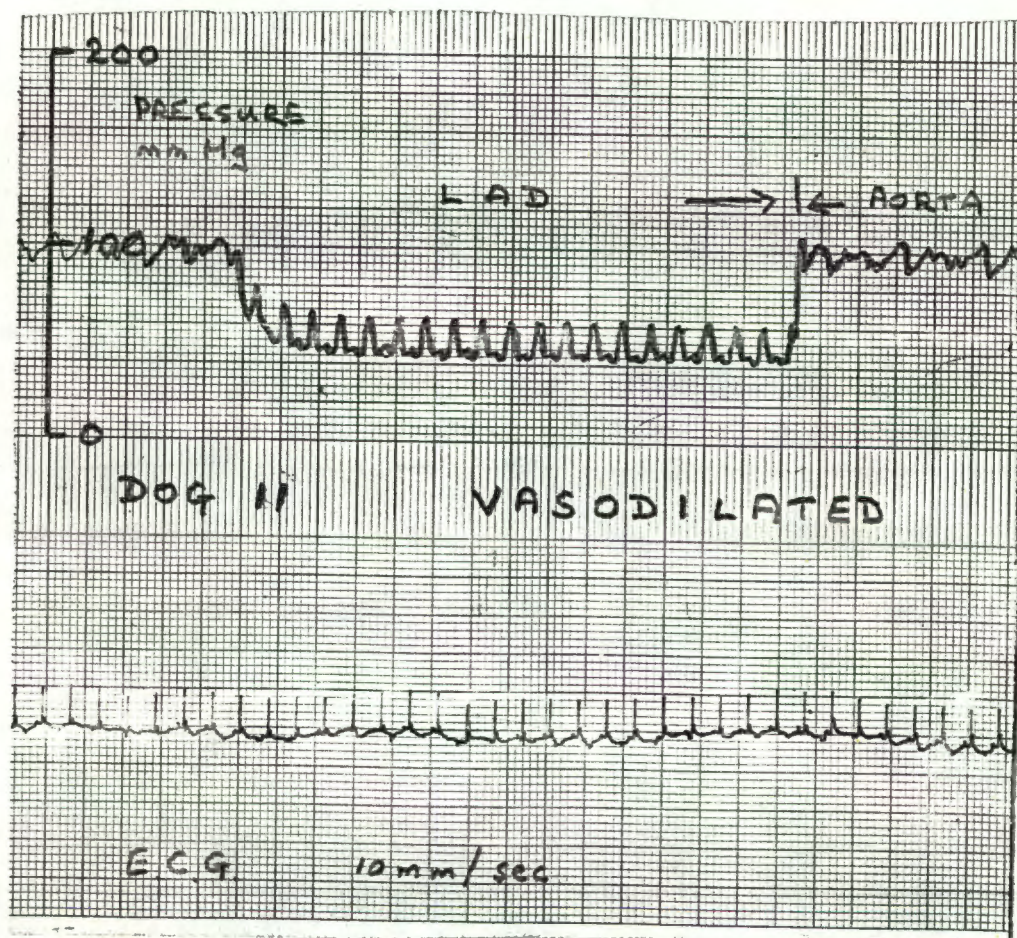


Figure 5b-3

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

75% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.02	1.10
S.D.	0.63	0.81
S.E.M.	0.11	0.26

PROGRAM: DJW (REV F)

DOG 11
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 4.00

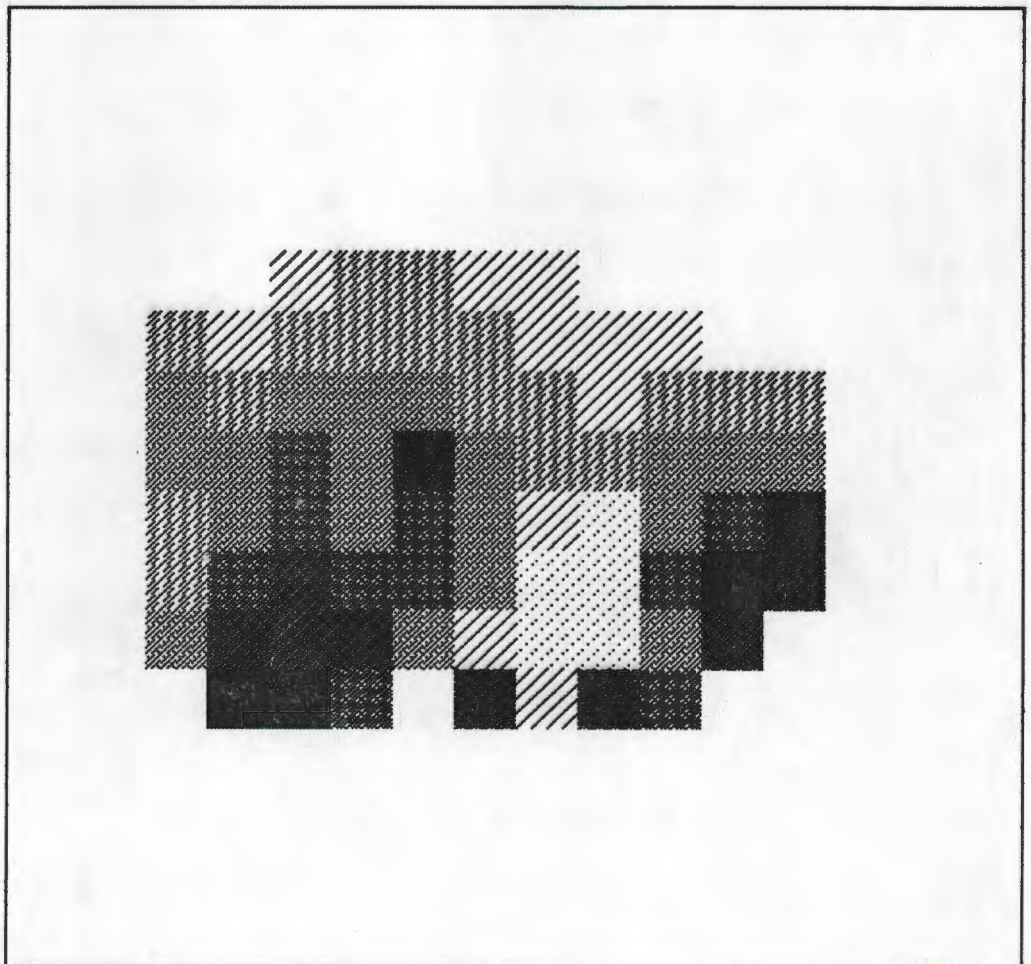


Figure 5b-4

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

75% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	4.32	1.88
S.D.	1.22	1.69
S.E.M.	0.21	0.53

PROGRAM: DJW (REV F)

DOG 11

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 4.00

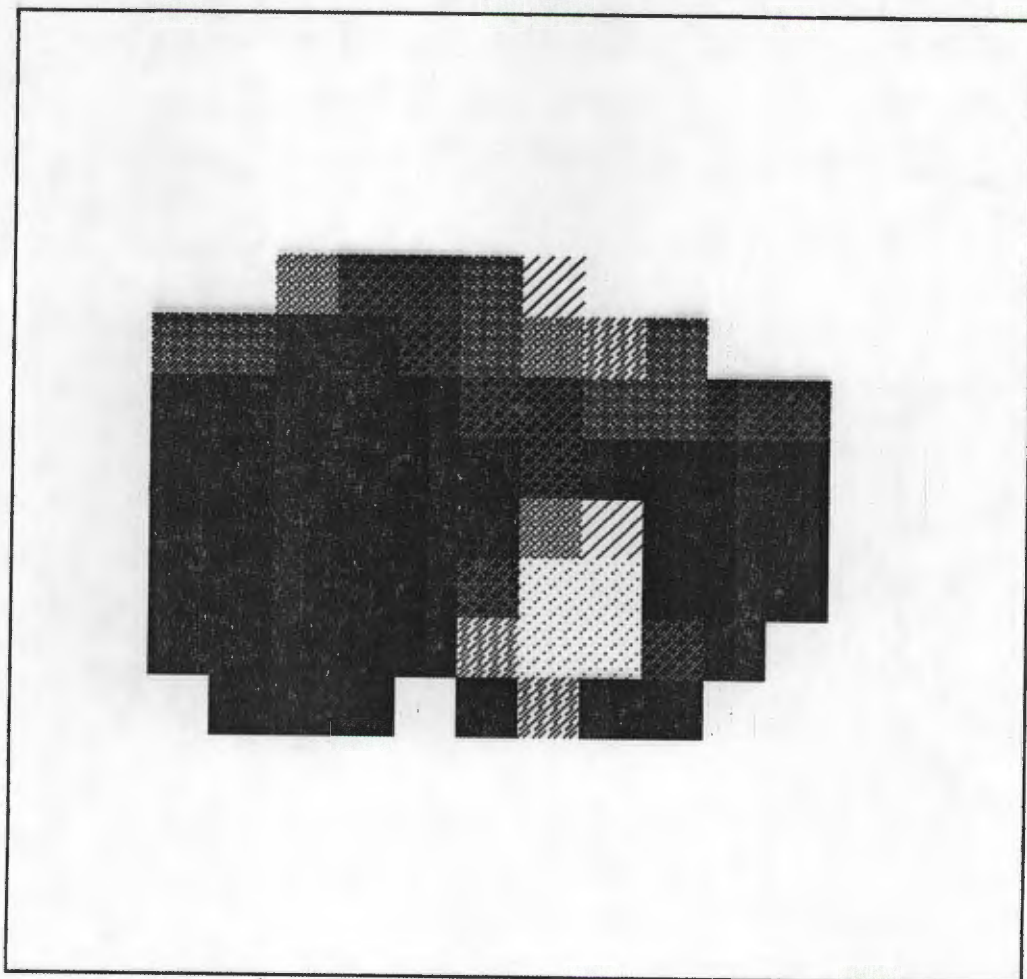


Figure 5b-5

Figure 5b-6 shows the 80% pressure drop measured across an 80% stenosis in the anterior descending artery on Dog 7, with resting vasomotor tone. Flow is very low (0.33 ml/Gm left ventricle/minute).

Figure 5b-7 shows a very similar pressure drop across the same lesion with coronary vasodilatation and higher flow (1.41 ml/Gm left ventricle/minute).

Figure 5b-8 shows the uniformly low flow regional myocardial perfusion map with no distinguishable perfusion deficit (although the flow of 0.27 ml/Gm/minute in the jeopardised anterior descending territory is significantly lower than the flow on 0.49 ml/Gm/minute in the control circumflex territory).

Figure 5b-9 shows the well marked perfusion deficit evoked by vasodilatation. There has been a 394% increase in flow in the control area but only 230% increase in flow in the jeopardised anterior descending area. This increase in flow in the jeopardised territory is due to increased flow in the blocks of myocardium near the periphery of the jeopardised area - it will be seen that the blocks in the centre remain perfused at the same level (the scaling factor is unchanged at 4.00 ml/Gm/minute and the central area is shaded at the "diagonal dotted line" level in Figures 5b-8 and 5b-9). The central area of the jeopardised territory thus has no coronary reserve and is unable to compensate for the effect of the severe fixed stenosis by further vasodilatation.

DOG 7

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

THIS RECORD SHOWS PRESSURE IN AORTA (108 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 80% STENOSIS (mean 20 mmHg). A PRESSURE DROP OF 80% IS PRESENT.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN

FIGURE 5b-8

TOTAL HEART BLOOD FLOW: 72 ml/min (CORONARY SINUS DRAINAGE)
 LEFT VENTRICULAR BLOOD FLOW: 57 ml/min (TRACER MICROSPHERE METHOD)
 TOTAL HEART WEIGHT: 241 Gm
 LEFT VENTRICULAR WEIGHT: 174 Gm

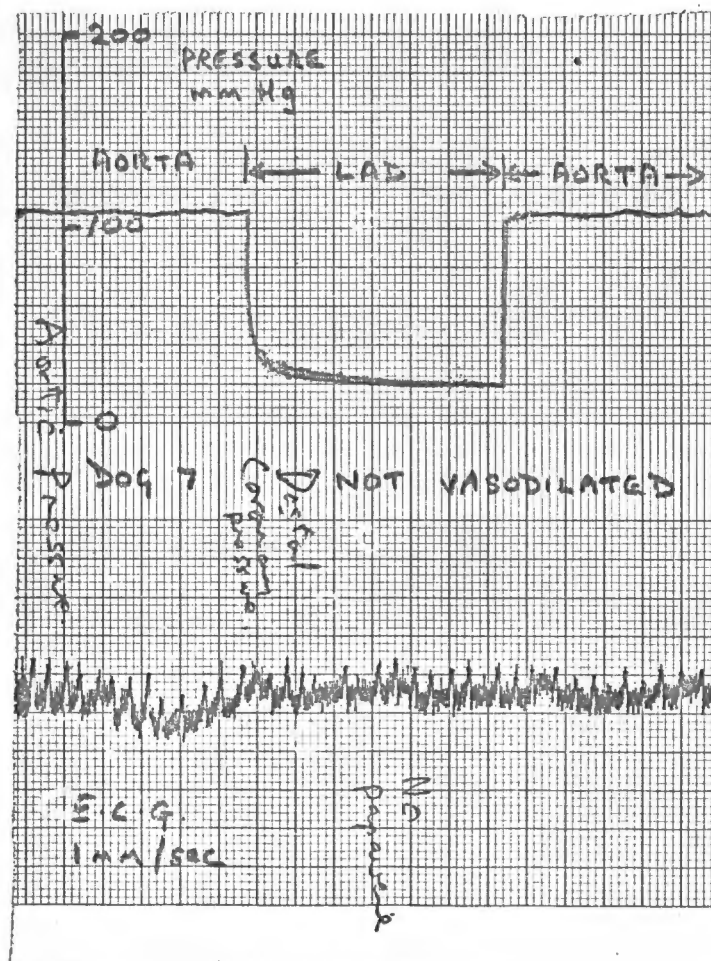


Figure 5b-6

EFFECT OF CORONARY VASOMOTOR TONE

DOG 7

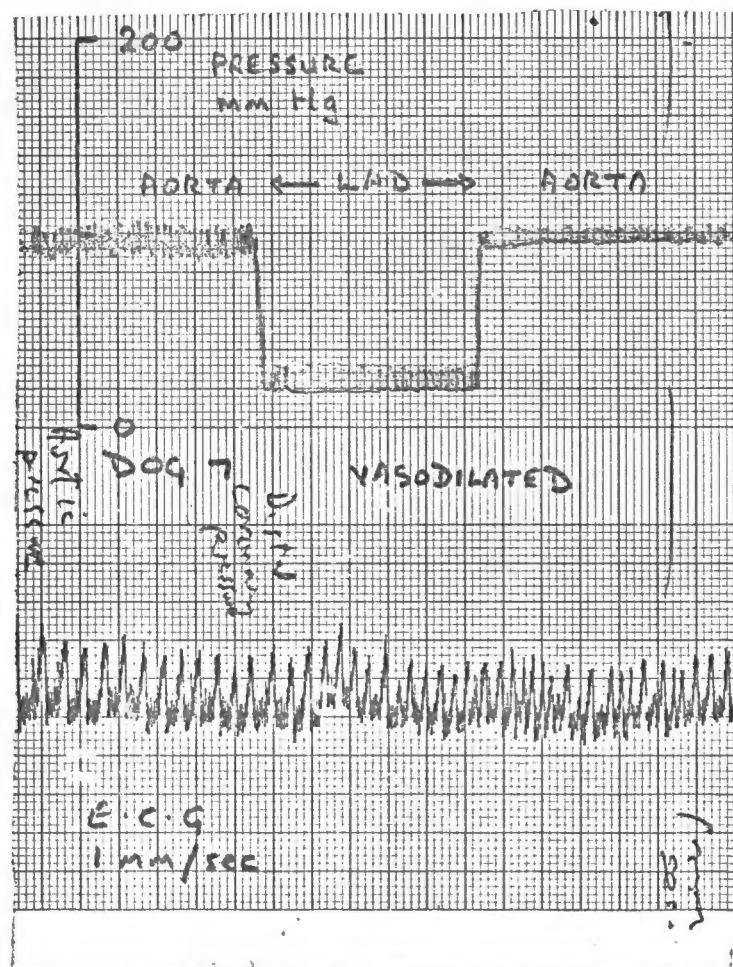
80% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION INDUCED WITH PAPAVERINE (1 mg/min)

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 80% STENOSIS (mean 24 mmHg). A PRESSURE DROP OF 76% IS PRESENT; DISTAL CORONARY PULSE PRESSURE IS INCREASED.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURE 5b-9

TOTAL HEART BLOOD FLOW:	260 ml/min (CORONARY SINUS DRAINAGE)
LEFT VENTRICULAR BLOOD FLOW:	245 ml/min (TRACER MICROSPHERE METHOD)
TOTAL HEART WEIGHT:	244 Gm
LEFT VENTRICULAR WEIGHT:	174 Gm



EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.49	0.27
S.D.	0.11	0.06
S.E.M.	0.02	0.01

PROGRAM: DJW (REV F)

DDOG 7
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 4.00

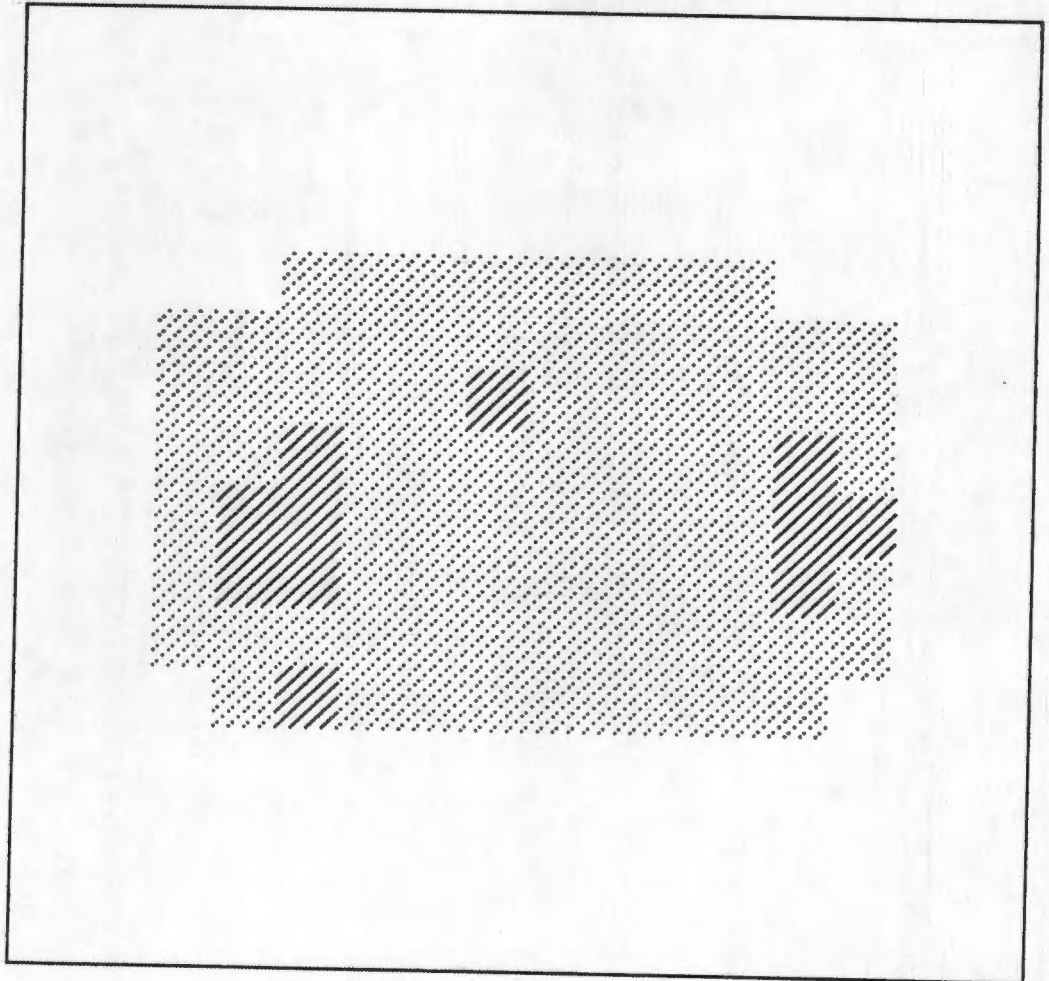


Figure 5b-8

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.93	0.62
S.D.	0.57	0.66
S.E.M.	0.10	0.13

PROGRAM: DJW (REV F)

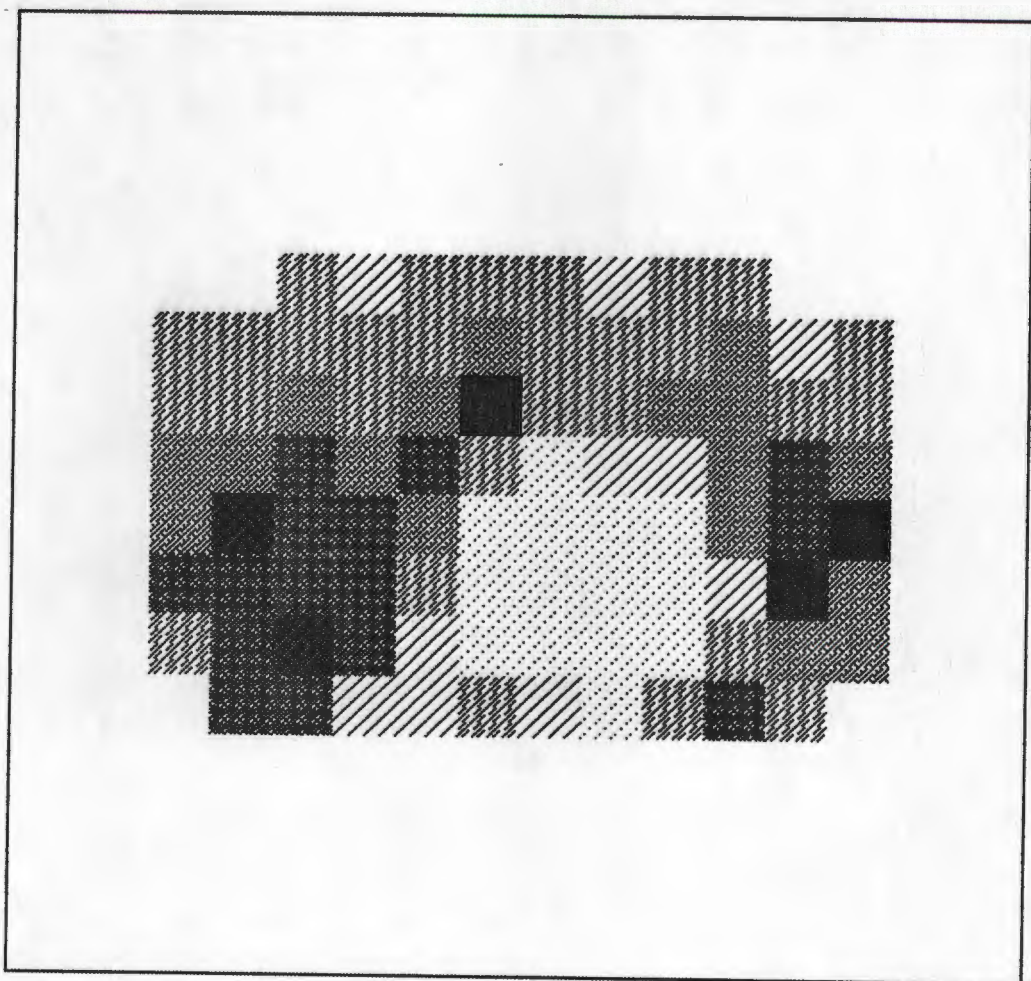
DDOG 7
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 4.00

Figure 5b-9

Figure 5b-10 shows the 74% pressure drop recorded across the 80% stenosis in the anterior descending artery of Dog 6 at low flow (0.65 ml/Gm left ventricle/minute).

Figure 5b-11 shows an identical pressure drop (but with slightly increased distal coronary pulse pressure) at high flow induced by vasodilatation with papaverine (2.69 ml/Gm left ventricle/minute).

Figure 5b-12 shows the regional myocardial perfusion map for Dog 6 with resting vasomotor tone. A perfusion deficit is not present and "test" and "control" area perfusion is not significantly different.

Figure 5b-13 shows the striking perfusion deficit in the jeopardised anterior descending territory revealed by inducing coronary vasodilatation.

EFFECT OF CORONARY VASOMOTOR TONE

DOG 6

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 80% STENOSIS (mean 26 mmHg). A PRESSURE DROP OF 74% IS PRESENT.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURE 5b-12

TOTAL HEART BLOOD FLOW:	170 ml/min (CORONARY SINUS DRAINAGE)
LEFT VENTRICULAR BLOOD FLOW:	134 ml/min
TOTAL HEART WEIGHT:	282 Gm
LEFT VENTRICULAR WEIGHT:	206 Gm

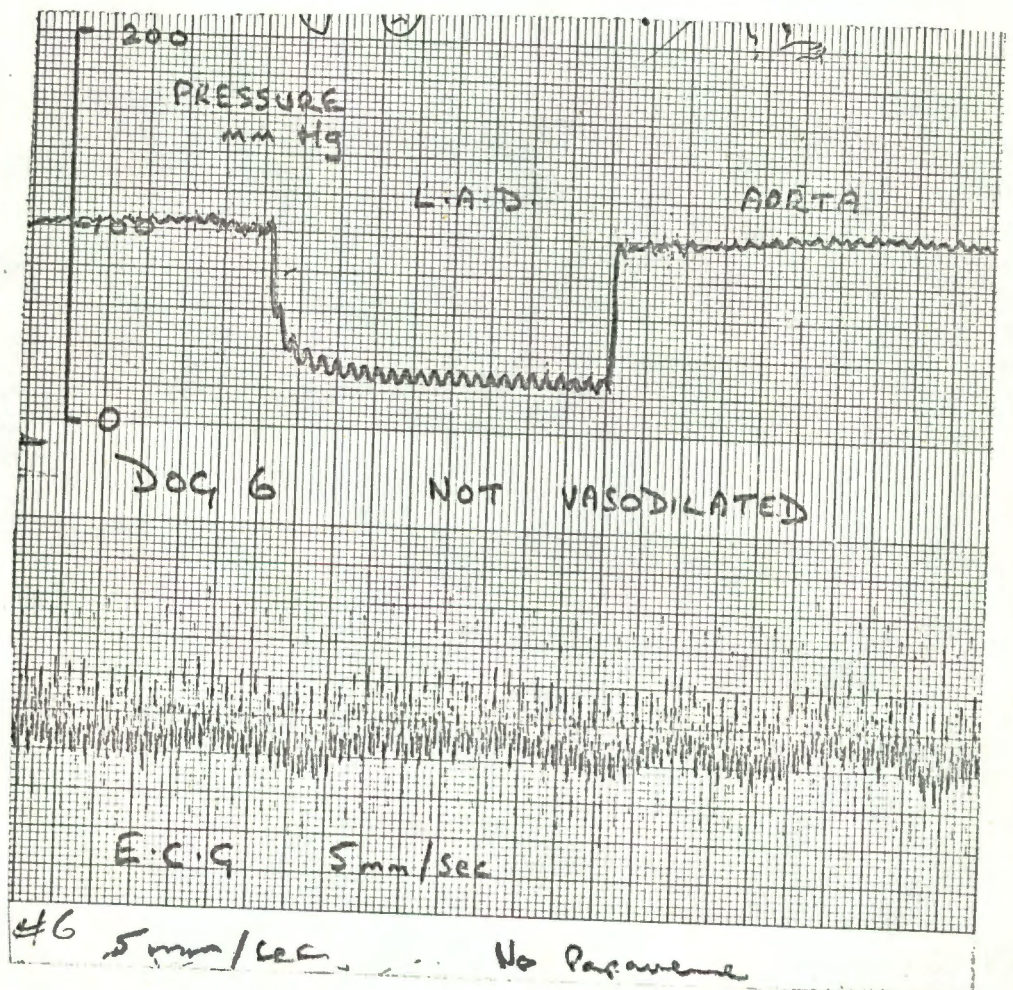


Figure 5b-10

EFFECT OF CORONARY VASOMOTOR TONE

DOG 6

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION INDUCED WITH PAPAVERINE (1 mg/minute)

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 80% STENOSIS (mean 26 mmHg). A PRESSURE DROP OF 74% IS PRESENT: DISTAL CORONARY PULSE PRESSURE IS SLIGHTLY INCREASED.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN

FIGURE 5b-13

TOTAL HEART BLOOD FLOW:	725 ml/min (CORONARY SINUS DRAINAGE)
LEFT VENTRICULAR BLOOD FLOW:	555 ml/min (TRACER MICROSPHERE METHOD)
TOTAL HEART WEIGHT:	282 Gm
LEFT VENTRICULAR WEIGHT:	206 Gm

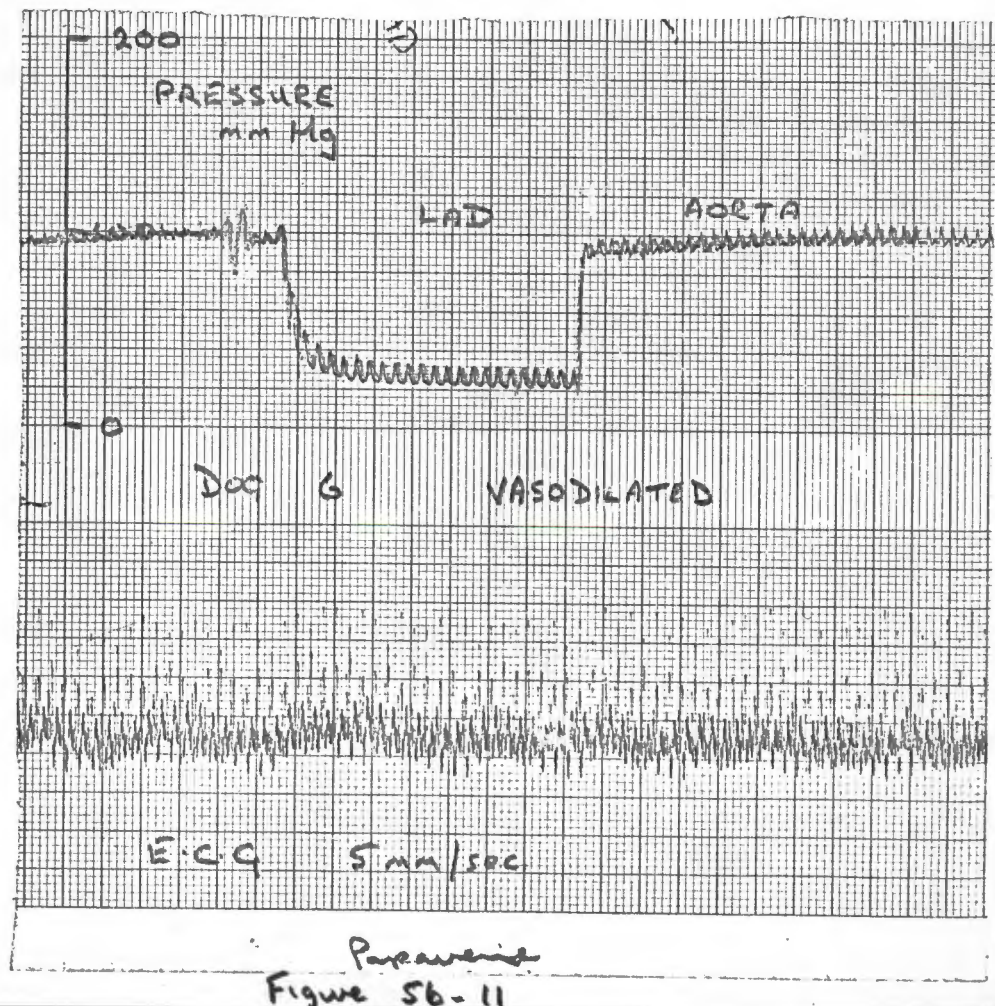


Figure 5b-11

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.71	0.70
S.D.	0.20	0.17
S.E.M.	0.03	0.04

PROGRAM: DJW (REV F)

DOG 6
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 3.00

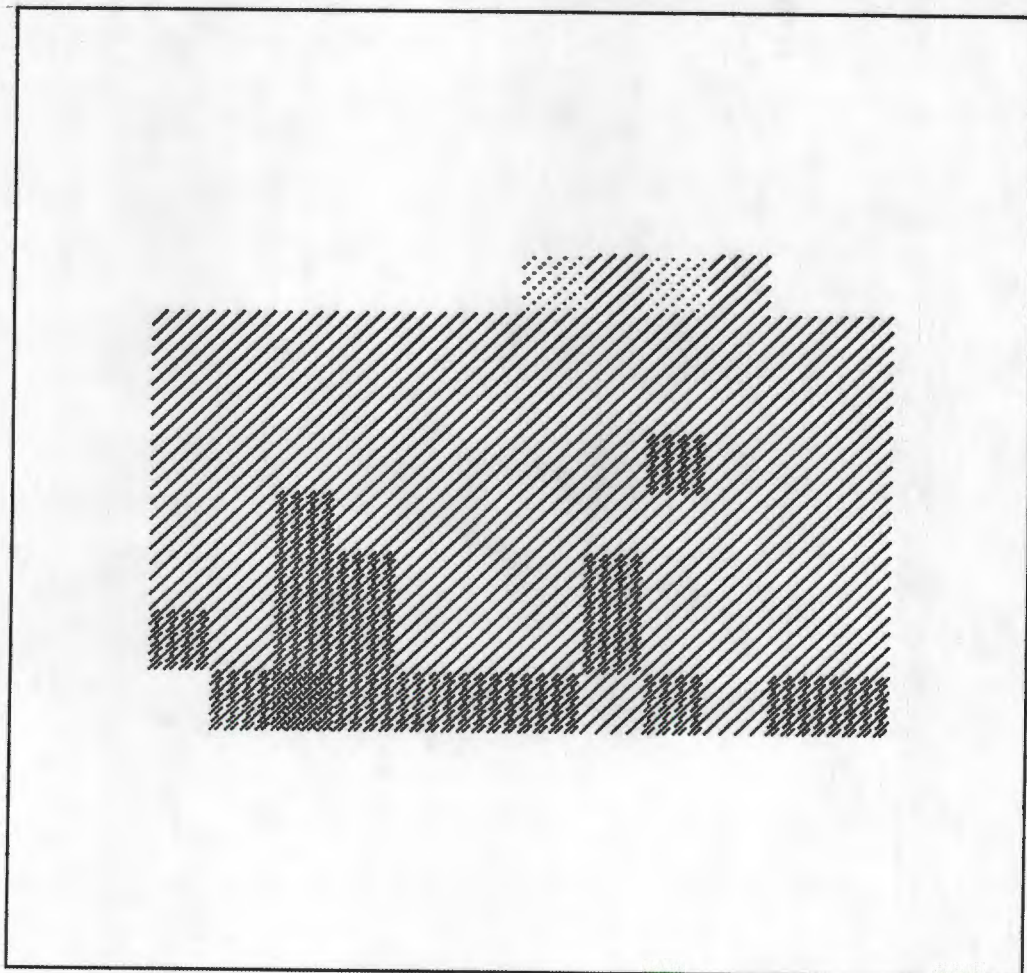


Figure 5b-12

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

80% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	3.00	2.02
S.D.	0.80	0.92
S.E.M.	0.11	0.23

PROGRAM: DJW (REV F)

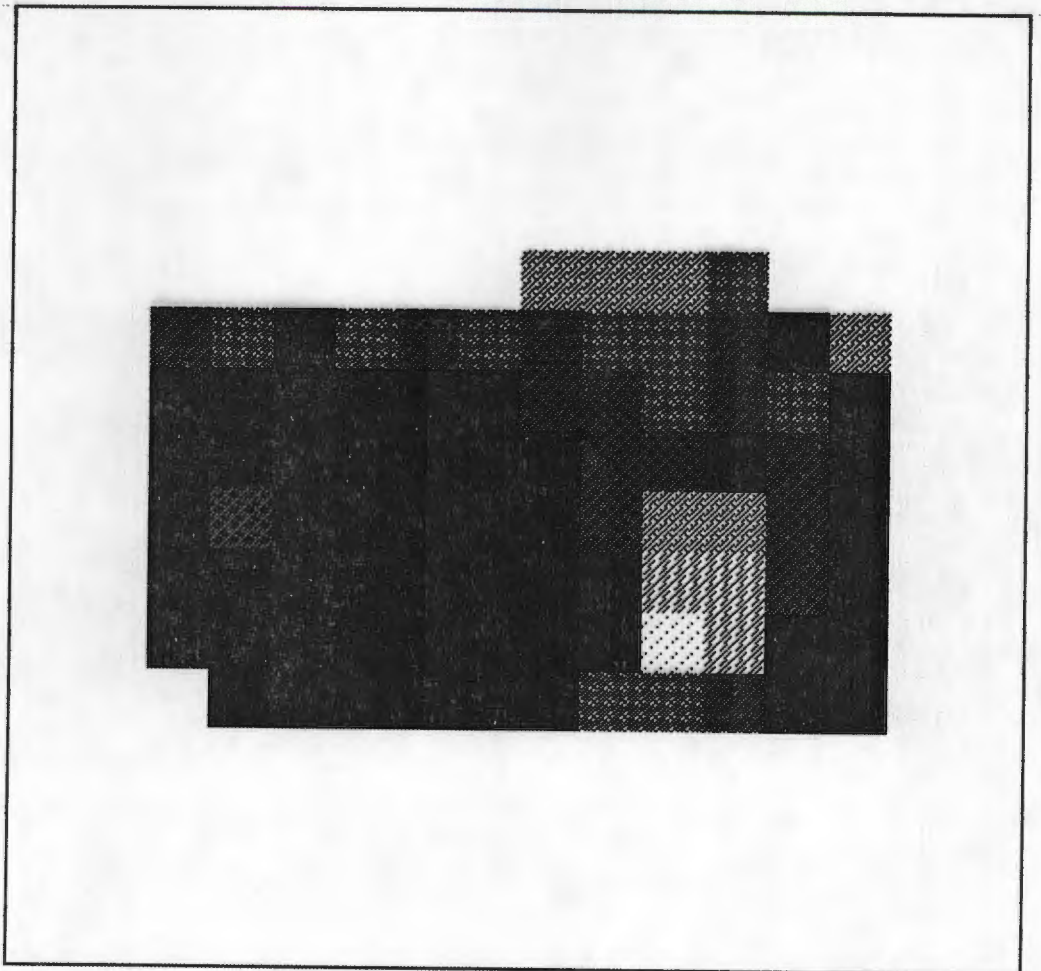
DOG 6
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 3.00

Figure 5b-13

Figures 5b-14 and 5b-15 show the pressure drop across the 70% stenosis of the anterior descending artery in Dog 14 for "resting" vasomotor tone and coronary vasodilatation respectively.

Figures 5b-16 and 5b-17 show respectively the regional myocardial perfusion maps for endocardial and epicardial halves of the left ventricle with resting vasomotor tone. The perfusion deficit is just distinguishable in the epicardial map.

Figures 5b-18 and 5b-19 show respectively the maps for endocardial and epicardial halves with coronary vasodilatation. The perfusion deficit is now obvious in both.

EFFECT OF CORONARY VASOMOTOR TONE

DOG 14

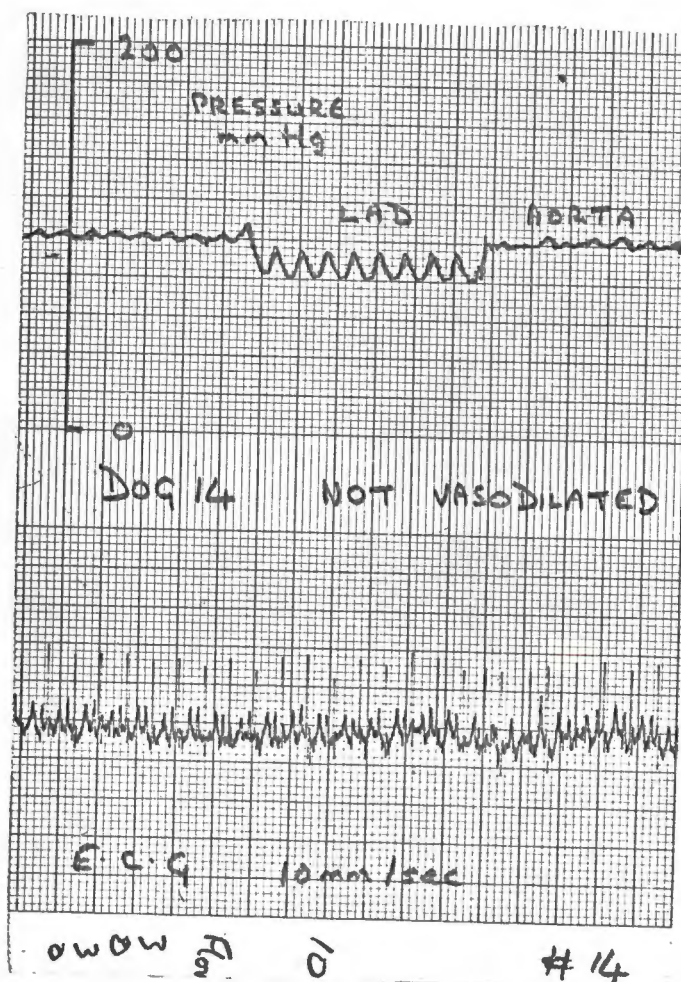
70% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 70% STENOSIS (mean 88 mmHg). A PRESSURE DROP OF 12% IS PRESENT.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURES 5b-16 and 5b-17.

TOTAL HEART BLOOD FLOW:	245 ml/min (CORONARY SINUS DRAINAGE)
LEFT VENTRICULAR BLOOD FLOW:	203 ml/min (TRACER MICROSPHERE METHOD)
TOTAL HEART WEIGHT:	215 Gm
LEFT VENTRICULAR WEIGHT:	160 Gm



EFFECT OF CORONARY VASOMOTOR TONE

DOG 14

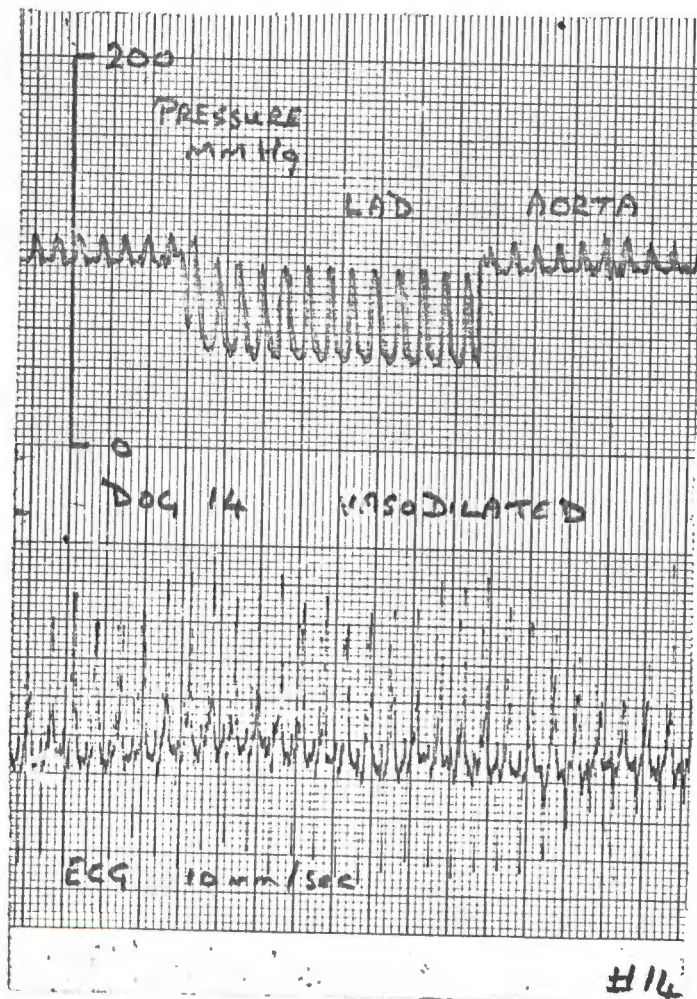
70% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION INDUCED WITH PAPAVERINE (1 mg/minute)

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 70% STENOSIS (mean 60 mmHg). A PRESSURE DROP OF 40% IS PRESENT; DISTAL CORONARY PULSE PRESSURE IS MARKEDLY INCREASED.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURES 5b-18 and 5b-19

TOTAL HEART BLOOD FLOW: 370 ml/min (CORONARY SINUS DRAINAGE)
 LEFT VENTRICULAR BLOOD FLOW: 352 ml/min (TRACER MICROSPHERE METHOD)
 TOTAL HEART WEIGHT: 215 Gm
 LEFT VENTRICULAR WEIGHT: 160 Gm



EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.61	1.18
S.D.	0.42	0.27
S.E.M.	0.09	0.07

PROGRAM: DJW (REV F)

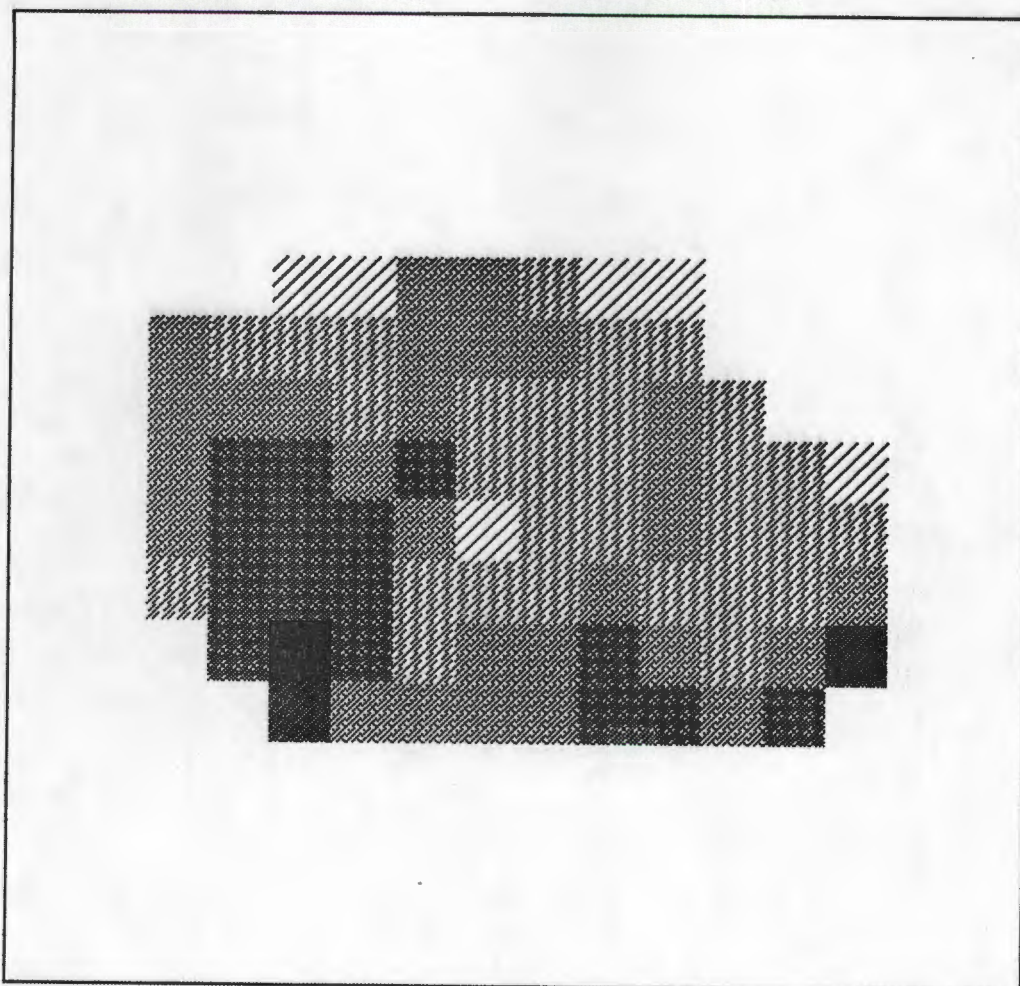
DOG 14
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 3.00

Figure 5b-16

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.03	0.75
S.D.	0.23	0.16
S.E.M.	0.05	0.04

PROGRAM: DJW (REV F)

DOG 14

EPICARDIUM BLOOD FLOWS FOR ENERGY 3. SCALED TO 3.00

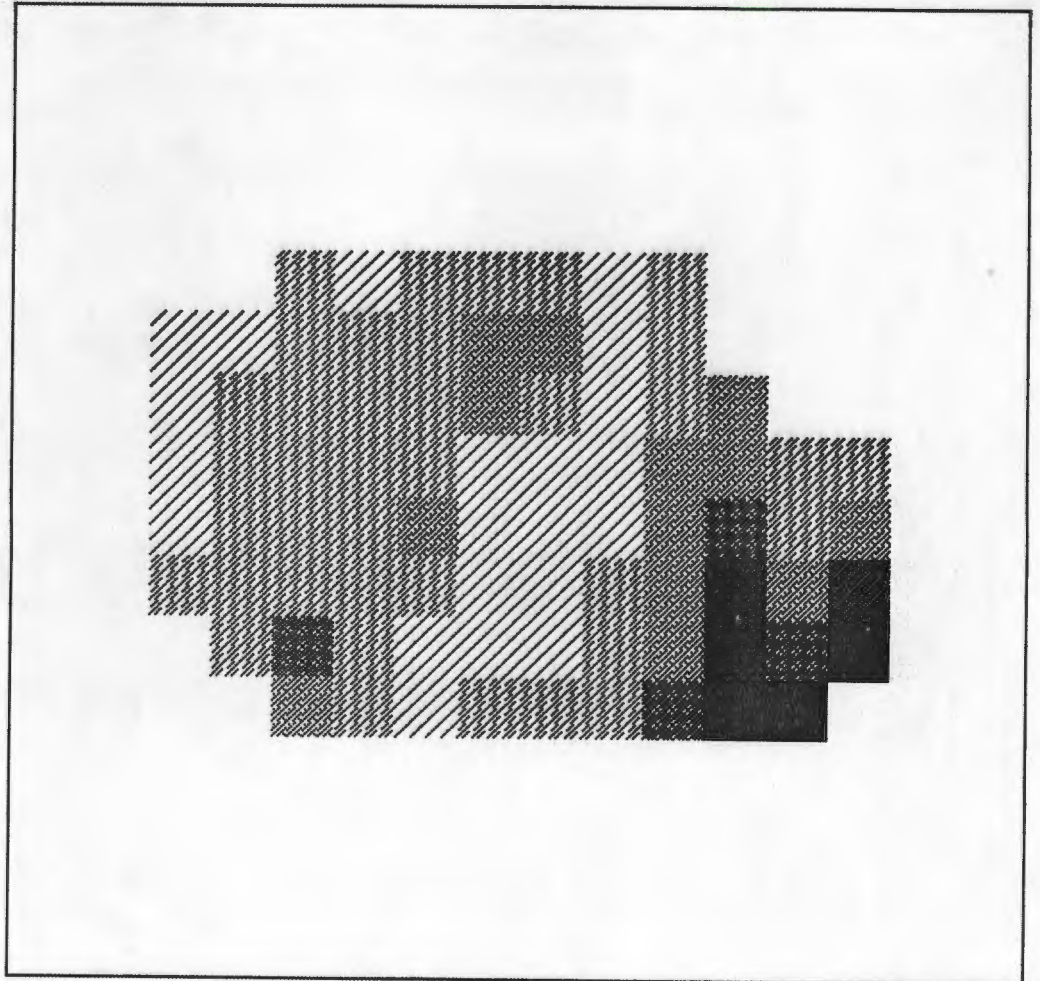


Figure 5b-17

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	3.12	1.41
S.D.	0.59	0.24
S.E.M.	0.13	0.07

PROGRAM: DJW (REV F)

DOG 14
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1. SCALED TO 3.00

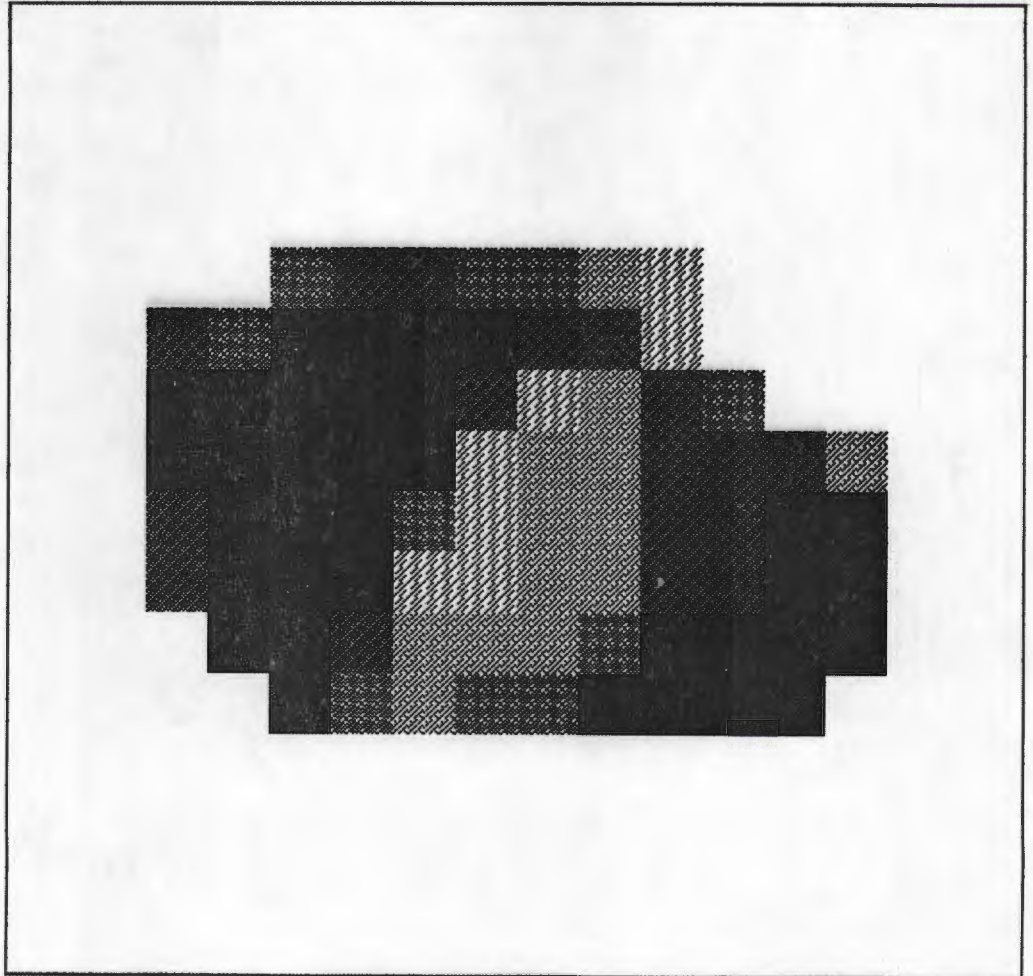


Figure 5b-18

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.23	1.05
S.D.	0.39	0.18
S.E.M.	0.08	0.05

PROGRAM: DJW (REV F)

DOG 14
EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 3.00

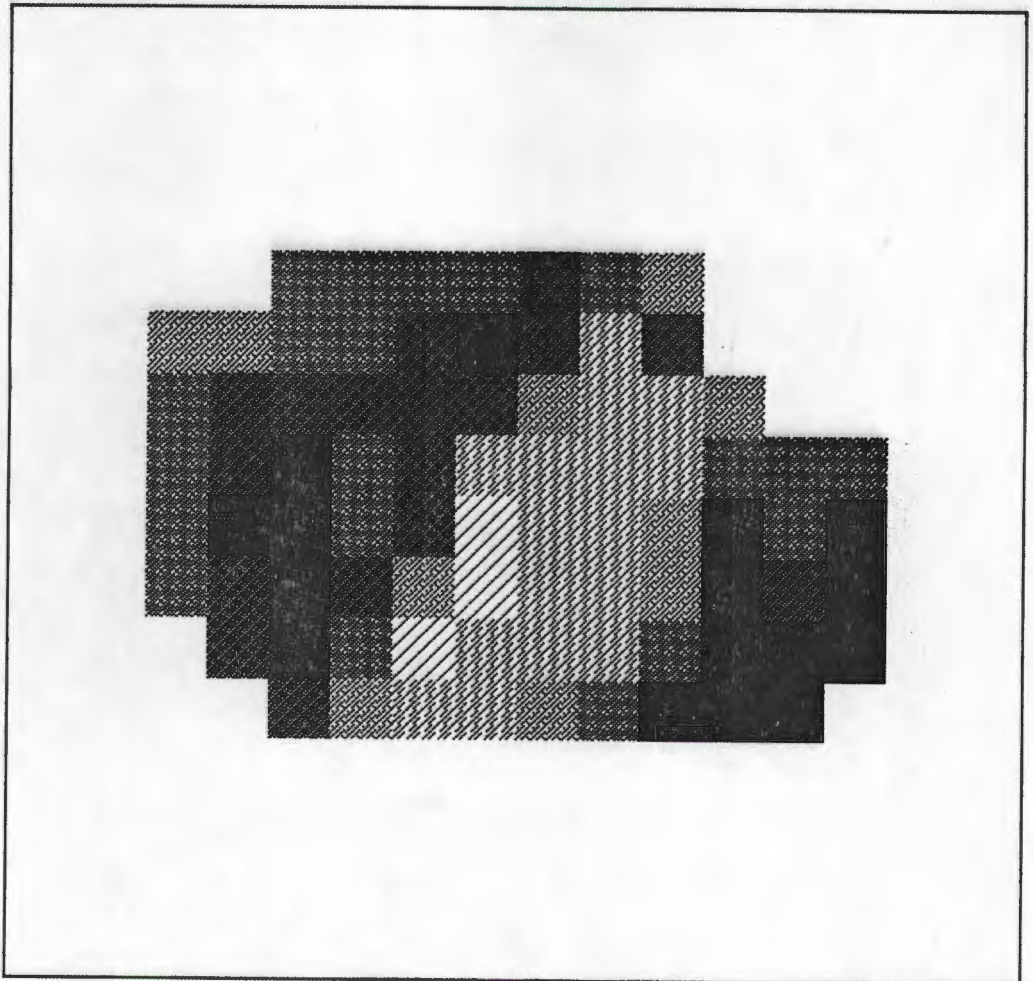


Figure 5b-19

Figure 5b-20 and 5b-21 show the pressure drop across the 65% stenosis in the anterior descending artery of Dog 12 in the state of resting vasomotor tone (flow of 0.72 ml/Gm left ventricle/minute) and coronary vasodilatation (Flow of 2.23 ml/Gm left ventricle/minute). The pressure drop is virtually identical in each case although vasodilatation is associated with increased distal coronary pulse pressure.

Figures 5b-22 and 5b-23 show respectively the endocardial and epicardial regional myocardial perfusion maps, with no apparent perfusion deficit with resting vasomotor tone.

Figures 5b-24 and 5b-25 show respectively the endocardial and epicardial maps with coronary vasodilatation. The perfusion deficit is marked. Although flow around the periphery of the jeopardised territory has increased with vasodilatation there is little increase in the central areas (in Figures 5b-22 and 5b-24 the central diagonally hatched areas are at the same scale).

EFFECT OF CORONARY VASOMOTOR TONE

DOG 12

65% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 65% STENOSIS (mean 70 mmHg). A PRESSURE DROP OF 30% IS PRESENT.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURES 5b-22 and 5b-23.

TOTAL HEART BLOOD FLOW: 96 ml/min (CORONARY SINUS DRAINAGE)
 LEFT VENTRICULAR BLOOD FLOW: 78 ml/min
 TOTAL HEART WEIGHT: 164 Gm
 LEFT VENTRICULAR WEIGHT: 109 Gm

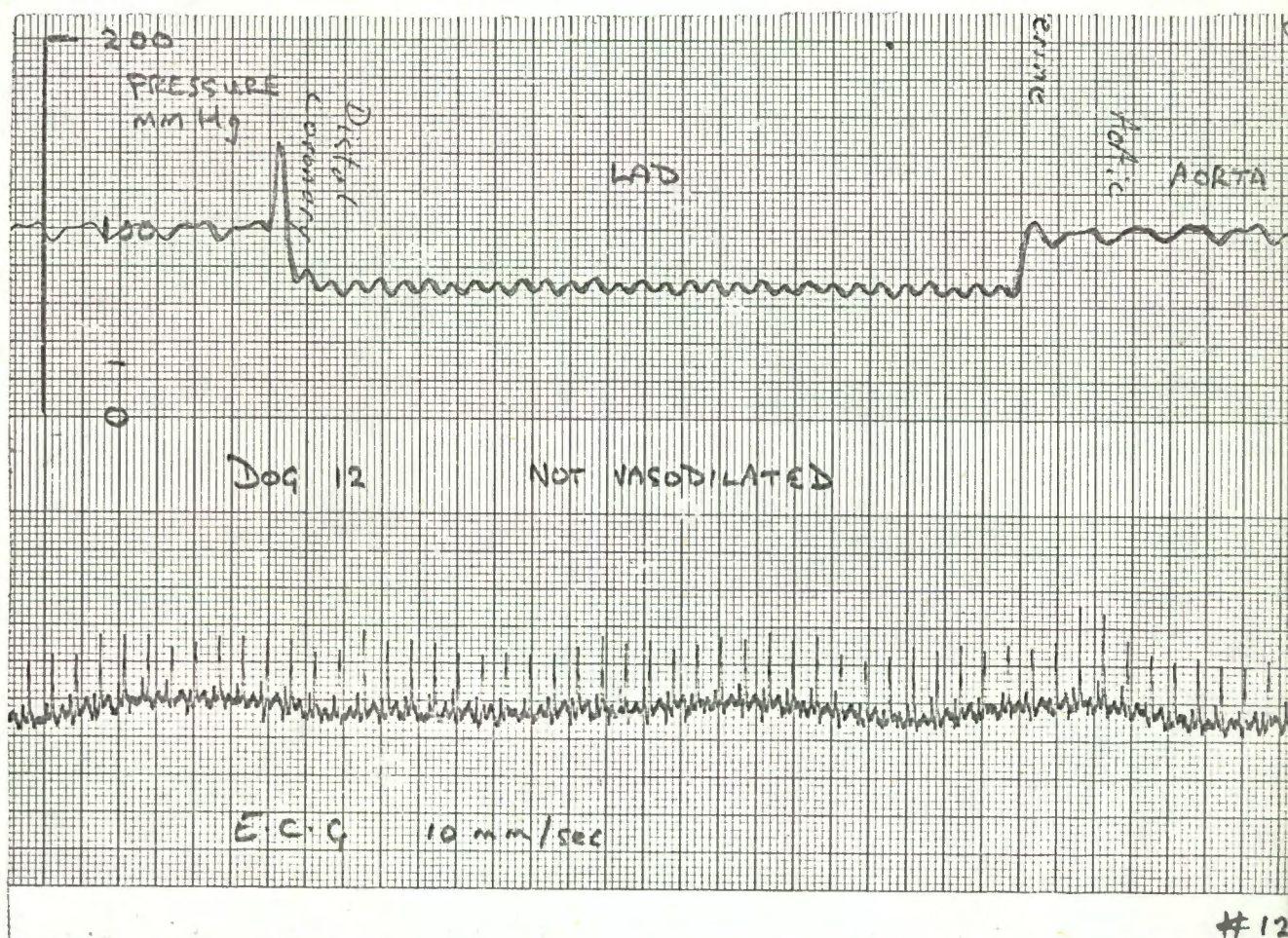


Figure 5b-20

EFFECT OF CORONARY VASOMOTOR TONE

DOG 12

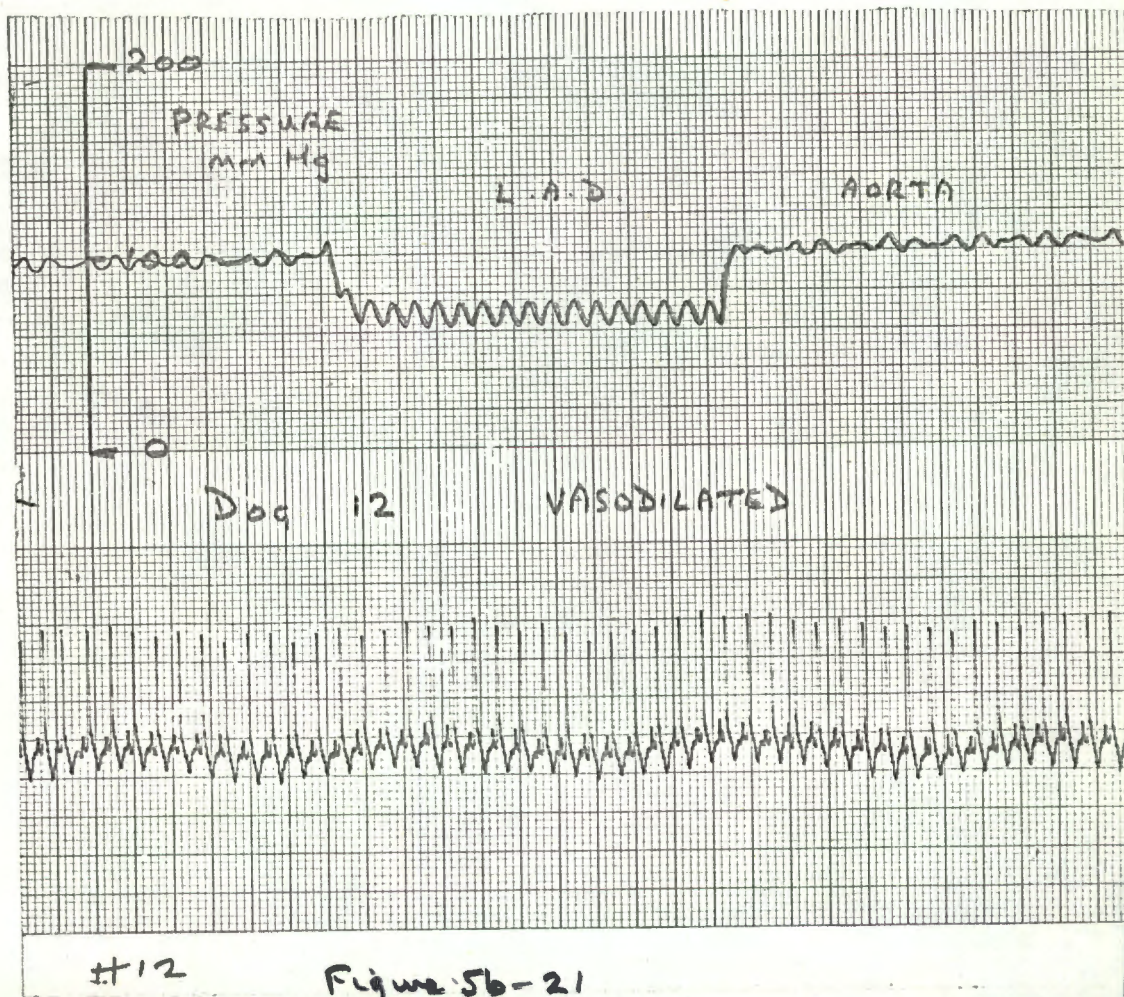
65% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION INDUCED WITH PAPAVERINE (1 mg/minute)

THIS RECORD SHOWS PRESSURE IN AORTA (100 mmHg mean) AND PRESSURE IN DISTAL ANTERIOR DESCENDING ARTERY (L.A.D.) BEYOND THE 65% STENOSIS (mean 68 mmHg). A PRESSURE DROP OF 32% IS PRESENT: DISTAL CORONARY PULSE PRESSURE IS INCREASED.

CORRESPONDING REGIONAL PERFUSION MAP IS SHOWN IN FIGURES 5b-24 and 5b-25

TOTAL HEART BLOOD FLOW: 355 ml/min (CORONARY SINUS DRAINAGE)
 LEFT VENTRICULAR BLOOD FLOW: 243 ml/min (TRACER MICROSPHERE METHOD)
 TOTAL HEART WEIGHT: 164 Gm
 LEFT VENTRICULAR WEIGHT: 109 Gm



EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

65% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.86	0.56
S.D.	0.20	0.14
S.E.M.	0.04	0.04

PROGRAM: DJW (REV F)

DOG 12

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 3.00

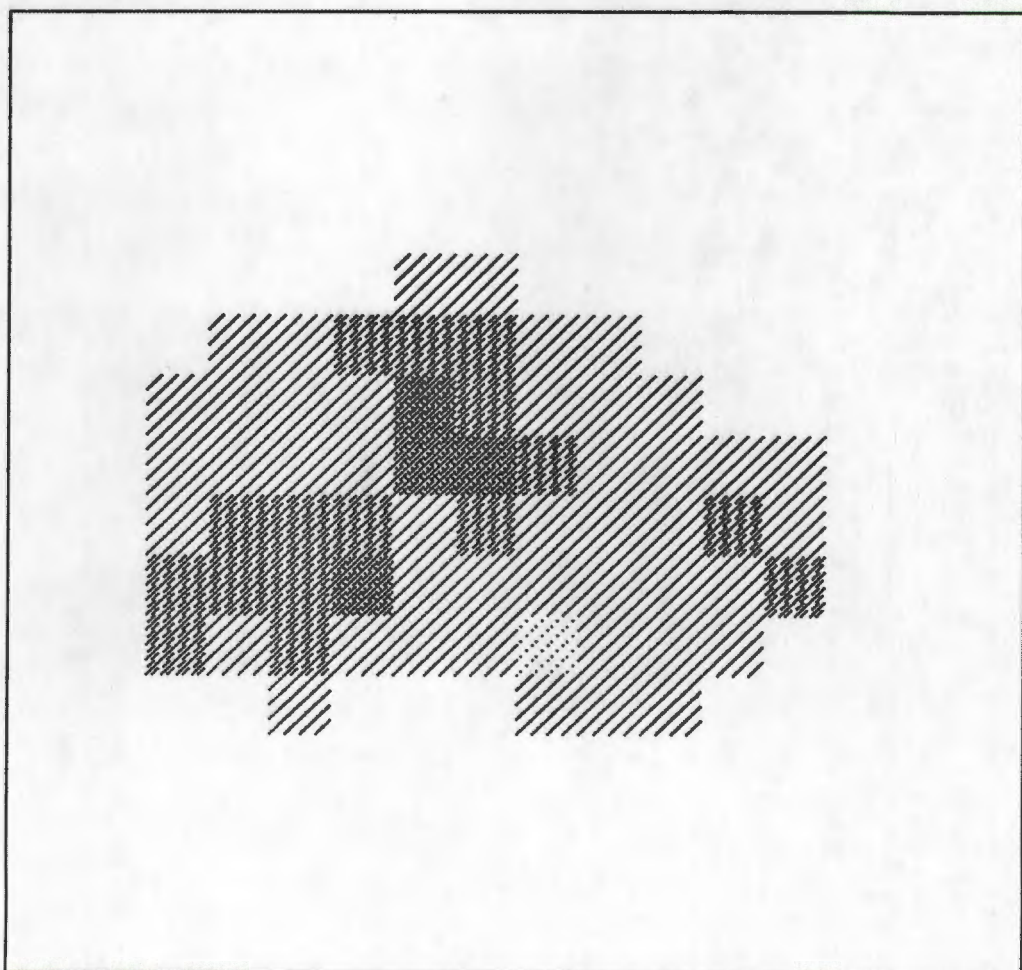


Figure 5b-22

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

65% STENOSIS OF ANTERIOR DESCENDING ARTERY

"RESTING" VASOMOTOR TONE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.60	0.56
S.D.	0.10	0.15
S.E.M.	0.02	0.04

PROGRAM: DJW (REV F)

DOG 12

EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 3.00

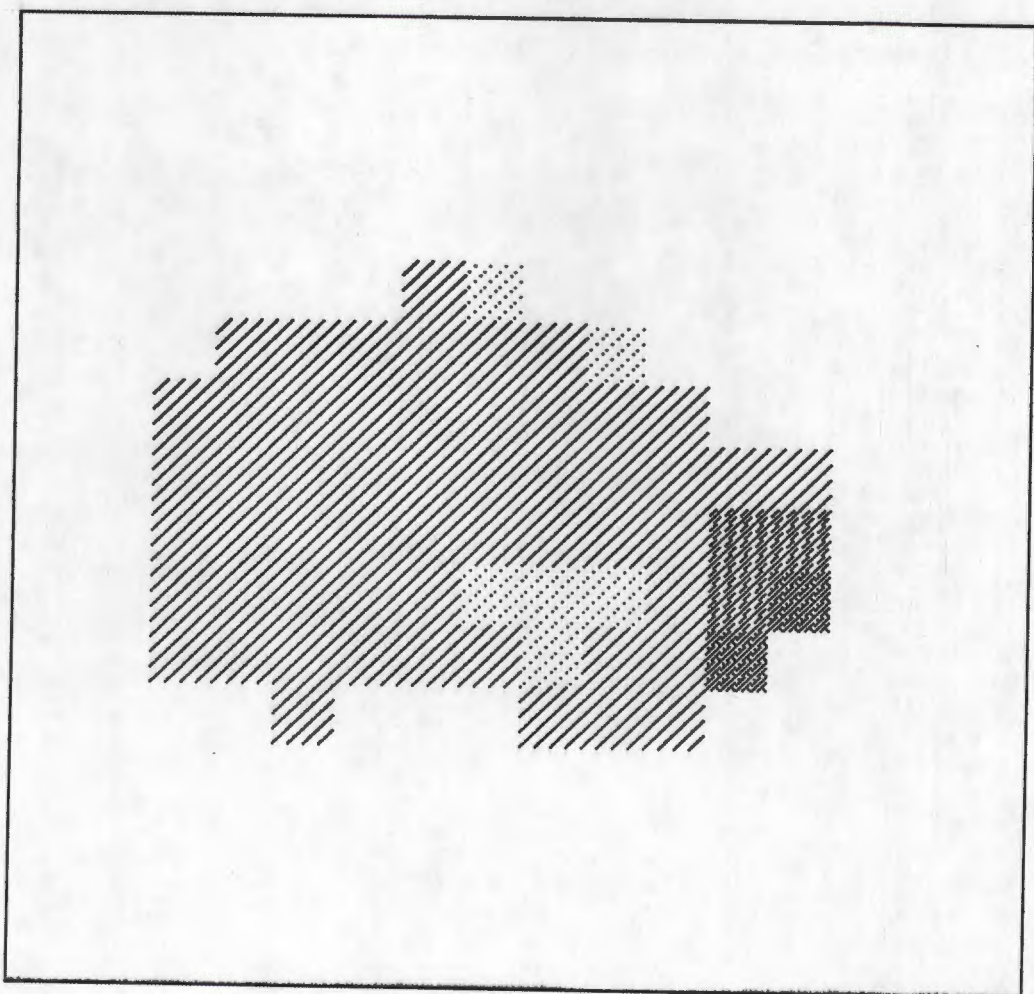


Figure 5b,23

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

65% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.79	1.17
S.D.	0.59	0.74
S.E.M.	0.12	0.19

PROGRAM: DJW (REV F)

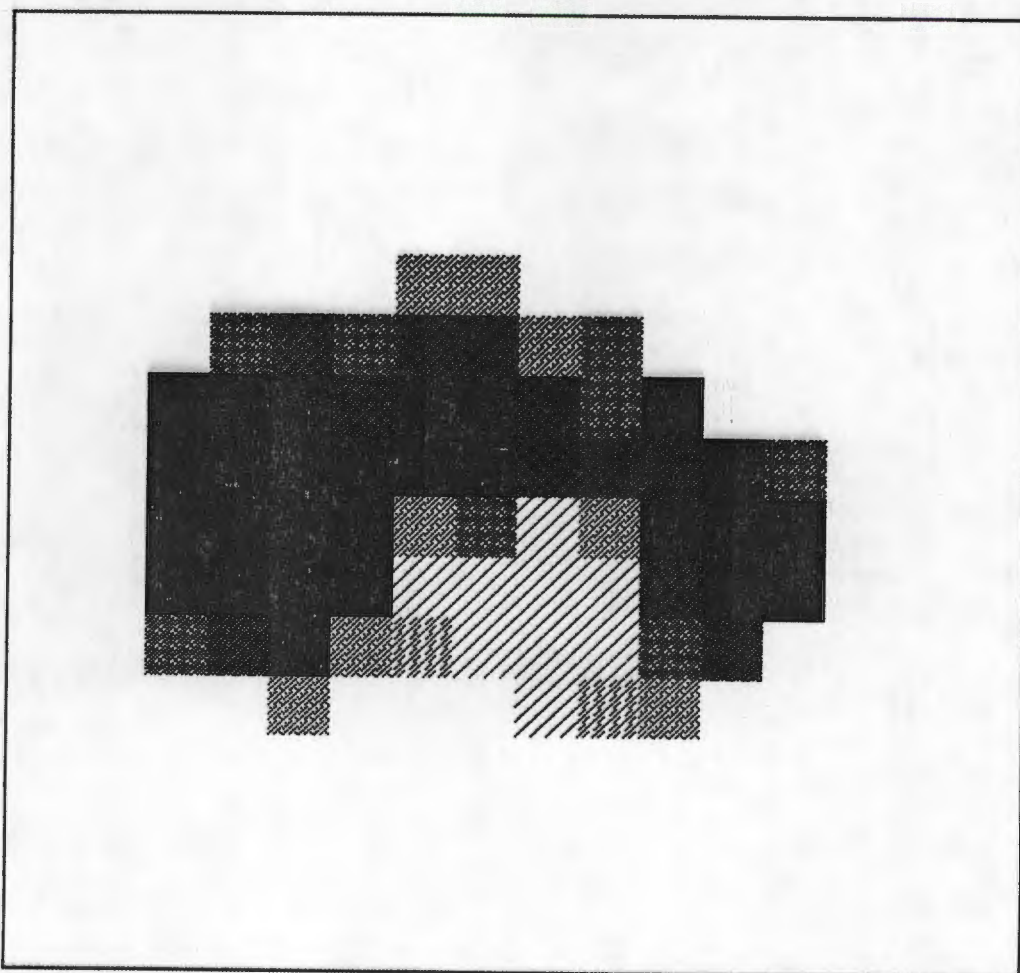
DOG 12
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3. SCALED TO 3.00

Figure 5b-24

EFFECT OF CORONARY VASOMOTOR TONE

REGIONAL MYOCARDIAL PERFUSION

65% STENOSIS OF ANTERIOR DESCENDING ARTERY

CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.69	1.22
S.D.	1.07	0.31
S.E.M.	0.22	0.08

PROGRAM: DJW (REV F)

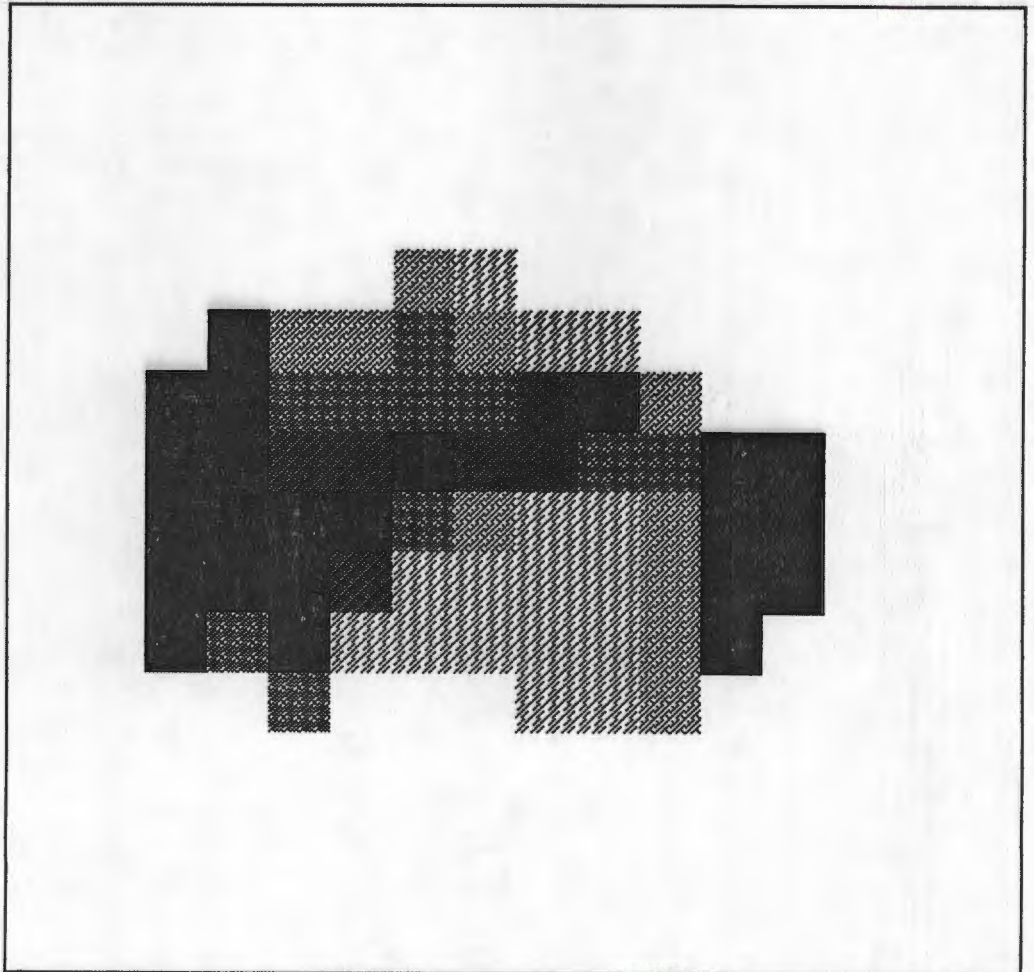
DOG 12
EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 3.00

Figure 5b-25

DISCUSSION

The animal model has shown that coronary vasodilatation with papaverine can increase myocardial perfusion considerably (between 204% and 414% in this study) and this is in keeping with other studies (Downey et al 1975).

The most striking effect of coronary vasomotor tone is the unmasking of perfusion deficits by coronary vasodilatation. This is in keeping with well known observations of clinical practice (Holman 1978). Because of this fact it is apparent that the assessment of the effect of coronary stenosis (as well as the effect of aorto-coronary bypass grafting) should take account of the state of coronary vasomotor tone.

It is clear that coronary vasodilatation induces or enhances non-homogeneous myocardial perfusion once a sufficiently severe coronary stenosis is present. The effect of coronary vasomotor tone (documented in terms of mean myocardial perfusion in the control area) in influencing myocardial perfusion in the territory jeopardised by a stenosed artery is shown in Figure 5d-30. It is clear from this that with low levels of coronary vasomotor tone (myocardial perfusion level in control area exceeding 2 ml/Gm/minute) that severe perfusion deficits arise with stenosis of 50%; and the degree of deficit is greater than with high levels of coronary vasomotor tone where stenosis of up to 80% may produce little or no perfusion deficit.

It is of considerable interest that pressure drop across the stenosis in this study was little influenced by the state of coronary vasodilatation. The pressure drop was found to be an accurate predictor of perfusion deficits under conditions of high coronary flow (whatever

the flow rate at which the pressure drop was measured). The relationship of pressure drop measured across the stenosis to myocardial perfusion in the jeopardised territory was unchanged by the state of coronary vasodilatation, and is shown for all dogs assessed in Section 5d, Figures 5d-31, 32, 33 and 34.

SECTION 5c
EFFECT OF PERFUSION PRESSURE

EFFECT OF PERFUSION PRESSURE

It is well recognised that perfusion pressure (diastolic aortic pressure in the normal working heart) is of great importance in determining the ability of the coronary tree to deliver sufficient blood to the myocardium for its needs (Gregg and Fisher 1963).

The influence of aortic perfusing pressure on myocardial perfusion in the non-working heart on cardio-pulmonary bypass is less well appreciated. It is known that in the usual range of arterial pressure the coronary circulation exhibits a degree of autoregulation which ensures appropriate myocardial perfusion in the working heart (Milnor 1974) but how this autoregulation copes on cardiopulmonary bypass over a frequently unphysiological pressure range, particularly in the presence of coronary obstruction, is of great practical significance to the coronary surgeon.

It is easy to demonstrate that flow in a graft to a coronary artery beyond an occlusion is markedly pressure-dependant. Figures 5c-1 and 5c-2 show two examples of this relationship between perfusion pressure in the aorta and flow in the bypass graft for a non-working heart on cardiopulmonary bypass.

In order to show the effect of aortic perfusion pressure on myocardial perfusion in the presence of coronary obstruction 3 dogs were investigated at different perfusion pressures, obtained by adjusting cardiopulmonary bypass flow rate. Figure 5c-3 shows the appearance of the epicardial perfusion map for Dog 29 in which a total occlusion of the anterior descending artery was present. An aortic perfusion pressure of 30 mmHg mean was maintained for 10 minutes prior to injection of tracer microspheres. Distal coronary pressure measured 20 mmHg.

No perfusion deficit is seen and all areas show exceedingly low flow. Mean control area (epicardial half) flow was 0.36 ml/Gm/minute (S.D. 0.09) but in the jeopardised anterior descending area the mean flow was only 0.04 ml/Gm/minute (S.D. 0.00).

Figure 5c-4 shows the angiographic appearances of Dog 29 - the total occlusion of the anterior descending artery is seen at the junction of block B9 and C9, and blocks D9, E8, E9, E10, F7, F8, F9, F10, G7, G9 and G10 are jeopardised and constitute the 'test' area. The myocardial perfusion map shows the regional blood flow for the endocardial half of the left ventricle. The very low flow masks the virtual absence of flow in the test area (Control area flow is 0.28 ml/Gm/minute (S.D. 0.07) and test area flow is 0.03 ml/Gm/minute (S.D. 0.01).

Figure 5c-5 shows the results with a perfusion pressure of 60 mmHg maintained for 10 minutes prior to injection of tracer microspheres. Distal coronary pressure measures 32 mmHg mean. The regional myocardial perfusion map for epicardial half of left ventricle shows a well-marked perfusion deficit in the jeopardised test area of totally occluded anterior descending territory. Epicardial flow in the control area is 2.35 ml/Gm/minute (S.D. 0.46) and in the test area is 0.39 ml/Gm/minute (S.D. 0.11).

Figure 5c-6 shows the angiographic appearance together with the regional myocardial perfusion map for the endocardial half of left ventricle at 60 mmHg perfusion pressure. Endocardial flow in the control area is 1.67 ml/Gm/minute (S.D. 0.30) and in the test area is 0.23 ml/Gm/minute (S.D. 0.09).

Figure 5c-7 shows the results with a perfusion pressure of 90 mmHg maintained for 10 minutes prior to injection of tracer microspheres. Distal coronary pressure measures 40 mmHg mean. The regional myocardial perfusion map for epicardial half of left ventricle shows

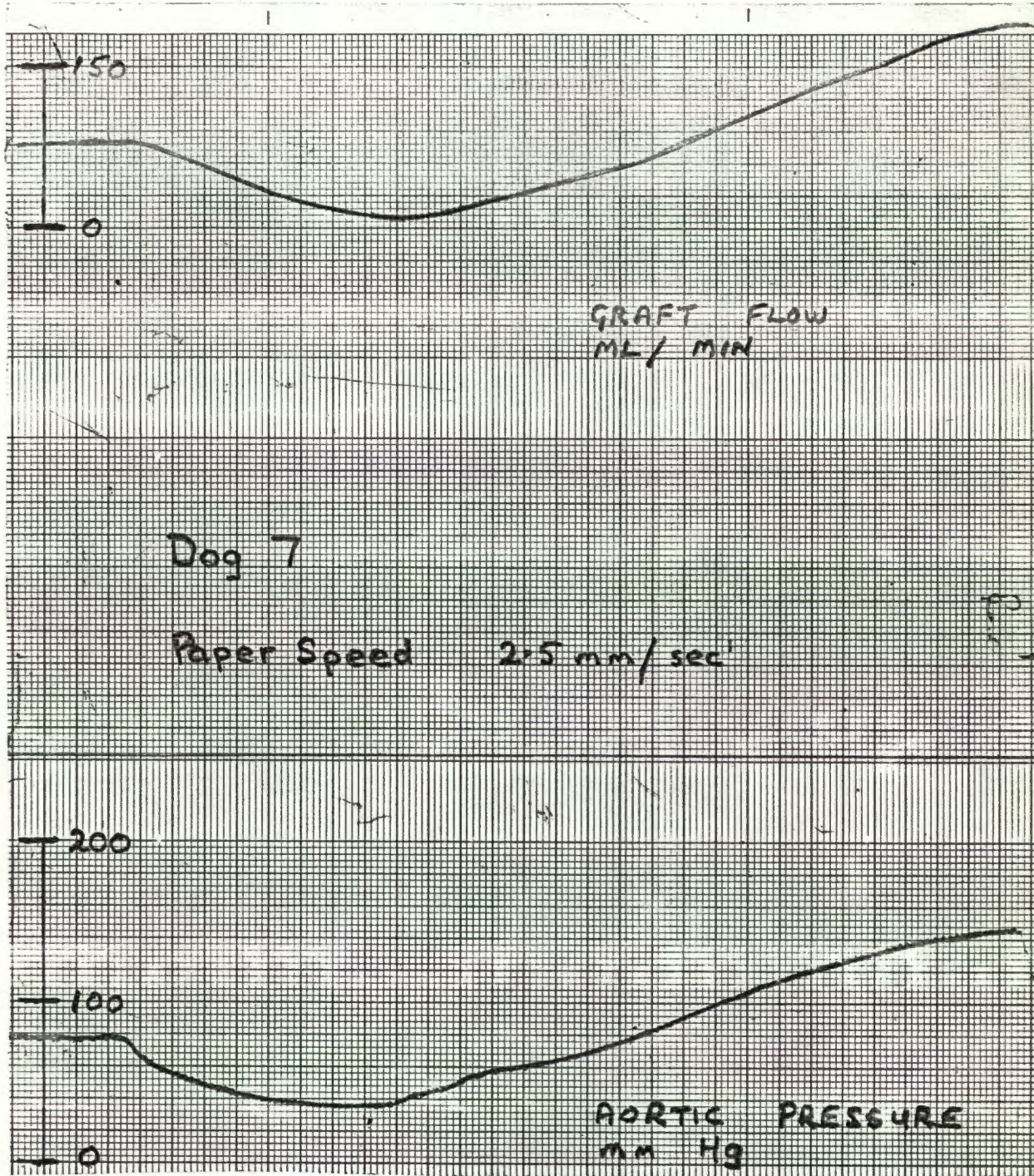
a marked perfusion deficit but with fairly high levels of flow in the test area. Epicardial flow in the control area is 3.21 ml/Gm/minute (S.D. 0.63) and in the test area 1.19 ml/Gm/minute (S.D. 0.25).

Figure 5c-9 shows again the angiographic appearances with a similar perfusion map for endocardial half of left ventricle. Endocardial flow in the control area is 2.43 ml/Gm/minute (S.D. 0.60) and in the test area is 0.78 ml/Gm/minute (S.D. 0.23).

Figure 5c-9 shows the results with a perfusion pressure of 120 mmHg maintained for 10 minutes prior to injection of tracer microspheres. Distal coronary pressure is 50 mmHg mean. The regional myocardial perfusion map (all are at the same scaling factor of 5.00) shows high flow even in the test area for epicardial half of left ventricle. Epicardial flow in the control area is 4.11 ml/Gm/minute (S.D. 0.90) and in the test area is 1.80 ml/Gm/minute (S.D. 0.41).

Figure 5c-10 shows the perfusion map for endocardial half of left ventricle at this high pressure. Endocardial flow in the control area is 4.82 ml/Gm/minute (S.D. 0.63) and in the test area is 1.09 ml/Gm/minute (S.D. 0.45).

EFFECT OF PERFUSION PRESSURE ON CORONARY BLOOD FLOW

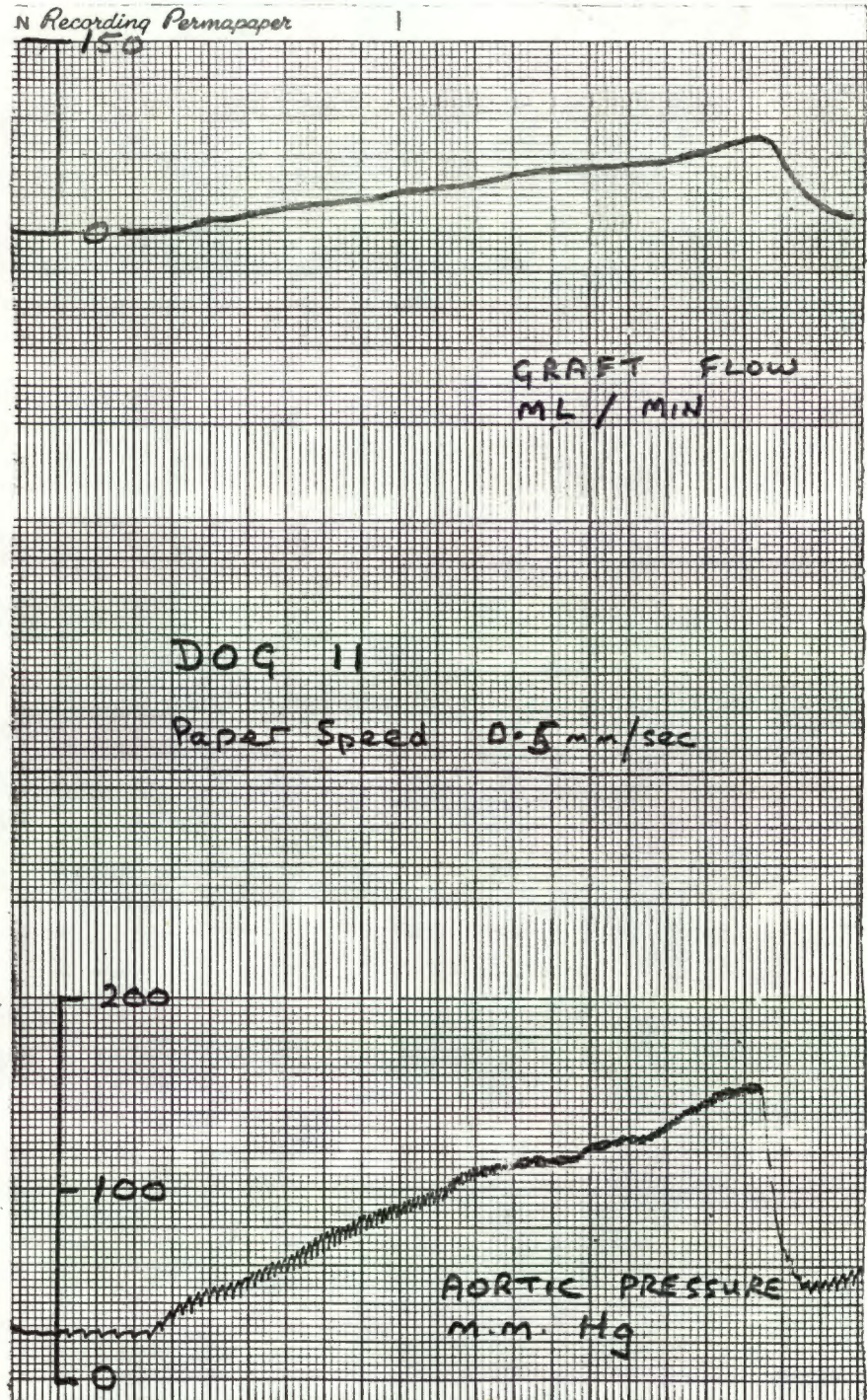


Dog 7

This shows mean blood flow (ml/minute) in a graft to the anterior descending artery just beyond a total occlusion with varied aortic pressure

Figure 5c-1

EFFECT OF PERFUSION PRESSURE ON CORONARY BLOOD FLOW



Dog 11

This shows mean blood flow (ml/minute) in a graft inserted into the anterior descending artery just beyond a 75% stenosis with varied aortic pressure

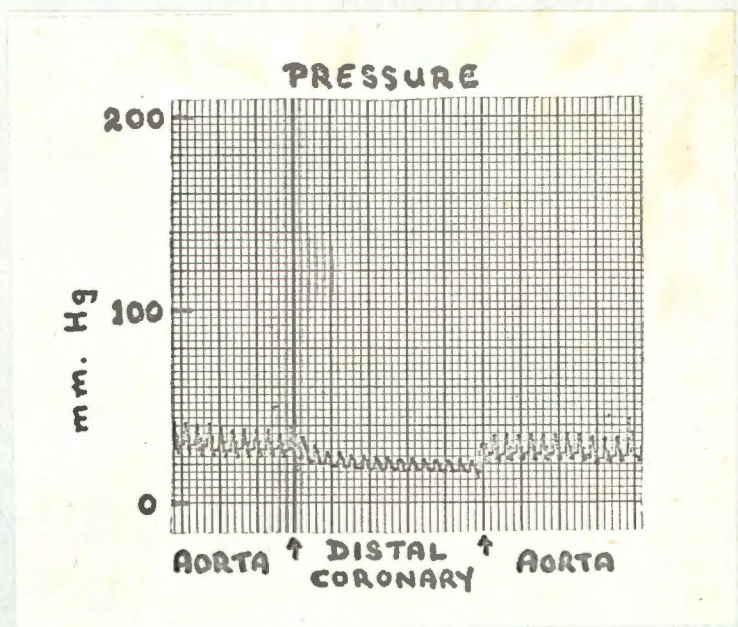
REGIONAL MYOCARDIAL PERFUSION
EFFECT OF PERFUSION PRESSURE

TOTAL OCCLUSION OF
ANTERIOR DESCENDING
CORONARY ARTERY

HEART RATE 180/MIN

LEFT VENTRICULAR
CAVITY PRESSURE 0

AORTIC PRESSURE
30 mm Hg mean



PROGRAM: DJW (REV F)

DOG 29
EPICARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 5.00

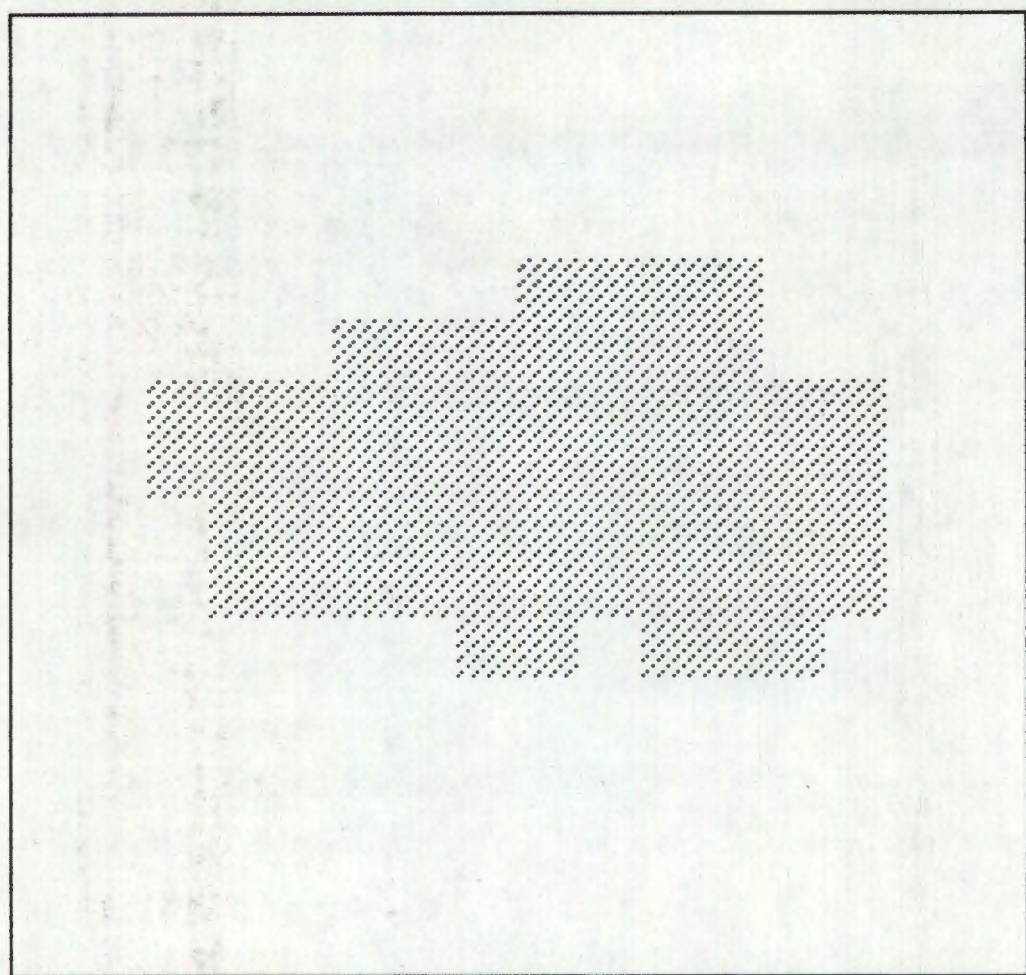


Figure 5c-3

29

187

A
B
C
D
E
F
G
H

1 2 3 4 5 6 7 8 9 10 11 12

DOG 29

MEAN AORTIC PRESSURE 30 mm Hg

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4. SCALED TO 5.00

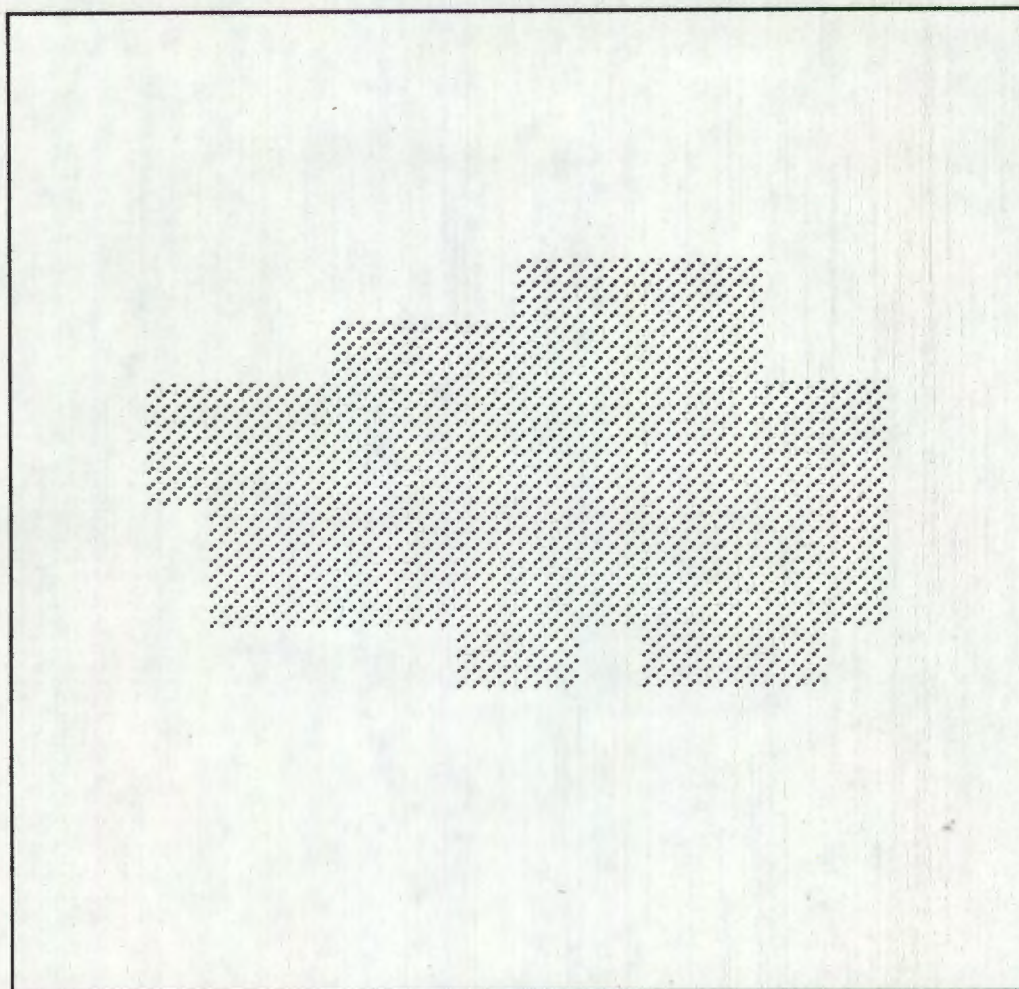


Figure Sc-4

REGIONAL MYOCARDIAL PERFUSION

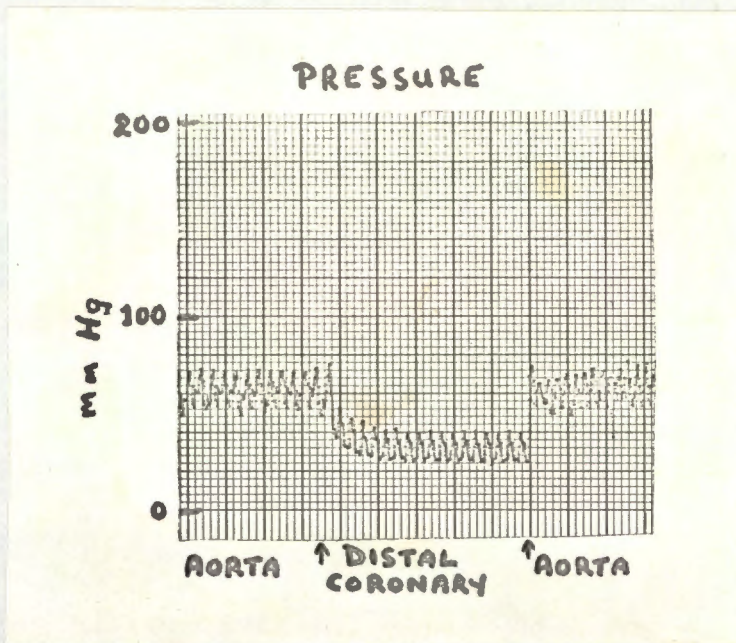
EFFECT OF PERFUSION PRESSURE

TOTAL OCCLUSION OF
ANTERIOR DESCENDING
CORONARY ARTERY

HEART RATE 180/MIN

LEFT VENTRICULAR
CAVITY PRESSURE 0

AORTIC PRESSURE
60 mm Hg mean



PROGRAM: DJW (REV F)

DOG 29
EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 5.00

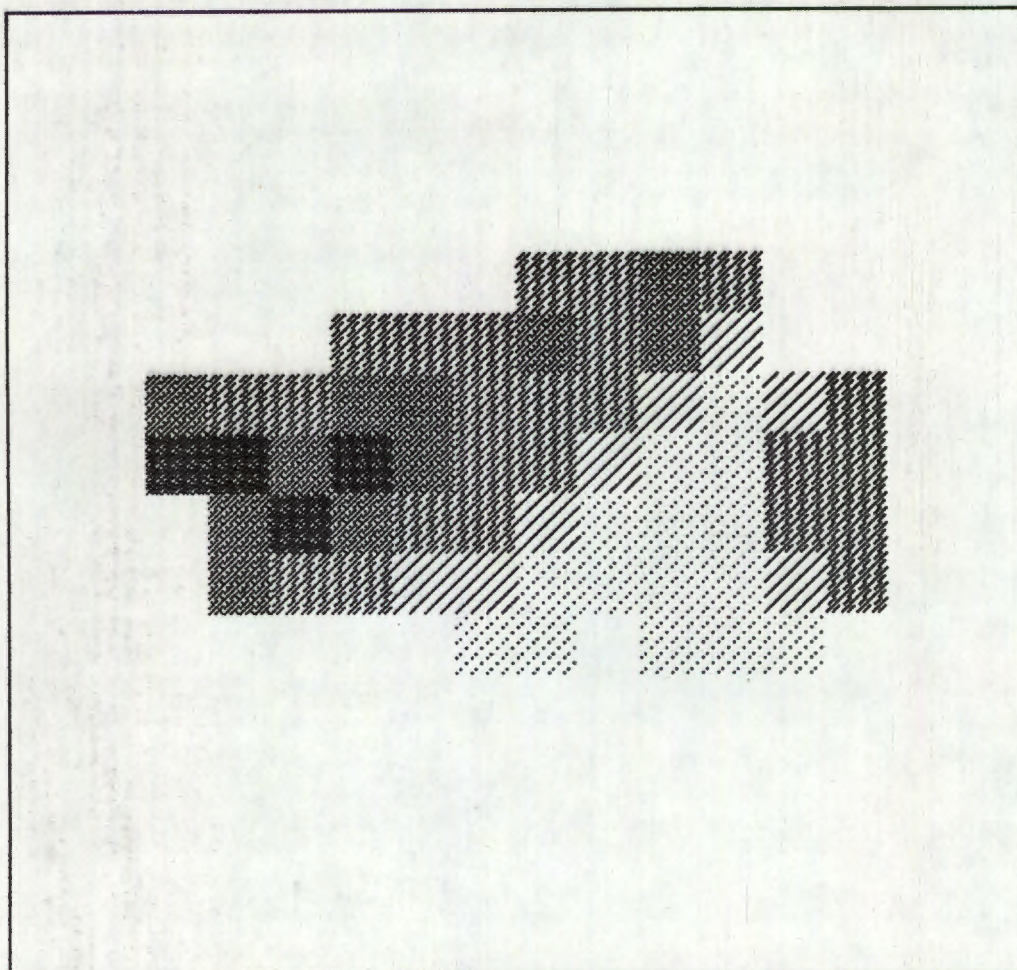


Figure Sc-5

29

A
B
C
D
E
F
G
H

1 2 3 4 5 6 7 8 9 10 11 12

DOG 29

MEAN AORTIC PRESSURE 60 mm Hg

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1. SCALED TO 5.00

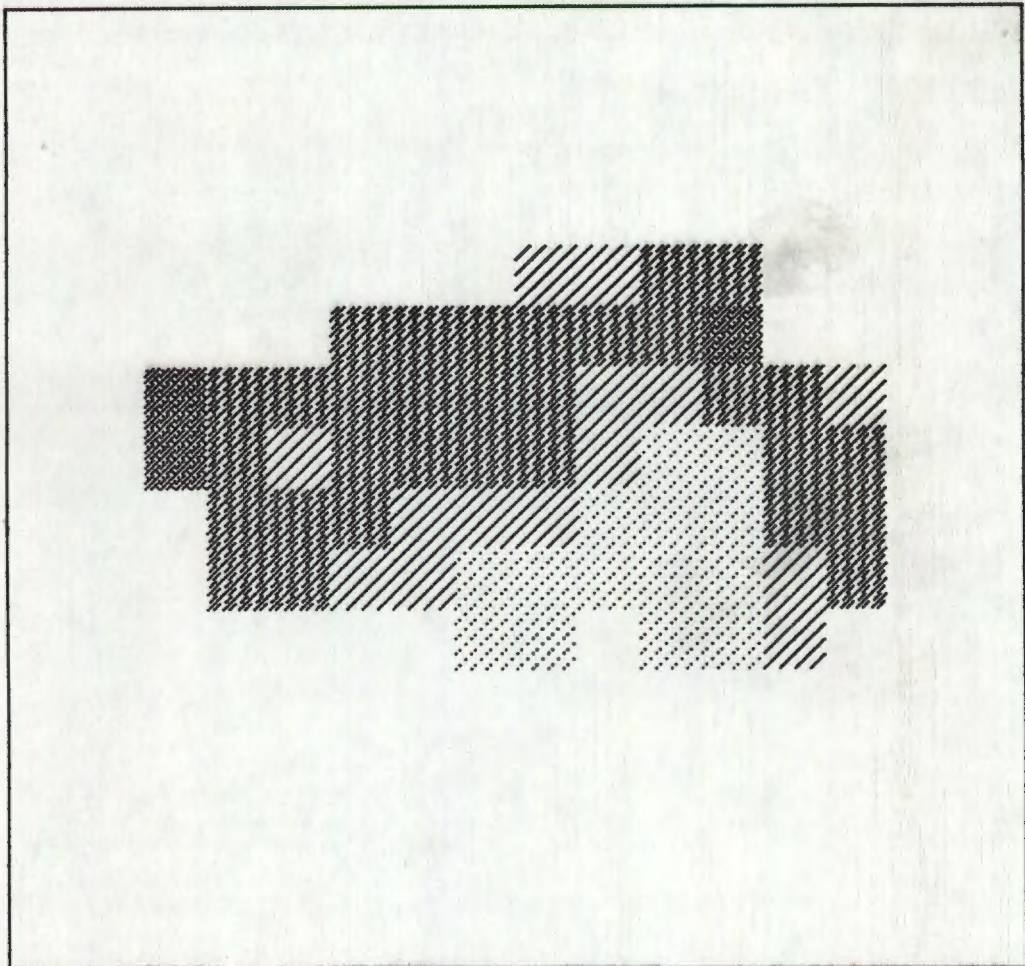


Figure 5c-6

REGIONAL MYOCARDIAL PERFUSION

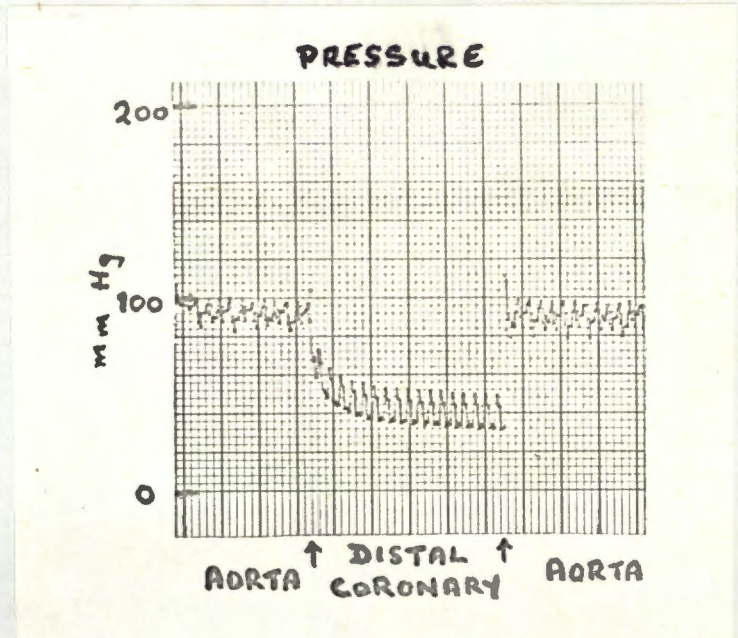
EFFECT OF PERFUSION PRESSURE

TOTAL OCCLUSION OF
ANTERIOR DESCENDING
CORONARY ARTERY

HEART RATE 180/MIN

LEFT VENTRICULAR
CAVITY PRESSURE 0

AORTIC PRESSURE
90 mm Hg mean



PROGRAM: DJW (REV F)

DOG 29

EPICARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 5.00

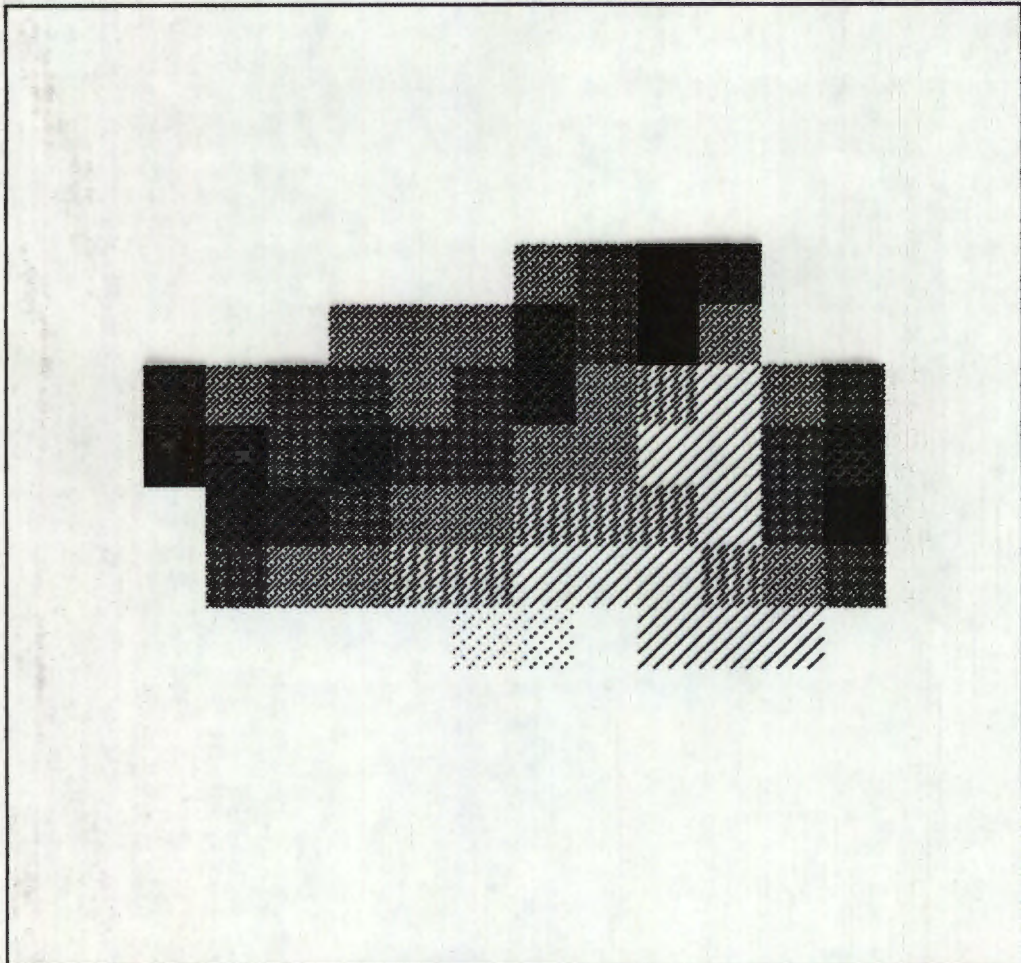


Figure 5c-7

29

191

A
B
C
D
E
F
G
H

1 2 3 4 5 6 7 8 9 10 11 12

DOG 29

MEAN AORTIC PRESSURE 90 mm Hg

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 5.00

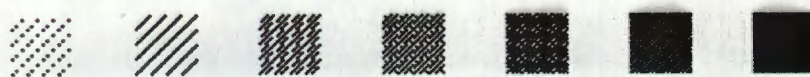
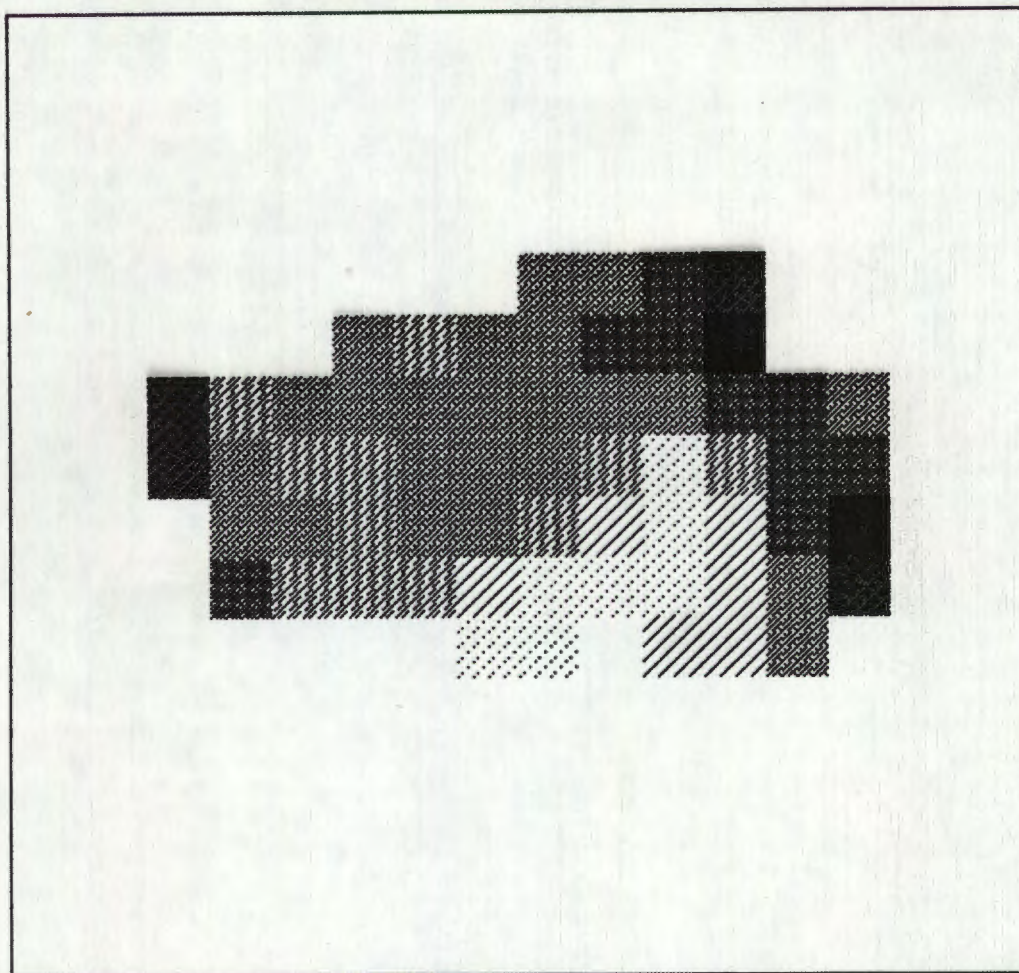


Figure 5c-8

REGIONAL MYOCARDIAL PERFUSION

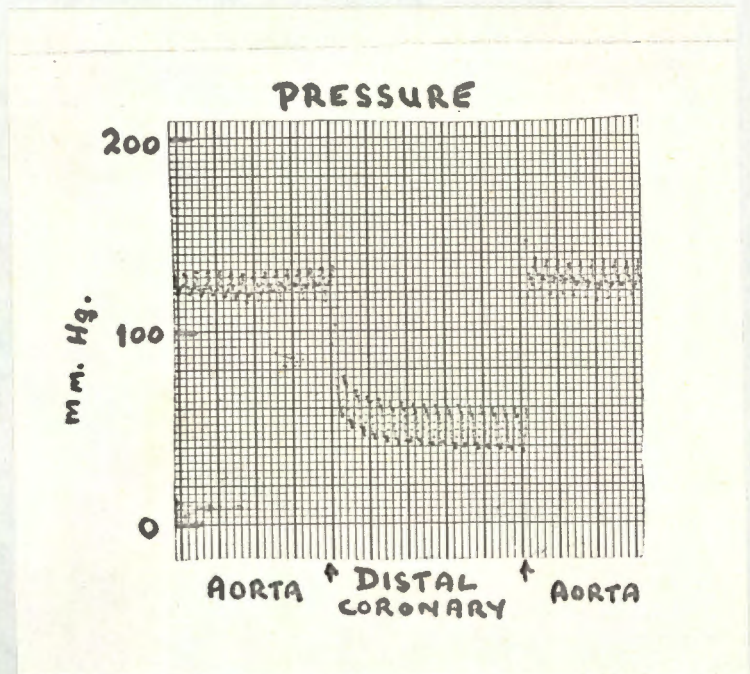
EFFECT OF PERFUSION PRESSURE

TOTAL OCCLUSION OF
ANTERIOR DESCENDING
CORONARY ARTERY

HEART RATE 180/MIN

LEFT VENTRICULAR
CAVITY PRESSURE 0

AORTIC PRESSURE
120 mm. Hg mean



PROGRAM: DJW (REV F)

DOG 29
EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 5.00

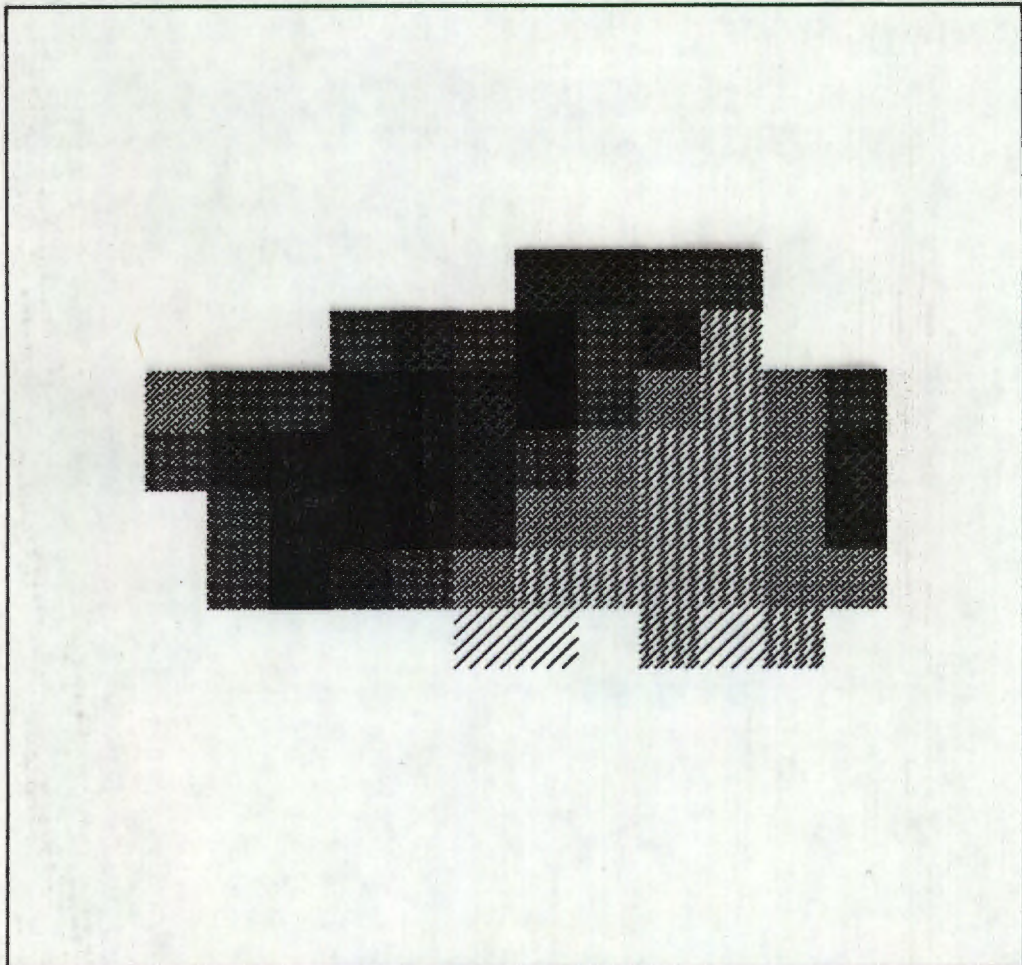
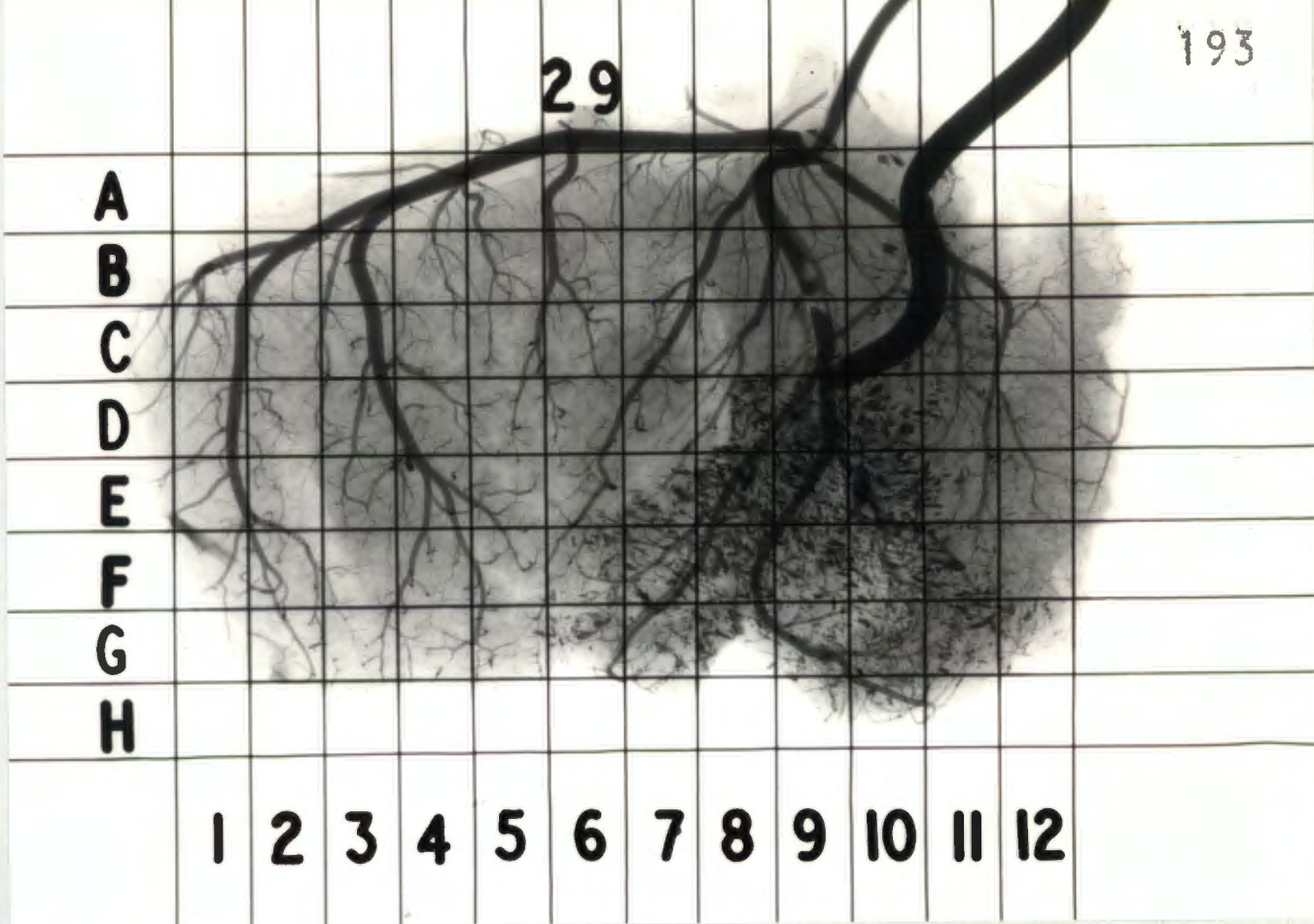


Figure 5c-9

29



DOG 29

MEAN AORTIC PRESSURE 120 mm Hg

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 5.00

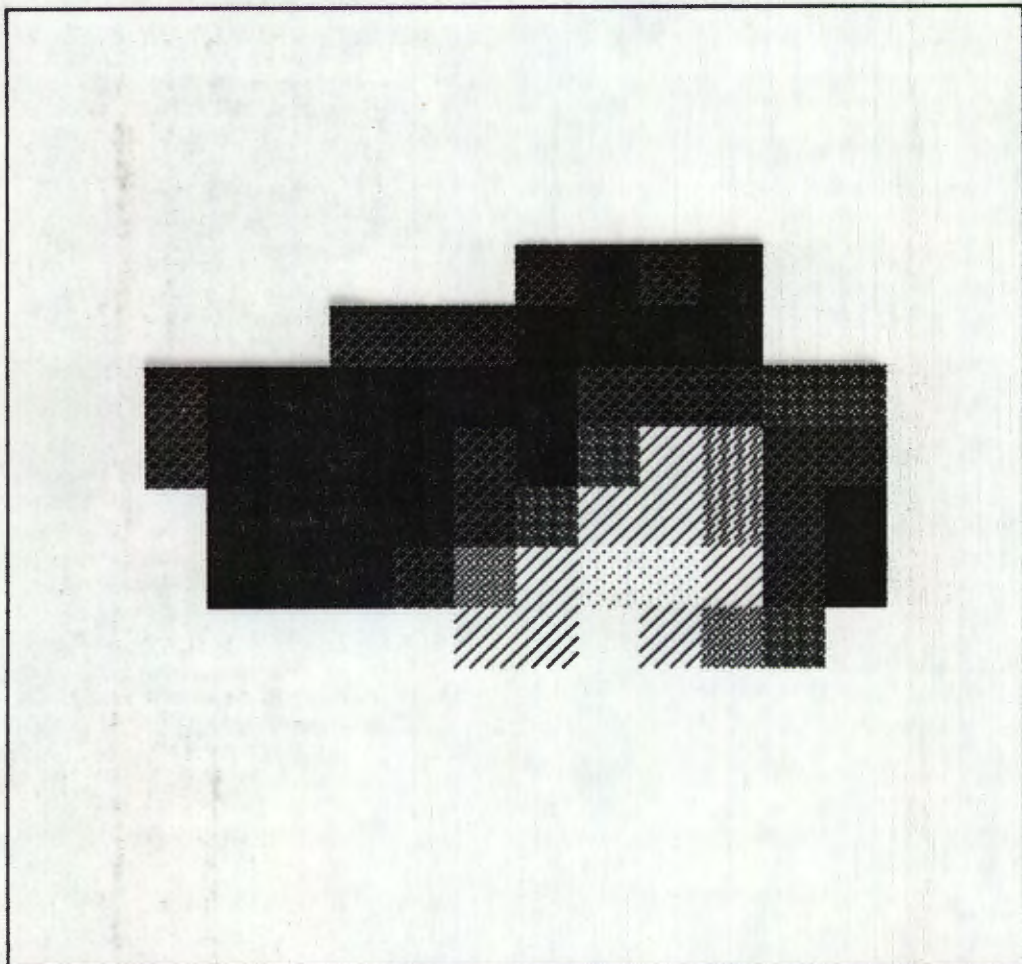


Figure Sc-10

DISCUSSION

Although the relation of graft flow to perfusion pressure (Figures 5c-1 and 5c-2) is often recognised by coronary surgeons, the much more striking relationship of jeopardised myocardial flow to perfusion pressure is not as widely appreciated. In this study, the level of perfusion to the jeopardised territory was markedly reduced at 30 mmHg perfusion pressure. Even allowing for the fact that this is in a non-working heart the low flow is unlikely to sustain normal viability and metabolism of the jeopardised myocardium. However, with levels of perfusion pressure of 90 mmHg or 120 mmHg perfusion of the jeopardised area via the naturally occurring collaterals of the dog succeed in maintaining mean flow in excess of normal requirements for a working heart at rest. (Gregg and Fisher 1963).

The considerable variation in perfusion pressure obtainable at clinical surgery makes these observations of great practical significance (see Section 6a and Section 7).

SECTION 5d
EFFECT OF VARIED STENOSES

EFFECT OF VARIED STENOSES

Knowledge of the functional effect of stenosis in a coronary artery is fundamental to logical application of surgical treatment. Current investigations rely on the angiographic demonstration of areas of narrowing in the coronary arteries (Section 3b). In spite of the considerable efforts in developing clinical means of assessing regional perfusion for clinical use (Holman 1977; Resnekov 1977; Miller 1977) the techniques are not yet in widespread use, and do not give the surgical information necessary - the surgeon can only "revascularise" vessels, not areas of underperfusion.

In order to study the effect of varied stenoses on myocardial perfusion 28 dogs were assessed for myocardial perfusion by the tracer microsphere method as described in Section 4c with varied vasomotor tone (vasodilatation induced by papaverine as described in Section 5b). Each animal was assessed with an anatomically normal coronary tree; with two different degrees of coronary constriction produced by accurately tying a ligature around each of two accurately sized drill-bit obturators introduced into the coronary lumen via the arteriotomy used for insertion of the bypass graft (Section 4c); and with total coronary occlusion produced by tying a ligature at the stenosis site. The degree of stenosis was estimated as a percentage reduction of vessel diameter by measuring the vessel diameter from its angiographic appearance with a vernier gauge and having micrometer measurements of the drill-bit obturators. Further documentation of the degree of stenosis was obtained by measuring the pressure drop across the artificial stenosis with a constant 100mmHg mean aortic pressure (See Figure 4-2).

The technique has been described in detail for experiment 27 in Section 4c. Further examples are illustrated here.

Figure 5d-1 shows the appearance of the opened left ventricle of Dog 20 in which varied stenoses of the anterior descending coronary artery were assessed.

Figure 5d-2 shows the same heart superimposed on the grid. The drill-bit obturators used for producing the two different stenoses (calculated from the angiographic appearance to be 58% and 70% of lumen diameter loss) are seen in the lower right corner. The anatomical extent of the jeopardised myocardium was assessed as comprising blocks E7, E8, E9, F6, F7, F8, F9, F10, G6, G7, G8, G9, G10, H6, H7, H8, H9, H10 - and these blocks were assessed numerically for calculation of quantitative changes.

Figures 5d-3 to 5d-8 inclusive show the qualitative data in the form of regional myocardial perfusion maps, together with the quantitative data for each degree of coronary stenosis and for endocardial and epicardial halves of the myocardium.

Figure 5d-9 shows the pressure drop across the stenoses assessed in this experiment.

It can be seen from Figure 5d-3 that a 58% stenosis of the anterior descending artery produces a mild perfusion deficit in spite of vasodilatation and high coronary flow. The perfusion deficit is just apparent, but is by no means marked. There is a reduction in perfusion in the "test" area to 71% of control value (1.52 ml/gm/min in test area; 2.13 ml/gm/min in control area). Figure 5d-4 shows similar data for the epicardial half of the myocardium ("test" area perfusion 78% of control value)

Figures 5d-5 and 5d-6 show the data for a 70% stenosis - the perfusion deficit is more marked ("test" area 35% and 61% of control values for endocardial and epicardial halves respectively).

Figures 5d-7 and 5d-8 show the data for total occlusion. The perfusion deficit is both more extensive anatomically and of greater degree ("test" area 22% and 24% of control values for endocardial and epicardial halves respectively).

Figure 5d-9 shows the pressure drop across the 58% stenosis, the 70% stenosis and the total occlusion.

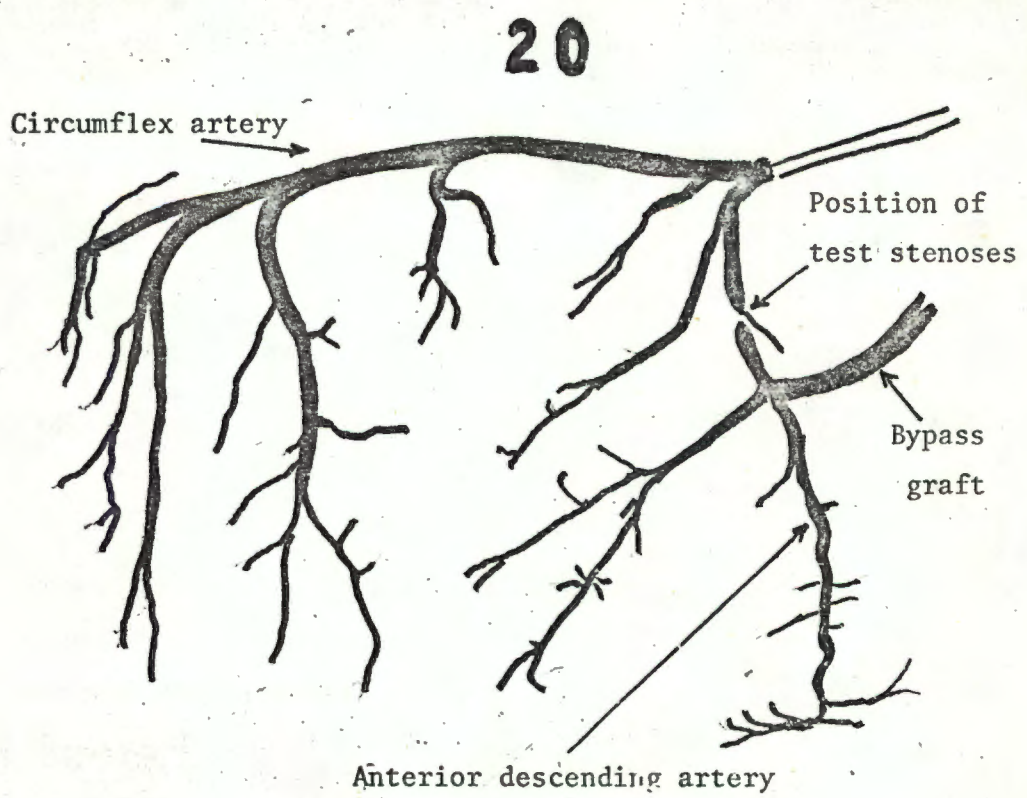
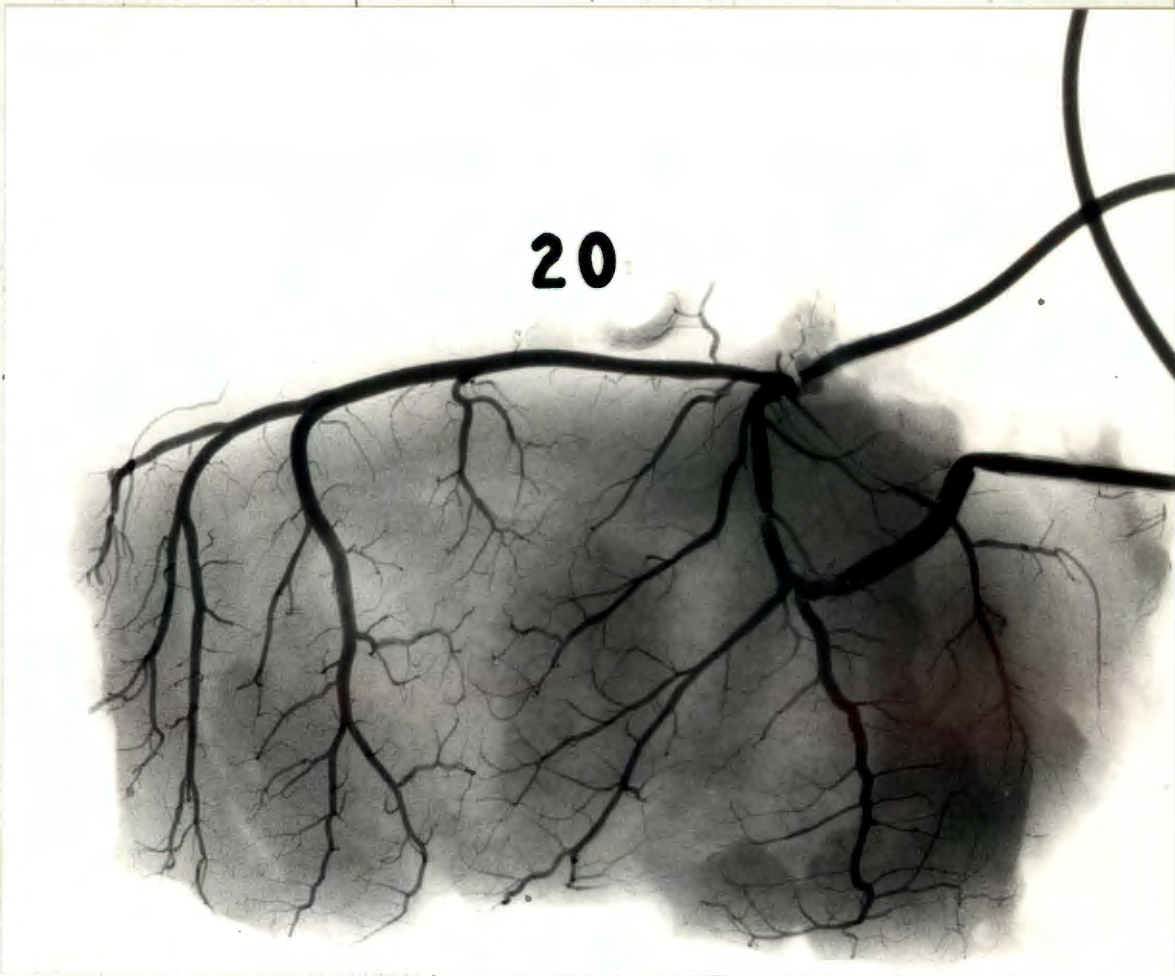
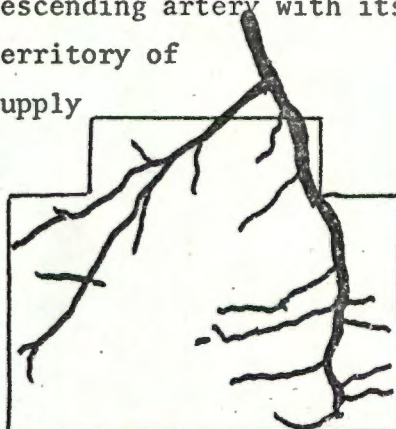


Figure 5d - 1

20

A
B
C
D
E
F
G
H

Jeopardised anterior
descending artery with its
territory of
supply



1 2 3 4 5 6 7 8 9 10 11 12

Drill-bit obturators
used for producing stenoses

20

A
B
C
D
E
F
G
H

1 2 3 4 5 6 7 8 9 10 11 12

Figure 5d - 2

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

58% STENOSIS OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.13	1.52
S.D.	0.65	0.38
S.E.M.	0.12	0.09

PROGRAM: DJW (REV F)

DOG 20
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 5.00

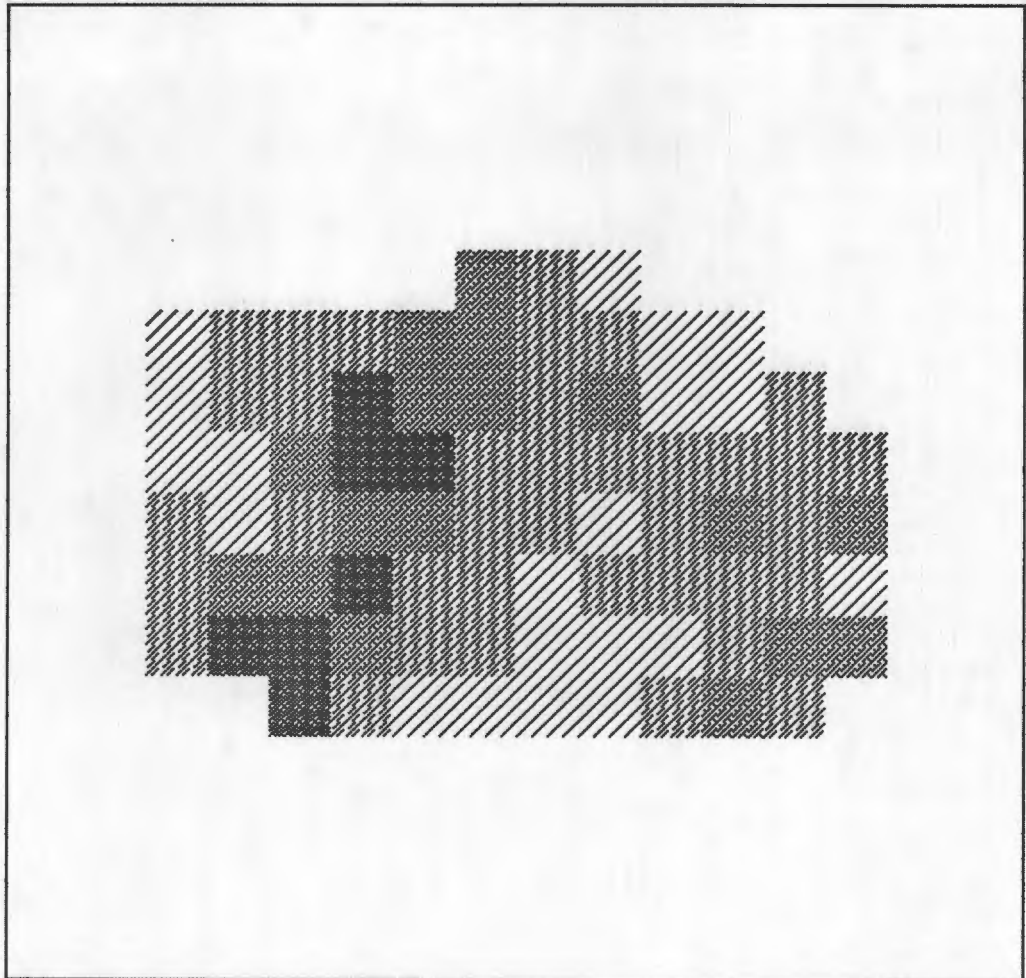


Figure 5d-3

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

58% STENOSIS OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.43	1.12
S.D.	0.23	0.32
S.E.M.	0.04	0.08

PROGRAM: DJW (REV F)

DOG 20

EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 5.00

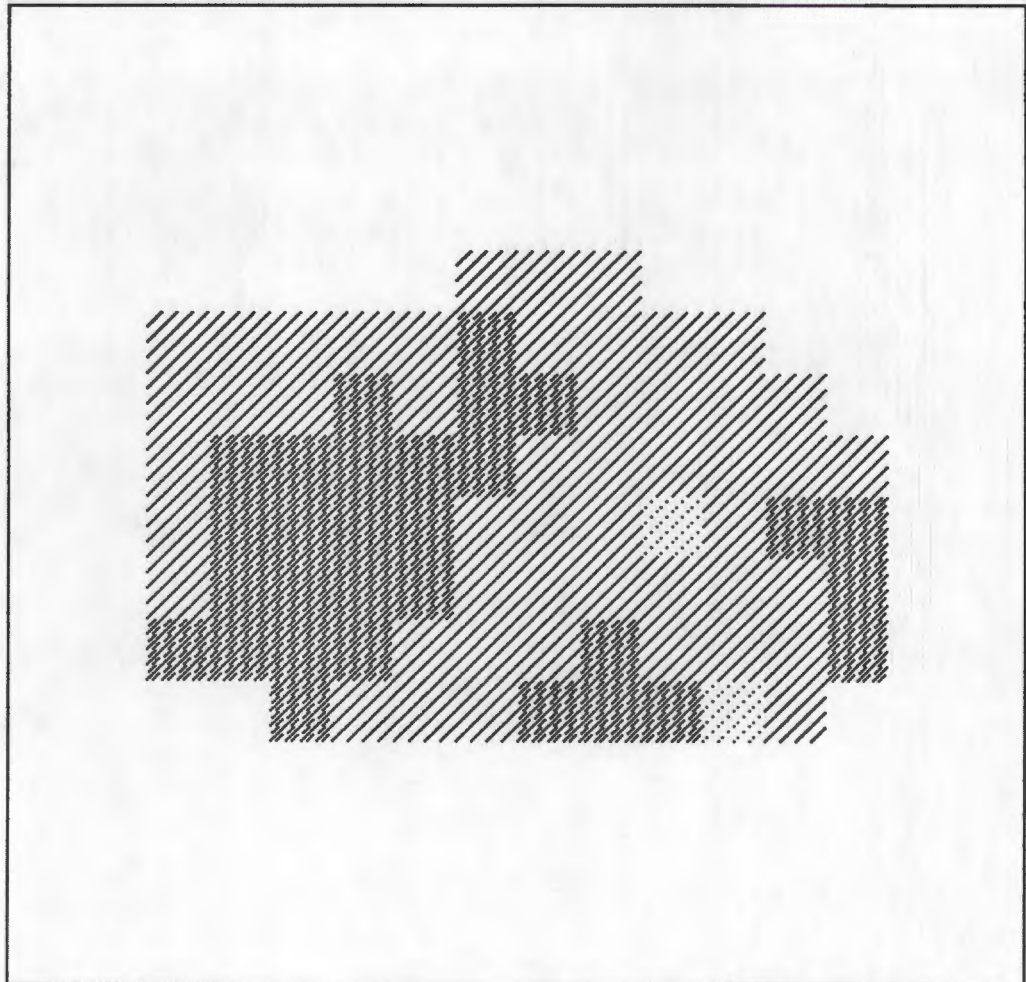


Figure 5d-4

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	3.02	1.07
S.D.	0.97	0.71
S.E.M.	0.19	0.17

PROGRAM: DJW (REV F)

DOG 20

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 5.00

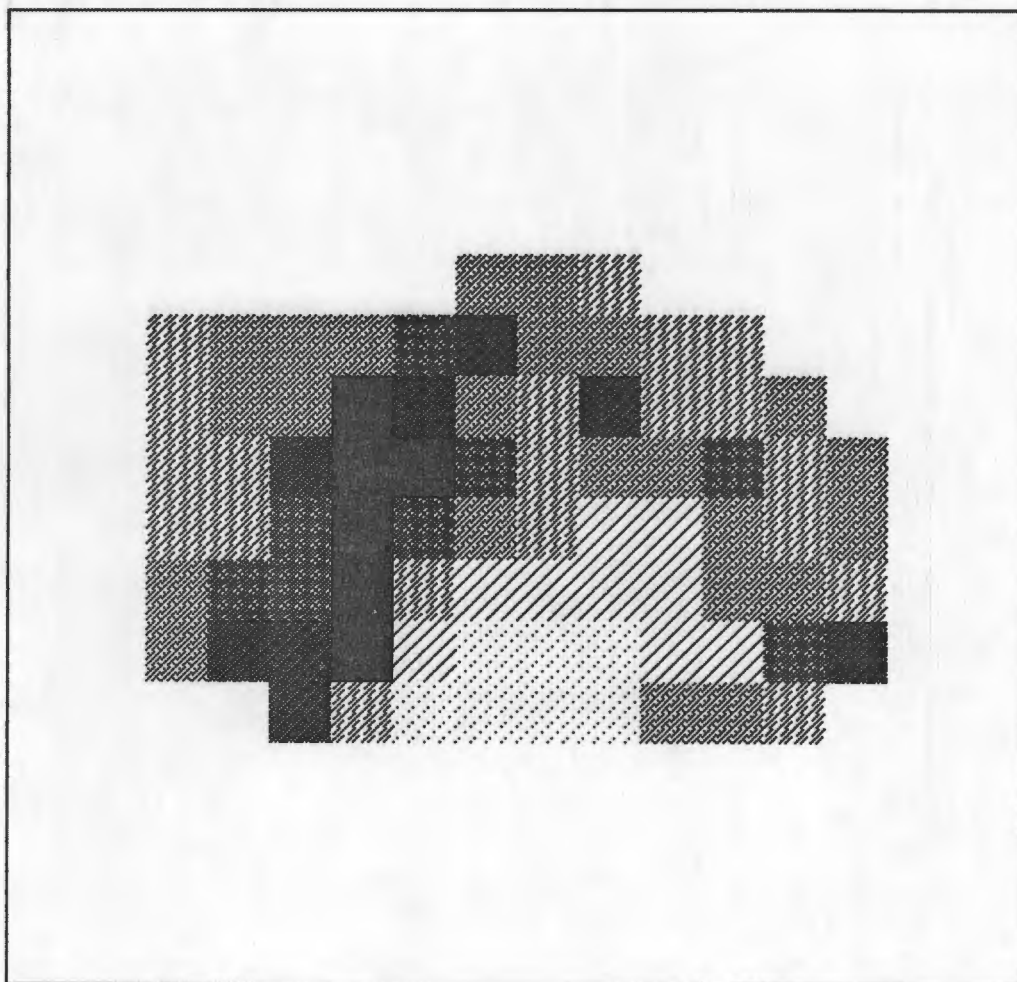


Figure 5d-5

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

70% STENOSIS OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.74	1.07
S.D.	0.34	0.22
S.E.M.	0.07	0.05

PROGRAM: DJW (REV F)

DOG 20
EPICARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 5.00

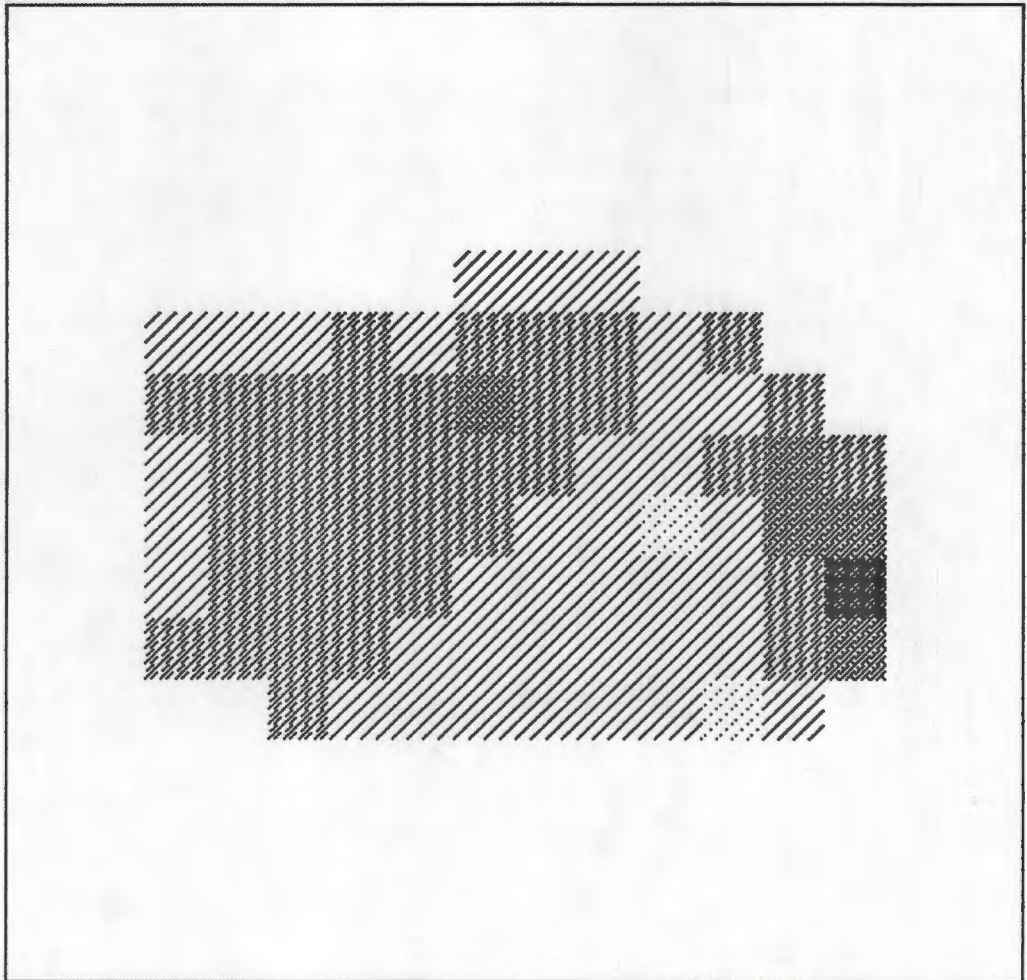


Figure 5d-6

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.07	0.45
S.D.	0.55	0.57
S.E.M.	0.11	0.13

PROGRAM: DJW (REV F)

DOG 20

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 5.00

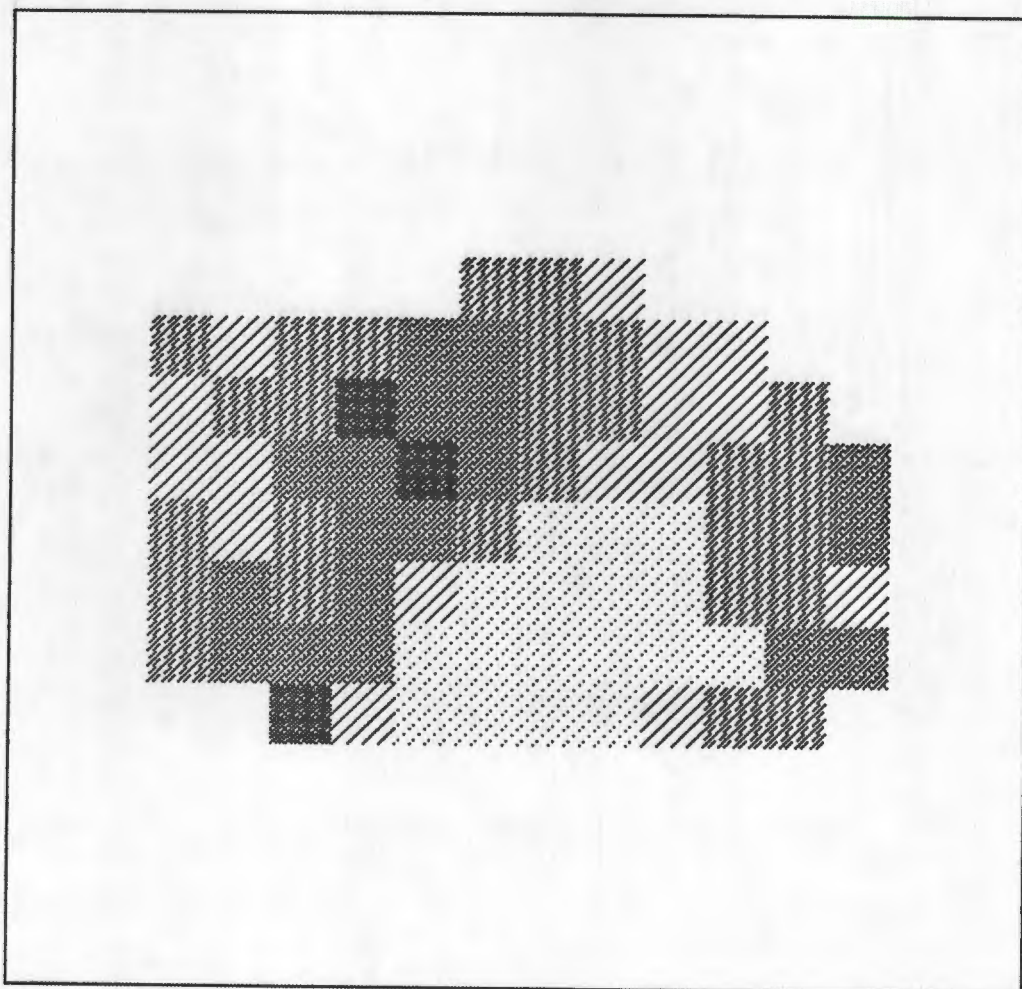


Figure 5d-7

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.56	0.37
S.D.	0.25	0.11
S.E.M.	0.05	0.03

PROGRAM: DJW (REV F)

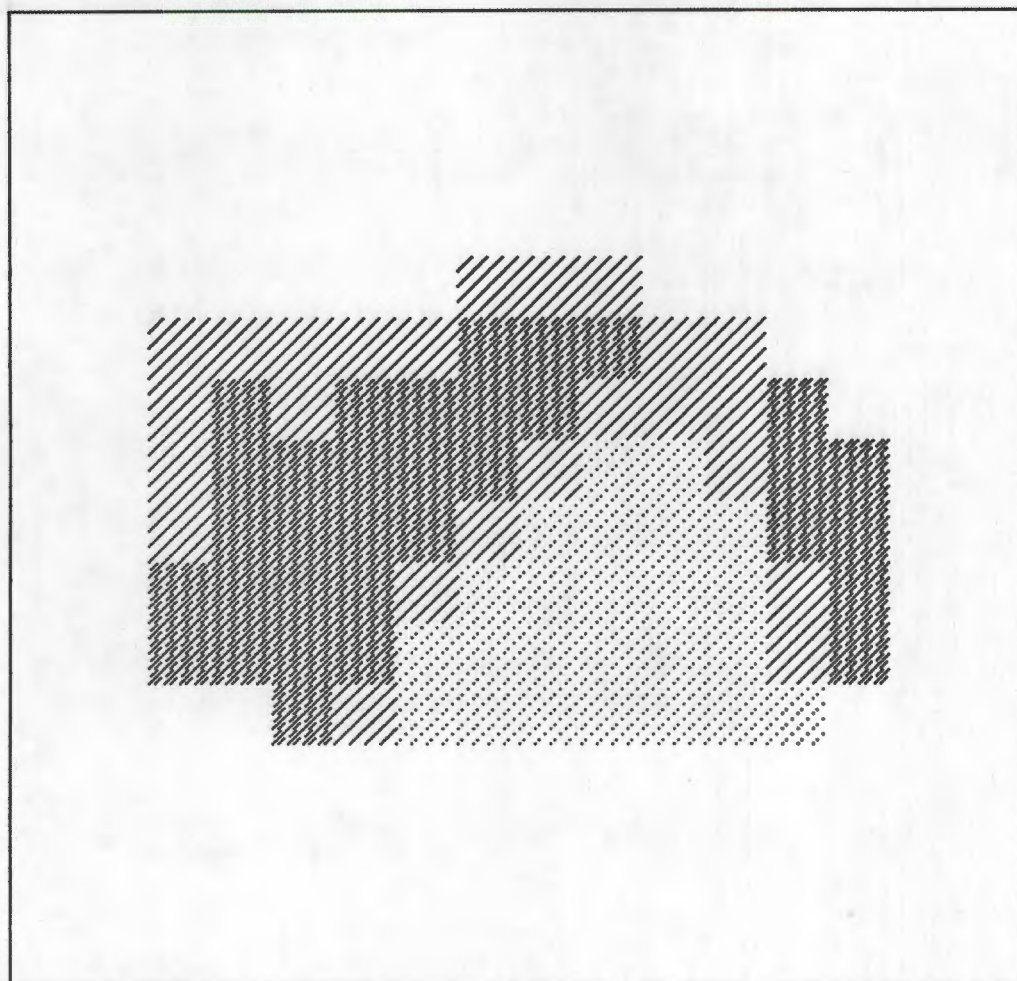
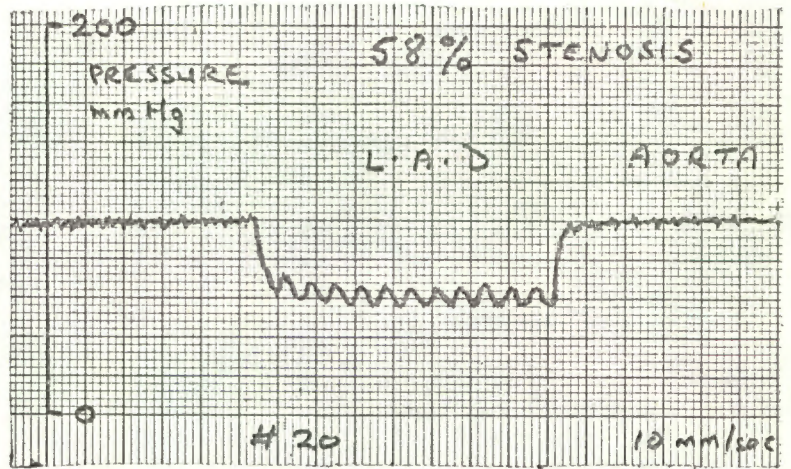
DOG 20
EPICARDIUM BLOOD FLOWS FOR ENERGY 4. SCALED TO 5.00

Figure 5d-8

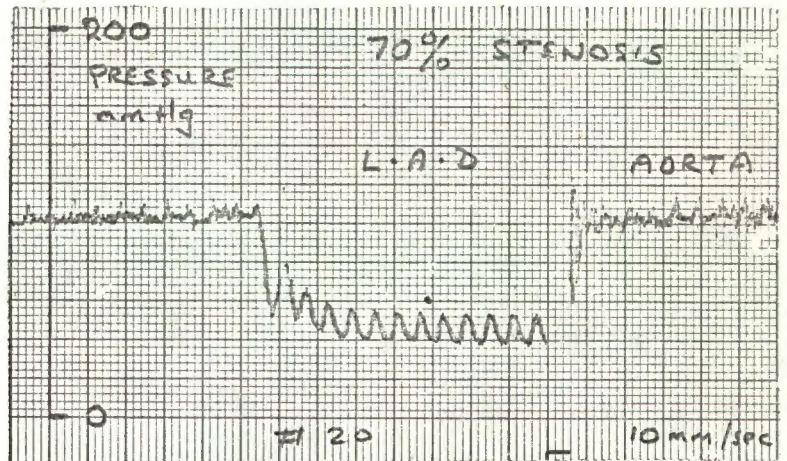
PRESSURE DROP FROM AORTA TO DISTAL ANTERIOR DESCENDING ARTERY
(L.A.D.) BEYOND OBSTRUCTION

DOG 20



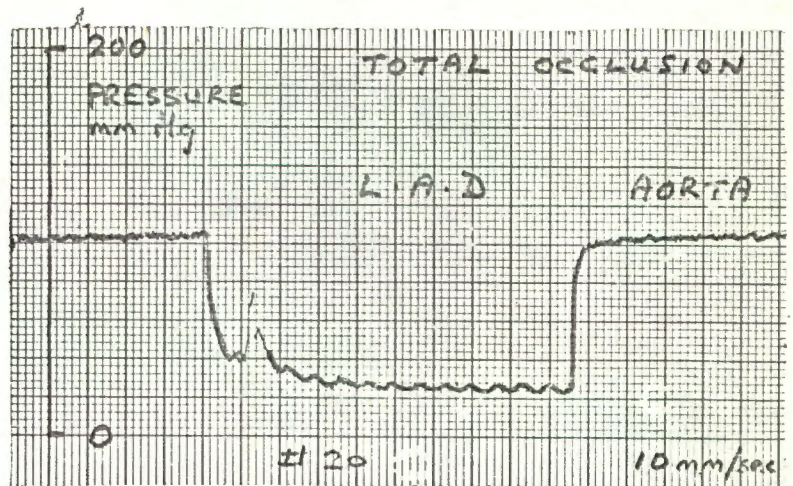
58% STENOSIS

Aorta mean 100 mmHg
L.A.D. mean 60 mmHg
40% PRESSURE DROP



70% STENOSIS

Aorta mean 100 mmHg
L.A.D. mean 45 mmHg
55% PRESSURE DROP



TOTAL OCCLUSION

Aorta mean 11 mmHg
L.A.D. mean 25 mmHg
75% PRESSURE DROP

Figure Sd-9

Figure 5d-10 shows the appearance of the opened left ventricle of Dog 24 in which varied stenoses of the circumflex coronary artery were assessed.

Figure 5d-11 shows the same heart superimposed on the grid. The drill-bit obturators used for producing the two different stenoses (calculated from the angiographic appearance to be 48% and 67% of lumen diameter loss) are seen in the lower right corner. The anatomical extent of the jeopardised myocardium was assessed as comprising blocks B2, B3, B4, B5, C2, C3, C4, C5, D2, D3, D4, D5, E2, E3, E4, F2, F3, G2 - and these blocks were assessed numerically for calculation of quantitative changes.

Figures 5d-12 to 5d-17 inclusive show the qualitative data in the form of regional myocardial perfusion maps, together with the quantitative data for each degree of coronary stenosis and for endocardial and epicardial halves of the myocardium.

Figure 5d-18 shows the pressure drop across the stenoses assessed in this experiment.

It can be seen from Figure 5d-12 that a 48% stenosis of the circumflex artery produces a well marked perfusion deficit. In this example there is considerable vasodilatation with high flow (control flow 3.16 ml/gm/min). There is a reduction in perfusion in the "test" area to 42% of control value (1.33 ml/gm/min in test area; 3.16 ml/gm/min in control area). Figure 5d-13 shows similar data for the epicardial half of the myocardium ("test" area perfusion 49% of control value).

Figures 5d-14 and 5d-15 show the data for a 67% stenosis - the perfusion deficit is more marked ("test" area 25% and 19% of control values for endocardial and epicardial halves respectively).

Figures 5d-16 and 5d-17 show the data for total occlusion - a similar marked perfusion deficit is seen ("test" area 24% and 36% of control values for endocardial and epicardial halves respectively).

Figure 5d-18 shows the pressure drop across the 48% stenosis, the 67% stenosis and the total occlusion.

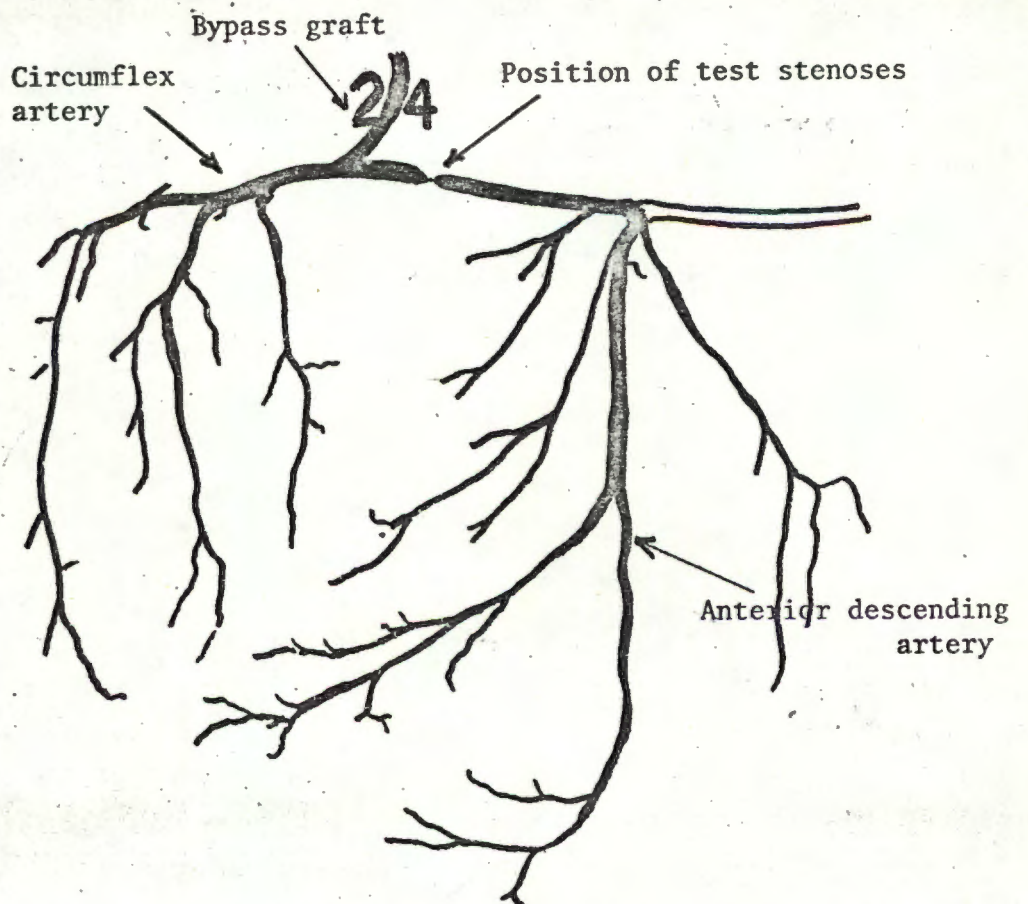
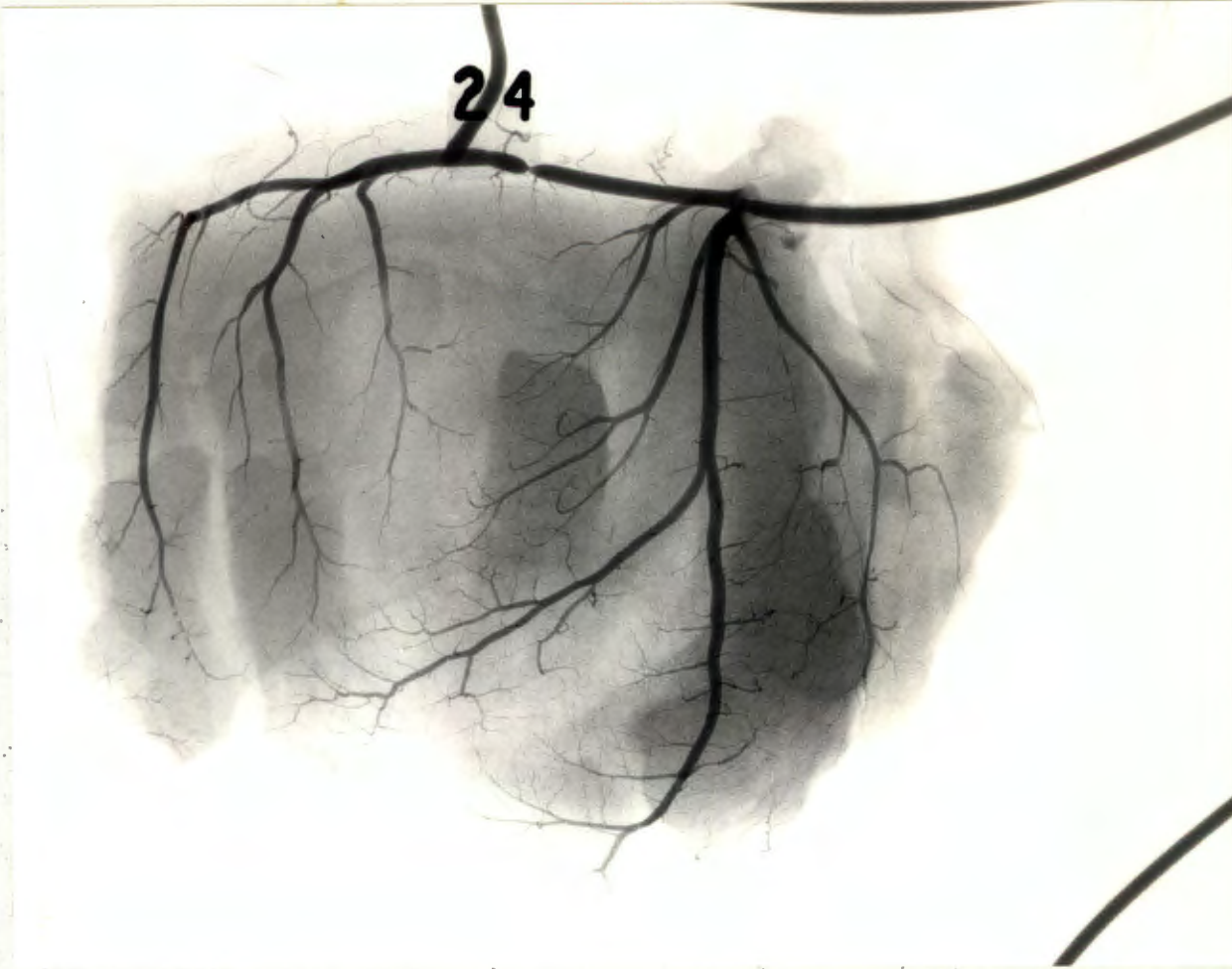
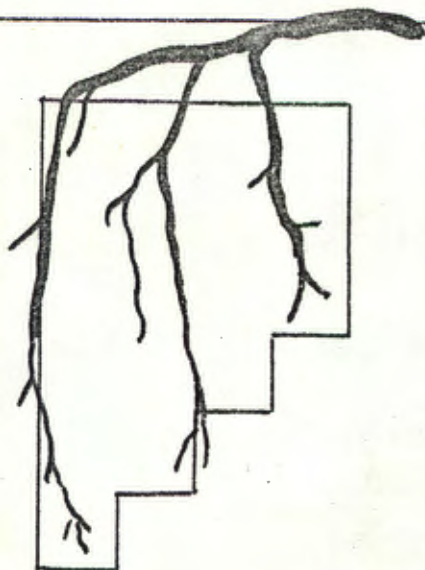


Figure 5d - 10.

24

A
B
C
D
E
F
G
H



Jeopardised
circumflex artery
with its territory
of supply

1 2 3 4 5 6 7 8 9 10 11 12

Drill-bit obturators
used for producing stenoses

24

A
B
C
D
E
F
G
H

1 2 3 4 5 6 7 8 9 10 11 12

Figure 5d - 11

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

48% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.33	3.16
S.D.	0.40	0.66
S.E.M.	0.09	0.13

PROGRAM: DJW (REV F)

DOG 24

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 2.50

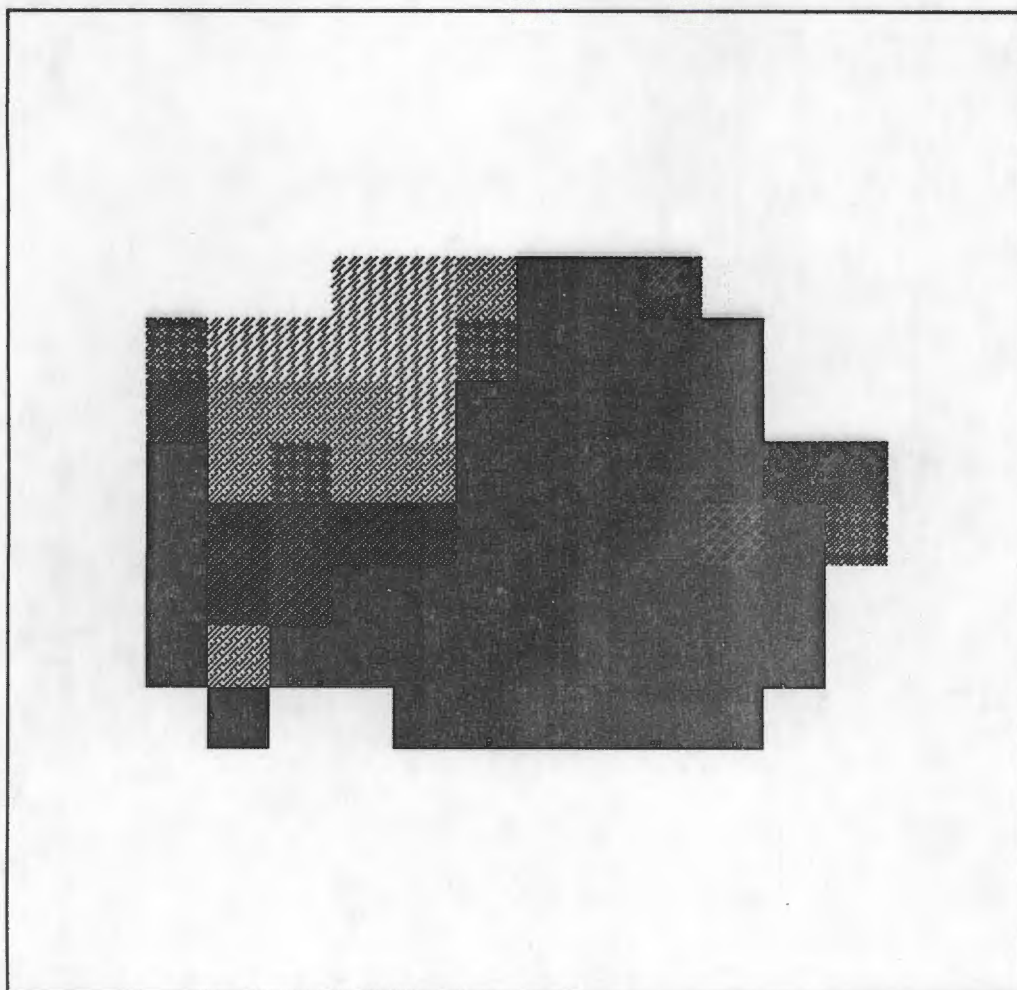


Figure 5d-12

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

48% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.29	2.63
S.D.	0.46	0.62
S.E.M.	0.11	0.12

PROGRAM: DJW (REV F)

DOG 24

EPICARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 2.50

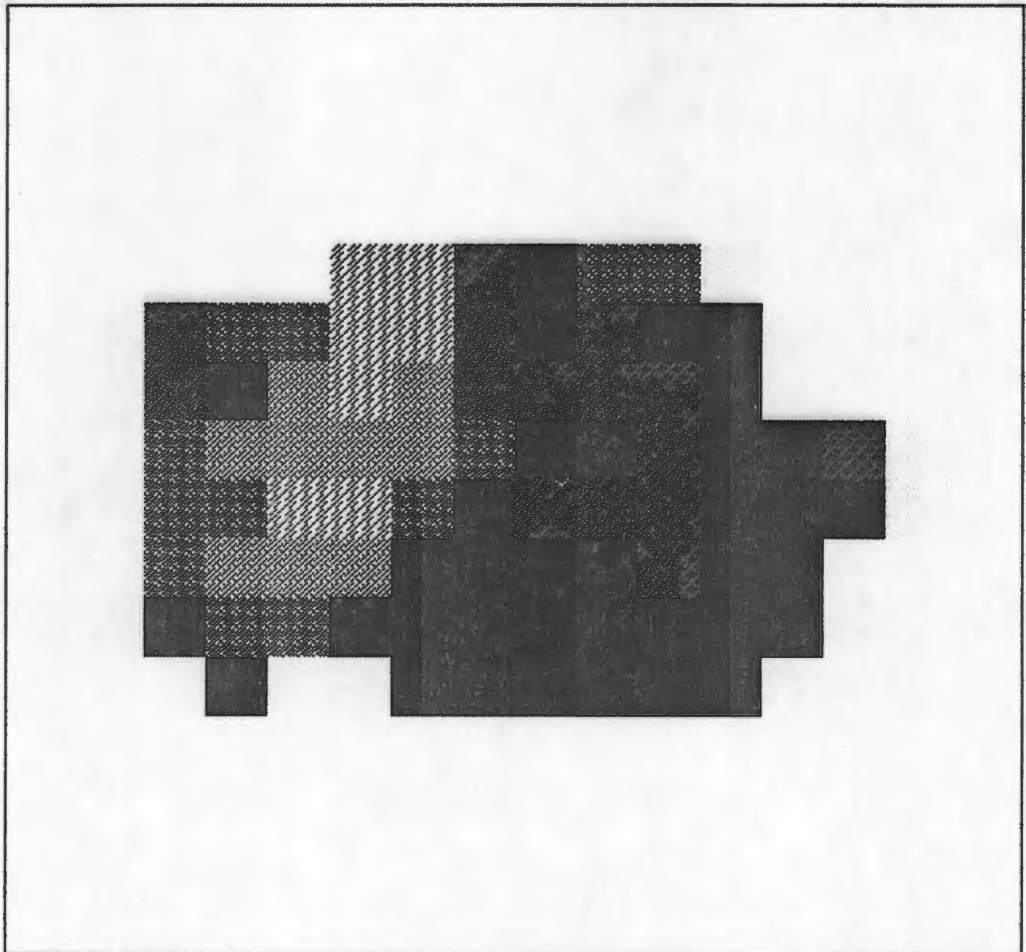


Figure 5d-13

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

67% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.40	1.62
S.D.	0.17	0.41
S.E.M.	0.04	0.08

PROGRAM: DJW (REV F)

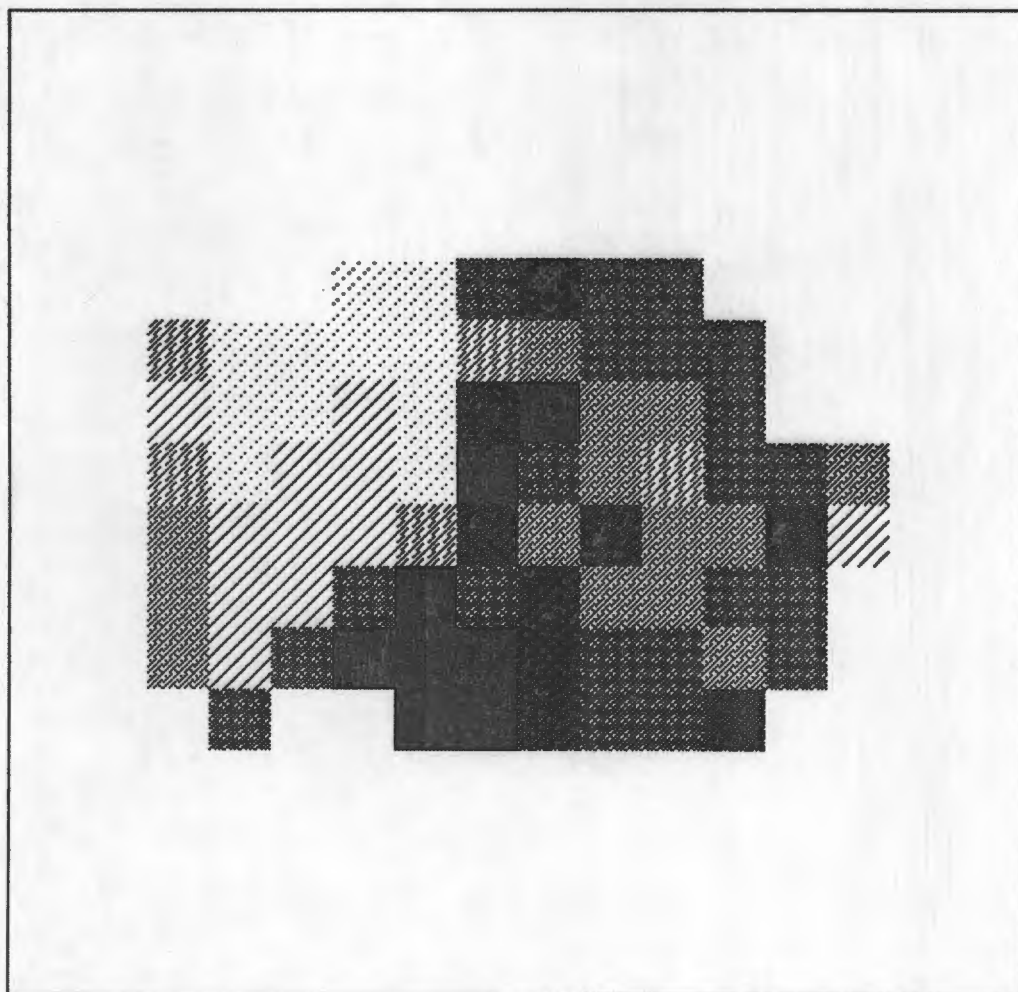
DOG 24
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.50

Figure 5d-14

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

67% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.37	1.96
S.D.	0.13	0.53
S.E.M.	0.03	0.10

PROGRAM: DJW (REV F)

DOG 24

EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.50

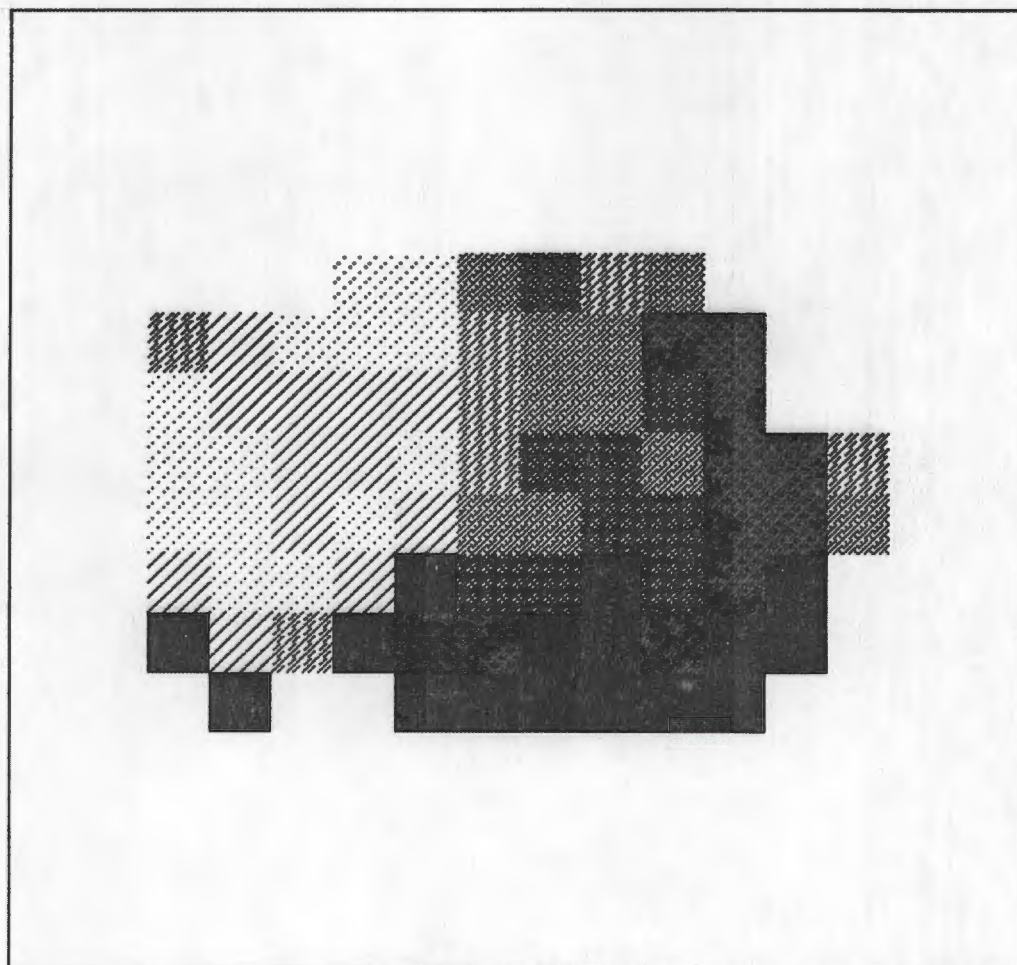


Figure 5d-15

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.65	2.70
S.D.	0.22	0.70
S.E.M.	0.05	0.14

PROGRAM: DJW (REV F)

DOG 24

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 2.50

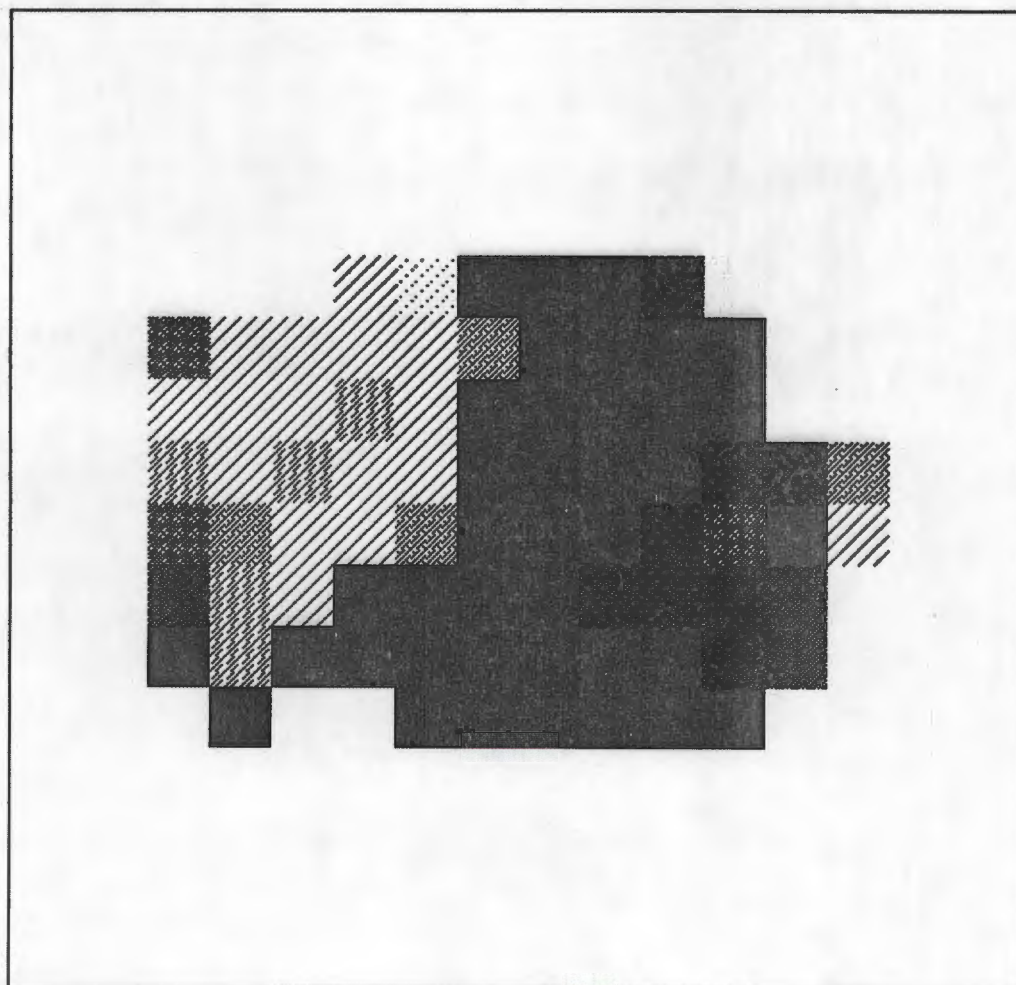


Figure 5d - 16

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.86	2.42
S.D.	0.32	0.55
S.E.M.	0.07	0.11

PROGRAM: DJW (REV F)

DOG 24

EPICARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 2.50

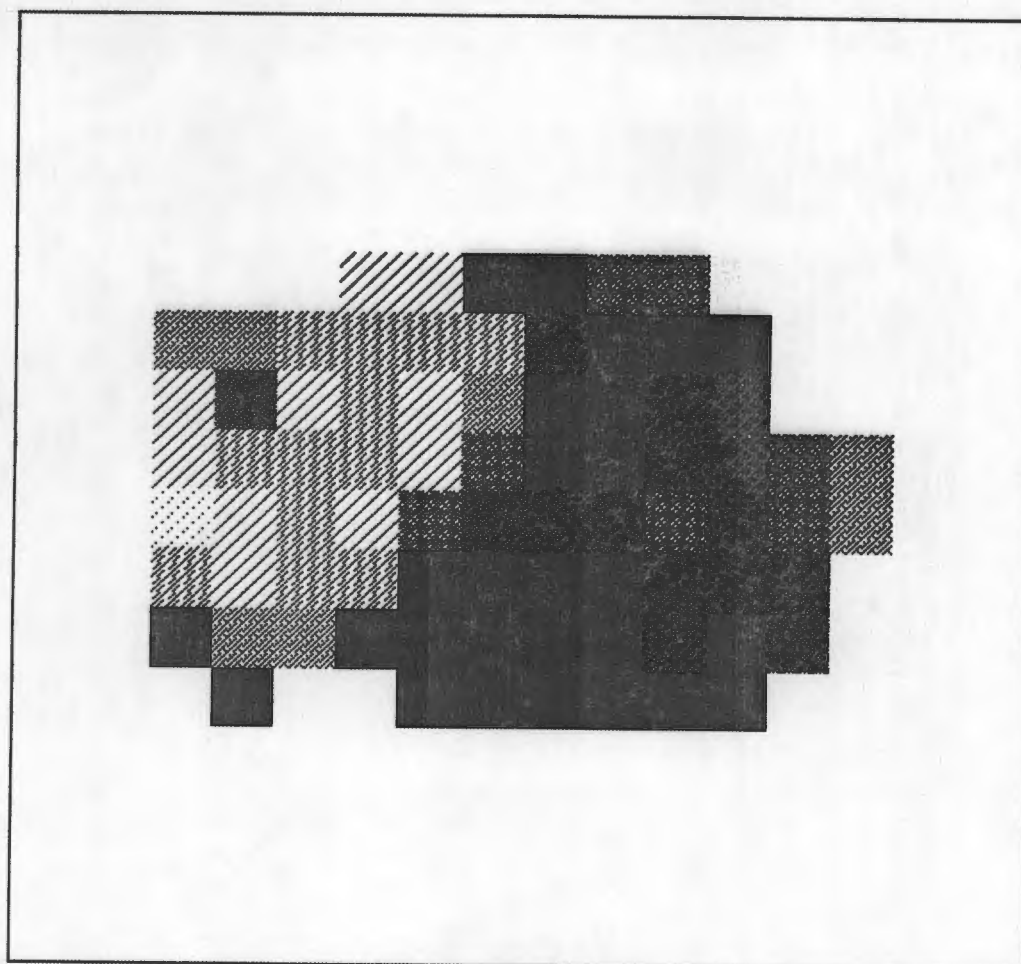


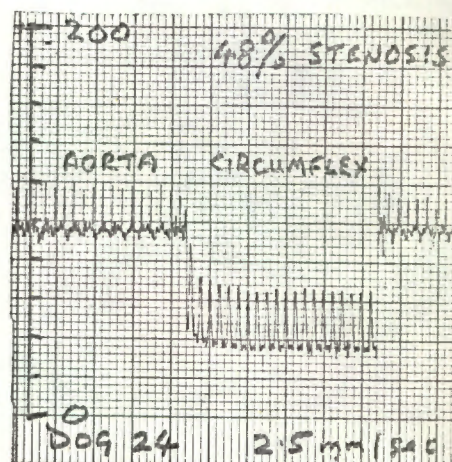
Figure 5d-17

EFFECT OF VARIED STENOSESDOG 24

48% STENOSIS OF CIRCUMFLEX

AORTA 100 mmHg CIRCUMFLEX
50 mmHg (mean)

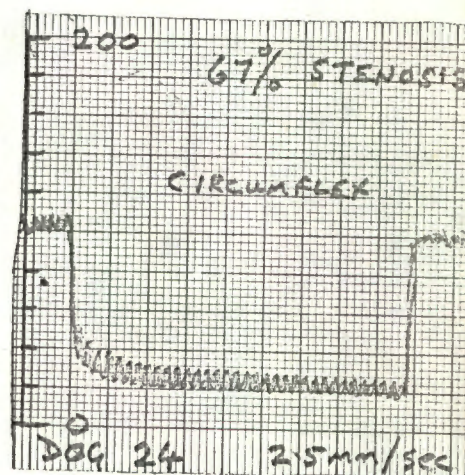
PRESSURE DROP 50%



67% STENOSIS OF CIRCUMFLEX

AORTA 100 mmHg CIRCUMFLEX
22 mmHg (mean)

PRESSURE DROP 78%



TOTAL OCCLUSION OF CIRCUMFLEX

AORTA 100 mmHg CIRCUMFLEX
20 mmHg (mean)

PRESSURE DROP 80%

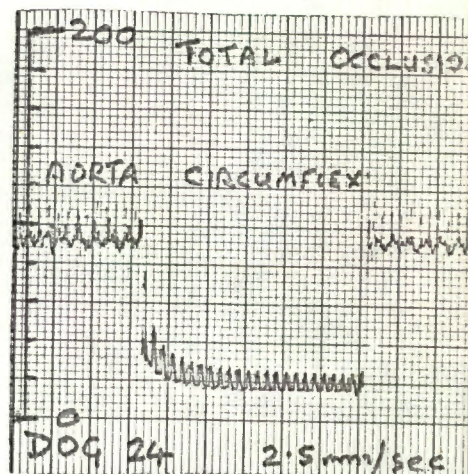


Figure 5d-18

Dog 26 illustrates a further example of the effect of varied stenoses. Figure 5d-19 shows the angiographic appearance of the coronary tree superimposed on the grid. The site of test stenoses in the circumflex artery, together with the territory of supply jeopardised by the stenoses is shown.

Figure 5d-20 shows a fairly well marked perfusion deficit resulting from a 50% loss of lumen diameter at the test site. There is a reduction to 43% of control perfusion level. Figure 5d-21 shows a similar perfusion deficit in the epicardial half of myocardium (42% of control perfusion level).

Figure 5d-22 shows a very marked perfusion deficit resulting from a 68% loss of lumen diameter at the test site - the endocardial map shows reduction of perfusion in the test area to 6% of control level. Figure 5d-23 shows reduction to 8% of control level for the epicardial half of myocardium.

Figure 5d-24 shows virtually no perfusion with total occlusion of the circumflex area - 1% of control level for endocardium; and in Figure 5d-25, 2% of control level for epicardium.

Figure 5d-26 shows the pressure drop measured across the 50% stenosis, the 68% stenosis, and the total occlusion.

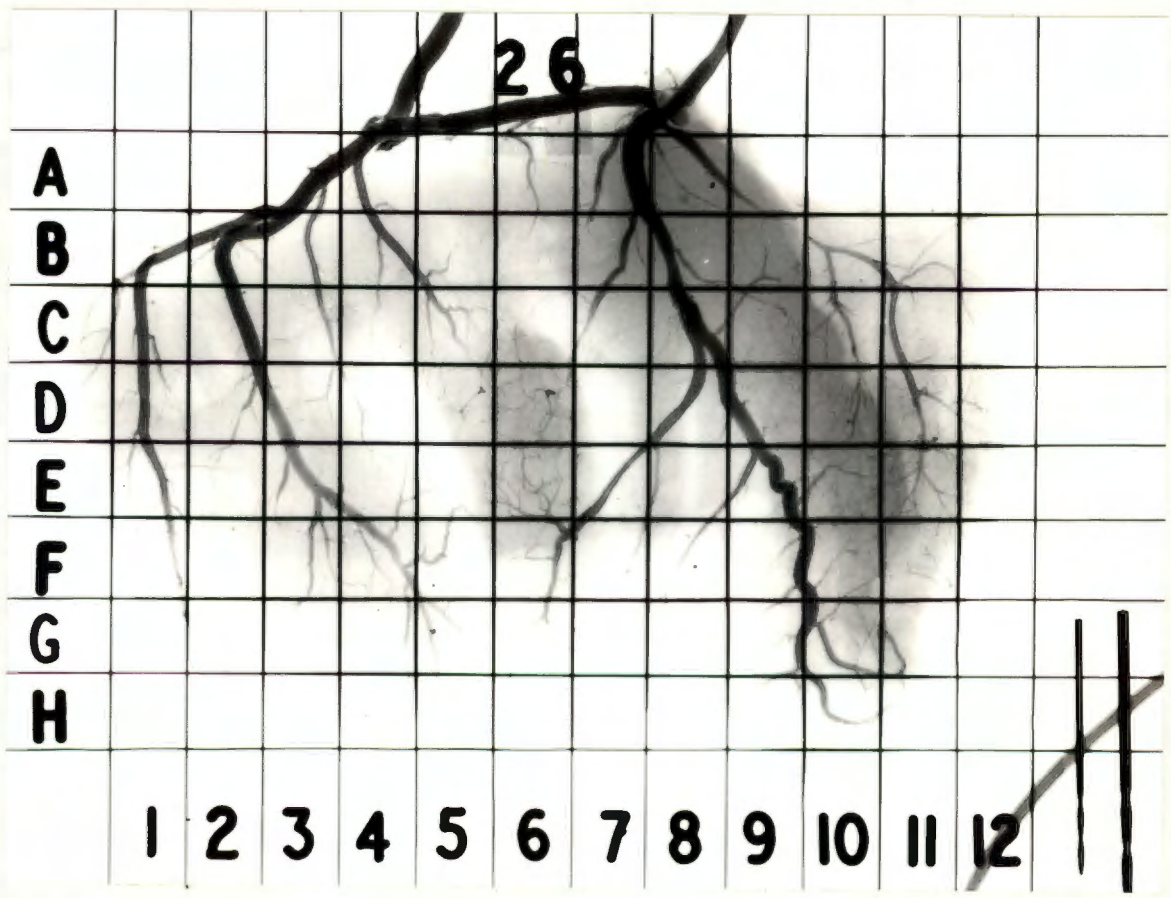
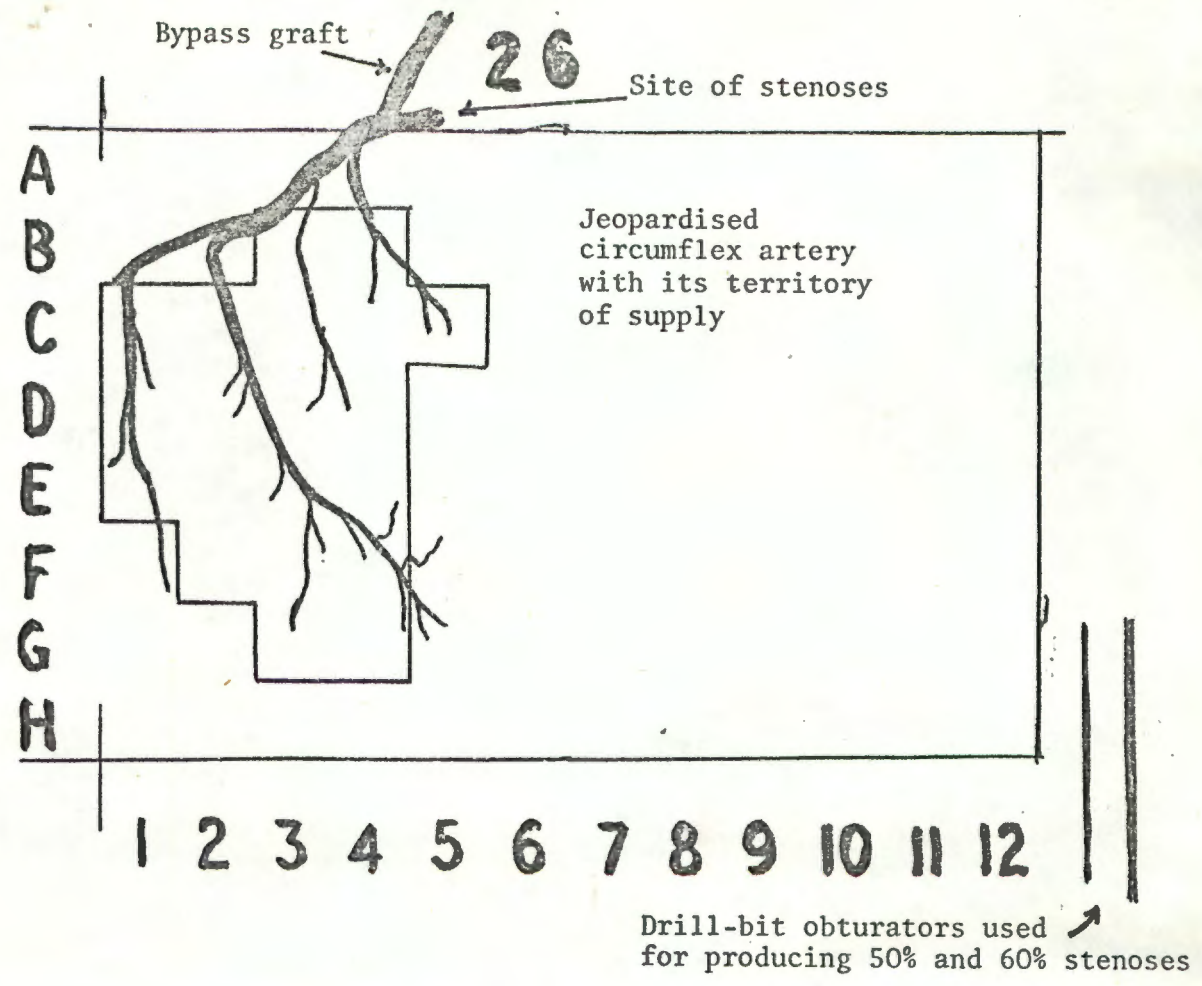


Figure 5d - 19

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

50% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.00	2.34
S.D.	0.36	0.32
S.E.M.	0.08	0.07

PROGRAM: DJW (REV F)

DOG 26

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 2.50

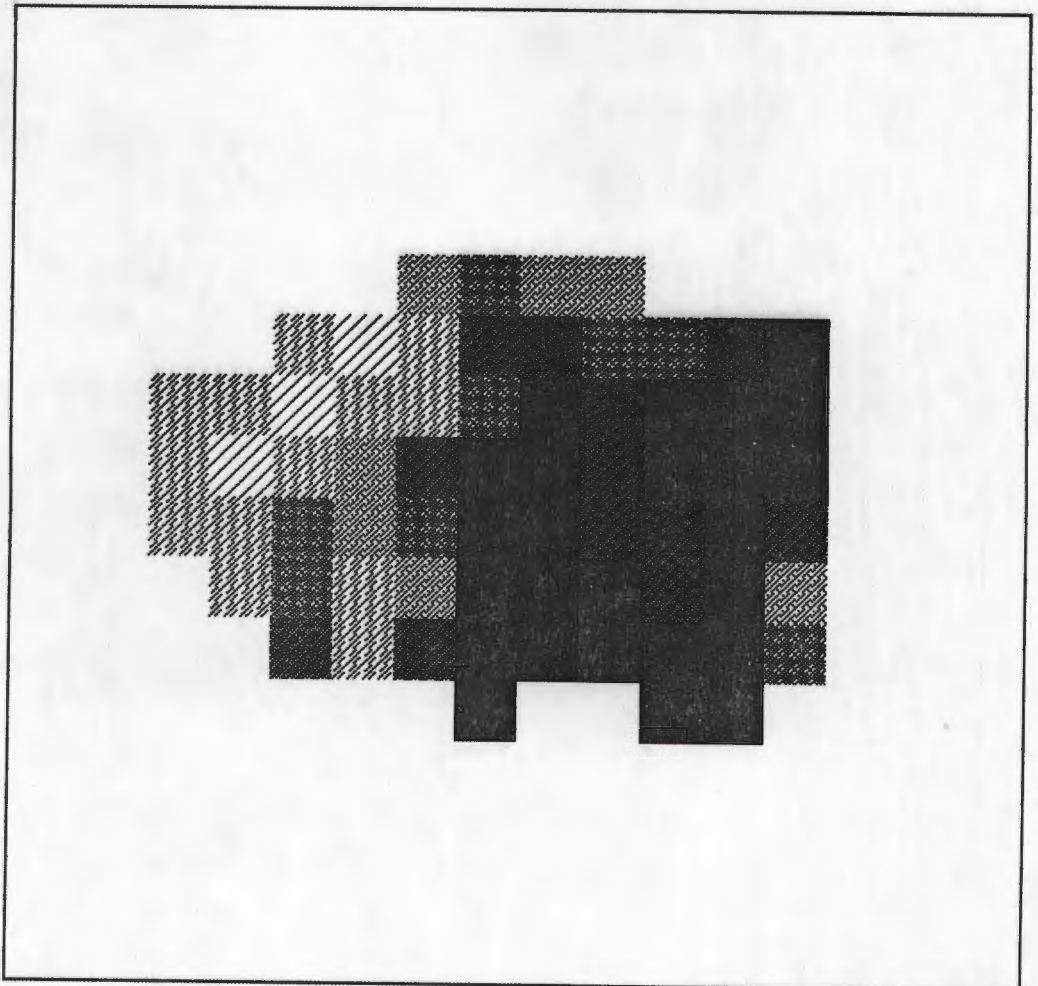


Figure 5d-20

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

50% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.82	1.94
S.D.	0.14	0.28
S.E.M.	0.03	0.06

PROGRAM: DJW (REV F)

DOG 26
EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 2.50

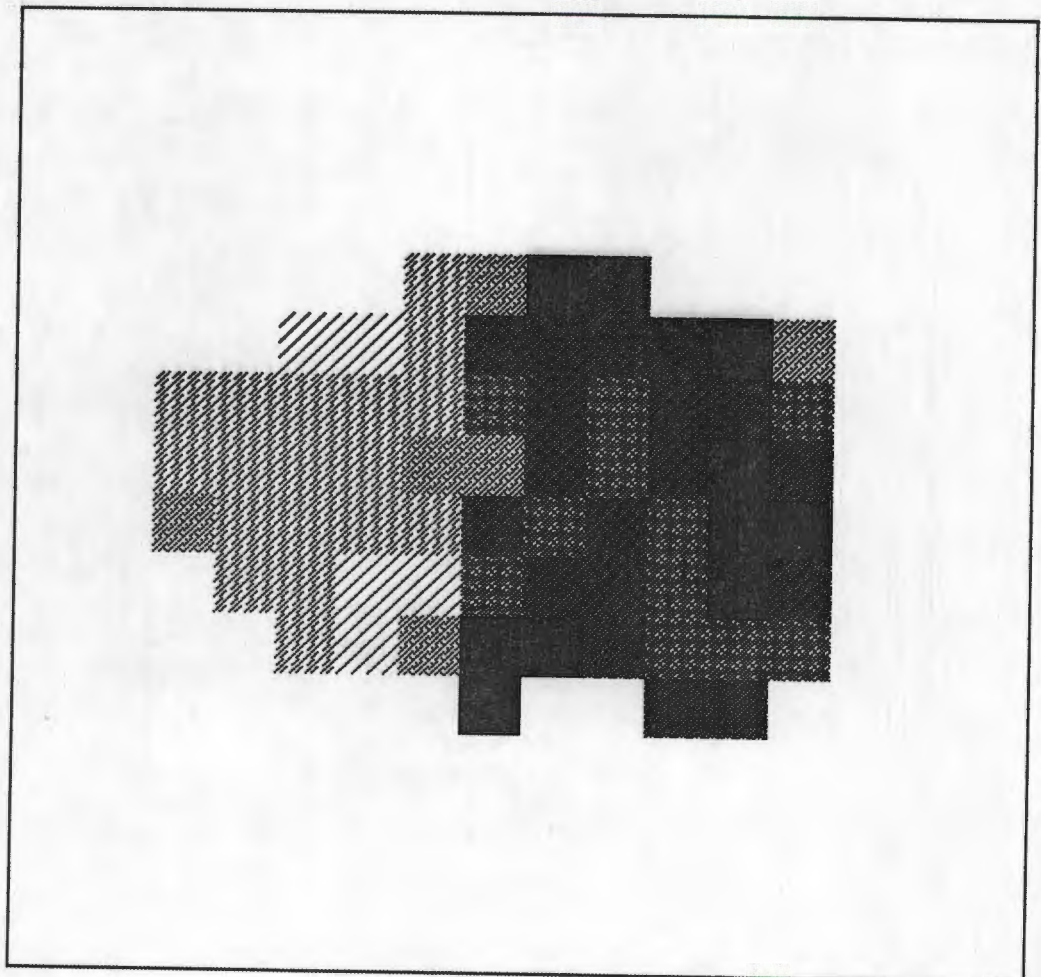


Figure 5d-21

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

68% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.11	1.94
S.D.	0.07	0.25
S.E.M.	0.02	0.06

PROGRAM: DJW (REV F)

DOG 26

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.50

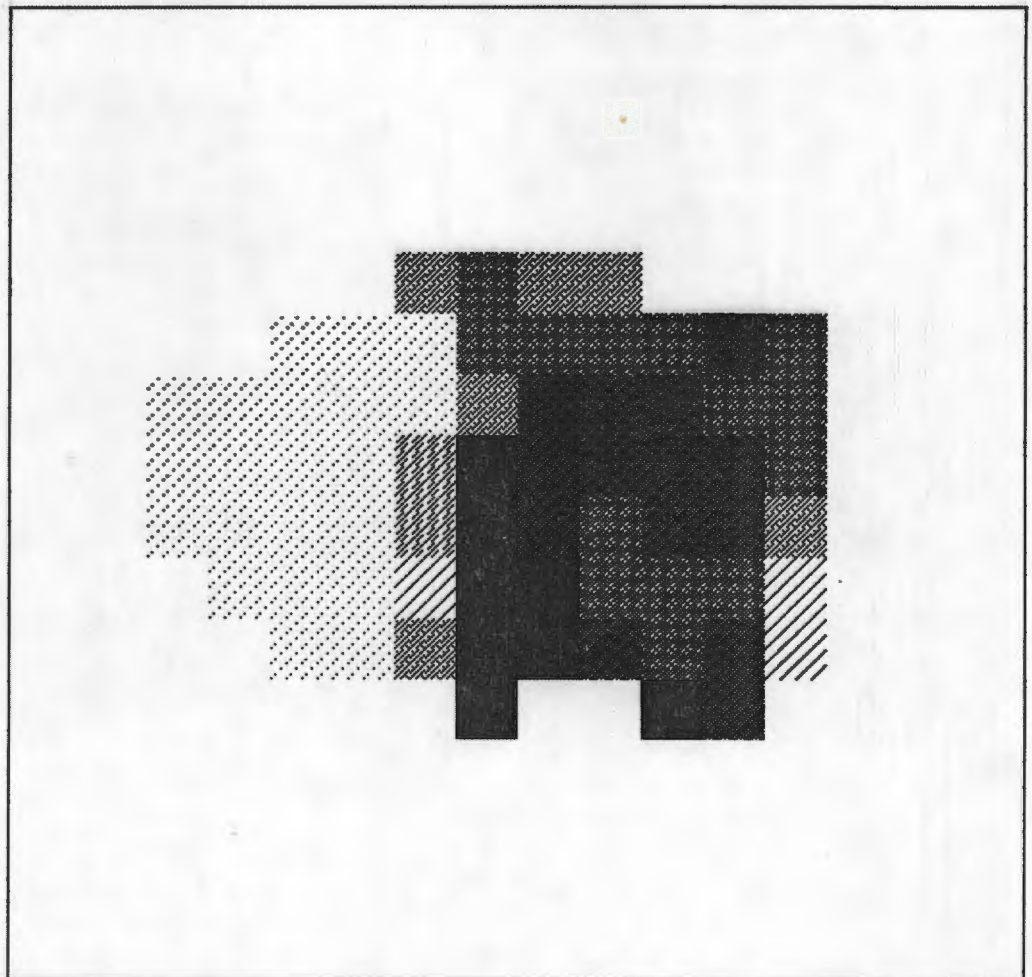


Figure 5d-22

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

68% STENOSIS OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.14	1.75
S.D.	0.11	0.24
S.E.M.	0.02	0.05

PROGRAM: DJW (REV F)

DOG 26
EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.50

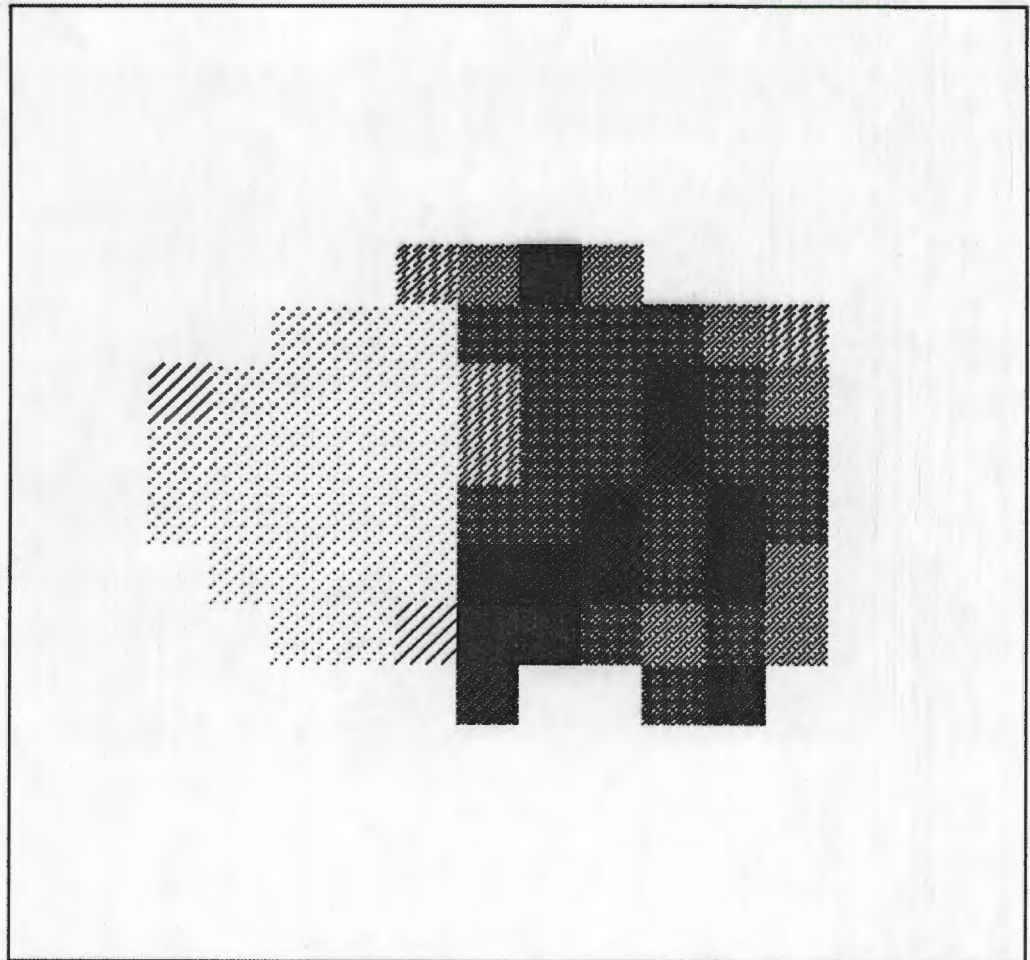


Figure 5d-23

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.03	2.54
S.D.	0.05	0.30
S.E.M.	0.01	0.07

PROGRAM: DJW (REV F)

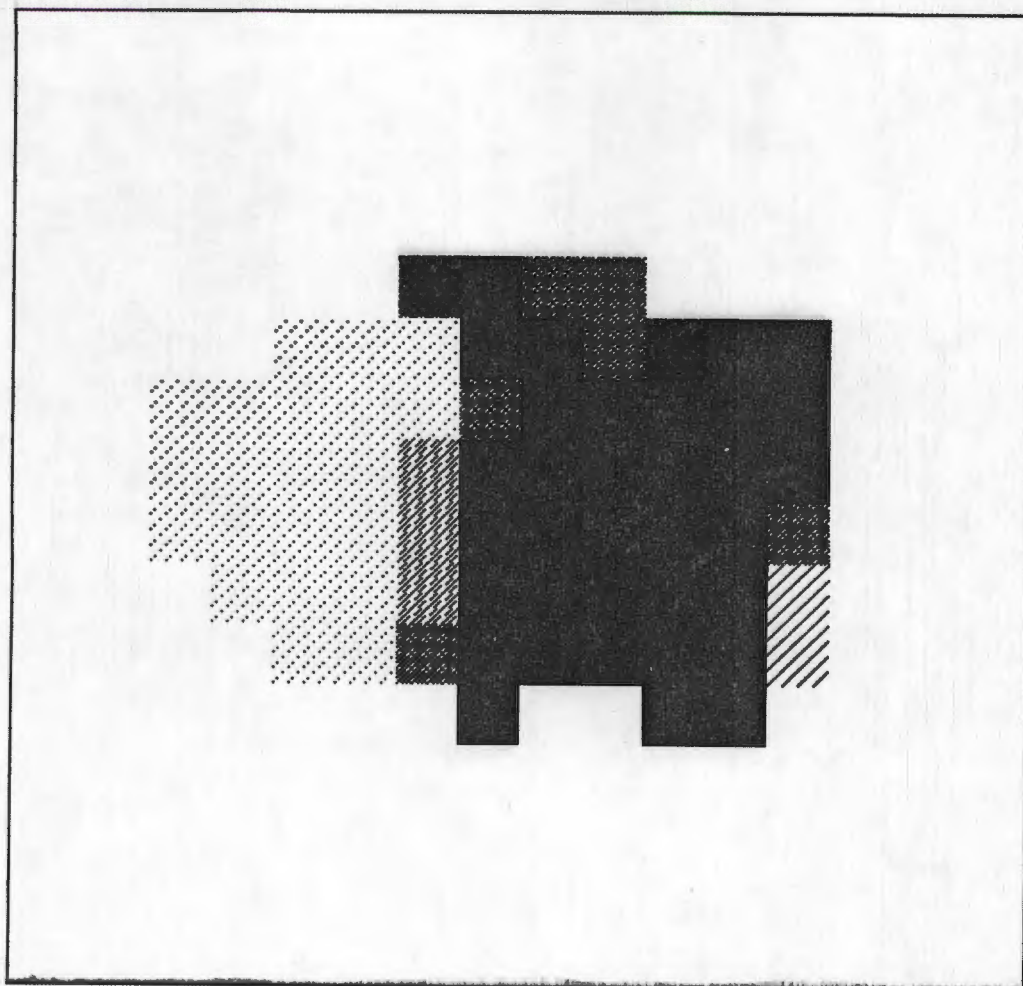
DOG 26
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 2.50

Figure 5d-24

EFFECT OF VARIED STENOSES

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF CIRCUMFLEX ARTERY

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.04	2.03
S.D.	0.09	0.27
S.E.M.	0.02	0.06

PROGRAM: DJW (REV F)

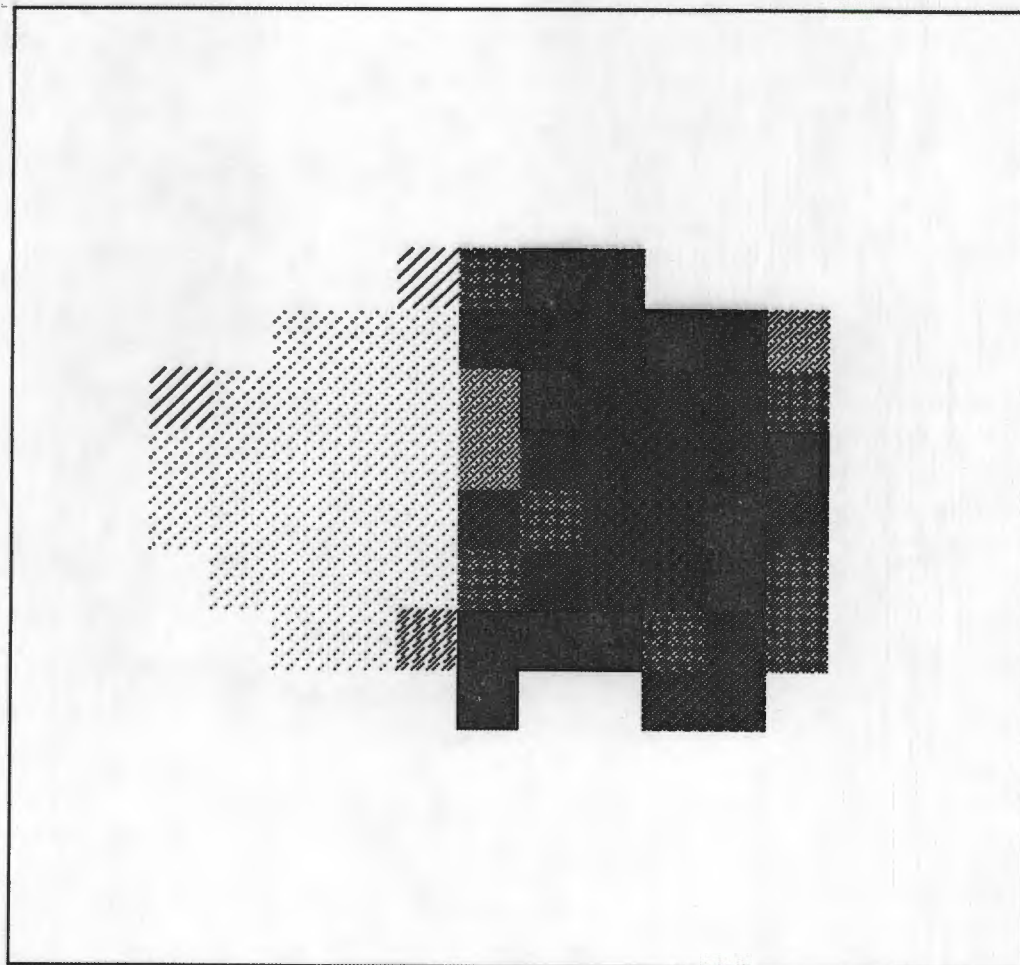
DOG 26
EPICARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 2.50

Figure 5d-25

EFFECT OF VARIED STENOSES

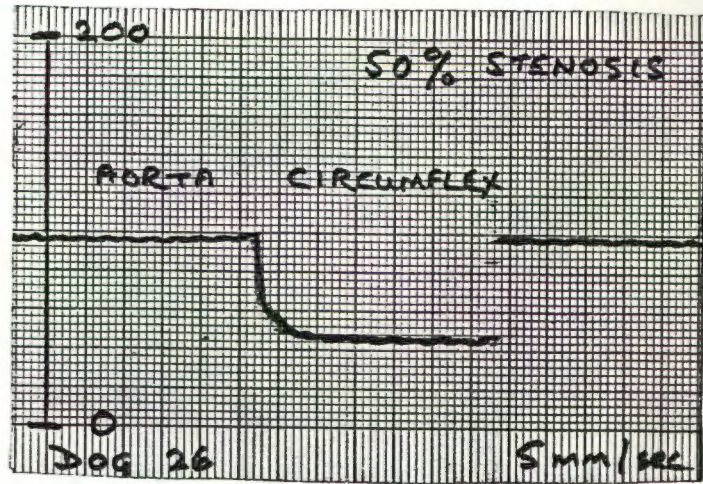
DOG 26

50% STENOSIS OF CIRCUMFLEX

AORTA 100 mmHg

CIRCUMFLEX 45 mmHg (mean)

PRESSURE DROP 55%

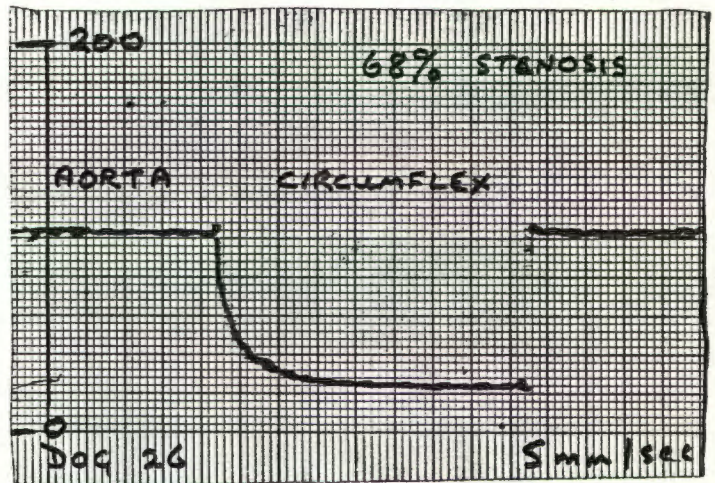


68% STENOSIS OF CIRCUMFLEX

AORTA 100 mmHg

CIRCUMFLEX 25 mmHg (mean)

PRESSURE DROP 75%



TOTAL OCCLUSION OF CIRCUMFLEX

AORTA 100 mmHg

CIRCUMFLEX 10 mmHg (mean)

PRESSURE DROP 90%

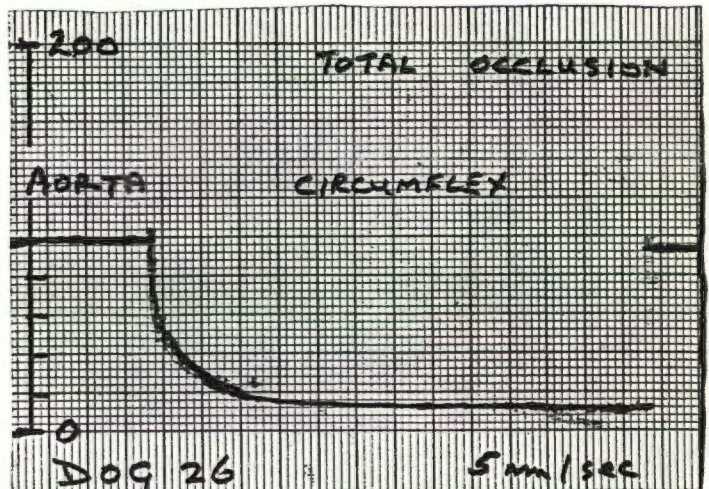


Figure 5d - 26

The preceding illustrations of data from dogs 20, 24 and 26 are typical examples of the effect of varied stenoses. In each there was considerable coronary vasodilatation, as confirmed by the high level of perfusion in the control areas. In Section 5b it has been shown that unless high coronary flow is present perfusion deficits may be absent or mild.

The data for all 28 dogs assessed in this way for the effect of varied stenoses is shown in graph form in Figures 5d-27 to 5d-33 inclusive.

Figures 5d-27 to 5d-30 show the mean value for myocardial perfusion in the "test" area (expressed as a percentage of the mean value for myocardial perfusion in the "control" area - for endocardial and epicardial halves together) plotted against the angiographically calculated degree of stenosis (expressed as percentage loss of lumen diameter).

Figure 5d-27 shows that with low levels of myocardial perfusion (less than 1 ml/gm/minute) the perfusion may not be significantly reduced in the test area with obstructions as severe as 80% loss of lumen diameter.

Figure 5d-28 shows the same data with intermediate levels of myocardial perfusion (1 to 2 ml/gm/minute). Reduction in perfusion is apparent at lower levels of percentage loss of lumen diameter.

Figure 5d-29 shows the data with high levels of myocardial perfusion (over 2 ml/gm/minute). Here 50% or more loss of lumen diameter consistently resulted in significant reduction in myocardial perfusion in the test area.

Figure 5d-30 summarises this data for both low and high myocardial blood flow levels. The range of levels of perfusion is fairly wide (reflecting in large part the difficulty of calculating the loss of

lumen diameter angiographically with precision). It is clear that with low levels of myocardial flow 70-80% loss of lumen diameter is required to make a significant difference to myocardial perfusion (and then only causing approximately 25% reduction in perfusion). However, with high levels of myocardial flow even 50% loss of lumen diameter results in marked reduction of myocardial flow.

When the mean value for myocardial perfusion in the "test" area (expressed as a percentage of the mean value for myocardial perfusion in the "control" area - for endocardial and epicardial halves together), is plotted against the percentage pressure drop across the stenosis a far more constant relationship is seen, and this relationship is remarkably constant for all three groups of myocardial flow rate.

Figure 5d-31 shows this relationship with low levels of myocardial perfusion (less than 1ml/gm/minute). Figure 5d-32 shows the relationship with intermediate levels of perfusion (1 to 2 ml/gm/minute); and Figure 5d-33 shows the relationship with high levels of perfusion (over 2 ml/gm/minute).

Figure 5d-34 shows the best-fit line which most accurately describes the relationship between percentage pressure drop over a stenosis and resultant myocardial perfusion deficit for all levels of coronary vasodilatation.

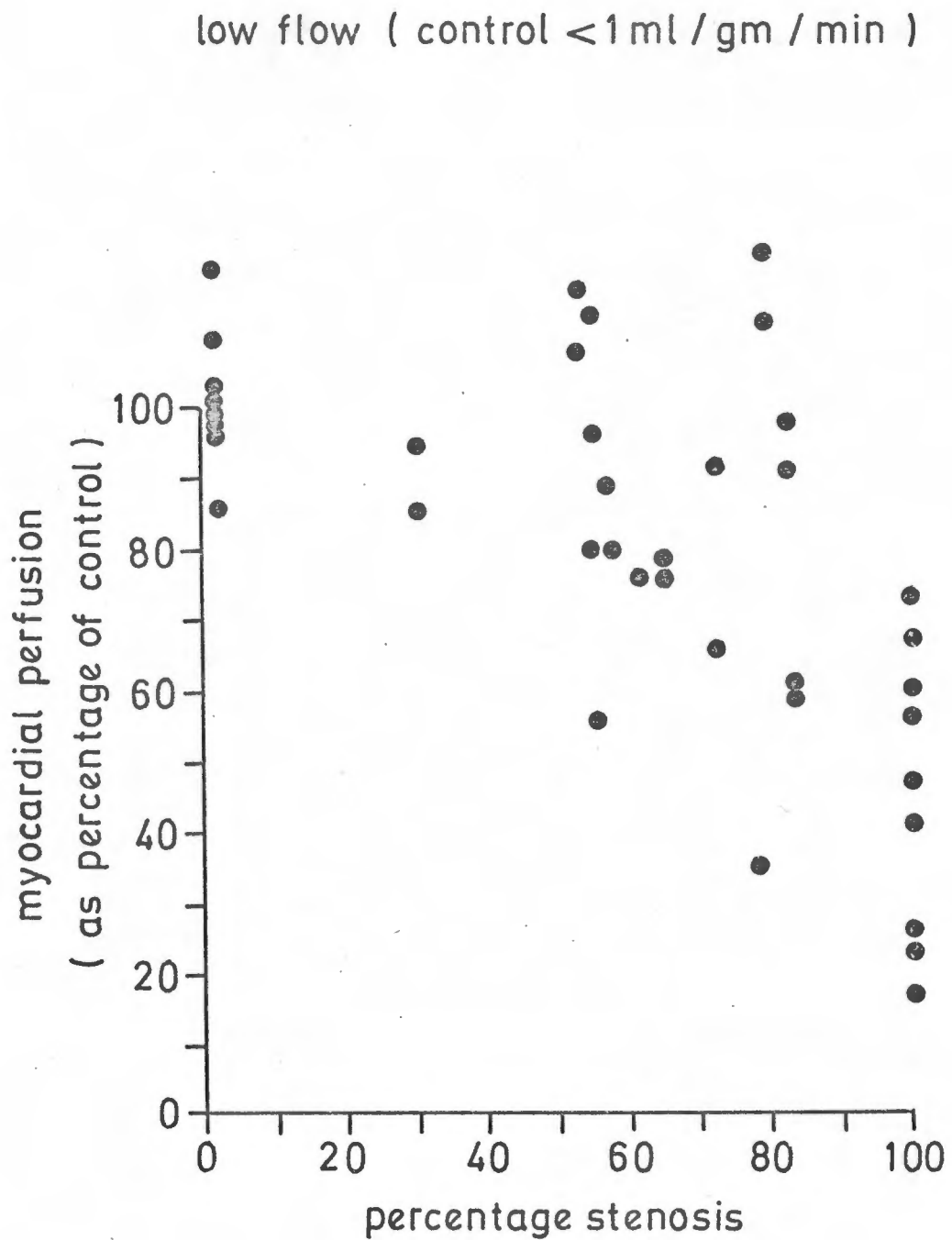
RELATIONSHIP BETWEEN PERCENTAGE DIAMETER
STENOSIS AND MYOCARDIAL PERFUSION

Figure 5d-27

RELATIONSHIP BETWEEN PERCENTAGE DIAMETER
STENOSIS AND MYOCARDIAL PERFUSION

intermediate flow (control 1-2 ml / gm / min)

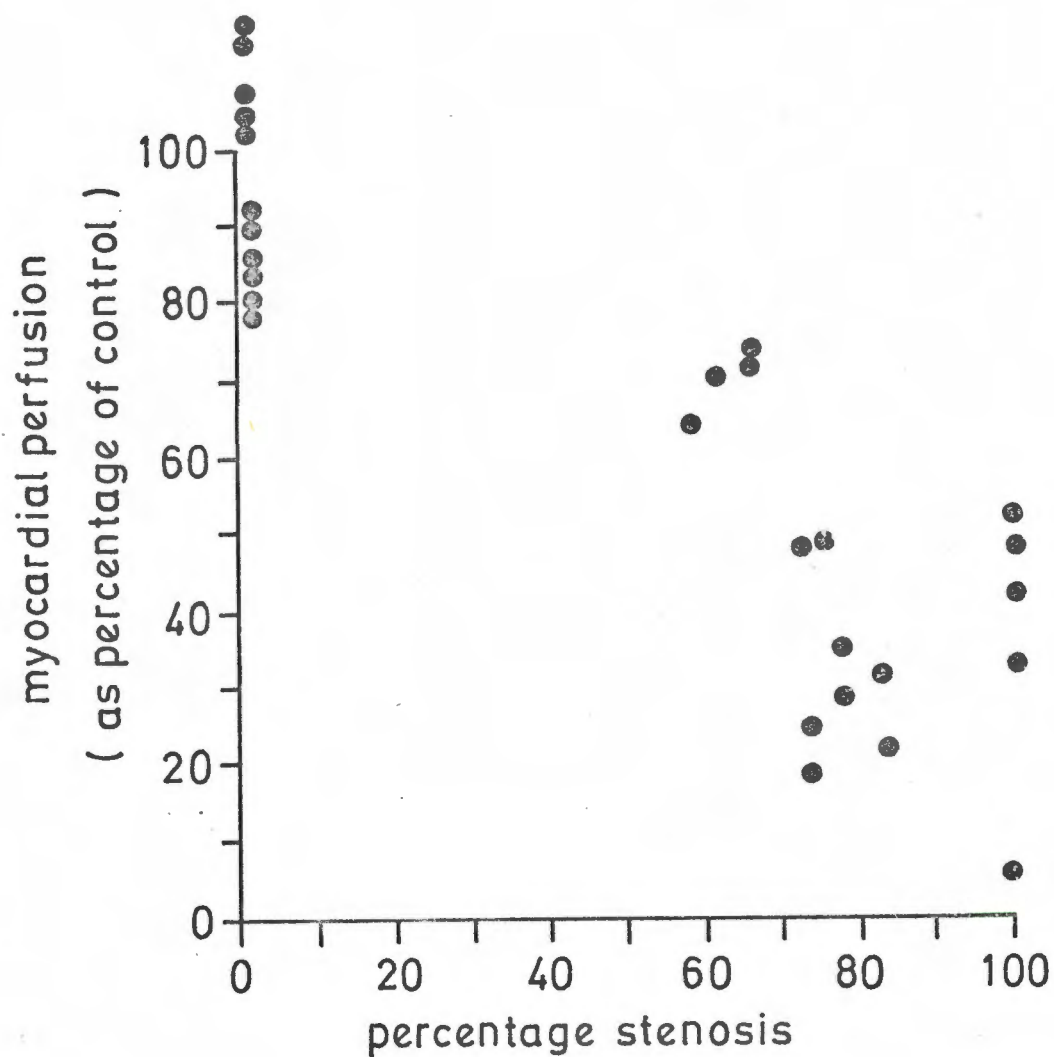


Figure 5d-28

RELATIONSHIP BETWEEN PERCENTAGE DIAMETER STENOSIS AND MYOCARDIAL PERFUSION

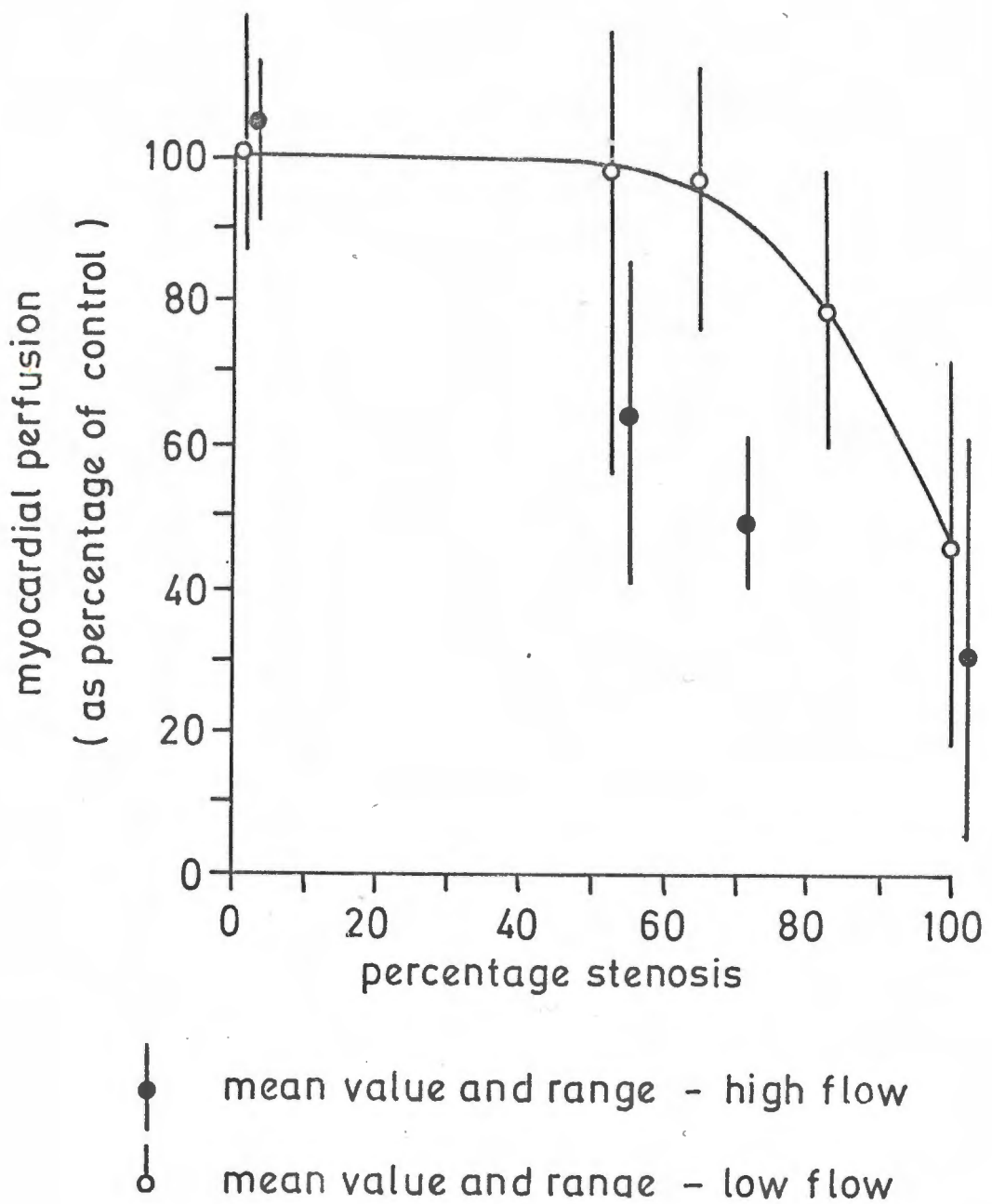


Figure 5d-30

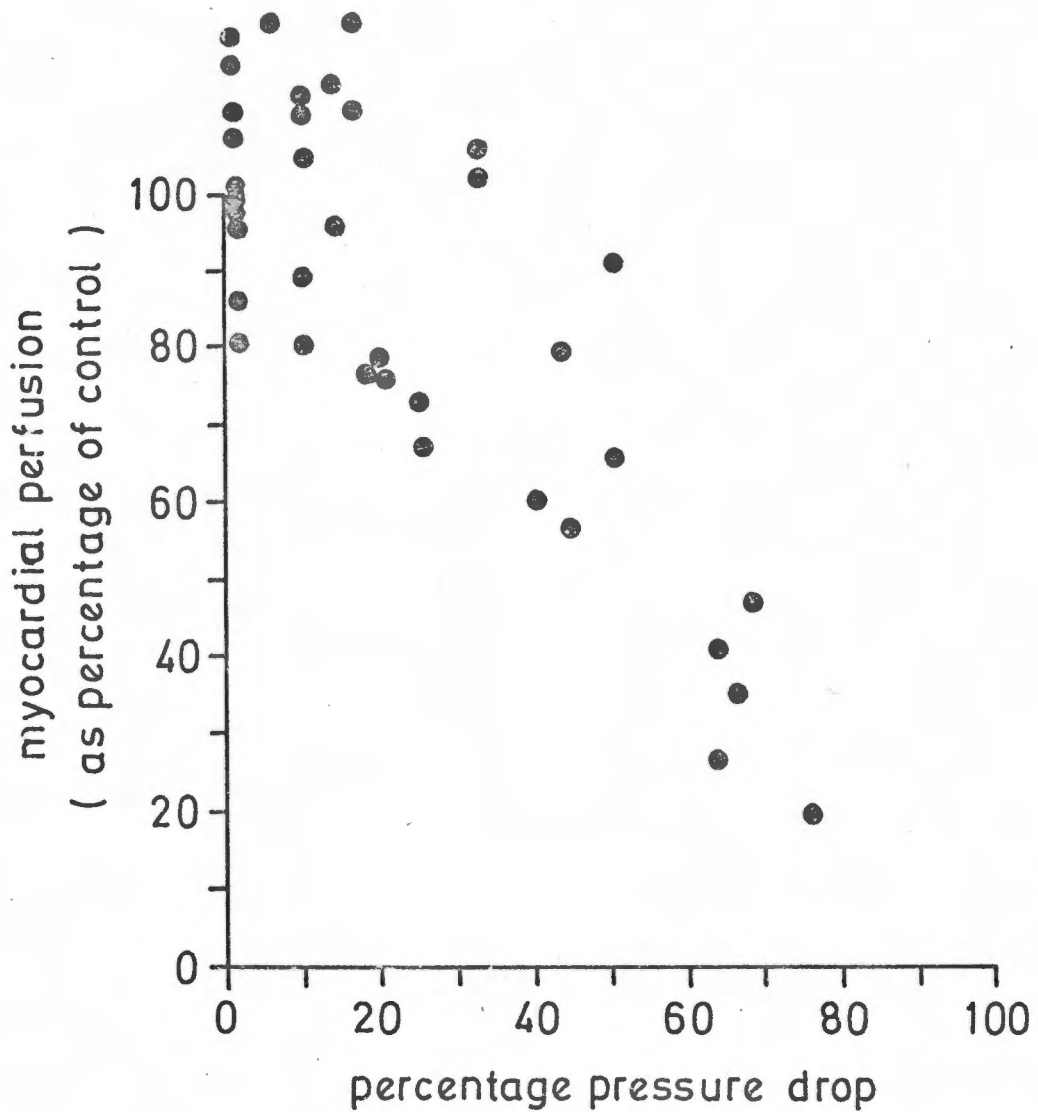
RELATIONSHIP BETWEEN DISTAL CORONARY PRESSURE
AND MYOCARDIAL PERFUSIONlow flow (control < 1 ml / gm / min)

Figure 5d-31

RELATIONSHIP BETWEEN DISTAL CORONARY
PRESSURE AND MYOCARDIAL PERFUSION

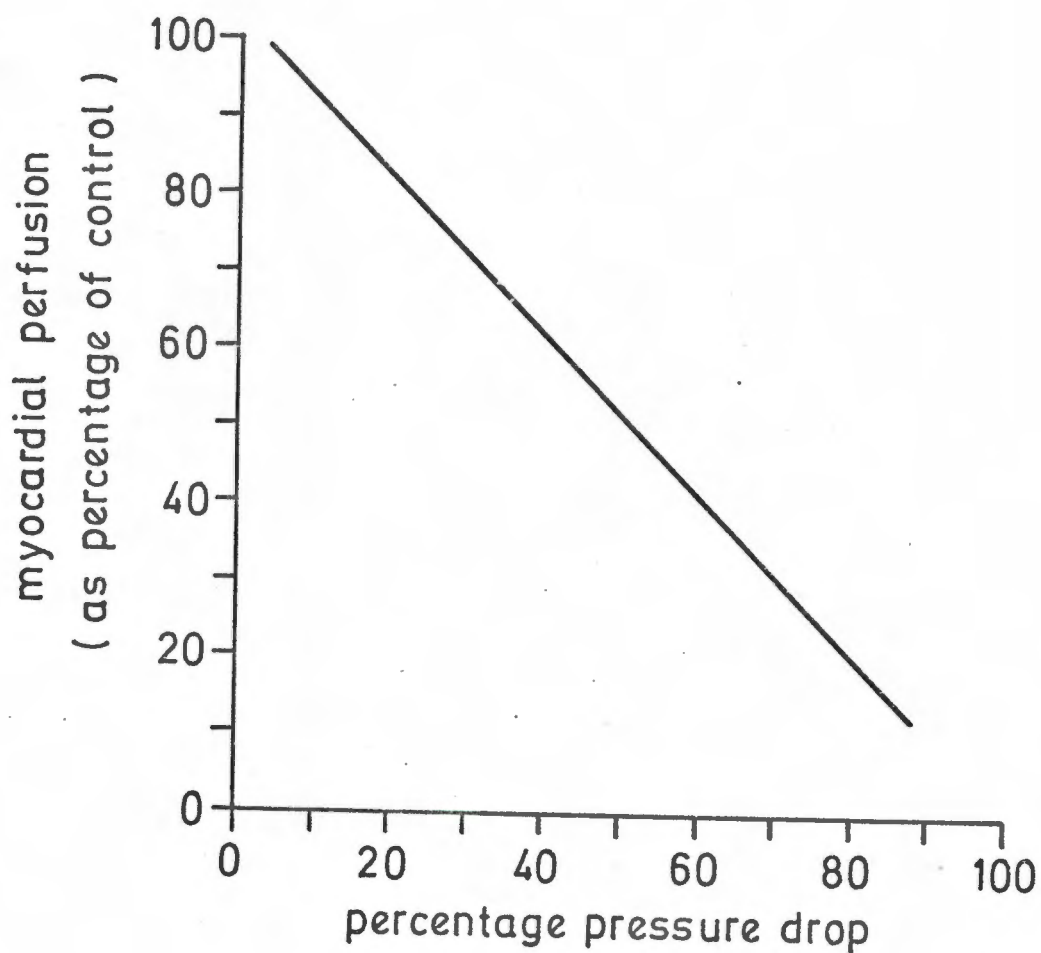
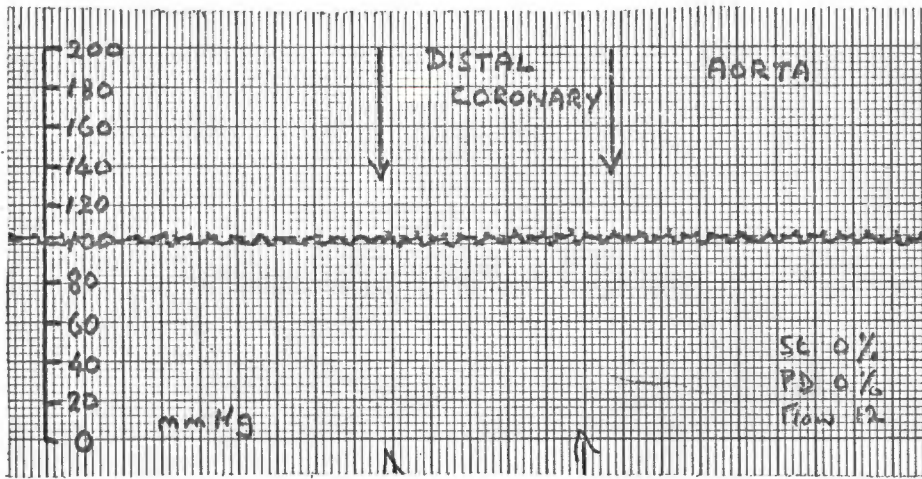


Figure 5d-34

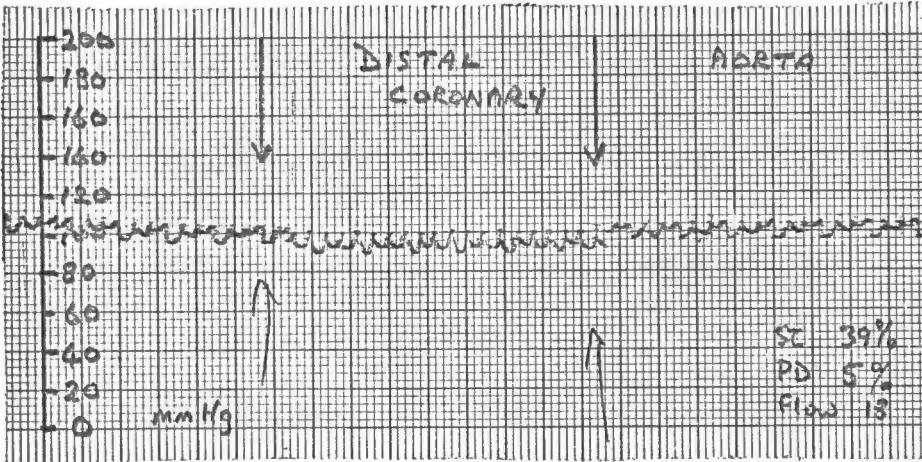
The pressure drop across a coronary stenosis can be readily measured in the experimental model, and is also easy to measure clinically once a bypass graft has been inserted (see Section 6a). As shown in Figure 5d-34, the pressure drop bears a more predictable relationship to the perfusion deficit than does the angiographic estimate of lumen diameter loss (which is less easy to calculate with accuracy - particularly with clinically obtained angiograms).

Not only did pressure drop appear of value in predicting perfusion deficit in this model, but it also predicted the likely aorto-coronary bypass flow in a graft placed to correct for the stenosis.

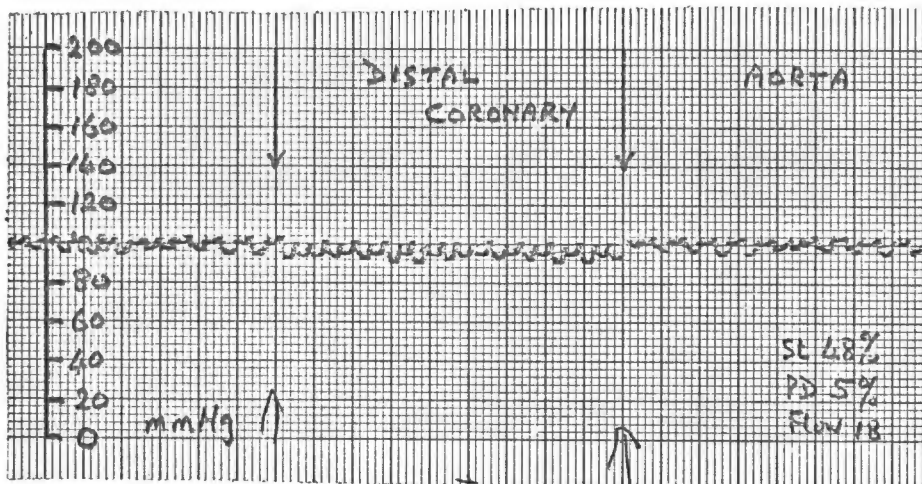
Figures 5d-35, 5d-36 and 5d-37 show the records of pressure drop from aorta to distal coronary artery in the same dog with varying degrees of stenosis of the anterior descending coronary artery produced by tying a ligature around the artery while an accurately sized drill-bit was held alongside it, with subsequent withdrawal of the drill-bit. It can be seen that a pressure drop is not detectable when there is no stenosis; and that a large pressure drop only develops with severe stenosis, and that flow in the aorto-coronary bypass graft is markedly influenced by the distal coronary artery pressure. This provides one explanation for disappointingly low graft flow measured at surgery - a coronary stenosis must be of sufficient severity to drop distal coronary pressure before high flow can be anticipated in a corrective bypass graft.



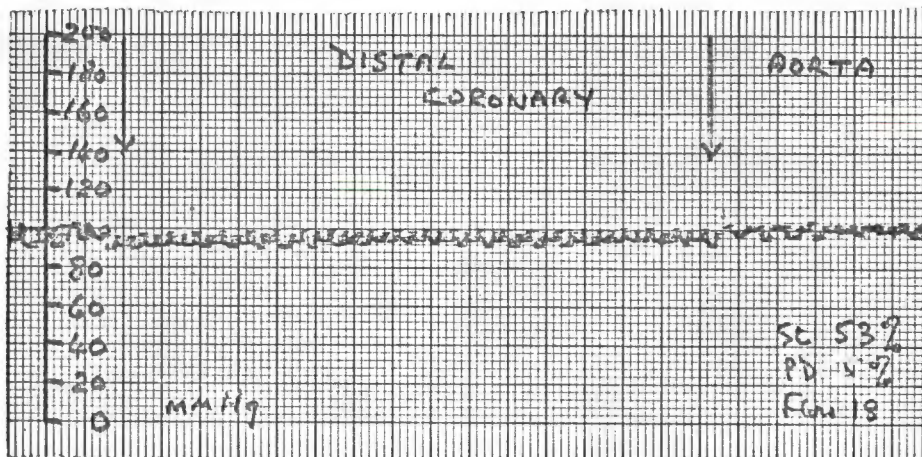
0% STENOSIS
0% PRESSURE DROP
12 ml/minute
bypass graft
flow



39% STENOSIS
5% PRESSURE DROP
18 ml/minute
bypass graft
flow

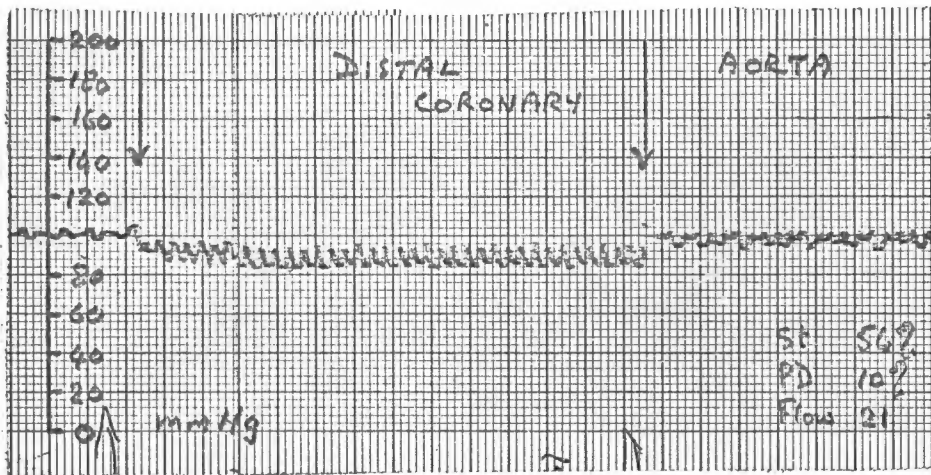


48% STENOSIS
5% PRESSURE DROP
18 ml/minute
bypass graft
flow

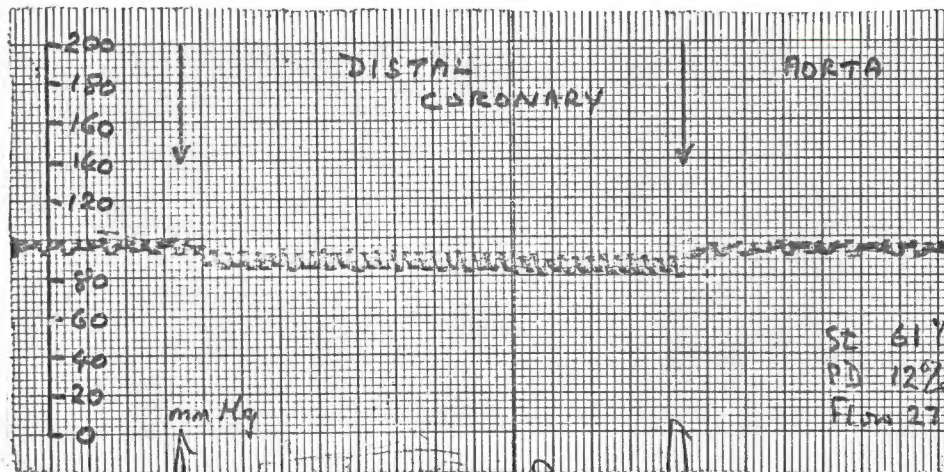


53% STENOSIS
5% PRESSURE DROP
18 ml/minute
bypass graft
flow

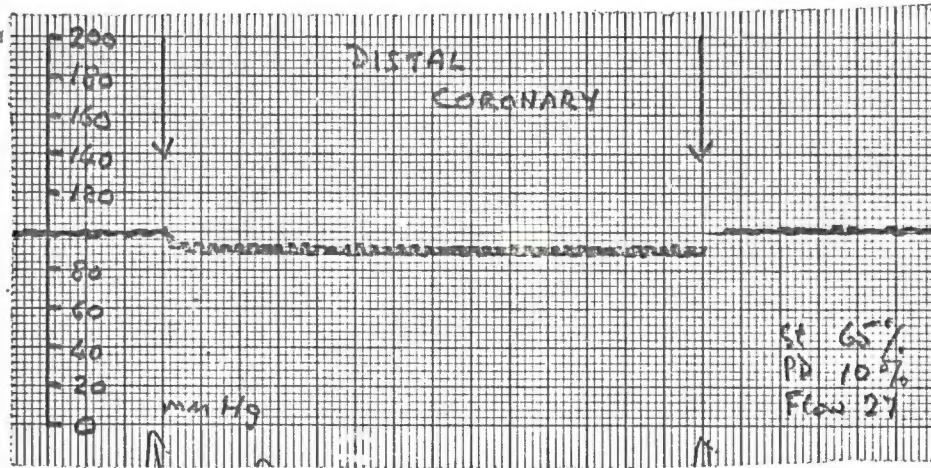
Figure 5d-35



56% STENOSIS
10% PRESSURE DROP
21 ml/minute
bypass graft
flow

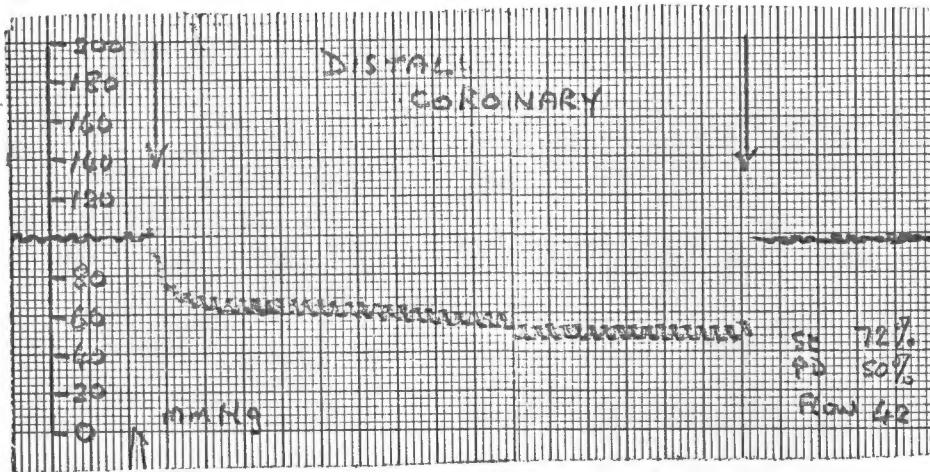


61% STENOSIS
12% PRESSURE DROP
27 ml/minute
bypass graft
flow

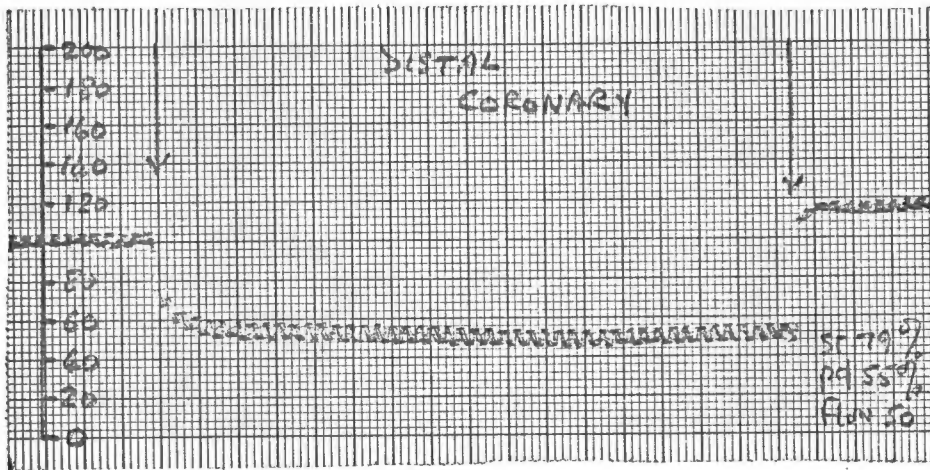


65% STENOSIS
10% PRESSURE DROP
27 ml/minute
bypass graft
flow

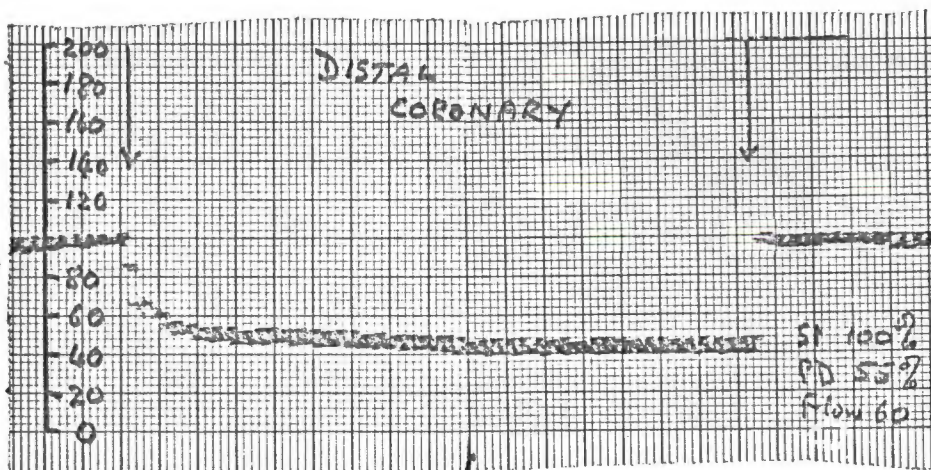
Figure 5d-36



72% STENOSIS
50% PRESSURE DROP
42 ml/minute
bypass graft
flow



79% STENOSIS
55% PRESSURE DROP
50 ml/minute
bypass graft
flow



100% STENOSIS
55% PRESSURE DROP
60 ml/minute
bypass graft
flow

Figure 5d-37

DISCUSSION

It has long been known that a considerable reduction in the lumen of an artery is required before it is possible to measure a reduction in pressure or flow beyond the obstruction (Mann et al 1938; Shipley and Gregg, 1944; May et al 1963). A "critical" level of stenosis is often described beyond which small additional degrees of stenosis produce great fall in distal pressure and flow (Berger and Hwang 1974). The problem of predicting the effects of arterial stenosis are considerable as pathological lesions rarely produce isolated stream-line stenoses and blood behaves as a non-Newtonian fluid (Byar et al 1963).

Although for the practical reasons of clinical angiographic assessments coronary stenosis are defined as percentage reduction in lumen diameter (see Section 3b). There are problems in using this as a measure of severity without accounting for other and often critical geometric characteristics such as stenosis length, absolute diameter, divergence angles (degree of streamlining) and eccentricity which may have equal or greater effects on pressure and flow (Young et al 1975). The effect of coronary vasodilatation has been shown in coronary stenoses by Gould (1978) in a dog model.

Coronary arteriography has limitations such as interobserver and intraobserver error in interpretation (Gilbert and Harthorne 1976; De Rouen et al 1977; Detre et al 1975; Bjork et al 1975). This is reflected in the poor correlation with postmortem or surgical assessment of severity (Vlodaver et al 1973; Grondin et al 1974).

Gregg and Bedynek (1978) point out the difficulties of estimation of luminal dimensions in experimental preparations. They show that a very large reduction in vessel lumen is needed to reduce coronary flow,

and this observation has been made by many workers (Folts et al 1974; Hillis et al 1975; Elzinga and Skinner 1975; Furuse et al 1975; Levinsky et al 1974). Gregg and Bedynek (1978) show that reactive hyperaemic coronary flow begins to fall at a 42% decrease in internal diameter, but that reduction of about 70% in internal diameter is necessary for reduction in control flow to appear - findings very similar to those in this study (Figure 5d-30). These workers also show similar findings with respect to distal coronary pressure and flow to those in this study. During reactive hyperaemia (in this study papaverine induced vasodilatation) flow is extremely sensitive to reduction in perfusion pressure - a deficit becoming apparent with about 6% pressure drop over a stenosis. In contrast, resting coronary flow is relatively unresponsive to marked reduction in coronary perfusion pressure.

It would appear therefore that reduction in perfusion pressure beyond a coronary stenosis is a good indication of the likely effect on regional perfusion, and that this reduction in pressure (or stenosis gradient) is relatively independent of flow rate in the range of flows encountered in the dog model. The superiority of this parameter over estimates of lumen diameter loss (even with the superior accuracy possible in an animal model compared with clinical angiography) in predicting perfusion deficit as well as likely aorto-coronary bypass graft flow in a "corrective" graft has been shown (Figures 5d-27, to 5d-34; and 5d-35 to 5d-37).

SECTION 5e
EFFECT OF VARIED
HEART RATE

EFFECT OF VARIED HEART RATE

In five dogs a total occlusion of the anterior descending artery was assessed for its effect on myocardial perfusion at varied heart rate.

Heart rate was initially slowed by giving intravenous practolol (50 mg intravenously over half an hour), together with deep anaesthesia. In this way it was possible to obtain a spontaneous heart rate in sinus rhythm of 75/minute (68 - 80 range) in all. Repeated attempts at sinus node crushing and infiltration of the sinus node with lignocaine were unsuccessful in achieving a slower rate.

Once satisfactory slow rate had been achieved the anterior descending artery was totally occluded for 10 minutes and the first injection of tracer microspheres was given with a beating, vented heart with perfusion pressure of 100 mmHg. The anterior descending occlusion was released after this for 10 minutes recovery before the next assessment.

The heart was next paced atrially at 100/minute and following 10 minutes of occlusion of the anterior descending artery the second tracer microsphere injection was given under conditions identical to the first injection (except for heart rate).

With similar recovery and occlusion periods third and fourth tracer microsphere injections were given at atrially paced heart rates of 150 and 200/minute respectively.

No significant alteration of mean myocardial blood flow could be demonstrated in the control areas at any of the heart rates tested. The values obtained in the model are shown on the next page.

Mean myocardial blood flow at 100 beats/minute:

endocardial half: 1.89 ml/Gm/min (S.D. 0.50)

epicardial half: 0.92 ml/Gm/min (S.D. 0.19)

Mean myocardial blood flow at 200 beats/minute:

endocardial half: 1.89 ml/Gm/min (S.D. 0.63)

epicardial half: 0.81 ml/Gm/min (S.D. 0.16)

Endocardial/epicardial flow ratio was similarly unchanged by heart rate in this model. At 100 beats/minute it was 2.05; at 200 beats/minute it was 2.32.

It must be emphasised that this is a beating, non-working heart with zero left ventricular cavity pressure (vented heart). These factors clearly explain both the high endocardial-epicardial flow ratio and also the failure of tachycardia to limit the flow in a demonstrable way in this model.

Figure 5e-1 shows the angiographic appearance of one of the dogs in this study.

Figure 5e-2 and 5e-3 show the left ventricular perfusion maps for endocardial half and epicardial half respectively at a heart rate of 75/minute. There is a flow rate in the test area of 45% and 50% of control value for endocardial and epicardial halves respectively.

Figure 5e-4 and 5e-5 show the left ventricular perfusion maps for endocardial half and epicardial half respectively at a heart rate of 105/minute. There is a flow rate in the test area of 35% and 16% of control value for endocardial and epicardial halves respectively. Furthermore, the anatomical extent of the perfusion deficit is greater at the more rapid rate.

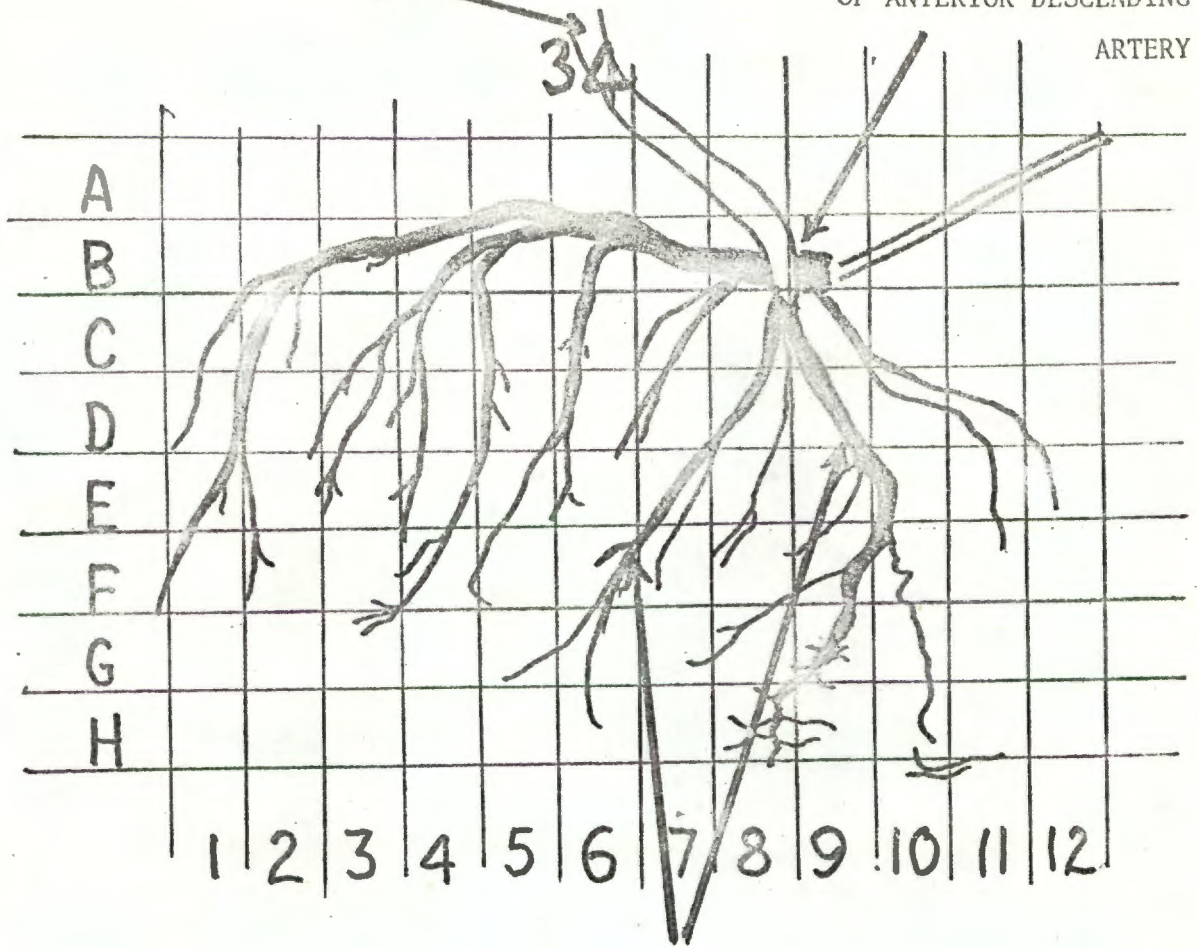
The amelioration of the consequences of coronary obstruction were only evident at the lowest rate tested (75/minute). There was a significant difference in all dogs between the perfusion deficit at 75/minute and at 100/minute. However, there was no significant difference between

the perfusion deficits at 100, 150 and 200-minute. Furthermore, the endocardial/epicardial ratio was not altered by the variation in heart rate at these levels, but was closer to one than the control areas.

The results for the 5 dogs are shown in graph form in Figure 5e-6.

SITE OF TOTAL OCCLUSION
OF ANTERIOR DESCENDING
ARTERY

GRAFT



Dog 34

THESE VESSELS JEOPARDISED

EFFECT OF VARIED HEART RATE

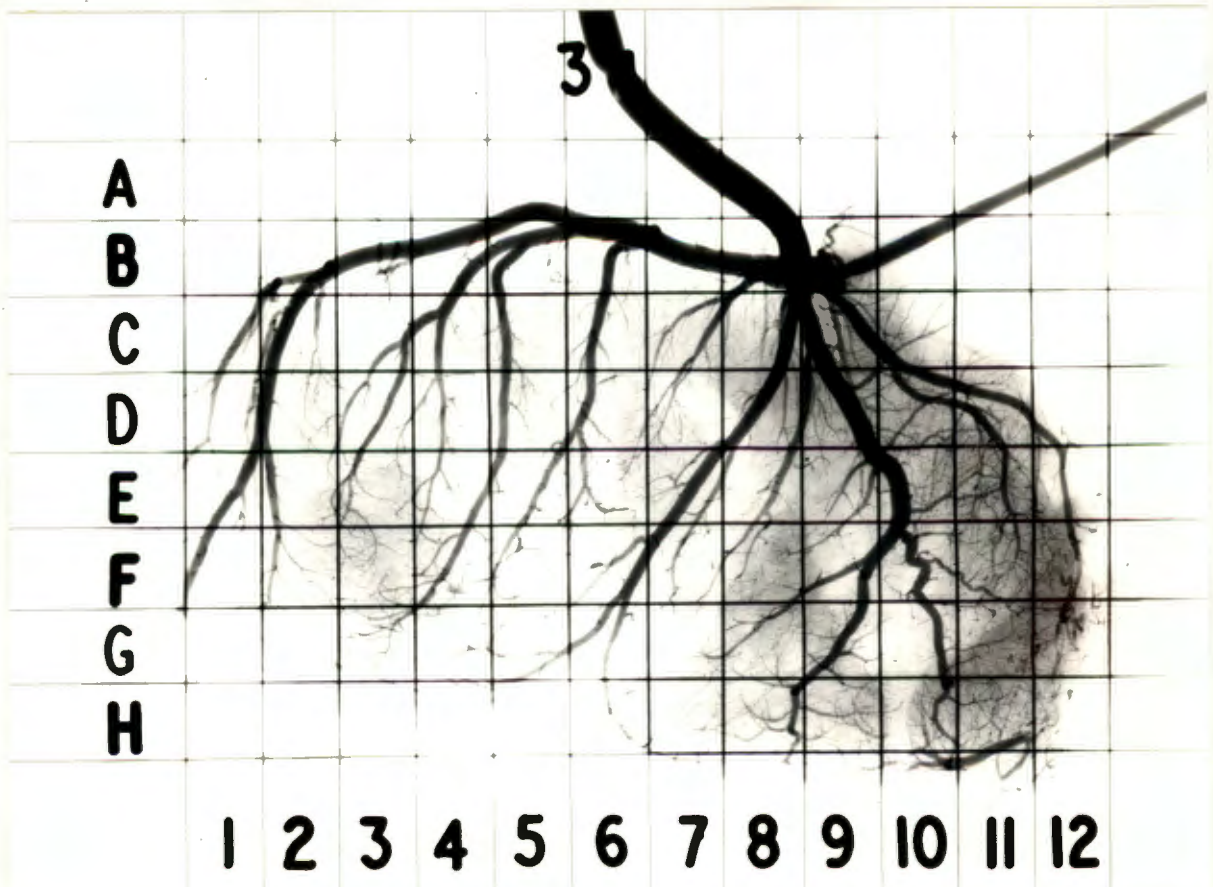


Figure 5e - 1

EFFECT OF VARIED HEART RATE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

HEART RATE ; 75/MINUTE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.63	0.74
S.D.	0.22	0.50
S.E.M.	0.05	0.15

PROGRAM: DJW (REV F)

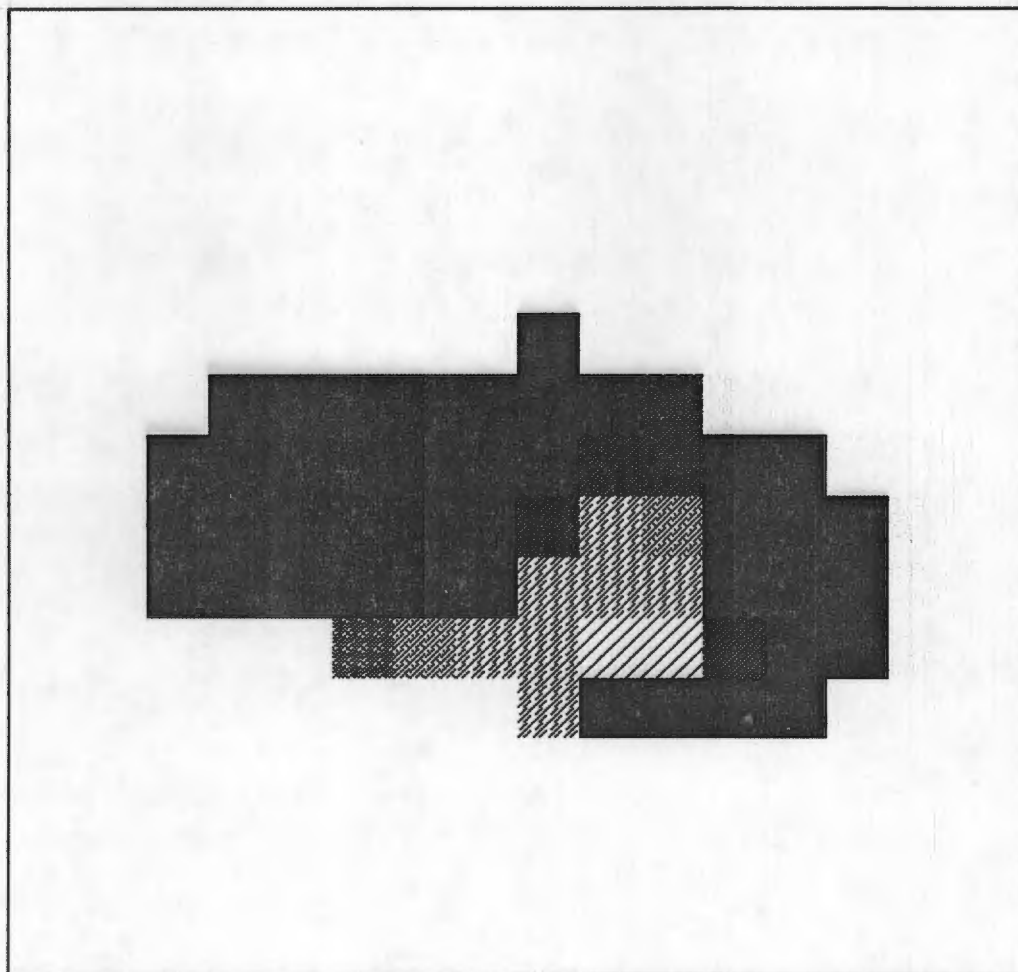
DOG 34 EFFECT OF VARIED HEART RATE
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 1.20

Figure 5e-2

EFFECT OF VARIED HEART RATE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

HEART RATE : 75/MINUTE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0,86	0,43
S.D.	0,21	0,13
S.E.M.	0,05	0,04

PROGRAM: DJW (REV F)

DOG 34 EFFECT OF VARIED HEART RATE
 EPICARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 1.20

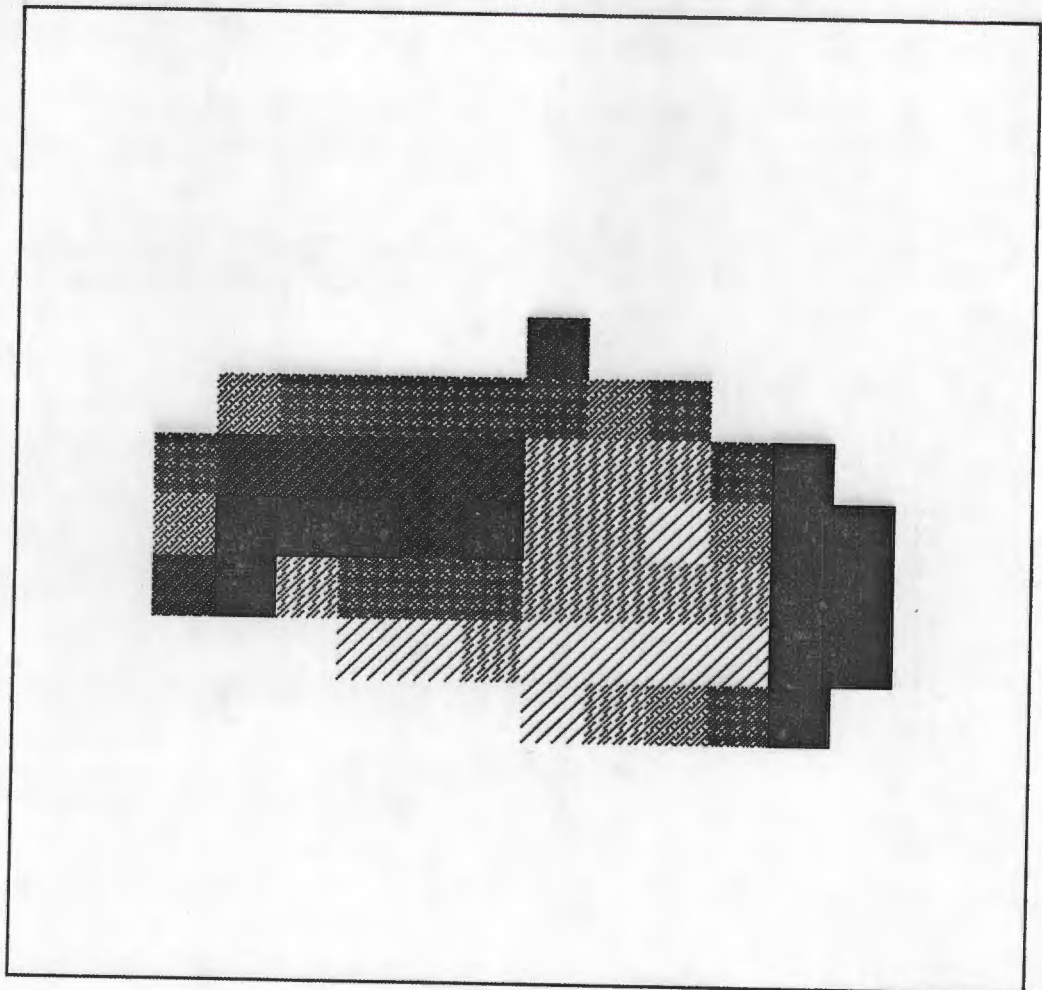


Figure 5e-3

EFFECT OF VARIED HEART RATE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

HEART RATE ; 105/MINUTE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.19	0.42
S.D.	0.20	0.42
S.E.M.	0.04	0.12

PROGRAM: DJW (REV F)

DOG 34 EFFECT OF VARIED HEART RATE
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 1.20

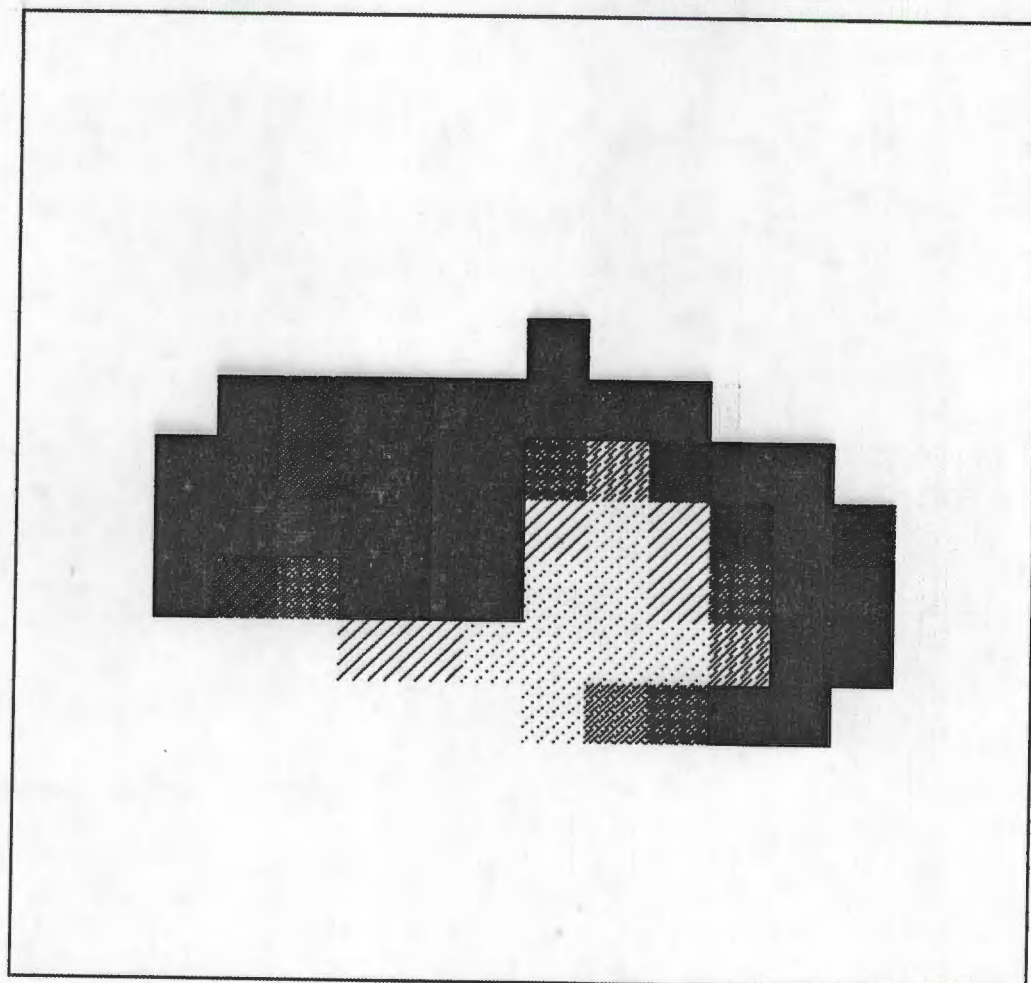


Figure 5e-4

EFFECT OF VARIED HEART RATE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

HEART RATE : 105/MINUTE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1,46	0,24
S.D.	0,34	0,37
S.E.M	0,07	0,11

PROGRAM: DJW (REV F)

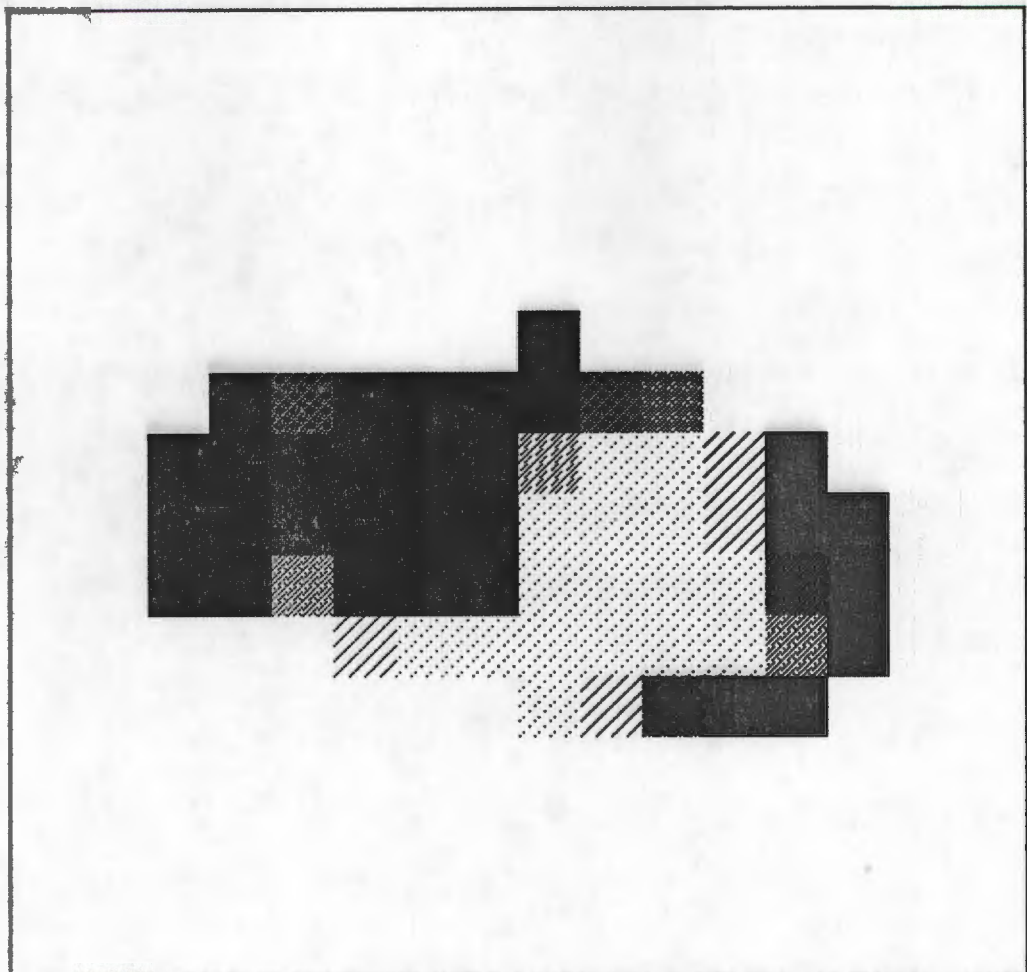
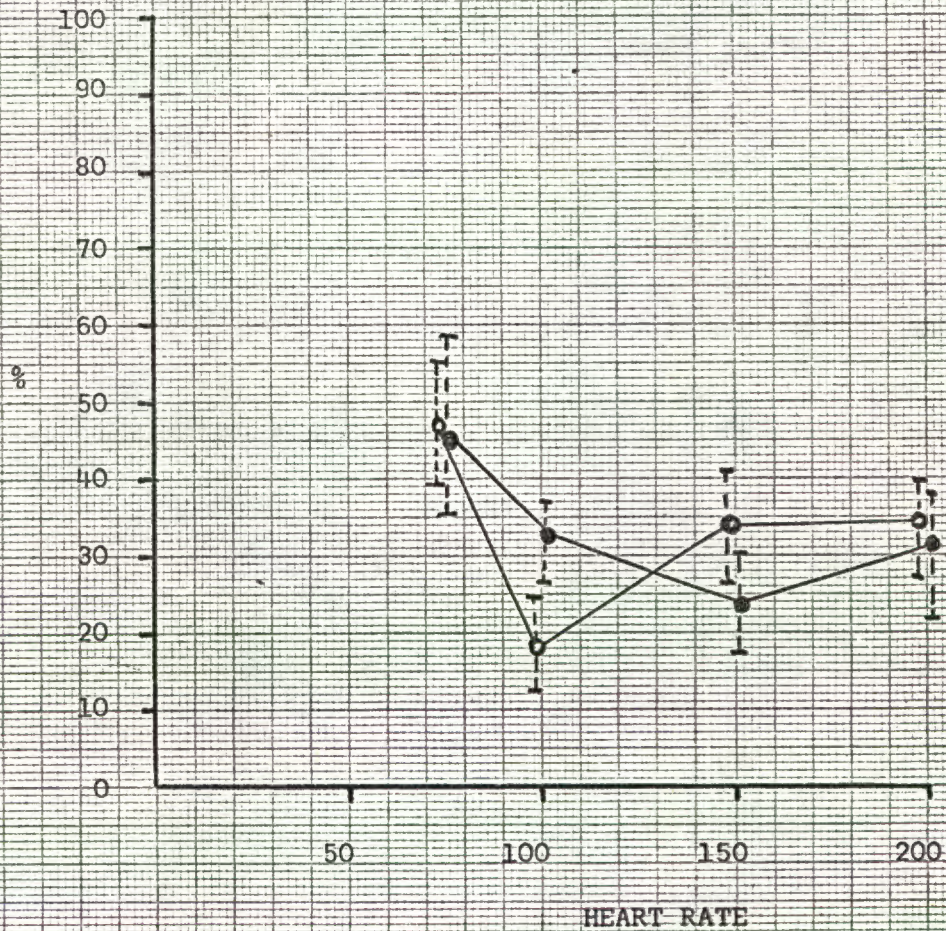
DOG 34 EFFECT OF VARIED HEART RATE
EPICARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 1.20

Figure 5e-5

EFFECT OF VARIED HEART RATE

Beating, vented, non-working hearts on cardio-pulmonary bypass. Heart rate varied by atrial pacing. Occlusion of anterior descending artery.

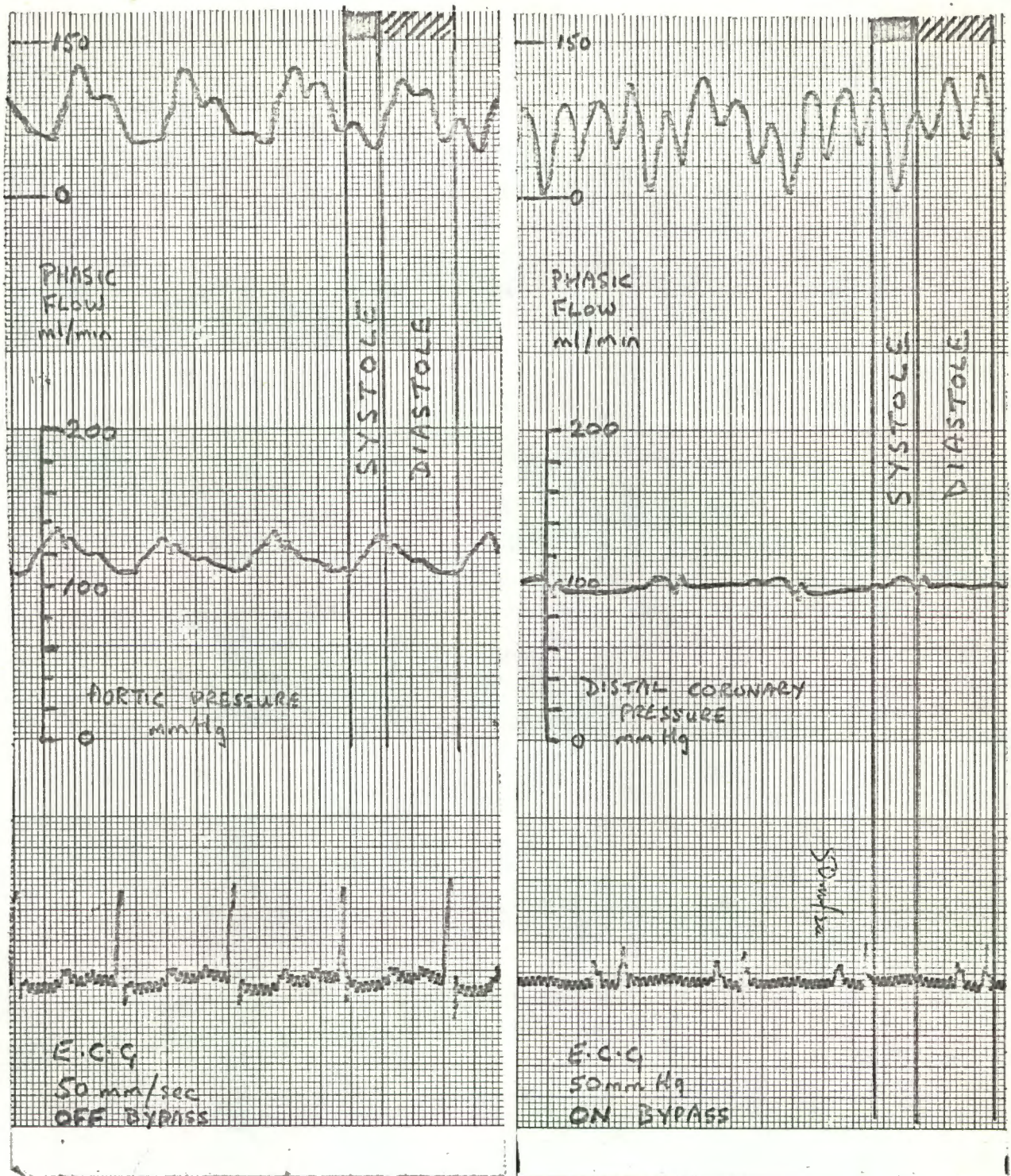
Graph shows perfusion of jeopardised territory (expressed as percentage of control area value)



- - epicardial perfusion
- - endocardial perfusion

Perfusion expressed as percentage of control area value
Mean value and range for 5 dogs shown

Figure 5e - 6



The left hand trace shows phasic flow in the anterior descending coronary artery in a working heart off cardio-pulmonary bypass.

The right hand trace shows phasic flow in the anterior descending coronary artery of the same heart, not working, on cardio-pulmonary bypass.

Figure 5e - 7

EFFECT OF HEART RATE

It is well known, and Figure 5e-7 shows this in a typical example from one dog, that coronary blood flow is reduced during systole (L'Abbate et al 1978). Sabiston and Gregg (1957) showed an increase in coronary flow in the arrested heart compared with beating heart at constant perfusion pressure. An intramyocardial pressure gradient from epicardium to endocardium is created by systolic myocardial contraction (Johnson and Di Palma, 1939; Kirk and Honig, 1964; Brandi and McGregor, 1969). There is general agreement that pressures in the subendocardium equal or exceed left ventricular cavity pressure in systole and become lower nearer the epicardium (Downey and Kirk 1974; Hess and Bache 1976). This is assumed to compress intramyocardial vessels during systole, accounting for systolic limitation of myocardial perfusion, which is most marked in the deepest layers - the subendocardium, where systolic intramyocardial pressure is highest.

Griggs and Nakamura (1968) showed that the ratio of subendocardial to subepicardial flow could be predicted from coronary and left ventricular pressure curves. The concept of subendocardial vulnerability to relative ischaemia due to low diastolic pressure, or shortened diastolic perfusion time, (as in tachycardia) increased systolic pressure in the left ventricle, (as in aortic stenosis or hypertension) has been tested by Buckberg et al (1972) and is now widely accepted (Hoffman et al 1978).

L'Abbate et al (1978) showed that abolition of contraction in a normally perfused segment of left ventricular myocardium caused subendocardial blood flow to increase. As subendocardial flow is equal to or exceeds subepicardial flow in a beating normal heart a

greater vascularity of the subendocardial region is suggested (Myers et al 1964; Weiss et al 1974). Hoffman et al (1978) however produced evidence which supported that of Buckberg et al (1972) suggesting that differential autoregulation is an important factor in monitoring the subendocardial/subepicardial ratio close to one. However, when autoregulation is abolished and coronary perfusion pressure is maintained, transmural blood flow distribution remains even (L'Abbate et al 1974; Klassen et al 1978; Cobb et al 1974; Downey et al 1975). This suggests that autoregulation does not play a part in evening out transmural flow. This observation is supported by findings in this study - the subendocardial/subepicardial ratios were not related to the state of coronary vasodilatation (See Figure 5a-8).

It would seem logical to expect that tachycardia would be disadvantageous to myocardial perfusion, particularly in the presence of coronary obstruction already prejudicing blood flow; and that bradycardia would be advantageous. However, the results obtained in this model suggest that for a non-working vented heart the effect of tachycardia is largely absent; and that to obtain a benefit from bradycardia in terms of myocardial perfusion it may be necessary to have fairly well marked bradycardia (in the dog 75 beats/minute is clearly better than 100 beats/minute).

However, myocardial oxygen demand is related to heart rate (Wolfson and Gorlin, 1969; Goodman and Gilman, 1975) and can be advantageously influenced by beta-blockade - a standard cardiological practice now carried over into surgical management (Section 3c - Shorthouse and Parker 1978).

SECTION 5f
EFFECT OF LEFT VENTRICULAR
CAVITY PRESSURE

EFFECT OF LEFT VENTRICULAR CAVITY PRESSURE

Left ventricular cavity pressure is known to influence the transmural distribution of myocardial blood flow in the normally working heart (Hoffman et al 1978; Griggs and Nakamura 1968; Buckberg et al 1972).

During cardiopulmonary bypass it is usual practice to vent the left ventricle to prevent left ventricular distension (Miller 1977) and the importance of left ventricular venting in preventing sub-endocardial ischaemia is emphasised by Hottenrott et al (1974).

In order to assess the effect of left ventricular cavity pressure on regional myocardial perfusion in the presence of coronary obstruction a balloon was tied over the end of the left ventricular vent which was inserted into the left ventricle via the left atrial appendage in three dogs.

With total occlusion of the anterior descending artery and an aortic perfusion pressure on cardiopulmonary bypass of 100 mmHg for 10 minutes with no pressure in the intracavitary balloon the first tracer microsphere injection was given.

Following a 10 minute recovery period the anterior descending artery was again occluded totally and the balloon in the left ventricle was inflated with air to 20 mmHg pressure. After 10 minutes a second tracer microsphere injection was given.

Following a further 10 minute recovery period the anterior descending artery was again occluded totally and the balloon in the left ventricle was inflated with air to 40 mmHg pressure. After 10 minutes a third tracer microsphere injection was given.

Maintaining sinus rhythm for all three injections was not possible and it was therefore elected to induce ventricular fibrillation

electrically before each experimental run rather than have the heart fibrillate spontaneously with the inflation of the balloon (as occurred repeatedly with the first attempted dog). A balloon was necessary as attempts to distend the left ventricle with blood failed as the heart ejected its contents into the aorta, and further more it was important to avoid the possibility of left ventricular contents (devoid of microspheres) getting into the aortic root during tracer microsphere injection.

Figure 5f-1 shows the endocardial perfusion map for one of the dogs (Dog 31). with zero left ventricular cavity pressure. The anticipated perfusion deficit in the anterior descending territory is present. Myocardial blood flow in the endocardial half of the "test" anterior descending area is 21% of control level.

Figure 5f-2 shows the endocardial perfusion map for the same dog with 20 mmHg left ventricular cavity pressure. A similar perfusion deficit is present with myocardial blood flow in the test area being 14% of control level.

Figure 5f-2 shows the endocardial perfusion map for the same dog with 40 mmHg left ventricular cavity pressure. The perfusion deficit is similar with myocardial blood flow in the test area being 14% of control level.

Similar changes were observed in the epicardial flow maps. The endocardial/epicardial flow ratios were as follows:

Endocardial/Epicardial Flow Ratio

LV Cavity Pressure	Control	Test
Zero	1.72	4.46
20 mmHg	1.49	0.72
40 mmHg	1.42	0.85

EFFECT OF LEFT VENTRICULAR CAVITY PRESSURE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

LV CAVITY PRESSURE - ZERO

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.13	0.24
S.D.	0.08	0.45
S.E.M.	0.02	0.13

PROGRAM: DJW (REV F)

DOG 31

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.00

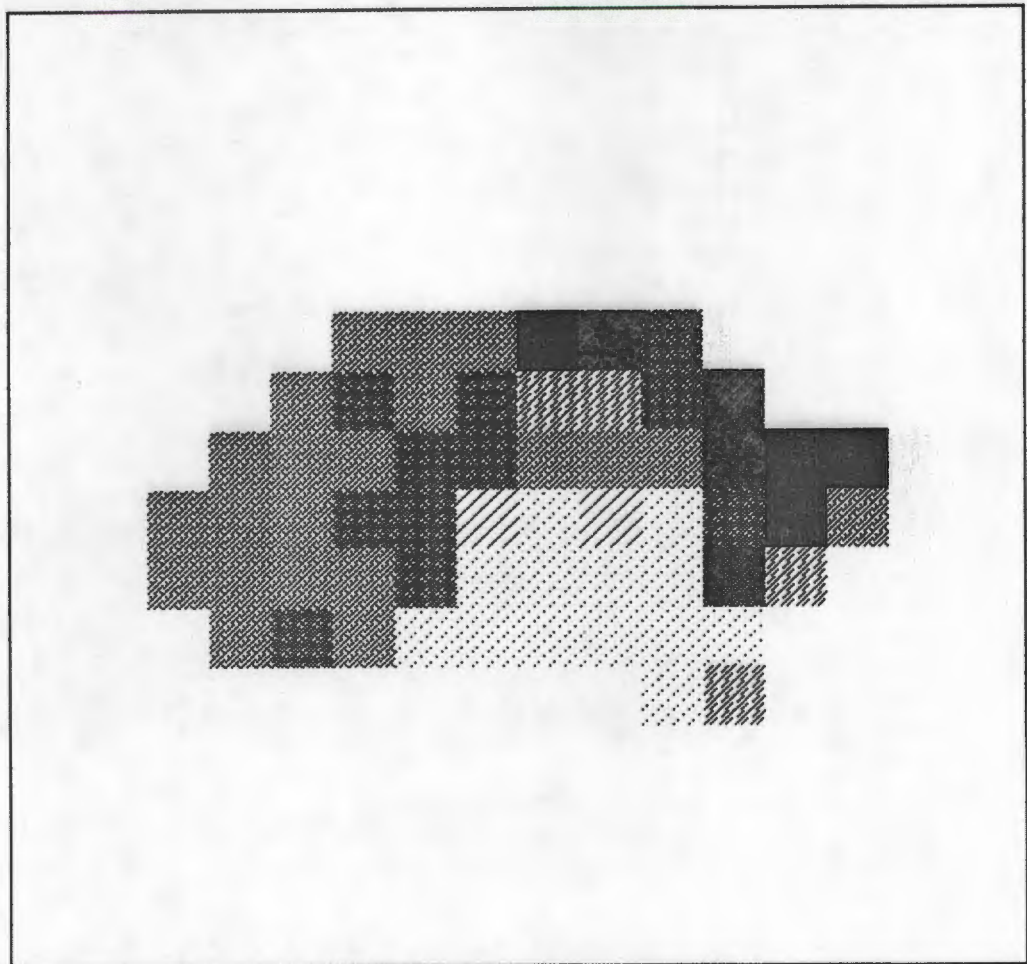


Figure Sf-1

EFFECT OF LEFT VENTRICULAR CAVITY PRESSURE
 REGIONAL MYOCARDIAL PERFUSION
 TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY
 LV CAVITY PRESSURE 20 mmHG

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.57	0.22
S.D.	0.22	0.22
S.E.M.	0.05	0.06

PROGRAM: DJW (REV F)

DOG 31
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 2.00

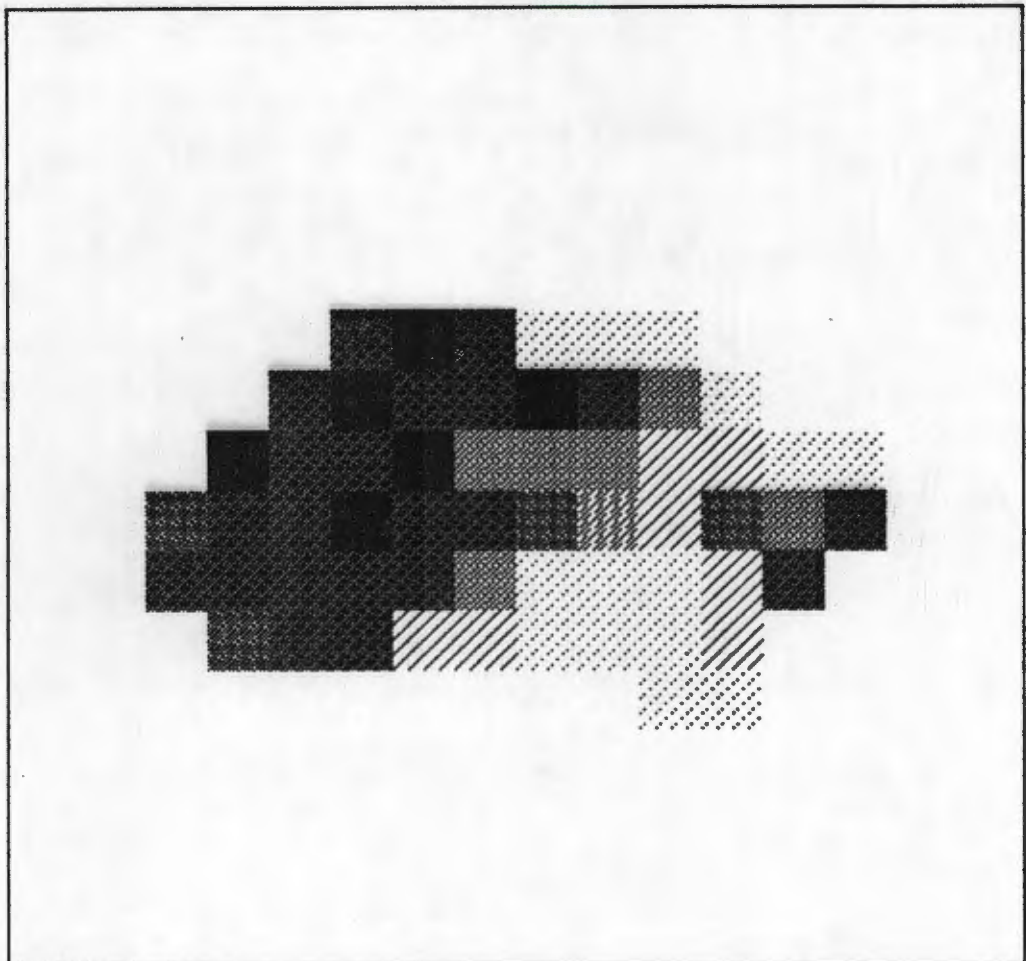


Figure Sf-2

EFFECT OF LEFT VENTRICULAR CAVITY PRESSURE

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

LV CAVITY PRESSURE 40 mmHg

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.68	0.24
S.D.	0.22	0.24
S.E.M.	0.05	0.07

PROGRAM: DJW (REV F)

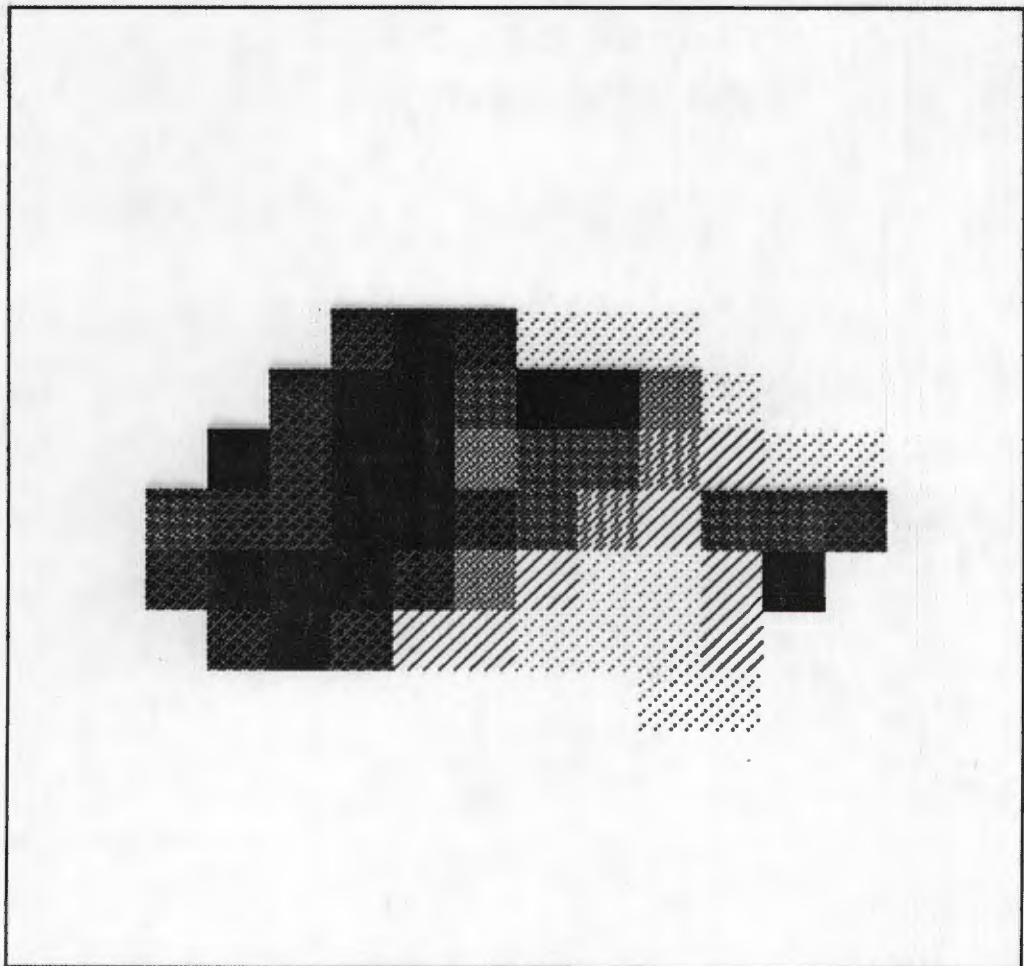
DOG 31
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 4, SCALED TO 2.00

Figure 5f-3

DISCUSSION

The importance of avoiding left ventricular distension during cardiopulmonary bypass has been emphasised (Hottenrott et al 1974); and clearly the ill-effects of left ventricular distension include mechanical stretching of myocardial fibres and pulmonary venous engorgement.

However, this experiment in the animal model for coronary surgery was not able to demonstrate a striking effect with raised left ventricular cavity pressure. There was no significant change in endocardial/epicardial ratio nor in absolute blood flow over the range of left ventricular cavity pressures measured (zero to 40 mmHg). This may well be due to the aortic perfusing pressure being considerably higher at 100 mmHg. Clearly there is a point at which, with lowered arterial pressure or further elevated left ventricular cavity pressure the driving pressure for blood flow to subendocardial regions would be reduced, but in this model with the pressures tested this did not occur.

SECTION 5g
EFFECT OF VENTRICULAR
FIBRILLATION

EFFECT OF VENTRICULAR FIBRILLATION

In three dogs the effect of ventricular fibrillation was assessed in the presence of total occlusion of the anterior descending artery.

Figure 5g-1 shows the endocardial perfusion map of one dog (Dog 31) in which an injection of tracer microspheres was made on cardiopulmonary bypass with 100 mmHg perfusion pressure and a beating (160/minute), vented heart. The anticipated perfusion deficit is present in the territory of the occluded anterior descending artery, with endocardial blood flow in this region being 17% of control level.

Figure 5g-2 shows the endocardial perfusion map of the same dog after 10 minutes of electrically induced, spontaneous ventricular fibrillation, with perfusion pressure and left ventricular cavity pressure being unchanged. There is increased flow to both "test" and control areas. The endocardial flow in the jeopardised test area is 21% of control level.

The increase in myocardial perfusion in the fibrillating heart was seen in each case and was a significant increase, involving both normally perfused and jeopardised areas.

Change in myocardial perfusion with
ventricular fibrillation compared
with beating heart (150-160/minute)

Control Areas (normally perfused)		Test Areas (totally occluded artery)	
Endocardium	Epicardium	Endocardium	Epicardium
134% increase	135% increase	168% increase	56% decrease

Mean endocardium/epicardium flow ratio remained unchanged with the onset of ventricular fibrillation in the control areas at 1.63.

*In the test areas the low flow made reliable estimation impossible (the endocardium/epicardium ratio in fact changed from 4.47 to 17).

EFFECT OF VENTRICULAR FIBRILLATION

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

BEATING HEART RATE - 160/MINUTE

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.81	0.14
S.D.	0.06	0.23
S.E.M.	0.01	0.06

PROGRAM: DJW (REV F)

DOG 31

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 2.00

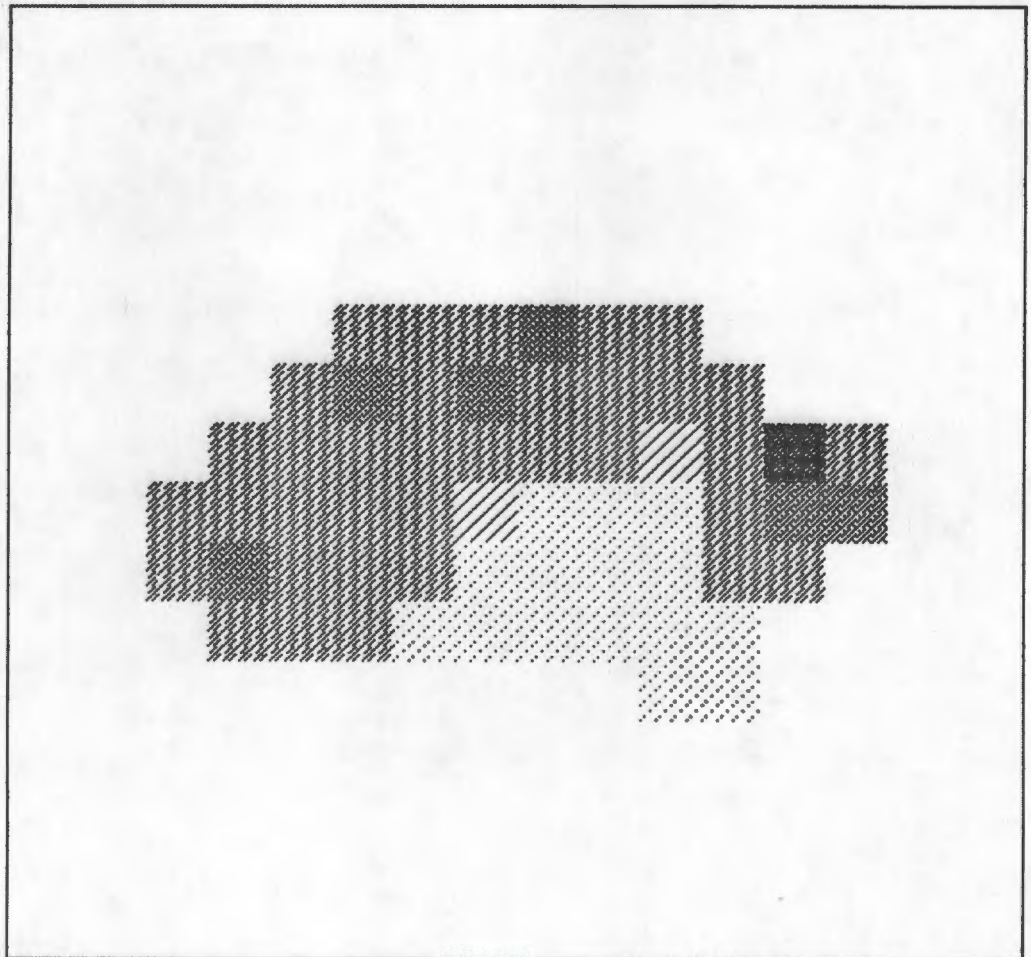


Figure 5g-1

EFFECT OF VENTRICULAR FIBRILLATION

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

VENTRICULAR FIBRILLATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.13	0.24
S.D.	0.08	0.45
S.E.M.	0.02	0.13

PROGRAM: DJW (REV F)

DOG 31

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 2.00

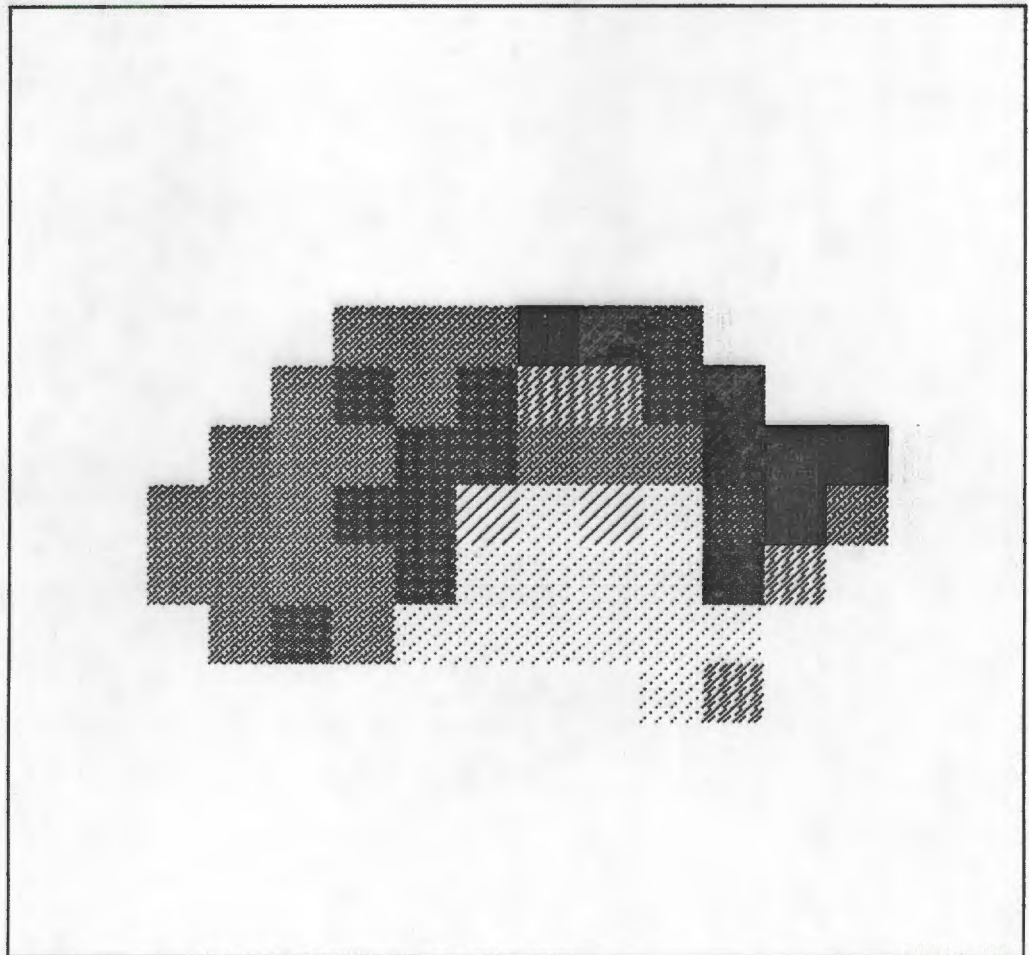


Figure 5g-2

DISCUSSION

Ventricular fibrillation is frequently used during coronary surgery to obtain an immobile operating field (Hottenrott et al 1974; Wheatley and Davis 1975; Race et al 1964). Hottenrott et al (1974) showed that for a non-hypertrophied heart spontaneous fibrillation (ie, ventricular fibrillation induced with a 60 cycle AC stimulus which is then withdrawn) resulted in significant increase in blood flow to the subendocardium. This compensated for the increase in oxygen consumption of the fibrillating heart compared with the empty, beating heart. The increase in flow to the endocardial region in that work was about 290%; for flow to the whole left ventricle 240%, with ventricular fibrillation, an even greater increase than that observed in this study.

Kleinman and Wechsler (1978) showed an increase in flow to subendocardium of normally perfused left ventricle with ventricular fibrillation but no change in flow to the subendocardium of left ventricle supplied only by collateral flow. They concluded that during cardiopulmonary bypass ventricular fibrillation exaggerates existing subendocardial perfusion deficits in collateral regions. While this present study does not show this it is important to note that collateral flow in Kleinman and Wechsler's study was through collaterals developed over 4 to 5 weeks of ameroid constriction and in this study the collateral flow is through the normally present but "undeveloped" collaterals of the dog heart. The resultant low flow in totally occluded territory makes it impossible to calculate changes in flow in these regions with certainty.

Thus the study confirms that increase in flow occurs to normally perfused myocardium with onset of ventricular fibrillation. Although a similar increase is shown for jeopardised endocardium there is a decrease for epicardium, but the low flow areas make the significance difficult to assess. The findings of no change in collaterally-supplied areas by Kleinman and Wechsler therefore appear wholly in keeping with results from this study.

SECTION 5h
EFFECT OF BYPASS GRAFT

EFFECT OF BYPASS GRAFT

As pointed out in Section 5b the assessment of adequacy of an aorto-coronary bypass graft in correcting for coronary obstruction should take account of coronary vasomotor tone - the graft should cope with high coronary flow requirements to be truly effective.

The examples that follow are therefore shown in a state of coronary vasodilatation and high coronary flow.

Figure 5h-1 shows the endocardial perfusion map of Dog 11, in which a corrective aorto-coronary bypass graft was inserted to bypass a 75% stenosis of the anterior descending artery (see Figure 5b-1). The perfusion deficit consequent on the 75% stenosis has been shown in Figures 5b-4 and 5b-5. Figure 5h-1 shows that with the bypass graft open and functioning there is restoration to normal uniform perfusion (no significant difference between circumflex (control) area and anterior descending (test) area, with high coronary flow level.

EFFECT OF BYPASS GRAFT
 REGIONAL MYOCARDIAL PERFUSION
 75% STENOSIS OF ANTERIOR DESCENDING ARTERY
 "CORRECTIVE" AORTO-CORONARY BYPASS GRAFT FUNCTIONING
 CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.67	2.96
S.D.	0.87	0.55
S.E.M.	0.15	0.17

PROGRAM: DJW (REV F)

DOG 11
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1. SCALED TO 4.00

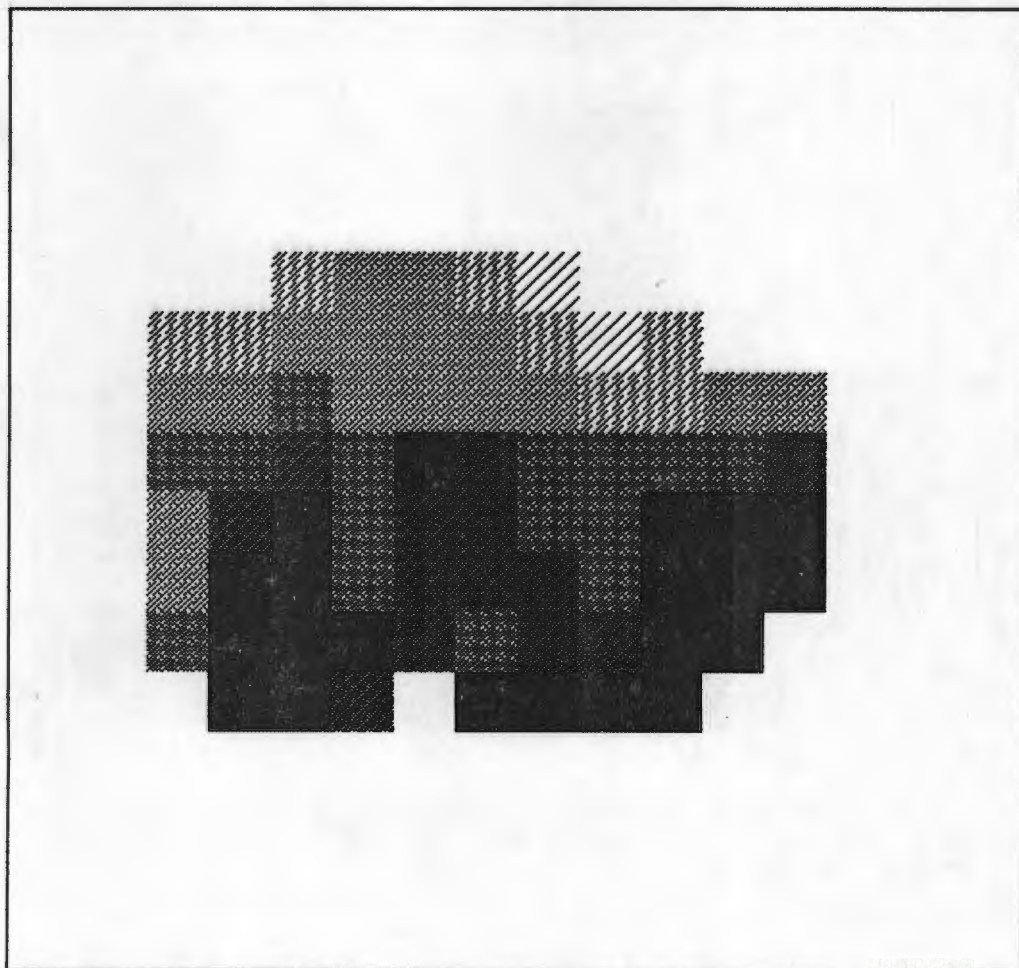


Figure 5h-1

Figure 5h-2 shows the endocardial perfusion map for Dog 7, in which an aorto-coronary bypass graft is open and functioning to correct for an 80% stenosis of the anterior descending artery at a high coronary flow level.

The perfusion deficit resulting from the stenosis in this dog is shown in Figure 5b-9. With the bypass graft functioning there is no significant difference between the circumflex (control) and anterior descending (test) areas.

EFFECT OF BYPASS GRAFT
 REGIONAL MYOCARDIAL PERFUSION
 80% STENOSIS OF ANTERIOR DESCENDING ARTERY
 "CORRECTIVE" AORTO-CORONARY BYPASS GRAFT FUNCTIONING
 CORONARY VASODILATATION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	3.46	3.88
S.D.	1.19	0.87
S.E.M.	0.22	0.17

PROGRAM: DJW (REV F)

DDOG 7
 ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2. SCALED TO 4.00

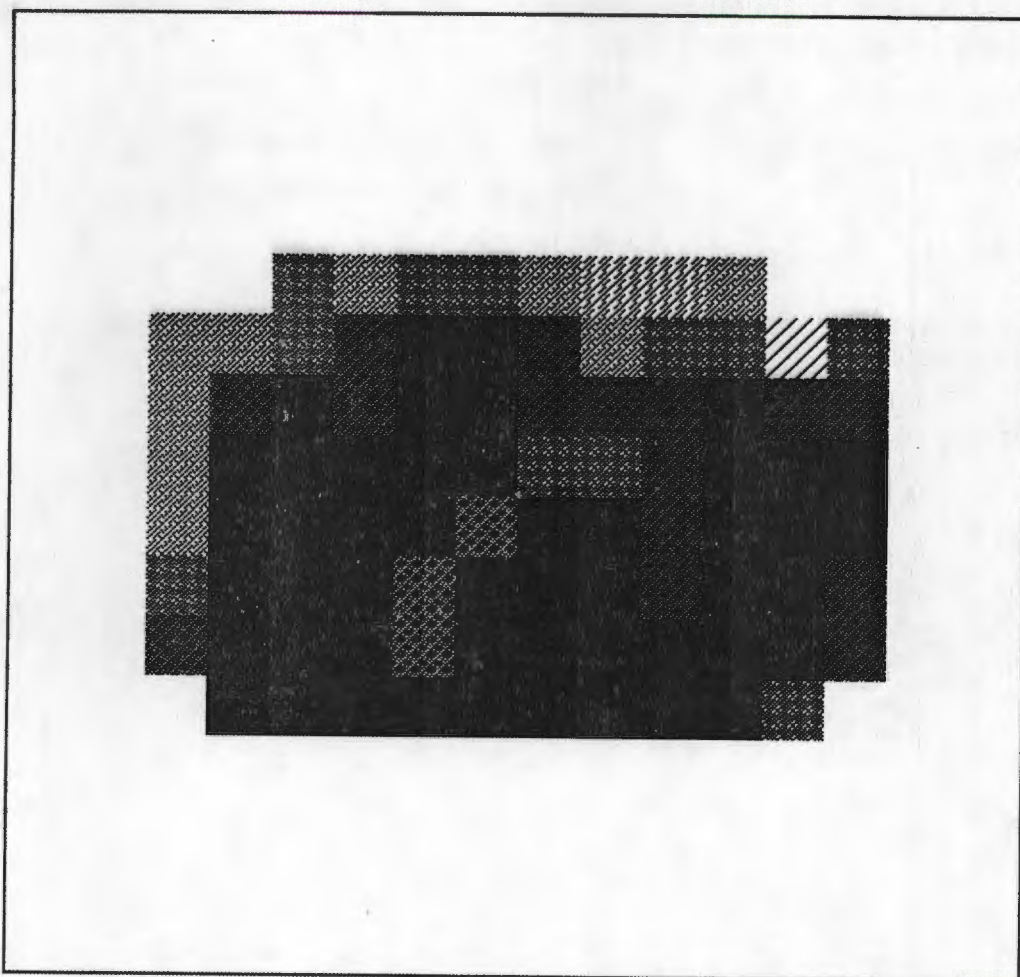


Figure 5h-2

Figures 5h-3 and 5h-4 show respectively the myocardial perfusion maps for endocardial and epicardial halves of left ventricle of Dog 20 in which total occlusion of the anterior descending artery was corrected by an aorto-coronary bypass graft.

The angiographic appearances are shown in Figures 5d-1 and 5d-2 and the myocardial perfusion deficit consequent on the total anterior descending occlusion is shown for endocardium in Figure 5d-7 and for epicardium in Figure 5d-8.

The bypass graft restores uniform flow even at very high perfusion levels and there is no significant difference between control and test areas.

EFFECT OF BYPASS GRAFT

REGIONAL MYOCARDIAL PERFUSION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	3.77	5.26
S.D.	1.46	1.09
S.E.M.	0.28	0.26

PROGRAM: DJW (REV F)

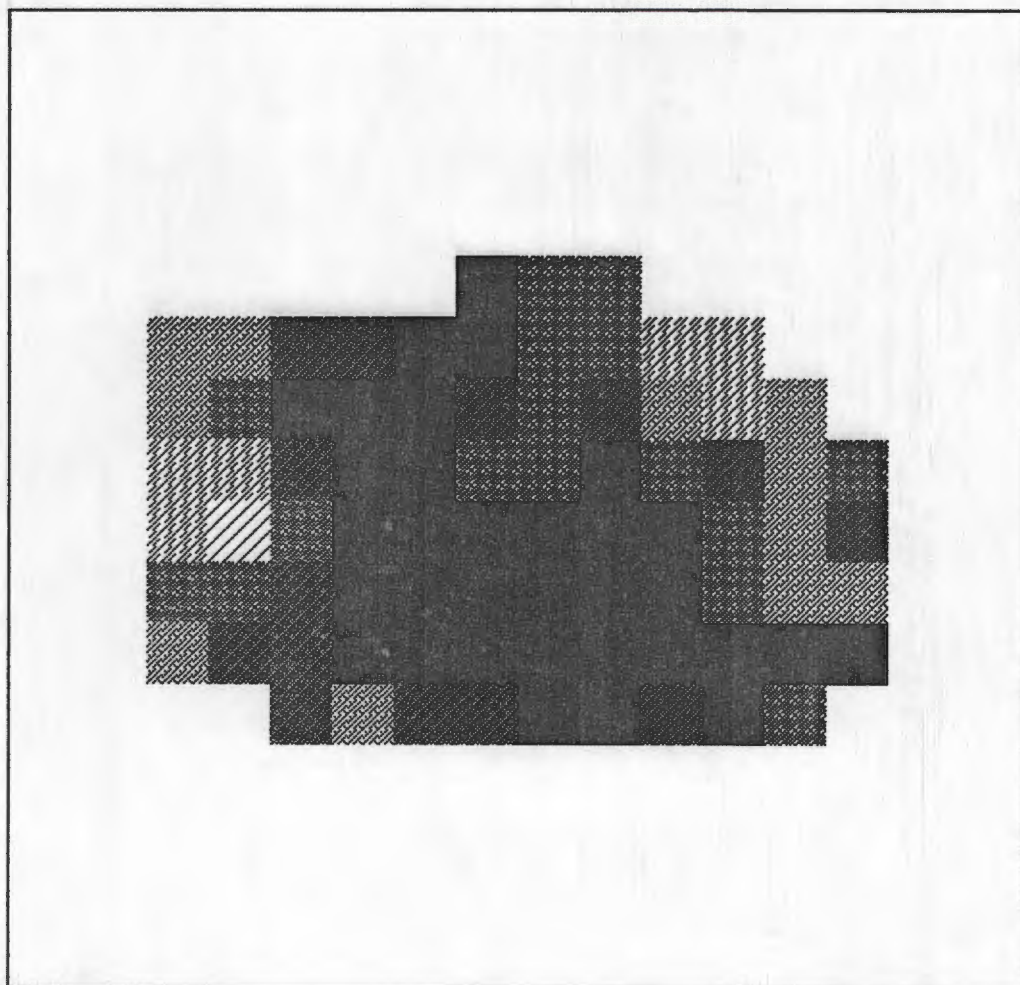
DOG 20
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 5.00

Figure 5h-3

EFFECT OF BYPASS GRAFT

REGIONAL MYOCARDIAL PERFUSION

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.47	3.35
S.D.	0.62	1.05
S.E.M.	0.12	0.25

PROGRAM: DJW (REV F)

DOG 20

EPICARDIUM BLOOD FLOWS FOR ENERGY 1, SCALED TO 5.00

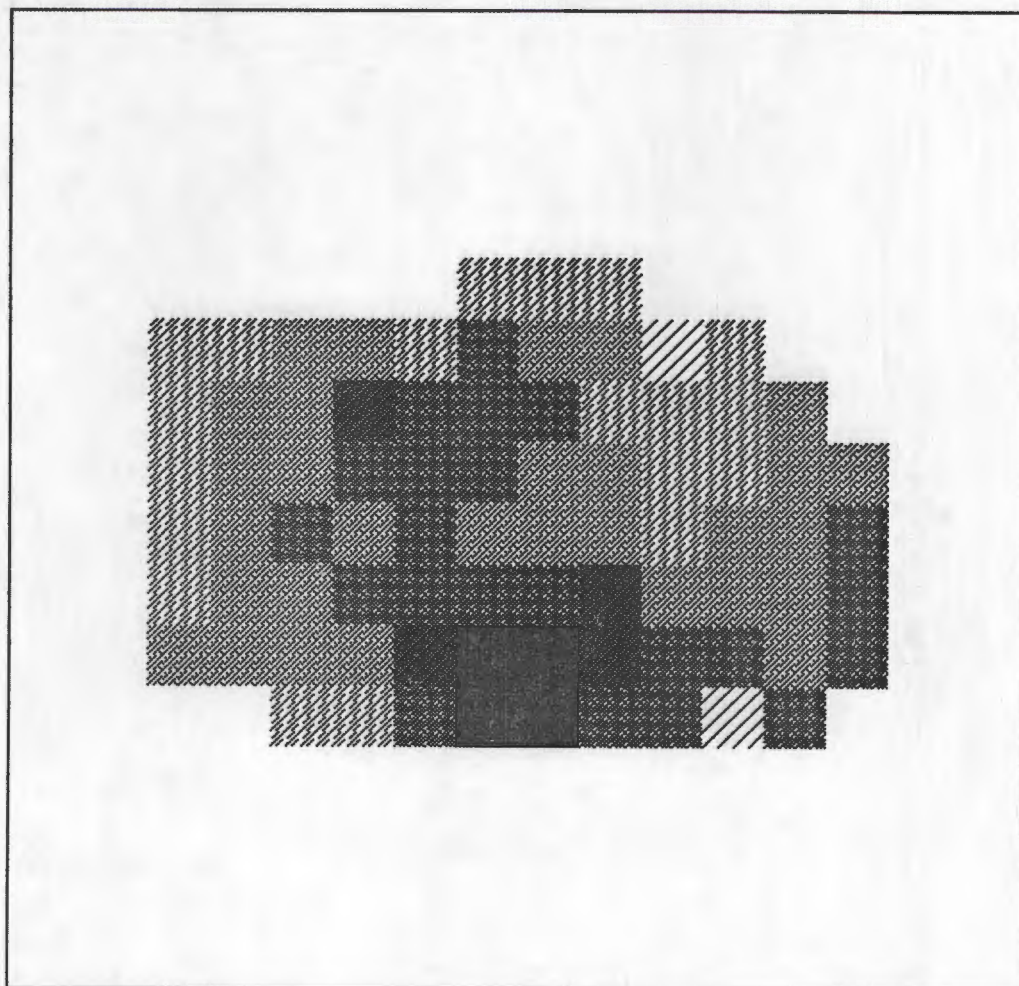


Figure 5h-4

Figures 5h-5 and 5h-6 show respectively the myocardial perfusion maps for endocardial and epicardial halves of left ventricle of Dog 24, in which total occlusion of the circumflex artery was corrected by an aorto-coronary bypass graft.

The angiographic appearances are shown in Figures 5d-10 and 5d-11 and the myocardial perfusion deficit consequent on the total circumflex occlusion is shown for endocardium in Figure 5d-16 and for epicardium in Figure 5d-17.

The bypass graft restores uniform flow, even at high perfusion level, and there is no significant difference between control and test areas.

EFFECT OF BYPASS GRAFT
REGIONAL MYOCARDIAL PERFUSION
TOTAL OCCLUSION OF CIRCUMFLEX ARTERY
WITH BYPASS GRAFT FUNCTIONING

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	1.69	1.64
S.D.	0.37	0.28
S.E.M.	0.08	0.05

PROGRAM: DJW (REV F)

DOG 24

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 2.50

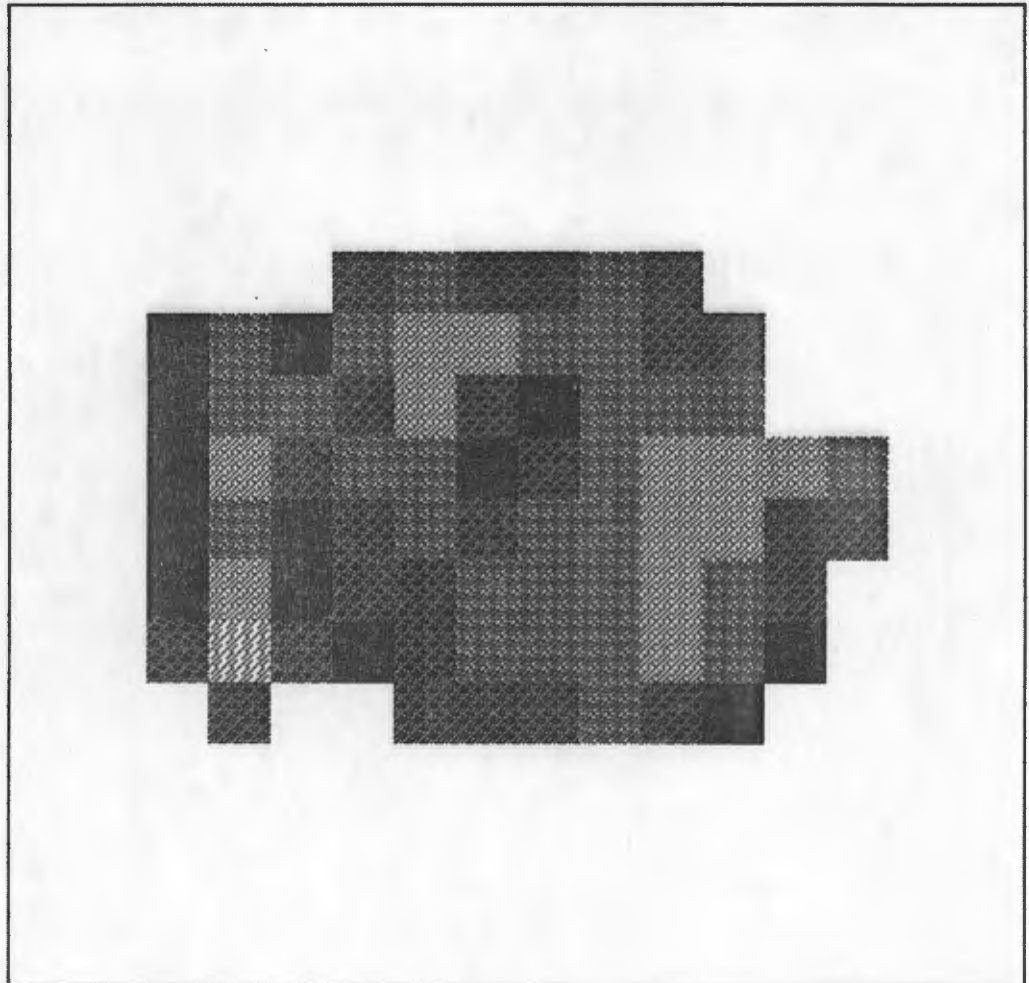


Figure 5h-5

EFFECT OF BYPASS GRAFT

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF CIRCUMFLEX ARTERY
WITH BYPASS GRAFT FUNCTIONING

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	2.38	2.29
S.D.	1.10	0.37
S.E.M.	0.26	0.07

PROGRAM: DJW (REV F)

DOG 24

EPICARDIUM BLOOD FLOWS FOR ENERGY 3. SCALED TO 2.50

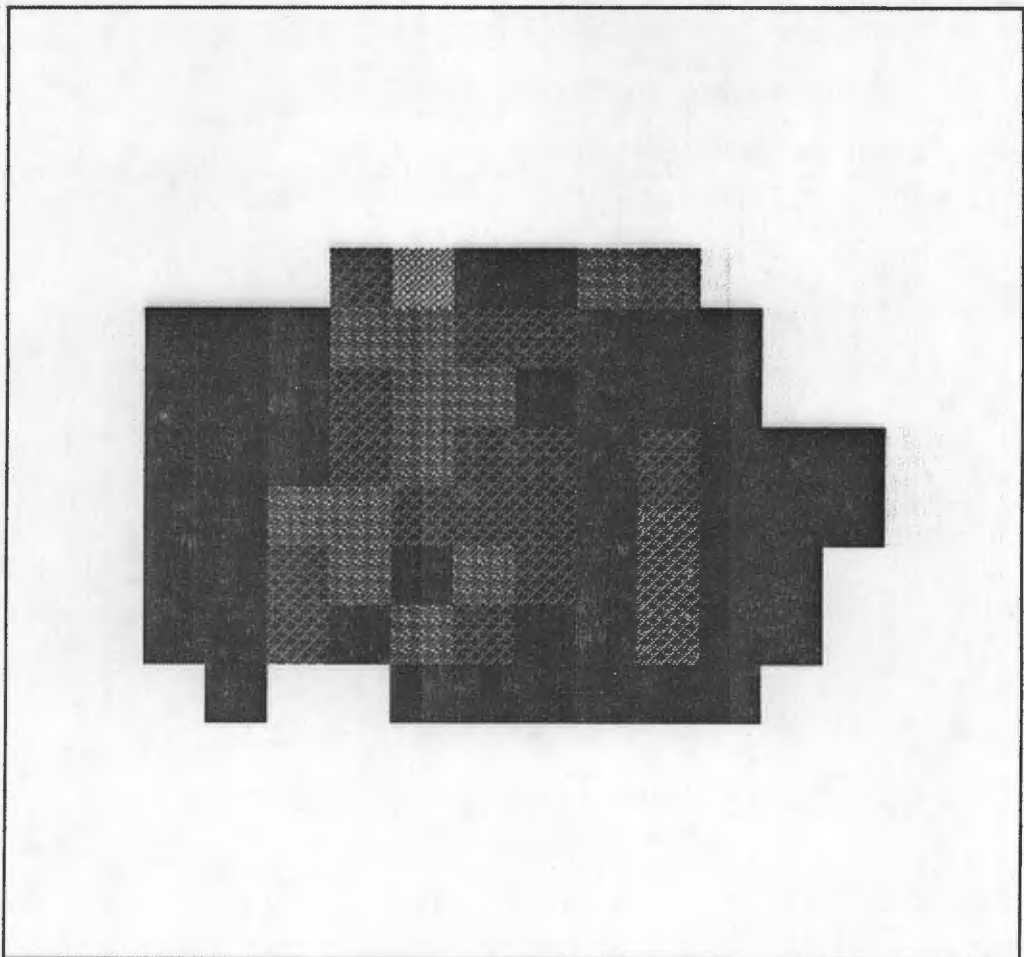


Figure 5h-6

Figure 5h-7 shows the perfusion deficit consequent on a fairly distal total occlusion of the anterior descending artery in Dog 18.

Figure 5h-8 shows the abolition of the perfusion deficit when an aorto-coronary bypass graft is functioning.

Complete correction of perfusion deficits was demonstrable in all 14 dogs in which aorto-coronary bypass graft function was assessed.

EFFECT OF BYPASS GRAFT

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

BYPASS GRAFT OCCLUDED

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.96	0.55
S.D.	0.15	0.27
S.E.M.	0.05	0.08

PROGRAM: DJW (REV F)

DOG18
ENDOCARDIUM BLOOD FLOWS FOR ENERGY 3, SCALED TO 1.20

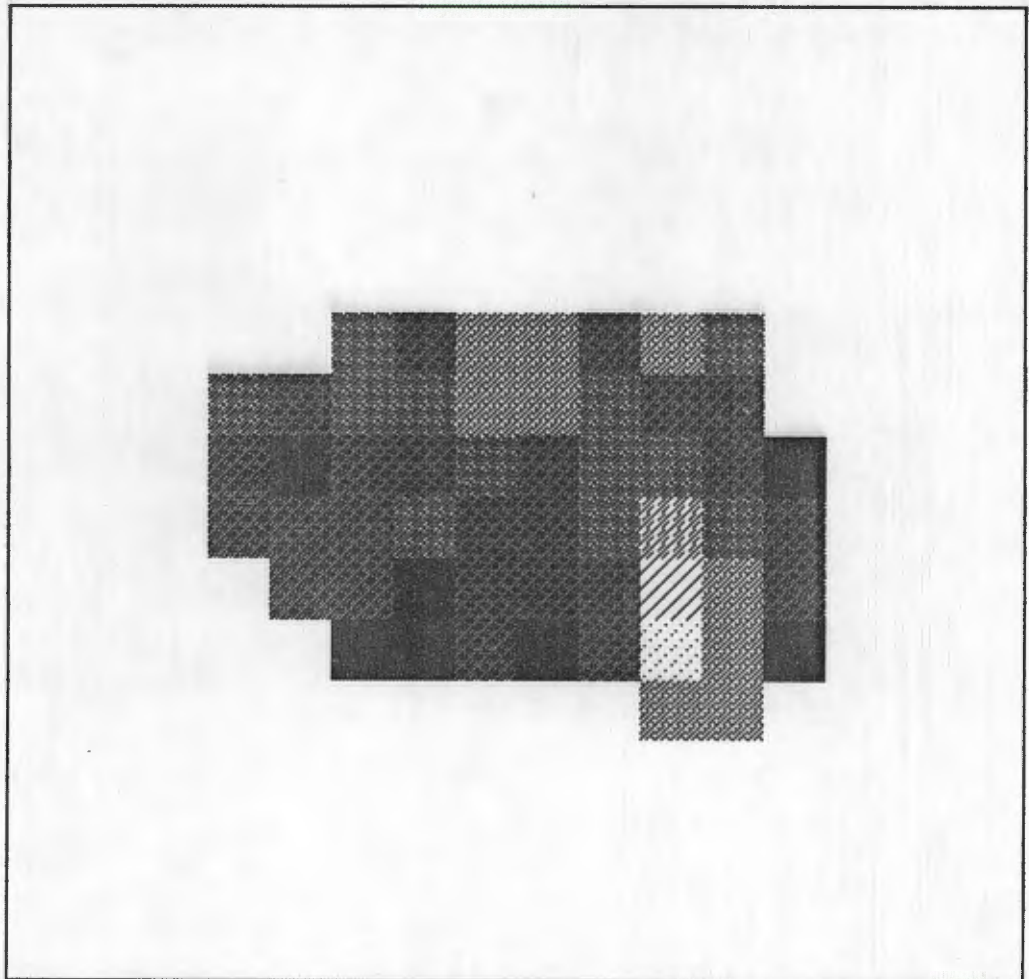


Figure 5h-7

EFFECT OF BYPASS GRAFT

REGIONAL MYOCARDIAL PERFUSION

TOTAL OCCLUSION OF ANTERIOR DESCENDING ARTERY

BYPASS GRAFT FUNCTIONING

	CIRCUMFLEX TERRITORY	ANTERIOR DESCENDING TERRITORY
MEAN FLOW (ML/GM/MIN)	0.93	1.42
S.D.	0.15	0.47
S.E.M.	0.05	0.15

PROGRAM: DJW (REV F)

DOG18

ENDOCARDIUM BLOOD FLOWS FOR ENERGY 2, SCALED TO 1.20

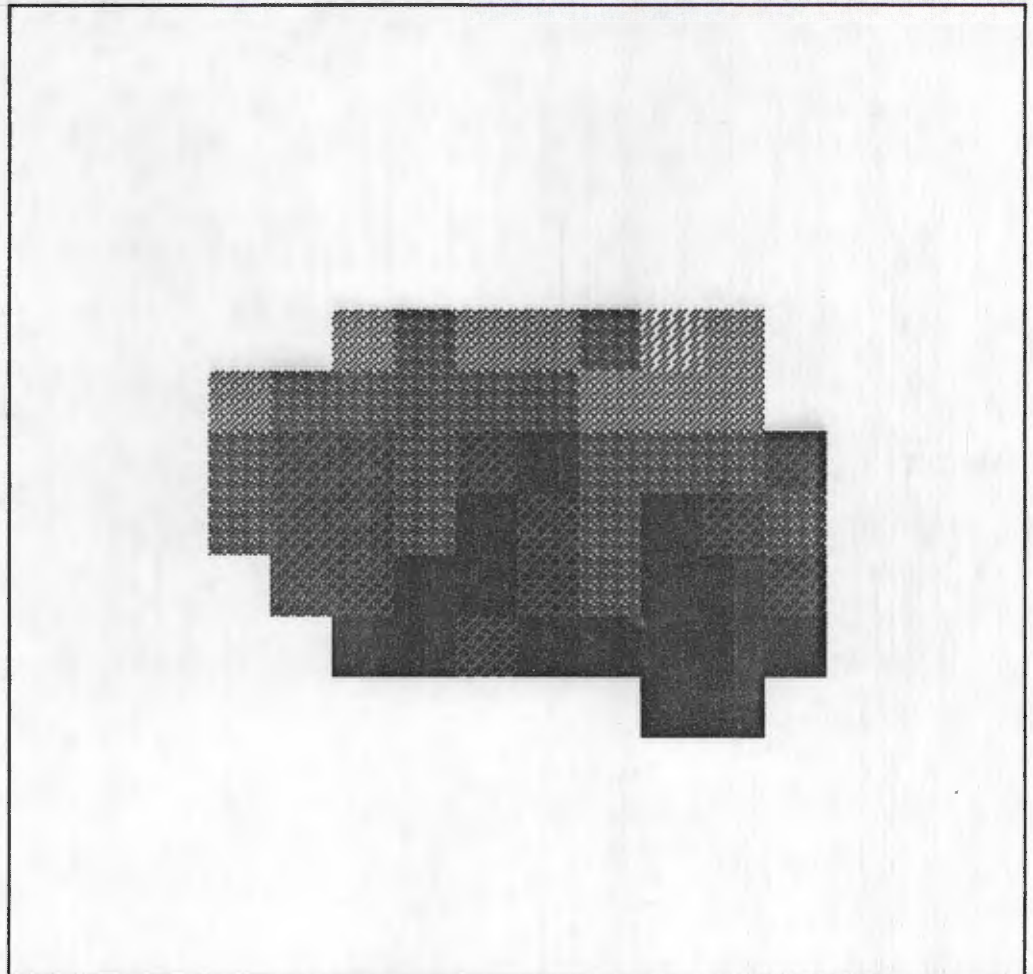


Figure 5h-8

In assessing the effect of aorto-coronary bypass grafts in correcting perfusion deficits consequent on coronary obstruction (whether the artificial variety described in this experimental study or the naturally occurring variety of clinical coronary surgical practice) it has been assumed that the technical aspects of conduit-to-coronary artery anastomosis have ensured that the conduit is in fact capable of supplying blood at ascending aortic pressure without any obstruction, to the coronary artery.

Most cardiac surgeons assume their anastomotic techniques to be "perfect" but this assumption is not necessarily always justified. Griffith et al. (1977) describe clearly the occlusive changes which may be seen in post mortem specimens of hearts which had earlier had aorto-coronary bypass grafts inserted. Using stereoscopic radiographic techniques as well as histological examination of the graft-to-coronary anastomotic site they showed frequent loss of lumen circumference at the proximal and distal ends of the anastomosis. They further described how easy it is to produce just such narrowing during construction of the anastomoses. Earlier catheterisation studies shown that most severe narrowings in coronary arteries after grafting occurred immediately adjacent to the proximal and distal ends of the anastomosis (Griffith et al. 1973).

The anastomotic technique personally adopted has been described in Section 3c and it is believed that the technique takes careful note of the need to avoid narrowing the coronary artery adjacent to the proximal and distal ends of the anastomotic site by having a clear view and taking fine suture bites close to the arteriotomy edge.

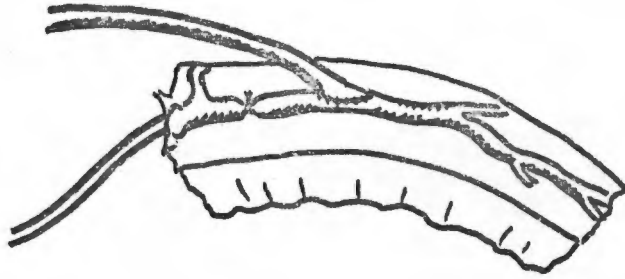
It is however not immediately obvious that the suture technique that has been used in the experimental series is equally meticulous.

The reason for this is that the angiographic demonstration of the coronary arteries in a single plane on a grid necessitates compressing the left ventricular muscle mass into a flat sheet. This inevitably distorts the anastomotic site to some degree. In this way an anastomosis, seen to be technically highly satisfactory at the time of its construction, may appear less than ideal on the angiogram in single plane.

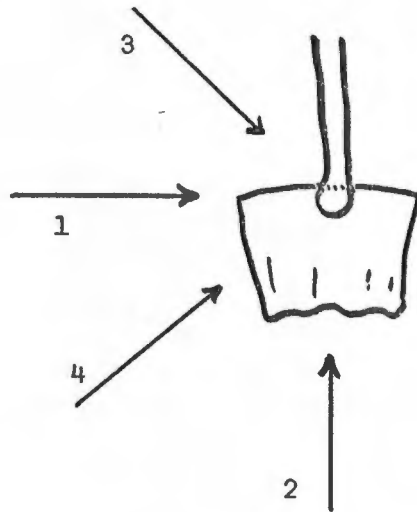
In order therefore to check carefully on personal operative technique a number of different suture techniques were assessed in construction of vein to coronary artery anastomosis using sheep or dog hearts. The anastomotic area was then filled with micropaque-gelatin solution (as described in Section 4) and a block of adjacent tissue containing the anastomosis was then set in gelatin and removed for radiological examination in four planes. It was not possible to demonstrate superiority of multiple interrupted suture technique or continuous technique - with clear view and care in placing sutures a very satisfactory anastomosis could always be achieved.

A representative result of radiological examination in four planes of vein-to-coronary anastomosis by the continuous suture technique described in Section 3c is shown in the following illustrations.

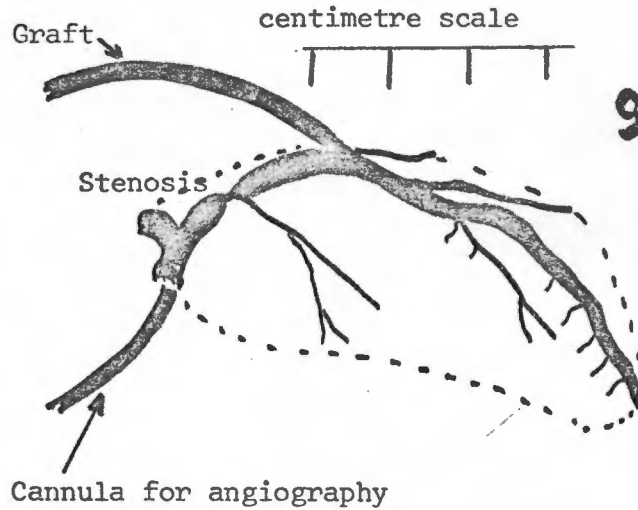
EXAMINATION OF ANASTOMOTIC TECHNIQUE



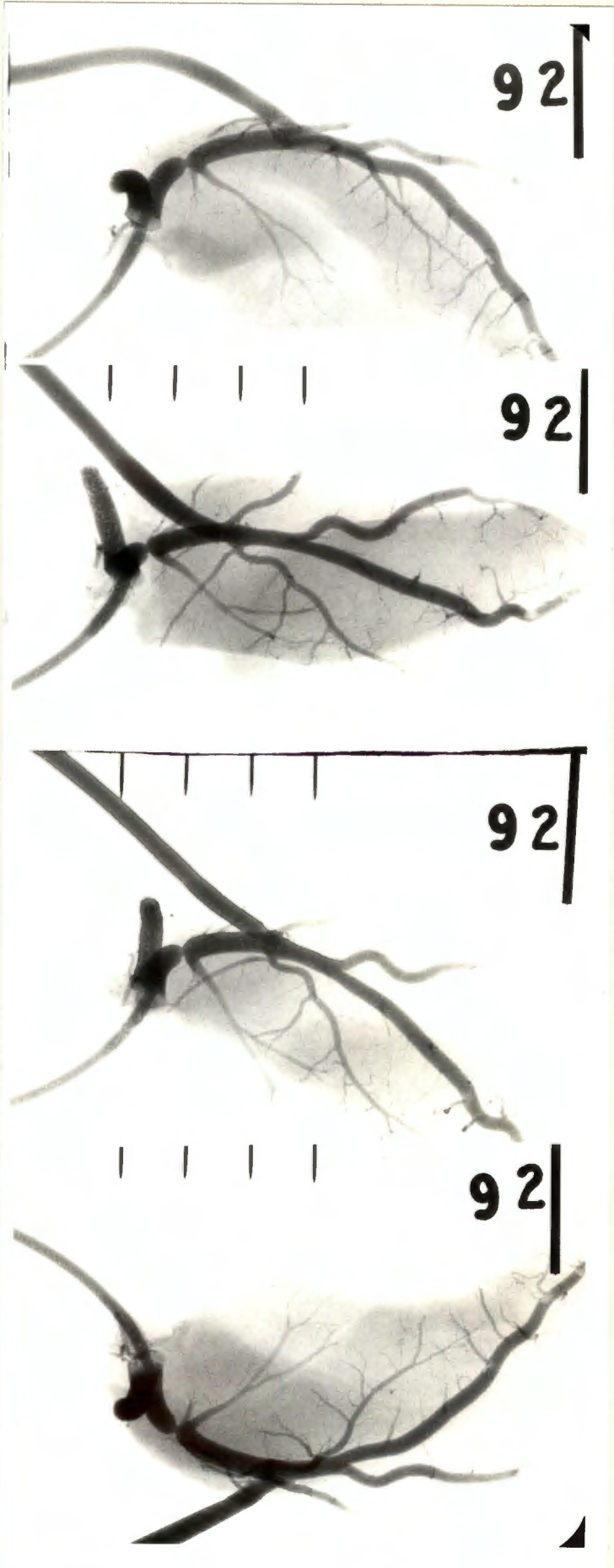
Myocardial tissue block containing graft-to-coronary anastomosis is cut from heart filling coronary tree with micropaque-gelatin.



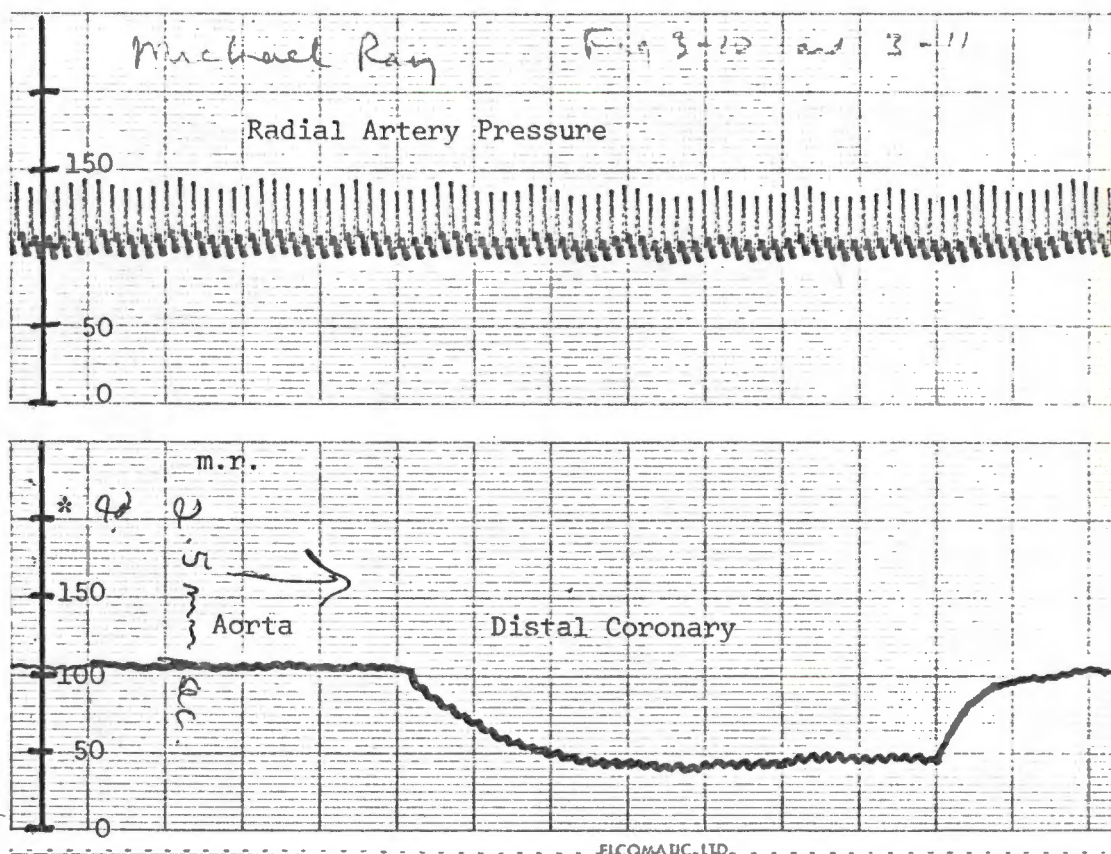
Radiographs of the tissue block are taken in four planes



92 | Drill-bit obturator used for creating stenosis



SECTION 6a
APPLICATION TO CLINICAL
PRACTICE



This shows the pressure drop across the severe stenosis of the proximal anterior descending artery which is illustrated in Section 3b in Figures 3b - 10 and 3b - 11. The pressure measured in the lower record is obtained through a 23 gauge needle inserted into the aorto-coronary bypass graft at the completion of surgery. Occlusion of the graft between the needle and the aorta produces the record of distal coronary pressure.

There is a pressure drop from a mean aortic pressure of 105 mm Hg to approximately 45 mm Hg. Graft flow was measured with an electromagnetic flow probe and mean flow was 90 ml/minute.

This clinical example shows considerable similarity with the experimental models.

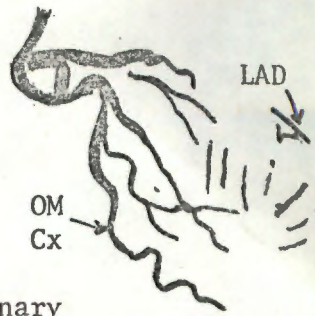
Figure 6a-1 shows the appearance at coronary angiography of the left coronary artery in a man of 50 years of age with severe, chronic angina. The late, and faint, filling of the anterior descending artery via collateral vessels in the septum is just visible. There was no clinical doubt about the need for grafting this vessel.

Figure 6a-2 shows the angiographic appearance in the same man, showing a narrowing at the junction of proximal and mid third of the right coronary artery. A degree of uncertainty was expressed about the need for bypass grafting to the distal right artery. A graft was inserted however at surgery.

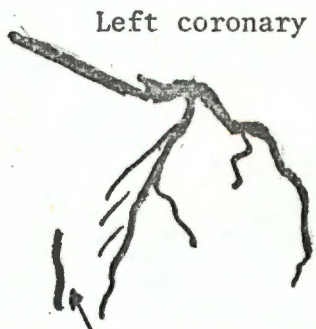
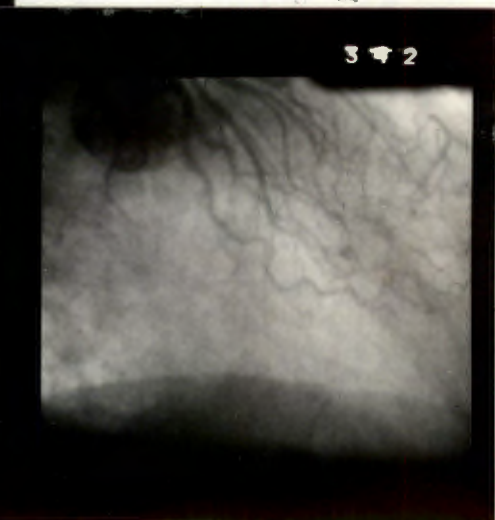
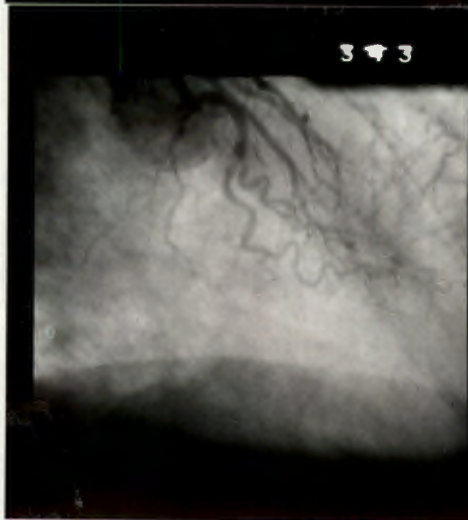
Figure 6a-3 shows the pressure drop across the anterior descending obstruction - it is about 56% - in keeping with a total occlusion with good collateral development. The lower trace shows the pressure drop across the right coronary stenosis - it is about 26% - suggesting that the stenosis was indeed likely to cause a perfusion deficit in its territory of supply.

The routine measurement of distal coronary pressure in this way has given greater confidence that clinical assessment of coronary stenosis from angiographic appearance is correct in most cases. There is no longer any doubt about the need for bypass grafting of lesions such as that illustrated in Figure 6a-2.

The meticulous attention to detail in constructing aorto-coronary bypass grafts stimulated by the study (Section 5h) can reasonably be expected to have improved operative techniques. Figure 6a-4 shows a re-study of a technically satisfactory bypass graft which is interesting to compare with the photographs of grafts constructed in the laboratory in Section 5h.



Left coronary
Distal anterior descending
(LAD) fills via collaterals
OM Cx: Obtuse marginal branch



Distal anterior
descending fills late via
collateral vessels

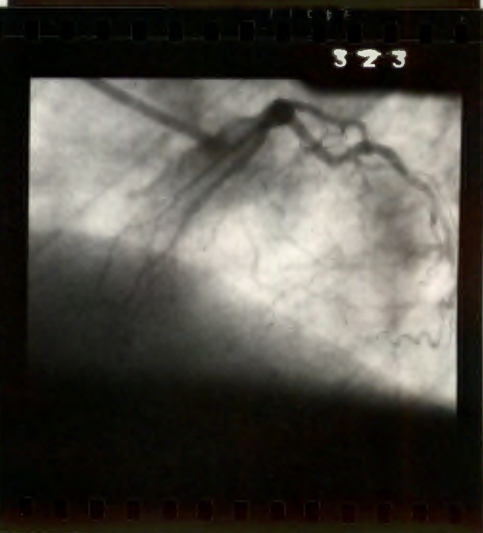
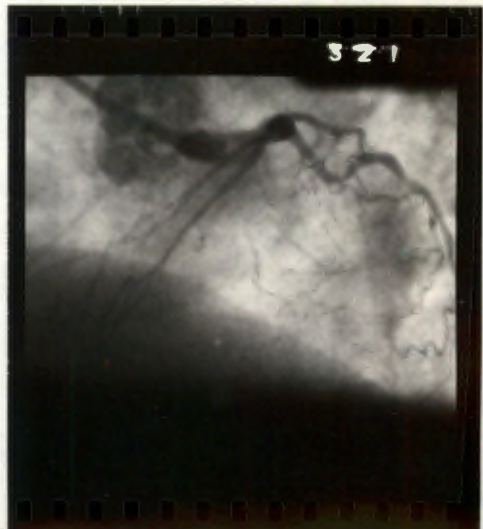
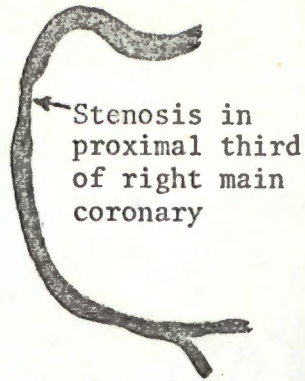
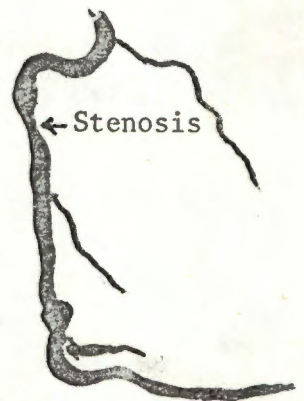


Figure 6a-1

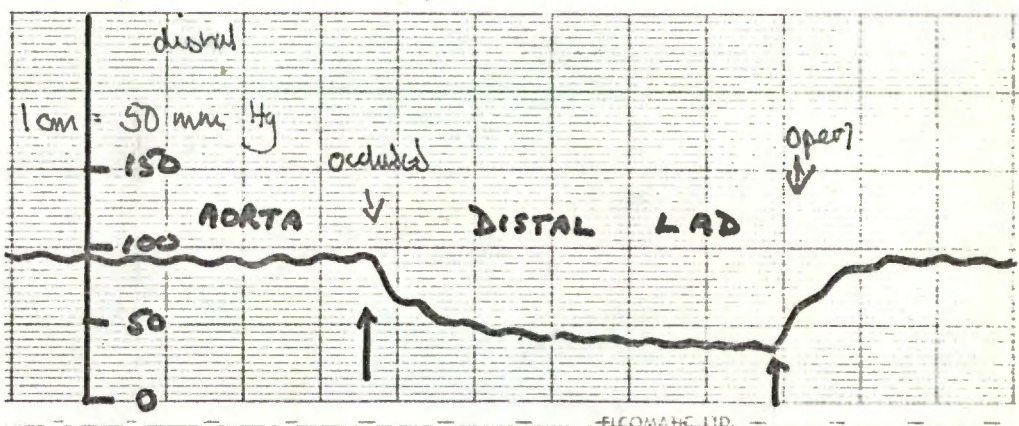
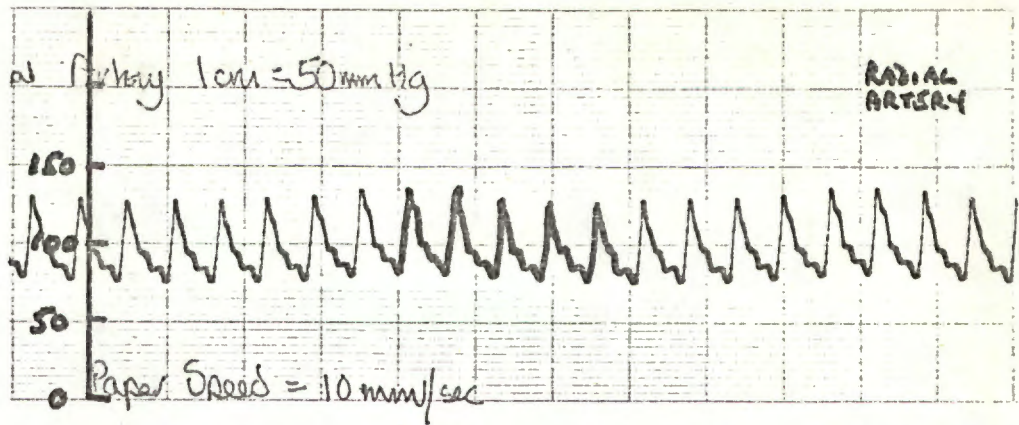


Left anterior oblique view

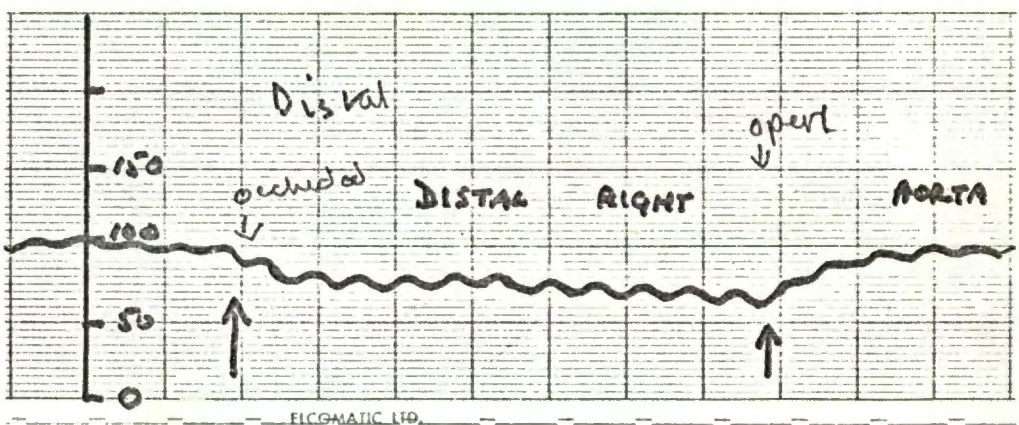
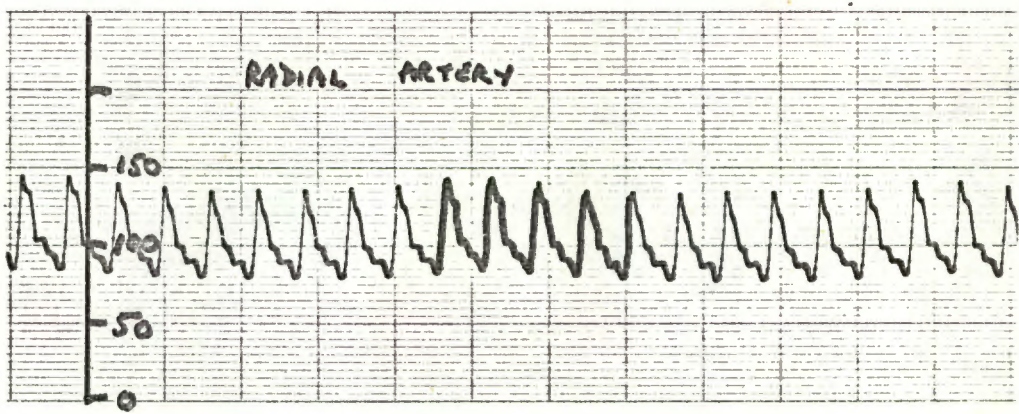


Right coronary artery
Right anterior oblique view



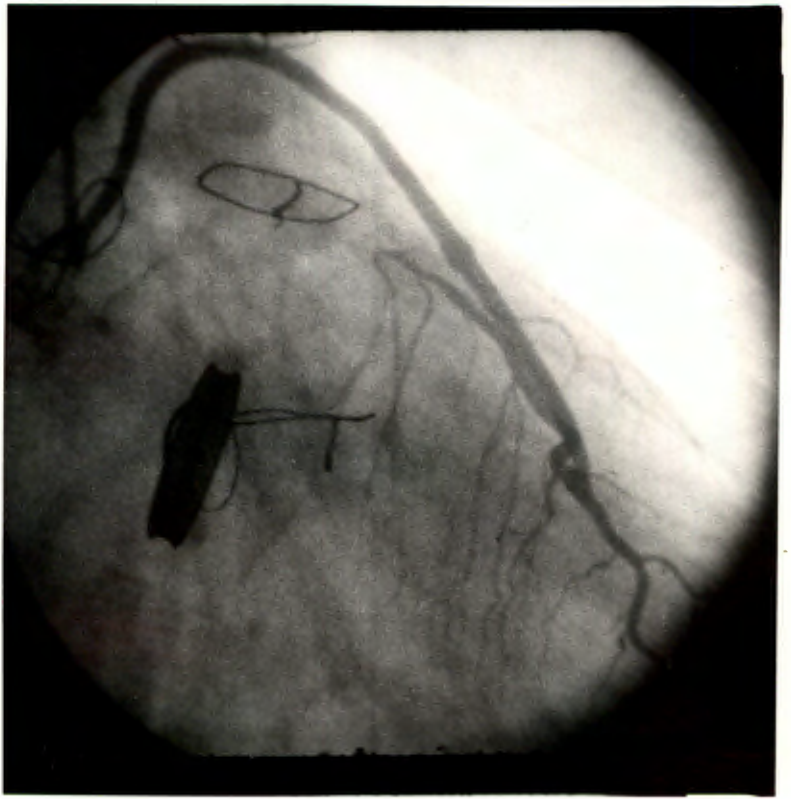


This shows the pressure trace obtained through a 23 gauge needle inserted into the aorto-coronary bypass graft to the anterior descending artery shown angiographically to fill poorly and late via collateral. Aortic mean pressure is 90 mm Hg; distal coronary pressure 40 mm Hg



This shows the pressure trace from the graft to the right coronary artery with stenosis of uncertain significance. Aortic mean pressure is 95 mm Hg; distal coronary pressure 70 mm Hg - suggesting that the stenosis was "significant."

Figure 6a-3



Elective cardiac catheter study of a symptom-free patient 18 months after mitral valve replacement and aorto-coronary bypass grafting to the anterior descending artery. The cardiac catheter is seen in the graft ostium (encircled with Raytec marker) filling the graft and the anterior descending artery and its branches, both proximal and distal to the graft-coronary anastomosis.

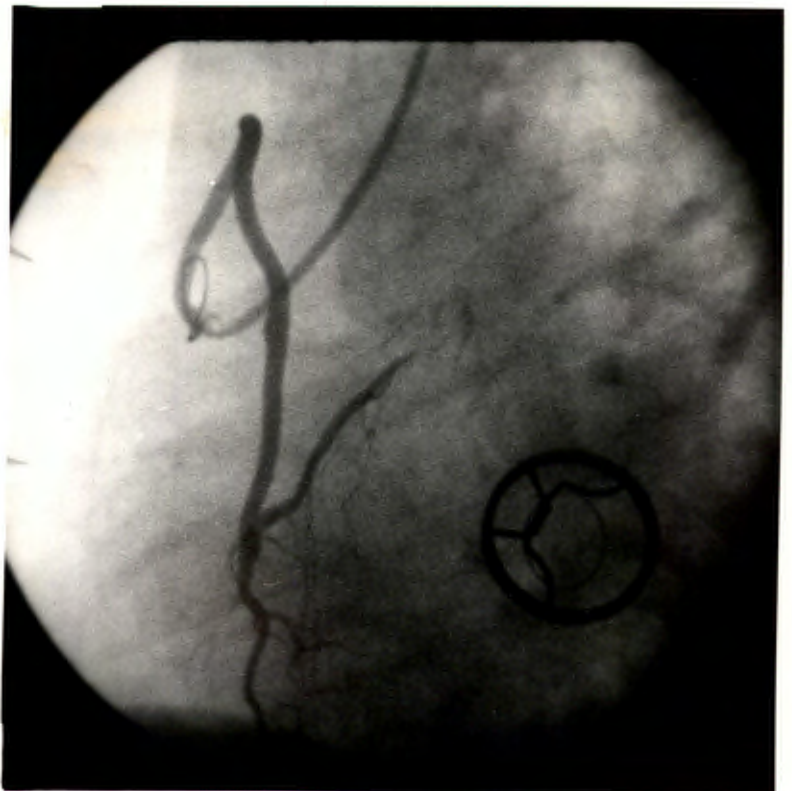


Figure 6a-4

APPLICATION TO CLINICAL PRACTICE

The technique personally adopted for clinical surgery is reviewed in Section 3c, and has been arrived at by modification of earlier practice as a result of this experimental study. In particular, the recognition of the importance of a high perfusion pressure (Section 5c) and slow heart rate are factors which have been altered in clinical practice as a consequence of the study.

The angiographic assessment of coronary stenosis is not always easy. In view of the finding that measurement of pressure drop across a stenosis reliably predicts its haemodynamic effect in the dog model, it has become routine to make the identical assessments in clinical practice.

The 8 hospital deaths occurring in 1976 and 1977 in 189 patients (4.2%) are reviewed in Section 3a. 7 of these deaths occurred in 1976; 1 in 1977; and in the next 100 cases there was no hospital mortality. Although it is impossible to prove, it is believed that recognition of factors covered in this study by all members of the anaesthetic and surgical team involved in the peri-operative and operative phase has contributed to this improvement.

SECTION 6b
USE OF THERMOGRAPHY
IN
CORONARY SURGERY

THE USE OF THERMOGRAPHY IN CORONARY SURGERY

The experimental demonstration of areas of myocardial underperfusion, and the restoration of normal perfusion following bypass grafting to the jeopardised vessel by the tracer microsphere technique as described in Sections 4 and 5 is clearly not applicable to clinical practice.

Currently, the use of electromagnetic flow probes to confirm graft flow is the only practical technique for routine use at surgery to demonstrate the function of the graft (Miller 1977; Marco et al 1976).

The use of radioactive Xenon-133 injected into a bypass graft at surgery with measurement of myocardial washout has been described by Kruelen et al (1974) but the technique is not suitable for routine use, and does not delineate anatomically the areas of underperfusion.

The use of thallium 201 for myocardial imaging with a gamma scintillation camera is in use in some centres for assessment of myocardial perfusion before and after surgery. The imaging requires to be undertaken after exercise and the demonstration of "cold" spots of underperfusion, with restoration to normal after successful bypass grafting is well described, but is expensive, and is not applicable at the time of surgery when the surgeon is able to modify the operation if necessary (Robinson, P.S. - St. Thomas's Hospital - personal communication 1978; Ritchie et al 1976; Resnekov, L. 1977).

Other radiopharmaceuticals are described for evaluation of myocardial perfusion (Walsh et al 1976) but are not currently suitable for use at surgery.

In an attempt to demonstrate graft function and delineate the anatomical distribution of graft flow it seemed possible that injection of a cold bolus of fluid into a graft should produce myocardial cooling in the distribution of the grafted vessel, which might be detectable with a heat-

sensitive camera. A search of the literature on thermography in medical practice showed that the major problems besetting its use in conventional applications to body surface scanning were the small temperature variations produced by pathological processes deep to the skin, the non-specificity, and liability to artefacts inherent in the technique. Disenchantment with conventional medical surface thermography was all too evident when approaching manufacturers of thermal imaging equipment in the United Kingdom.

However, the direct viewing of the exposed heart at surgery, the superficial course of the major coronary vessels, and the large temperature gradients to be expected by injection of cold fluid suggested that thermographic scanning of the heart could be of value.

Two recent reports were found where such use is described, but the technique is not currently in widespread use.

2nd European Thermographic Congress 11 - 15 September 1978

The Use of thermography in coronary bypass surgery

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Series of experiments were carried out in pigs in order to study the changes in temperature in the myocardium after partial and total coronary occlusion. In these series both thermocouples and thermography were used for temperature measurements. The results of the experiments suggested the use of thermography (AGA 680) during open heart surgery in patients with coronary diseases. Patients were studied immediately after the thorax was opened and again 30 minutes after coronary surgery was completed. In each study thermographic pictures were synchronized with E.C.G. pattern. Thermography was also carried out during right atrial pacing. Although very promising functions were obtained thermography is not yet an easy applicable tool for evaluation of ischaemic myocardium during surgery.

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APPLICATION OF THERMOGRAPHY IN CORONARY SURGERY

F. Robicsek, T. N. Masters, R. H. Svenson, W. Daniel, A. Ferrari.

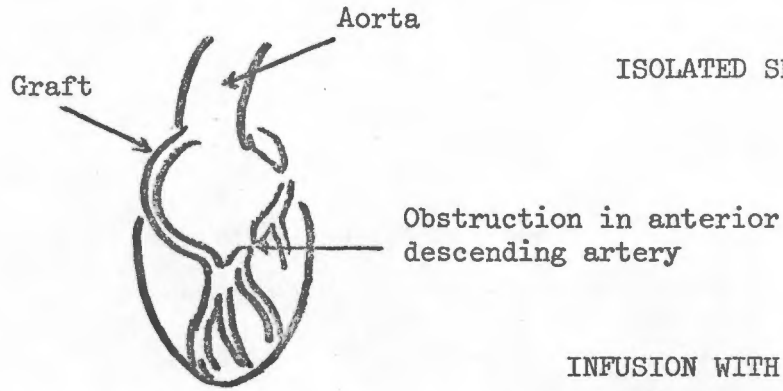
Charlotte Memorial Hospital; Charlotte, North Carolina (U.S.A.)

The technique presented in this paper is based on our previous observations in which we found that artificial decrease of blood flow to a portion of the heart muscle leads to an immediate and proportional drop in the regional myocardial temperature. It was a logical next step to apply the thermographic camera to a monitor and record such changes in the human during coronary surgery and use the data to draw conclusions applicable to regional blood supply and to blood flow through surgically inserted vein grafts. We found that on the normothermic heart there were well identifiable "cold" patches corresponding with areas of impaired coronary circulation. By infusion of blood to the ischemic myocardium through individual release of the bypass grafts, the thermogram responded by immediate appearance of "warm" spots corresponding with the areas supplied by the grafts. Even more dramatic demonstration of graft patency and outline of the area supplied by the graft was performed by injecting cold saline solution into the grafted saphenous veins. In our experience this most interesting new method proved to be a useful tool in coronary surgery both as an adjunct in delineating ischemic areas and proving the patency and efficiency of the grafts inserted.

Recent developments in the military field of thermal imaging and recent declassification of improved thermal sensors has made it possible to obtain small thermal scanners suitable for operating theatre use.

A preliminary study was made using an Aga Thermovision liquid nitrogen cooled detector which is in routine use for breast thermography in the Royal Infirmary of Edinburgh. Isolated sheep hearts were used to investigate the feasibility of the technique. A bypass graft was inserted into a major coronary vessel and 25 to 50 ml of cold saline was injected into the aortic root. The thermographic appearances of a typical study are illustrated in Figure 6b-1. The bulk of the Aga scanner precluded its use in an operating theatre, but the feasibility of the technique was clearly confirmed.

The next thermal scanner to be assessed was the Medical Thermal Scanning System IR II produced by Barr and Stroud Ltd, Glasgow. This scanner has a nitrogen gas cooled cadmium mercury telluride detector sensitive to the 8 - 13 micron spectral range, giving a temperature sensitive range of 22°C to 39°C. A grey scale image is produced on a



ISOLATED SHEEP HEART

INFUSION WITH 15°C FLUID

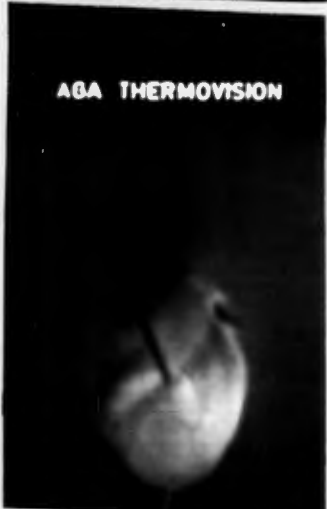
HEART TEMPERATURE 30 - 35°C



GRAFT OCCLUDED

AREA OF NON-PERFUSION REMAINS
WARM (WHITE) AFTER 2 MINUTES

COLD FLUID INJECTED INTO GRAFT ONLY

GRAFT AND DISTAL ANTERIOR DESCENDING
VESSEL AND BRANCHES COOL (BLACK)
AFTER 1 MINUTE

COLD FLUID INJECTED INTO AORTIC ROOT

UNIFORM COOLING SHOWN AFTER 2 MINUTES

GRAFT CORRECTING FOR ANTERIOR
DESCENDING OBSTRUCTION

Figure 6b - 1

5 inch television monitor and permanent records can be obtained on polaroid film. This is an extremely bulky scanner, not suitable for operating theatre use. However, it demonstrated the feasibility of the technique. Figures 6b-2 and 6b-3 illustrate representative examples of isolated sheep heart preparations.

In November 1978 a small military scanner was made available for trial by Thermal Imaging Limited. This was a prototype infra red video camera, light enough (6 Kg) to mount in a theatre lamp stand and which requires no supply of coolant gas. The pyro-electric vidicon tube, sensitive to wavelengths in the 8 to 14 micron band produces a moving picture output which can be displayed on a video monitor. The camera contains a mechanism which continuously changes the position of the image on the vidicon faceplate, enabling the tube, which is only sensitive to changes of light level, to image static scenes. After an initial warming up period of 2 to 3 minutes the camera can be used to produce a flicker-free, moving image which can be viewed at surgery, and which can also be stored on video tape for subsequent viewing.

Figure 6b-4 shows the appearance of the heart at surgery, lifted a little forward by the surgeon's hand. A cannula (C) has been left in the aorto-coronary bypass graft (G) to the anterior descending coronary artery (A). The centre photograph is from the video monitor during injection of cold saline (8 - 9°C) in a 20 ml bolus via the cannula. Filling of the graft, the anterior descending artery, and several large diagonal branches is clearly seen.

Figure 6b-5 shows sequences from two patients. Both illustrate the course of a 20 ml bolus of normal saline at 8 - 9 °C through the aorto-coronary graft to fill the anterior descending artery and its diagonal branches. Rewarming by aortic blood following the cold bolus through the graft is well seen as a white (warm) line in the graft and anterior

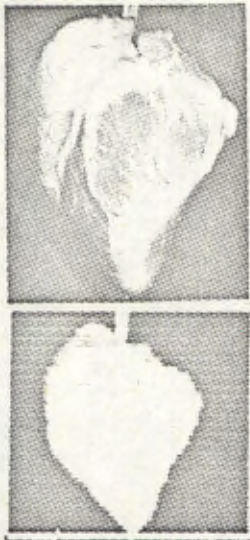
THERMAL IMAGING OF THE HEART

31st August 1978

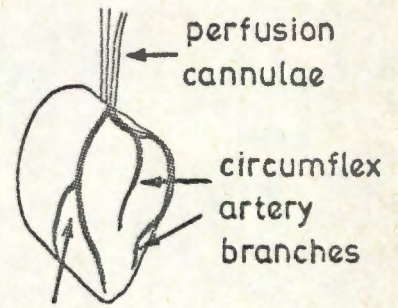
Barr and Stroud IR II Scanner

Heart perfused continuously via coronary ostia at 36°C

Cold saline 40 - 60 ml at 4°C injected over 10 - 20 seconds



control view
uniform 36°C
perfusion



ant. descending
artery with
diagonal branch

normal coronary filling



after 15 seconds

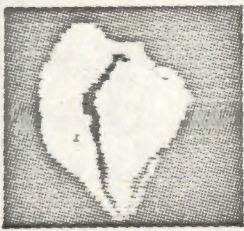


after 30 seconds



after 60 seconds

circumflex branch occluded



after 15 seconds



after 60 seconds

anterior descending artery occluded



after 15 seconds



after 60 seconds
retrograde filling of
anterior descending artery
distal to obstruction

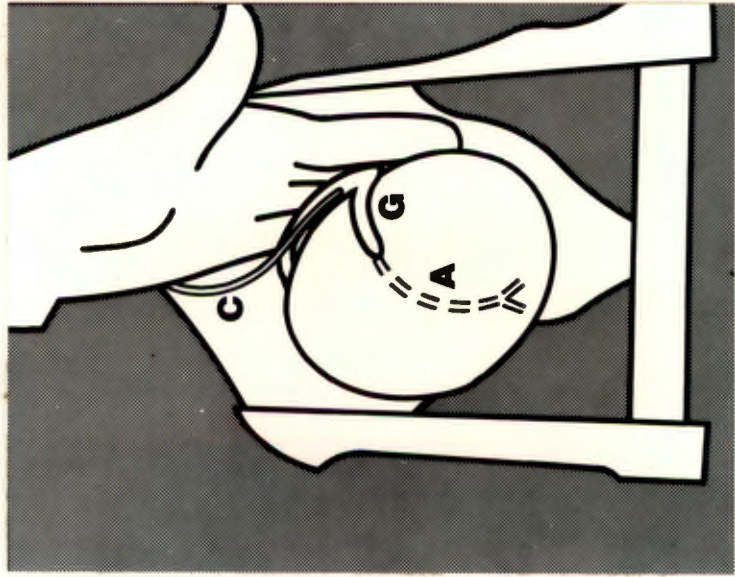


FIGURE 6b-4



0.25
seconds



1



8



20



35



45



0.5



1



10



26



45

FIGURE 6b - 5

descending artery and its branches at 45 seconds in the right-hand sequence.

Myocardial cooling (seen as a generalised dark area) did not reproduce well - it is discernable at 10 seconds in the right-hand sequence - and is likely to be better shown by improved camera design.

The technique has also been used for demonstration of function in grafts to the right and circumflex vessels. The promptness of graft filling and subsequent rewarming appears to reflect flow rates measured by electromagnetic flow probes. In Figure 6b-5 the patient illustrated in the left hand sequence had a measured anterior descending graft flow of 55 ml per minute - the patient illustrated in the right-hand sequence had a flow of 90 ml per minute under the same conditions at which the thermal scans were obtained.

The initial trial of the camera with eight patients has been completed. Visualisation of the coronaries filling via the grafts was possible in each case. Myocardial cooling as the cold fluid bolus passes through the myocardium was seen in each case, but with this camera is difficult to record. It is possible that this effect, if better demonstrated by improved camera design, could be used for a degree of quantitation of myocardial perfusion via aorto-coronary grafts. It is also possible that the technique may be able to demonstrate areas of underperfusion at surgery prior to insertion of grafts, and thus may aid in confirmation of angiographic diagnosis.

As a technique which demonstrates aorto-coronary graft function by cooling of perfused muscle, rather than by the more indirect measurement of graft flow alone, the technique has great physiological appeal. The delineation of the anatomical area of graft perfusion may well have practical surgical implications, as for example in dictating the need or otherwise for additional grafts (especially side to side grafts to

diagonal vessels - see Figure 3-15). Further evaluation is anticipated once an improved version of the thermal camera is available from Thermal Imaging Limited.

SECTION 7
SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

SURGERY FOR CORONARY ARTERY DISEASE

Edinburgh Clinical Experience

and

Experimental Studies

Section 1

Section 1 outlines the personal experience of coronary surgery that has preceded the work covered in this thesis. It indicates the advantages of an animal model for assessing surgical procedures in a way not possible in clinical practice with the aim of improving clinical practice. The aspects of the work performed personally and by others are indicated.

Section 2

Section 2a reviews the development of surgery for coronary artery obstruction. The lack of sound physiological and experimental evidence for much of the earlier surgery is apparent, and no doubt explains the multitude of short-lived procedures.

The comparatively recent advent of aorto-coronary bypass surgery and the considerable numbers of patients undergoing

such surgery have caused uncertainty and controversy about its role. Much of this uncertainty will only be resolved by the accumulation of further clinical experience over many years to come.

Section 2b describes the anatomy of the coronary arteries of man and dog, with particular reference to coronary surgery. The physiology of myocardial perfusion is briefly reviewed and pathology of coronary artery disease is discussed with reference to coronary surgery.

Section 3

Section 3a reviews personal experience of coronary surgery in Edinburgh during 1976 and 1977. 189 patients had coronary surgery in that period. The results are comparable to those obtained by North American centres. A review of clinical surgery is important both to document and assess this form of surgery in Scotland, and also to indicate why an experimental study was undertaken. The problem of maintaining and correcting myocardial perfusion in the presence of coronary obstruction by surgical means is an interesting experimental study- its important practical application is emphasised by review of the clinical counterpart.

Section 3b reviews coronary arteriography with particular reference to Edinburgh experience. This currently is the major basis of diagnosis for the coronary surgeon and its review is therefore relevant and important.

Section 3c reviews current personal Edinburgh surgical technique and is relevant for indicating the reasons for the

way the animal model was constructed. It also indicates the important points which it is believed have contributed to the success of this surgery, many of which have been assessed in the experimental model.

Section 4

Section 4 outlines the need for an experimental study and the aims of the study. The potential pitfalls in applying experience gained from acutely simulated conditions in dogs to naturally occurring disease in man are emphasised, but the advantages of such a study are indicated.

The design of the animal model is described in detail - including a description of the tracer microsphere technique, the description of the computing techniques and examples of the computed data obtained in a single experiment. Such data was obtained in each of the experiments but clearly cannot be illustrated for each for the reasons of space and time.

Section 5

Section 5 reviews the results of the animal study.

5a: Myocardial perfusion with a normal coronary tree is shown to be uniform in the animal model - a prerequisite for using part of the left ventricle as control area for another test area.

5b: The effect of coronary vasomotor tone is shown. The

accentuation of perfusion deficits by decreasing vasomotor tone, or the appearance of deficits not present with high degrees of vasomotor tone is of relevance to clinical symptoms, and to techniques of isotope scanning for perfusion deficits, which must be assessed at high levels of coronary flow. Similarly, in assessing the efficacy of surgical intervention high coronary flow must be present.

5c: The effect of perfusion pressure is shown to be striking. Low perfusion pressure on cardiopulmonary bypass results in low flow in the normally-perfused myocardium, but where coronary obstruction is present flow in jeopardised territory may be grossly reduced. Conversely, a high perfusion pressure was shown to provide levels of flow in excess of normal resting levels in territory of a totally occluded artery in the dog model where only the normally present collateral existed. The clinical application of this knowledge is indicated.

5d:

The effect of varied stenoses on regional myocardial perfusion and on pressure and flow in the distal coronary artery is shown. The influence of coronary vasomotor tone is indicated. The relevance to anticipated bypass graft function has practical application. The reliability of pressure drop over a stenosis in predicting the perfusion deficit in the animal model is so striking that its more widespread application clinically is suggested.

5e:

Varied heart rate could not be shown to markedly influence regional myocardial perfusion except with low heart rate where slight improvement in flow to jeopardised territory was demonstrable. The lowering of myocardial oxygen consumption by lowering heart rate was outside the scope of this study, but this is well-known, and is the major basis for the policy of clinical use of pre-operative beta-blockade to induce bradycardia.

5f:

The effect of left ventricular cavity pressure on regional myocardial perfusion in this model was not demonstrable and probably explains the freedom from problems in centres not using routine left-heart venting.

5g:

Ventricular fibrillation was shown to increase flow slightly in normally perfused areas- in jeopardised areas it could not be shown to convincingly affect flow.

5h:

Carefully constructed aorto-coronary bypass grafts could invariably be shown to totally correct for coronary obstruction. This does not of course mean that this goal is always achievable

clinically - diffuse disease, particularly obstructing septal arteries may be impossible to relieve totally by current techniques, but precision in constructing aorto-coronary bypass grafts is likely to improve results.

Section 6

Section 6 indicates how the experimental study has influenced personal clinical practice and demonstrates an example of the application of measurement of distal coronary pressure. The possibility of using thermography as an aid in coronary surgery is discussed and further development in this field is anticipated.

It is believed that the experimental study had improved personal practice of coronary surgery.

SECTION 8
ACKNOWLEDGEMENTS

ACKNOWLEDGEMENTS

A Thesis of this nature and magnitude is only possible with a considerable practical clinical experience and active surgical practice. For this I am indebted to my surgical teachers, most notable Professor N.M.A. Rogers of Durban, who first taught me the techniques of what was then pioneering surgery for coronary disease, and Mr Donald Ross and Mr Keith Ross of the National Heart Hospital in London, where most of my training in this surgery was obtained.

The enthusiasm and expertise of my Edinburgh cardiological colleagues, notably Dr Hugh Miller and Dr Arthur Kitchin, on whose patients I have operated, is gratefully acknowledged. My anaesthetic colleagues, Dr Calvin Hider and Dr Ian Davidson, have shared with me the operative treatment of this sometimes daunting group of patients where anaesthetic technique of greatest skill is a prerequisite for patient survival, let alone good results - their contribution is considerable.

I am indebted to Professor A.P.M. Forrest of the Department of Clinical Surgery, University of Edinburgh, for use of laboratory facilities, and encouragement in sustaining this work, and for providing a busy, academic and stimulating environment for me to work in. Mr Ian Ansell and Mrs Dorothy Gray have given great help in the laboratory.

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Miss M. Palmer and Miss J. Brown have undertaken much of the radiography for me. Many others in the Departments of Clinical Surgery, Medical Physics and Medical Engineering, Radiology, and Cardiology have contributed.

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The amount of time that this thesis has demanded over the past 3 years is incalculable- the patience of my wife and family in putting up with the consequences is appreciated and acknowledged.

SECTION 9
REFERENCES

- Anrep, G.V. (1936) Studies in Cardiovascular regulation. Lane Medical Lectures. Medical Science 3: 199
- Austen, W.G., Edwards, J.E. and Frye, R.L. (1975) A reporting system on patients evaluated for coronary artery disease: Circulation: 51, 5
- Bailey, C.P., May, A. and Lemmon, W.M.: (1957) Survival after coronary endarterectomy in man. Journal of American Medical Association: 164: 641
- Baird, R.J., Manktelow, R.T., Shah, P.A. and Ameli, F.M. (1970) Intramyocardial pressure: Study of its regional variations and its relationship to intraventricular pressure. Journal of Thoracic and Cardiovascular Surgery. 59: 810
- Baltaxe, H.A. and Levin, D.C. (1972) Coronary angiography: its role in the management of the patient with angina pectoris. Circulation. 46: 1161
- Baroldi, G., Mantero, O., and Scmozoni, G. (1956) The collaterals of the Coronary Arteries in Normal and Pathologic Hearts. Circulation Research 4: 223
- Bartrum, R.J., Berkowitz, D.M. and Hollenberg, N.K. (1974) A simple radioactive microsphere method for measuring regional blood flow and cardiac output. Investigative Radiology 9: 126
- Bassingthwaighte, J.B., Strandell, T. and Donald, D.E. (1968) Estimation of coronary blood flow by washout of diffusible indicators. Circulation Research 23: 259
- Beck, C.S. (1935) A new blood supply to the heart by operation. Surgery, Gynecology and Obstetrics 61: 407
- Beck, C.S. (1957) Coronary artery disease - physiologic concepts - surgical operation. Annals of Surgery 145: 439
- Beck, C.S., Hahn, R.S., Leighninger, D and McAllister, F.F. (1951) Operation for coronary artery disease. Journal of American Medical Association 147: 1726
- Beck, C.S. and Leighninger, D.S. (1955) Scientific basis for the surgical treatment of coronary artery disease. Journal of American Medical Association 159: 1294
- Beck, C.S. and Mako, A.E. (1941) Venous stasis in the coronary circulation. American Heart Journal 21: 767
- Beck, C.S. and Tichy, V.L. (1935) The production of a collateral circulation to the heart. American Heart Journal 10: 849
- Becker, L. (1976) Effect of tachycardia on left ventricular blood flow distribution during coronary occlusion. American Journal of Physiology 230: 1072
- Becker, L.C., Ferreira, R. and Thomas, M. (1973) Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. Cardiovascular Research 7: 391

- Becker, L.C., Ferreira, R. and Thomas, M. (1975) Effect of propranolol and isoprenaline on regional left ventricular blood flow in experimental myocardial ischaemia. *Cardiovascular Research* 9: 178
- Berguer, R. and Hwang, N.H.C. (1974) Critical arterial stenosis. A theoretical and experimental solution. *Annals of Surgery* 180: 39
- Berne, R.M. (1964) Regulation of coronary flow. *Physiological Reviews* 44: 1
- Bing, R.J. (1960) Determination of coronary blood flow. *Methods in Medical Research* 8: 269
- Bing, R.J. (1965) Cardiac Metabolism. *Physiological Reviews* 45: 171
- Bjork, L., Spindola-Franco, H., Van Houten, F.X., Cohn, F.P. and Adams, D.F. (1975) Comparison of observer performance with 16 mm cinefluorography and 70 mm camera fluorography in coronary arteriography. *American Journal of Cardiology* 36: 473
- Blair, E. (1961) Anatomy of the ventricular coronary arteries in the dog. *Circulation Research* 9: 333
- Blumgart, H.L., Schlesinger, M.J. and Davis, D. (1940) Studies on the Relation of the Clinical Manifestation of Angina Pectoris, Coronary Thrombosis, and Myocardial Infarction to the Pathologic Findings. *American Heart Journal* 19: 1
- Boardman, A.K. (1976) An inexpensive computer colour television system for the presentation of radionuclide scintigrams. *Physics in Medicine and Biology* 21: 289
- Brandi, G. and McGregor, M (1969) Intramural pressure in the left ventricle of the dog. *Cardiovascular Research* 3: 472
- Braunwald, E. (1971) Control of Myocardial Oxygen Consumption: Physiologic and Clinical Considerations. *American Journal of Cardiology* 27: 416
- Buckberg, G.D., Fixler, D.E., Archie, J.P. and Hoffman, J.I.E. (1972) Experimental Subendocardial Ischaemia in Dogs with normal Coronary Arteries. *Circulation Research* 30: 67
- Buckberg, G.D., Luck, J.C., Payne, D.B., Hoffman, J.I.E., Archie, J.P., and Fixler, D.E. (1971) Some sources of error in measuring regional blood flow with radioactive microspheres. *Journal of Applied Physiology* 31: 598
- Buckley, M. (1978) Personal communication
- Byar, D., Fiddian, R.V., Quereau, M., Hobbs, J.T. and Edwards, E.A. (1963) The Fallacy of Applying the Poiseuille Equation to Segmental Arterial Stenosis. *American Heart Journal* 70: 216
- Cannon, P.J., Dell, R.B., Dwyer, E.M. Jnr (1972) Measurement of regional myocardial perfusion in man with ¹³³xenon and a scintillation camera. *Journal of Clinical Investigation* 51: 964

- Christensen, G.C. and Campeti, F.D. (1959) Anatomic and functional studies of the coronary circulation in the dog and pig. *American Journal of Veterinary Research* 20: 18
- Cobb, F.R., Bache, R.J. and Greenfield, J.C.Jr (1974) Regional myocardial flow in awake dogs. *Journal of Clinical Investigation* 53: 1618
- Conn, H.L. (1955) Measurement of organ blood flow without blood sampling. *Journal of Clinical Investigation* 34: 916
- Cox, W.V. and Robertson, H.F. (1936) The effect of stellate ganglionectomy on the cardiac function of intact dogs. *American Heart Journal*, 12: 285
- Cutler, E.C. (1927) Summary of experience up to date in the surgical treatment of angina pectoris. *American Journal of Medical Science*, 173: 613
- DeBakey, M.E. and Lawrie, G. (1978) Invited commentary on Coronary Bypass Grafting and Longevity. *World Journal of Surgery* 2: 739
- De Marchi, G., Battezzati, M. and Gagliaferro, A. (1956) Influenza della legatura della arterie mammarie interne sulla insufficienza miocardica. *Minerva medica* 47: 1184
- De Rouen, T.A., Murray, J.A., Owen, W. (1977) Variability in the analysis of coronary arteriograms. *Circulation* 55:324
- Diethrich, E.B., Liddicoat, J.E., Kinard, S.A., Garrett, E.E., Lewis, J.M. and DeBakey, M.E. (1967) Surgical significance of Angiographic patterns in Coronary Arterial Disease. *Circulation* 35 and 36 (Supplement 1) 155
- Diguglielmo, L and Guttadauro, M. (1952) A roentgenologic study of the coronary arteries in the living. *Acta Radiologica* (Stockholm) Supplement 97)
- Domenech, R.J., Hoffman, J.I.E., Noble, M.I.M., Saunders, K.B., Henson, J.R. and Subijanto, S. (1969) Total and regional coronary blood flow measured by radio-active microspheres in conscious and anaesthetised dogs. *Circulation Research* 25: 581
- Dotter, C.T. and Frische, L.H. (1958) Visualisation of the coronary circulation by occlusion aortography. *Radiology*, 71: 502
- Downey, H.F., Bashour, F.A., Boatwright, R.B., Parker, P.E. and Edchejian, S.J. (1975) Uniformity of Transmural Perfusion in anaesthetised dogs with maximally dilated coronary circulations. *Circulation Research* 37: 111
- Downey, J.M. and Kirk, E.S. (1974) Distribution of the Coronary Blood Flow across the Canine Heart Wall during Systole. *Circulation Research* 34: 251
- Eckenhoff, J.E., Hafkenschield, J.H., Harmel, M.H., Goodale, W.T., Lubin, M., Bing, R.J., and Kety, S.S. (1948) Measurement of coronary blood flow by the nitrous oxide method. *American Journal of Physiology* 152: 356

- Eliot, R.S. and Edward, J.E. (1974) Pathology of Coronary Atherosclerosis and its Complications in The Heart, Arteries and Veins. Page 1003 Editor Hurst, J.W. McGraw-Hill Kogakusha Ltd. Tokyo
- Elzinga, W.E. and Skinner, D.B. (1975) Haemodynamic characteristics of critical stenosis in canine coronary arteries. Journal of Thoracic and Cardiovascular Surgery 69: 217
- Evans, C.L., Grande, F. and Hsu, F.Y. (1934) Two single heart oxygenator systems of the heart. Quarterly Journal of Experimental Physiology 24: 283
- Farrer-Brown, G. (1977) A Colour Atlas of Cardiac Pathology. Wolfe Medical Publications. Holland
- Favaloro, R.G., Effler, D.B., Groves, L.K. (1970) Severe segmental obstruction of the left main coronary artery and its divisions: surgical treatment by the saphenous vein graft technic. Journal of Thoracic and Cardiovascular Surgery 60: 469
- Flameng, W., Wiisten, B. and Schaper, W. (1973) The distribution of myocardial flow. Part 11 : Effects of arterial stenosis and vasodilatation. Basic Research in Cardiology 69: 435
- Folts, J.D., Gallagher, K.P. and Rowe, G.G. (1974) Physiologist 17: 223
- Foltz, E.L., Page, R.G., Sheldon, W.F., Wong, S.K., Tuddenham, W.J. and Weiss, A.J. (1950) Factors in variation and regulation of coronary blood flow in intact anaesthetised dogs. American Journal of Physiology 162: 521
- Forman, R., Kirk, E.S., Downey, J.M. and Sommerblick, E.H. (1973) Nitroglycerin and heterogeneity of myocardial blood flow. Journal of Clinical Investigation 52: 905
- Fortuin, N.J., Pitt, B. and Kahäara, S. (1968) Distribution of regional myocardial blood flow in the dog. (Abstr) Circulation 38: 77
- Friesinger, G.C. (1977) Haemodynamics. in Angina Pectoris. Editor Julian, D.C. Churchill Livingstone Edinburgh
- Fulton, W.F.M. (1965) The Coronary Arteries. Charles C. Thomas Springfield, USA
- Furuse, A., Klopp, E.H., Brawley, R.K. (1975) Haemodynamic determinations in the assessment of distal coronary artery disease. Journal of Surgical Research 19: 25
- Garrett, H.E., Dennis, E.W. and DeBakey, M.E. (1973) Aorto-coronary bypass with saphenous vein graft. Seven year follow up. Journal of American Medical Association. 223: 792
- Gensini, G.G. (1963) Coronary angiography. Progress in Cardiovascular Diseases, 6: 155
- Gilbert, J.P., Harthorne, J.W. (1976) Interobserver variability in coronary angiography. Circulation 53: 627

- Glover, R.P., Davila, J.C., Kyle, R.K., Beard, J.C. Jr., Trout, R.G. and Kitchell, J.R. (1957) Ligation of the internal mammary artery as a means of increasing blood supply to the myocardium. *Journal of Thoracic Surgery* 34: 661
- Goodman, L.S. and Gilman, A. (1975) *The Pharmacological Basis of Therapeutics*. Macmillan Publishing Co. New York - page 547 - 552
- Gorlin, R. (1974) *Physiology of the Coronary Circulation*, in *The Heart, Arteries and Veins* Editor Hurst, J.W. McGraw-Hill Kogakusha Ltd
- Gorlin, R. (1960) Measurement of Coronary Blood Flow in Health and Disease, in *Modern Trends in Cardiology*, editor Jones, A.M. page 191. Butterworth and Co Ltd. London
- Gould, K.L. (1978) Pressure - Flow Characteristics of Coronary Stenoses in Unsedated Dogs at rest and during coronary vasodilatation. *Circulation Research* 43: 242
- Grant, R.T. and Regnier, M. (1926) The comparative anatomy of the cardiac coronary vessels. *Heart* 13: 285
- Gregg, D.E. and Bedynek, J.L. Jr (1978) Compensatory Changes in the Heart during Progressive Coronary Artery Stenosis, in *Primary and Secondary Angina Pectoris*, Editors: Maseri, A., Klassen, G.A., Lesch, M. Grune and Stratton Inc. New York
- Gregg, D.E. and Dewar, D (1938) Immediate effect of coronary sinus ligation on dynamics of coronary circulation. *Proceedings of Society of Experimental Biology and Medicine* 39: 202
- Gregg, D.E. and Fisher, L.C. (1963) *Blood Supply to the Heart*, in *Handbook of Physiology: Section 2 Circulation Volume II* American Physiological Society, Washington.
- Griffiths, L.S.C., Achuff, S.C., Conti, C.R., Humphries, J.O., Brawley, R.K., Gott, V.L. and Ross, R.S. (1973) Changes in Intrinsic Coronary Circulation and Segmental Ventricular Motion after Saphenous vein Coronary Bypass Graft Surgery *New England Journal of Medicine* 288: 589
- Griffith, L.S.C., Bulkley, B.H., Hutchins, G.M. and Brawley, R.K. (1977) Occlusive changes at the coronary artery - bypass graft anastomosis. *Journal of Thoracic and Cardiovascular Surgery*. 73: 668
- Griggs, D.M. and Nakamura, Y (1968) Effects of coronary constriction on myocardial distribution of iodoantipyrine 131 *American Journal of Physiology* 215: 1082
- Grondin, C.M., Dyrda, I., Pasternac, A., Campeau, L., Bourassa, M.G. and Lesperance (1974) Discrepancies between cineangiographic and postmortem findings in patients with coronary disease and recent myocardial revascularisation. *Circulation* 49: 703
- Gross, L. (1921) *The blood supply to the Heart*. Oxford University Press. New York

- Gross, L. and Blum, L. (1935) Effects of coronary artery occlusion on dogs's heart with total coronary sinus ligation. Proceedings of Society of Experimental Biology and Medicine 32: 1578
- Hammond, G.L. and Austen, W.G. (1967) Drainage patterns of coronary arterial flow as determined from the isolated heart. American Journal of Physiology 212: 1435
- Hedley-Brown, A. and Krause, B.L. (1978) Pre-operative low-dosage propranolol: Its effect on left ventricular function and its protective value from ischaemia. Paper read at Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland. Leeds. September 1978
- Helmsworth, J.A., McGuire, J. and Felson, B. (1950) Arteriography of the aorta and its branches by means of the polyethylene catheter. American Journal of Roentgenology, Radium Therapy and Nuclear Medicine. 64: 196
- Herd, J.A., Hollenberg, M., Thorburn, G.D., Kopald, HH., and Barger, A.C. (1962) Myocardial blood flow determined with drypton⁸⁵ in unanaesthetised dogs. American Journal of Physiology 203: 122
- Hess, D.H. and Bach, R.J. (1976) Transmural Distribution of Myocardial Blood Flow during systole in the awake dog. Circulation Research 38: 5
- Hillis, W.S., Faulkner, S.L., Fisher, R.D. (1975) Significance of severity of coronary arterial stenosis: metabolic studies and correlation with hyperemic response. Journal of Surgical Research 18: 125
- Hoffman, J.I.E., Boerboom, L.E., Rouleau, J.R. and Surjadhana (1978) Factors influencing transmural flow distribution, in Primary and Secondary Angina Pectoris. Editors: Maseri, A., Klassen, G.A. and Lssch, M. Pages 13 - 20 Grune and Stratton New York
- Holman, B.L. (1977) Disturbances in blood flow in Coronary Artery Disease, in Current Cardiovascular Topics Vol III Angina Pectoris. Edited by Donoso, E and Gorlin, R. Georg Thieme Publishers Stuttgart
- Holman, B.J., Adams, D.F., Jewitt, D. (1974) Measuring regional myocardial blood flow with ¹³³Xe and the Anger camera. Radiology 112: 99
- Hottenrott, C., Maloney, J.V., and Buckberg, G. (1974) Studies of the effects of ventricular fibrillation on the adequacy of regional myocardial flow I Electrical vs. spontaneous fibrillation. Journal of Thoracic and Cardiovascular Surgery. 68: 615
- Hottenrott, C., and Buckberg, G. (1974) Studies of the effects of ventricular fibrillation on the adequacy of regional myocardial flow. II Effects of ventricular distention. Journal of Thoracic and Cardiovascular Surgery. 68: 626
- Hottenrott, C., Maloney, J.V. and Buckberg, G (1974) Studies of the effects of ventricular fibrillation on the adequacy of regional myocardial flow III Mechanisms of ischaemia. Journal of Thoracic and Cardiovascular Surgery 68: 634

- Hoyos, J.M. and Del Campos, C.G. (1948) Angiography of the thoracic aorta and coronary vessels. *Radiology*, 50, 211
- I.B.M. (1969) Technical Newsletter No: N20 - 1944 entitled "System#360 Scientific Subroutine Package Version III Programmer's Manual"
- James, T.N. (1961) *Anatomy of the Coronary Arteries*. Hoebner Medical Division, Harper and Row, Publishers Inc. New York
- James, T.N. and Burch, G.E. (1958) Blood supply of the human inter-ventricular septum. *Circulation* 17: 391
- Johnson, J.R. and DiPalma, J.R. (1939) Intramyocardial Pressure and its Relation to Aortic Blood Pressure. *American Journal of Physiology* 125: 234
- Johnson, W.D., Flemma, R.J., Lepley, D. Jr., Ellison, E.H. (1969) Extended treatment of severe coronary artery disease: a total surgical approach. *Annals of Surgery*. 170: 460
- Jones, J.W., Ochsner, J.L., Mills, N.L., Hughes, L. (1978) Impact of multiple variables on operative and extended survival following coronary artery surgery *Surgery*: 83: 20
- Jonnesco, T. (1920) Traitement chirurgical del'angine de potrine par la resection de sympatique cervico-toracique. *Bulletin de l'Academie Royale de Medecine de Belgique* 84: 93
- Jonsson, G. (1948) Visualisation of the coronary arteries - preliminary report. *Acta Radiologica* (Stockholm) 29: 536
- Judkins, M.P. (1967): Selective coronary arteriography: a percutaneous transfemoral technique. *Radiology* 89: 815
- Judkins, M.P. (1968) Percutaneous Transfemoral selective coronary arteriography. *Radiologic Clinics of North America* 6: 467
- Khoury, E.M., Gregg, D.E. and McGranahan, G.M. (1971) Regression and reappearance of coronary collaterals. *American Journal of Physiology* 220: 655
- Kirk, E.S. and Honig, C.R. (1964) Nonuniform distribution of blood flow and gradients of oxygen tension within the heart. *American Journal of Physiology* 207: 661
- Kirk, E.S. and Honig, C.R. (1964) Experimental and theoretical analysis of myocardial tissue pressure. *American Journal of Physiology*. 207: 361
- Klassen, G.A., Zborowska-Sluis, D.T., Sestier, F. and Mildenerber, R.R. (1978) The role of Autoregulation in the Genesis of Acute Myocardial Ischaemia, in Primary and Secondary Angina Pectoris. Editors: Maseri, A., Klassen, G.A. and Lesch, M. Publisher: Grune and Stratton Inc. New York
- Kleinman, L.H. and Wechsler, A.S. (1978) Pressure-Flow characteristics of the Coronary Collateral Circulation during Cardiopulmonary bypass. Effects of Ventricular Fibrillation. *Circulation* 58: 233

- Kreulen, T.H., Boue, A.A. and McDonough, M.T. (1975) The evaluation of left ventricular function in man: a comparison of methods. *Circulation*. 51: 677
- Kreulen, T.H., Kirk, H.S., Gorlin, R., Chon, L.H. and Collins, J (1974) Coronary artery bypass surgery: Assessment of revascularisation by determination of blood flow and myocardial mass. *American Journal of Cardiology*. 34: 129
- L'Abbate, Marzilli, M., Ballestra, and Camici, P. (1978) Myocardial Contraction : An additional determinant of transmural flow distribution. In *Primary and Secondary Angina Pectoris*, Editors: Maseri, A., Klassen, G.A. and Lesch, M. Publisher: Grune and Stratton Inc. New York
- L'Abbate, A., Mildenerger, R.R., Christie, L. (1974) Federation Proceedings: Federation of American Societies for Experimental Biology. 33: 414
- Lehman, J.S., Boyer, R.A. and Winter, F.S. (1959) Coronary arteriography. *American Journal of Roentgenology, Radium Therapy and Nuclear Medicine*. 81: 749
- Levinsky, R.A., Lewis, R.M., Laurie, D.J., Thompson, H.K., Cole, J.S. (1974) What is critical coronary artery stenosis : is it different in resting and stress conditions. *Circulation (III)* 49 - 50: 186
- Longmire, W.P. Jr., Cannon, A.J., Kattus, A.A. (1958) Direct-vision coronary endarterectomy for angina pectoris. *New England Journal of Medicine* 259: 993
- Love, W.D. (1964) Isotope clearance and myocardial blood flow. *American Heart Journal* 67: 579
- Love, W.D., Munford, R.S. and Abraham, R.E. (1965) Comparison of the effects of 1 - norepinephrine, angiotensin, dipyridamole, digitoxin, and reserpine on the regional distribution of coronary blood flow. *Journal of Laboratory and Clinical Medicine* 66: 423
- Mann, F.C., Herrick, J.F., Essex, H.E. and Baldes, E.J. (1938) The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel. *Surgery* 4: 249
- Marco, J.D., Barner, H.B., Kaiser, G.C., Codd, J.E., Mudd, J.G. and William, V. (1976) Operative Flow Measurements and Coronary bypass graft patency. *Journal of Thoracic and Cardiovascular Surgery*. 71: 545
- May, A.M. (1960) Surgical anatomy of the coronary arteries. *Diseases of Chest*. 38: 645
- May, A.G., DeWeese, J.A. and Rob, C.G. (1963) Haemodynamic effects of arterial stenosis. *Surgery* 53: 513
- McIntosh, H.D. and Garcia, J.A. (1978) The First Decade of Aorto-coronary Bypass Grafting, 1967 - 1977. A Review. *Circulation*. 57: 405

- Miller, D.W. (1977) *The Practice of Coronary Artery Bypass Surgery*. Plenum Medical Book Company. New York and London
- Milnor, W.R. (1974) in *Medical Physiology*. Edited: Mountcastle, V.B. C.V. Mosby Company. St.Louis. Pages 996 - 1000
- Miller, D.W., Hessel, E.A., Winterscheid, L.C., Merendino, K.A. and Dillard, D.H. (1977) Current practice of coronary artery bypass surgery. *Journal of Thoracic and Cardiovascular Surgery*. 73: 75
- Moir, T.W., Driscoll, T.E. and Eckstein, R.W. (1964) Thebesian drainage in the left heart of the dog. *Circulation Research* 14:245
- Moir, T.W. and DeBra, D.W. (1967) Effect of left ventricular hypertension, ischaemia and vasoactive drugs on the myocardial distribution of coronary flow. *Circulation Research* 21: 65
- Mundth, M.D. and Austen, W.G. (1975) Surgical measures for Coronary Heart Disease (Three parts) *New England Journal of Medicine*. 293: 13, 75, 124
- The New England Journal of Medicine - Editorial September 22, 1977
Coronary Artery Surgery at the Crossroads. 297: 661
- Ochsner, A. and DeBakey, M. (1937) The surgical treatment of coronary disease. *Surgery*. 2: 428
- Olson, R.E. (1962) *Physiology of Cardiac Muscle*. In *Handbook of Physiology*, editors: Hamilton, W.F. and Dow, P. Section 2 *Circulation*, page 199. American Physiological Society. Washington
- Paulin, S. (1964) *Coronary angiography. A technical, anatomic and clinical study*. *Acta Radiologica (suppl)* 233
- Pianetto, M.B. (1939) The coronary arteries of the dog. *American Heart Journal*. 18: 403
- Pitt, B. and Gregg, D.E. (1968) Coronary haemodynamic effects of increasing ventricular rate in unanaesthetised dog. *Circulation Research* 22: 753
- Porter, W.T. (1896) *The vasomotor nerves of the heart*. Boston Medical and Surgical Journal 134: 39
- Provenza, D.V. and Scherlis, S. (1959) Demonstration of muscle sphincters as a capillary component in the human heart. *Circulation* 20: 35
- Provenza, D.V. and Scherlis, S. (1959) Coronary circulation in dog's heart: demonstration of muscle sphincters in capillaries. *Circulation Research* 7: 318
- Race, D. Stirling, G.R. and Morris, K.N. (1964) Induced ventricular fibrillation in Open-Heart Surgery. *Journal of Thoracic and Cardiovascular Surgery*. 47: 271
- Radner, S. (1945) An attempt at the roentgenologic visualisation of coronary blood vessels in man. *Acta Radiologica (Stockholm)* 26: 497

- Regan, T.J., Binak, K., Gordon, S., Devazio, V. and Hellems, H.K. (1961) Myocardial blood flow and oxygen consumption during postprandial lipaemia and heparin-induced lipolysis. *Circulation* 23: 55
- Resnekov, L. (1977) Myocardial perfusion. In *Angina Pectoris*. Editor: Julian, D.G. Churchill Livingstone. Edinburgh
- Reynolds, S.R.M., Kirsch, M., and Bing, R.J. (1958) Functional capillary beds in the beating, KCl-arrested, and KCl-arrested-perfused myocardium of the dog. *Circulation Research* 6: 600
- Ricketts, H.J. and Abrams, H.L. (1962) Percutaneous selective coronary cine arteriography. *Journal of the American Medical Association*. 181: 620
- Ritchie, J.L., Trobaugh, G.B., Hamilton, G.W., Weaver, W.D., Williams, D.W., Gould, K.L. (1976) Rest and exercise myocardial imaging with Thallium-201 - correlation with EKG, coronary anatomy, and left ventricular function. *American Journal of Cardiology*. 37: 166
- Ross, R.S., Ueda, K., Lichtlen, P.R. and Rees, J.R. (1964) Measurement of myocardial blood flow in animals and man by selective injection of radioactive inert gas into the coronary arteries. *Circulation Research*. 15: 28
- Rowe, G.G. (1969) Myocardial perfusion and Measurement of Coronary Blood Flow. In *Clinical Cardiopulmonary Physiology*, Page 80 Editors, Gordon, B.L., Carleton, R.A. and Faber, L.P. Grune and Stratton Inc. New York
- Rudolph, A.M. and Heymann, M.A. (1967) The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circulation Research* 21:163
- Sabiston, D.C. Jr. (1974) The coronary circulation. The William F. Reinhoff Jr Lecture. *Johns Hopkins Medical Journal* 134: 314
- Sabiston, D.C. Jr. (1978) Surgical Treatment of Coronary Artery Disease - Introduction. *World Journal of Surgery* Vol 2 No 6: 673
- Sabiston, D.C. and Gregg, D.E. (1957) Effect of Cardiac Contraction on Coronary Blood Flow. *Circulation* 15: 14
- Salisbury, P.F., Cross, C.E., Oblath, R.W. and Rieben, P.A. (1962) Local circulation in heart muscle studied with Na 24 clearance method. *Journal of Applied Physiology* 17: 475
- Sandler, H. and Dodge, H.T. (1968) The use of single plane angiograms for the calculation of left ventricular volumes in man. *American Heart Journal* 75: 325
- Schaper, W. (1971) *The Collateral Circulation of the Heart*. North-Holland Publishing Company. Amsterdam.
- Selman, N.W. (1955) Experiences with the Beck operation for coronary artery disease. *Diseases of Chest* 28: 1

- Scheel, K.W., Granger, H.J., Brody, D.A. and Keller, F.W. (1973) Mechanisms of collateral development and haemodynamics of gradual coronary occlusion. *Basic Research in Cardiology*. 69: 338
- Schlesinger, M.J. (1938) An injection plus dissection study of coronary artery occlusions and anastomoses. *American Heart Journal* 15:528
- Sestier, F., Mildenerger, R. and Klassen, G.A. (1975) Cyclic changes in coronary blood flow: A consequence of autoregulation. *Circulation (II)* 52: 126
- Sheldon, W.C. (1977) Graft patency and survival following bypass graft surgery for coronary artery disease. In *Second Henry Ford Hospital International Symposium on Cardiac Surgery*, editor Davila, J.C.. Appleton-Century-Crofts. New York
- Shipley, R.E. and Gregg, D.E. (1944) The Effect of External Constriction of a Blood Vessel on Blood Flow. *American Journal of Physiology*. 141: 289
- Shorthouse, A. and Parker, D.J. (1978) Should Beta-Blockers be withdrawn prior to coronary artery surgery - recent experience. Paper read at meeting of Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland in Leeds. September 1978
- Sones, F.M., Jr. and Shirey, E.K. (1962) Cine coronary arteriography. *Modern Concepts of Cardiovascular Disease* 31:735
- Spencer, F.C. and Isom, O.W. (1978) The influence of coronary bypass grafting on longevity. *World Journal of Surgery* 2: 731
- Stiles, Q.R., Tucker, B.L., Lindesmith, G.G., Meyer, B.W. (1976) Myocardial Revascularisation. A Surgical Atlas. Publisher Little, Brown and Company, Boston.
- Ullyot, D.J., Wisneski, J., Sullivan, R.W. and Gertz, E.W. (1975) Coronary artery surgery improves survival in patients with extensive coronary artery disease. *Journal of Thoracic and Cardiovascular Surgery*. 70: 405
- Utley, J., Carlson, E.L., Hoffman, J.I.E., Martinez, H.M. and Buckberg, G.D. (1974) Total and regional myocardial blood flow measurements with 25u, 15u, 9u and filtered 1 - 10u diameter microspheres and antipyrine in dogs and sheep. *Circulation Research* 34: 391
- Vansant J.H., and Muller, W.H.Jr. (1959) Experimental evaluation of internal mammary artery ligation as a method of myocardial revascularisation. *Surgery*. 45: 840
- Vansant, J.H. and Muller, W.H. (1960) Surgical procedures to revascularise the heart. A review of the literature. *American Journal of Surgery*. 100: 572 - 583
- Vineberg, A.M. (1946) Development of an anastomosis between the coronary vessels and a transplanted internal mammary artery. *Canadian Medical Association Journal*. 55: 117
- Vineberg, A.M. (1949) Development of anastomosis between the coronary vessels and a transplanted internal mammary artery. *Journal of Thoracic Surgery*. 18: 839

- Vineberg, A.M. (1952) Treatment of coronary artery insufficiency by implantation of the internal mammary artery into the left ventricular myocardium. *Journal of Thoracic Surgery* 23: 42
- Vineberg, A. and Walker, J. (1957) Six months to six years experience with coronary artery insufficiency treated by internal mammary artery implantation. *American Heart Journal* 54: 851
- Vlodaver, Z and Edwards, J.E. (1971) Pathology of Coronary Atherosclerosis, *Progress in Cardiovascular Diseases*. 14: 256
- Vlodaver, Z, Frech, R., Van Tassel, R.A. and Edwards, J.E. (1973) Correlation of the antemortem coronary arteriogram and the postmortem specimen. *Circulation* 47: 162
- Wagner, H.N., Rhodes, B.A., Sasaki, Y. (1969) Studies of the circulation with radioactive microspheres. *Investigative Radiology*. 4:375
- Walsh, W.F., Harper, P.V., Resnekov, L., and Fill, H. (1976) Noninvasive evaluation of regional myocardial perfusion in 112 patients using a mobile scintillation camera and intravenous nitrogen-13 labelled ammonia. *Circulation* 54: 266
- Wearn, J.T., Mettier, S.R., Klumpp, T.G. and Zschiesche, L.J. (1933) The nature of the vascular communications between the coronary arteries and the chambers of the heart. *American Heart Journal*. 9: 143
- Weiss, H.R. and Winbury, M.M. (1974) Nitroglycerin and chromones on small vessel blood content of the ventricular walls. *American Journal of Physiology*. 226: 838
- Wheatley, D.J., Reid, J. and Coleman, E. (1975) Congenital coronary artery fistula. *Thorax* 39: 535
- Wiggers, C.J. (1936) *The Physiology of the Coronary Circulation. In Diseases of the coronary arteries and Cardiac pain.* Edited by Levy, R.L.. Macmillan, New York Pages 57 - 109
- Wiisten, B., Flameng, W. and Schaper, W. (1973) The distribution of myocardial flow Part 1: Effects of experimental coronary occlusion. *Basic Research in Cardiology*. 69: 422
- Wolfson, S. and Gorlin, R. (1969) Cardiovascular Pharmacology of propranolol in man. *Circulation*. 40: 501
- Wheatley, D.J. and Davis, P.D. (1975) A battery powered Cardiac Fibrillator. *Medical and Biological Engineering*. 13: 586
- Young, D.F., Cholvin, N.R., Roth, A.C. (1975) Pressure drop across artificially induced stenoses in the femoral arteries of dogs. *Circulation Research* 36: 735