APPROACHES TO THE ASSESSMENT OF COMBINED SEGMENT VASCULAR DISEASE

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2. Baker AR, Prytherch DR, Evans DH, Bell PRF.
   Doppler ultrasound assessment of the femoro-popliteal segment: comparison of different methods using ROC curve analysis.

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   Haemodynamic assessment of the femoro-popliteal segment: comparison of pressure and Doppler methods using ROC curve analysis.

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INTRODUCTION

Patients with co-existing aorto-iliac and femoro-popliteal arterial disease pose problems in assessment and management. Single plane arteriography is the only widely used investigation. This is known to underestimate aorto-iliac disease and when it shows combined segment disease, it gives no information on the relative importance of the two segmental components. Femoro-popliteal reconstructive surgery can not be successfully performed in the presence of uncorrected haemodynamically significant aorto-iliac disease. If proximal reconstruction alone is performed in combined segment disease, failure to relieve symptoms occurs in 20-50% of cases. Total repair in all cases may be attended by unacceptable increases in mortality and morbidity. Total repair would also involve unnecessary procedures in the large proportion of patients in whom proximal reconstruction alone provides symptomatic relief. It would be helpful to have haemodynamic information which would allow the group, in whom proximal reconstruction alone will be unsuccessful, to be identified preoperatively. If this were possible, total repair could be limited to this group alone.

In the first section of this thesis, the aetiology and distributions of atherosclerosis are reviewed together with the clinical presentations and therapeutic options in patients presenting with lesions affecting the legs (chapter 1). Arteriography and other imaging methods are described in chapter 2 and the effects of a stenosis on pressure and flow are discussed in chapter 3. Chapter 4 outlines the particular problems presented by patients with combined segment disease.
Section two deals with the aorto-iliac segment. Chapter 5 comprises a review of haemodynamic methods applied to this segment. Chapters 6 and 7 describe a flow monitored hyperaemic test which was developed in a canine model and then applied in the assessment of patients with vascular disease. Section three is devoted to the femoro-popliteal segment and is arranged in the same way. Chapter 8 is a review of haemodynamic methods in this segment, while chapters 9 and 10 describe haemodynamic tests in a canine model and in patients with vascular disease respectively.

Section four is the final section and consists of a short summary and concluding remarks.
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While the author has been actively involved in all stages of the work described in this thesis, it would not have been possible without the Department of Medical Physics.

I would like to thank Dr David Evans who has had a long interest in haemodynamic studies of vascular disease. He has studied the effects of arterial stenosis on pressure and flow and more recently has done a great deal of work on the analysis of Doppler waveforms. He has written the computer programs for all the Doppler analysis work in this thesis and has been a continuous source of support and stimulating discussion throughout.

My thanks go also to Dr David Prytherch who, together with Dr David Evans, designed the Doppler acquisition and analysis system used for these studies. He wrote the Doppler acquisition programs and also programs for data analysis and display. I am very grateful to Mr Stephen Bentley, Mr Michael Asher and Mr Michael Barton for their expert technical assistance during both the animal and patient studies. I would also like to thank Dr David Morton for his help with the animal studies and Dr Derek James for assistance in the classification of the arteriograms.

Lastly I am indebted to Professor Peter Bell for his continuing interest in applied vascular physiology and in particular the use of haemodynamic studies in clinical decision making. Almost all the
patients in the study were under his care and his comments have been stimulating throughout this work.
Atherosclerosis is a disease of uncertain aetiology which represents the major cause of death in the western world. It gives rise to lesions of the arterial intima which may be scattered widely throughout the vascular tree. Most of the deaths directly attributable to this disease result from lesions in the coronary and cerebral vessels. Considerable morbidity and mortality also results from lesions affecting the arteries supplying the legs and it is these which are the prime concern of this thesis.

The prevalence of atherosclerosis affecting leg arteries in western societies is approximately 2% of men and 1% of women aged between 45 and 69 years (Hughson et al 1978b). Women lag behind men by about 10 years in their incidence (Kannel et al 1970).

The aetiology of this condition is uncertain but there are several well recognised risk factors (Hughson et al 1978a). Based on these and the observed localisation of lesions, several hypotheses have been put forward. Risk factors include:

1. age
2. male sex
3. family history
4. smoking
There are three types of lesion classically recognised. The "fatty streak" is a lipid deposit containing cholesterol filled macrophages and smooth muscle cells. It is a yellow sessile lesion which causes no obstruction to flow and no symptoms. Such lesions can be found in the aorta of children of all races and environments by the age of 10 years. The "fibrous plaque" is the lesion characterising true atherosclerosis. These lesions are however not evenly distributed, either worldwide or throughout the arterial tree, and their relationship to fatty streaks is a matter of some controversy. The fibrous plaque is a white raised lesion which protrudes into the arterial lumen. Histologically it is similar to the fatty streak with the addition of collagen, elastic fibres, proteoglycans and cell debris. The fibrous plaque may develop into the third type of lesion known as the "complicated lesion". This may occur as a result of intramural haemorrhage, cell necrosis, calcification, ulceration and mural thrombosis. The complicated lesion is essentially a fibrous plaque with calcification and is often associated with symptomatic disease.

The controversy over aetiological mechanisms in the development of these lesions dates back to the rivalry between Virchow and Pokitansky in the middle of the nineteenth century. The filtration hypothesis propounded by Virchow attributed the formation of atherosclerotic lesions to imbibition of blood constituents by the arterial wall. The
localisation of the resulting lesions was supposed to be determined by tearing and stretching due to the "force of the blood". This theory gained a good deal of support from the experimental production of atherosclerosis-like lesions in animals by feeding cholesterol rich diets. The serum levels of cholesterol required to produce these lesions were however grossly unphysiological and there is some evidence that such cholesterol levels may themselves be damaging to the endothelial layer (Florentin et al 1969).

The encrustation hypothesis of Von Rokitansky, on the other hand, considered lesions to arise by a process of thrombotic fibrin deposition. These deposits were then thought to be covered by a new endothelial layer and so incorporated into the intimal layer.

As is so often the case in long standing scientific rivalries, it now appears that both of these hypotheses are correct to some extent. One of the most interesting recent observations which must be taken into account by any current hypothesis was made by Benditt (1973). He studied the cellular populations of aortic lesions in black women who were heterozygous for glucose-6-phosphate dehydrogenase. By looking at the iso-enzymes, he was able to show that the cells of any single lesion all expressed the same gene and were therefore derived by multiplication of a single cell. This might fit with imbibition of some mitogenic factor.

It has gradually been realised that whatever the aetiological mechanism of atherosclerosis, the endothelium is of prime importance
either by virtue of its permeability in the filtration hypothesis or for its adhesiveness in the encrustation hypothesis. The distribution of arterial lesions in relation to curving and branching of the arterial tree would certainly seem to be related in some way to haemodynamic forces (Fry 1968; Texon 1960; Texon 1972) and perhaps to endothelial wear and tear. The role of platelets in the maintenance of endothelial integrity has recently been realised and it has been shown that platelets are necessary for the development of atherosclerotic lesions in experimental animals. If animals are made thrombocytopenic before endothelial injury, intimal thickening and smooth muscle proliferation does not occur (Friedman et al 1977). Aggregating platelets have been shown to release a factor which stimulates smooth muscle proliferation (Ross 1980). The aggregation of platelets in response to endothelial injury seems to be controlled by the balance between Prostacyclin (PGI2) formed by the endothelium which inhibits platelet aggregation and Thromboxane A2 released by the platelets themselves which promotes their aggregation (Moncada & Vane 1979).

It would seem that the initiating event in the development of atheroma is haemodynamic injury to the endothelium. This allows some ingress of blood constituents and also initiates platelet adhesion and aggregation. There is then some imbalance in the normal platelet mediated repair process allowing increased platelet adhesion and subsequent stimulation of smooth muscle proliferation. The platelet thrombus is then re-endothelialised and incorporated into the arterial wall. The fibrous plaque thus formed may subsequently undergo ulceration and further thrombus formation and so grow according to the
encrustation theory.

Some at least of the known risk factors for development of atherosclerosis in man fit in with such a hypothesis. Smoking is known to increase platelet adhesiveness (Hawkins 1972). Arterial hypertension might be expected to increase the degree of endothelial trauma resulting from the pulse pressure wave and its reflection (Stephenson et al 1962). Hyperlipidaemia may increase the rate of intimal lipid accumulation at sites of increased endothelial permeability.

Sites of Predilection for Atherosclerosis

In 1962 Schwartz and Mitchell performed a post mortem survey in which they removed the aorta, carotid and iliac arteries from every fifth patient aged 35 years or more undergoing necropsy at their hospital. They examined 336 specimens and showed the predilection of certain sites for atheroma and noted a remarkably constant pattern of these sites. They discussed the relevance of haemodynamic factors to this distribution. DeBakey and his colleagues (1985) have recently published the results of analysing the records of 13,827 patients presenting with vascular disease and found that the characteristic distributions of atherosclerosis fall into 5 basic patterns:

I Coronary arteries
II Major branches of the aortic arch
III Visceral branches of the abdominal aorta
IV Terminal abdominal aorta and its branches
V Combinations of two or more of these

Among these categories, they found that category IV was the commonest
pattern accounting for approximately 40% of the patients. Category I was next most common and included a third of the patients. In all the categories, atheroma tended to be well localised in the middle portion of the arterial tree where it was amenable to surgery. Less commonly however disease was located in the distal part of all beds together and surgery had nothing useful to offer in this group. Interestingly they also found that patients in category IV had the highest incidence of development of disease in a new category, particularly category II.

Considering lesions in the arteries supplying the legs, it has been known for many years that the commonest lesion arises in the distal third of the superficial femoral artery as it passes through the adductor canal (Mavor 1956, Singer 1963). Kennedy Watt in 1965 reviewed femoral arteriograms in 264 patients with intermittent claudication. He stated that femoro-popliteal lesions arise at 3 principal sites: 70% at the adductor hiatus, 12% in the popliteal artery above the knee and 12% at the popliteal bifurcation. Plaque formation was uncommon in the proximal part of the superficial femoral artery and also in the popliteal artery below the knee. A year later (Watt 1966) he reviewed 100 translumbar aortograms and again found three common sites of origin of lesions. These were: the aortic bifurcation, the common iliac artery and the common iliac bifurcation. Of these, the commonest lesion was occlusion or stenosis of the common iliac artery.

Mavor (1956) noted the relative immunity of the profunda femoris to atherosclerosis and appreciated the great importance of this vessel as a collateral in the presence of superficial femoral occlusion. Singer
(1963) confirmed the sparing of profunda and also pointed out that the common femoral and popliteal artery below the knee were also usually relatively free of disease thus making them obvious sites for anastomosis of bypass grafts to give the best chance of long-term patency. Haimovici in 1967 published a very detailed analysis of the patterns of disease affecting the leg based on 321 limbs. The majority of patterns were diffuse particularly among diabetics in whom disease distal to the popliteal artery was relatively common.

Clinical presentations of occlusive arterial disease of the legs

Patients affected by atherosclerosis affecting the arterial supply of the legs present with one of two main complaints: intermittent claudication or ischaemic rest pain which may be associated with tissue necrosis.

Intermittent claudication is characterised by a cramp-like pain in the muscles of the leg associated with walking. Its precise location depends to some extent on the distribution of arterial disease causing it. The most striking feature of this pain is that in each affected individual it is produced by the same degree of exercise on each occasion and is completely relieved by a few minutes rest.

The pain of intermittent claudication occurs when arterial stenosis limits the capacity for reactive hyperaemia in response to exercise. The limb blood flow is usually normal at rest and tissue requirements are satisfied. However flow can not be increased sufficiently during exercise. The distal perfusion pressure falls and the metabolic demands
of the exercising muscle are not satisfied.

Ischaemic rest pain is severe and felt distally, usually in the fore-foot. It occurs when flow at rest falls below a level necessary to provide for the needs of the limb. In its least severe form, flow is reduced to a point where gravity can make the difference between a sufficient and an insufficient circulation at rest by increasing the distal perfusion pressure (Gaskell & Becker 1971) and blood flow (Eikhoff 1985). Such patients complain of pain at night when lying in bed and often find that hanging the foot down relieves the pain. They may sleep sitting in a chair to avoid the pain. As flow is reduced further, pain becomes continuous and is no longer affected by posture. Any decrease in flow beyond this point results in tissue necrosis, ulceration and gangrene.

Clinical assessment
The history gives some clue as to the location of occlusive lesions. Intermittent claudication occurs most commonly in the calf reflecting the frequency of femoro-popliteal disease. Patients with aorto-iliac lesions alone, however, may also present with calf claudication (Mavor 1956; Weslowski et al 1966). Aorto-iliac disease often results in thigh and buttock claudication which may be felt as an aching sensation together with profound weakness, rather than cramp-like pain. This is seen most classically associated with impotence in the syndrome of aortic occlusion described by Leriche (1948). Foot claudication is rare but it may occur in thromboangiitis obliterans.
Examination includes many physical signs such as muscle wasting and atrophic skin changes but the information of most help in determining the level of significant occlusive lesions is gained by palpation of the peripheral pulses. Of these the femoral pulse may be difficult to assess (Johnston et al 1981) particularly in obese subjects and the popliteal pulse is often difficult to feel even in patients of normal build. The pedal pulses are comparatively easy to feel. Nonetheless there is a large observer error in detection of both dorsalis pedis and posterior tibial pulses (Ludbrook et al 1962). Of the two, palpation of the posterior tibial is more reliable than dorsalis pedis which is impalpable in approximately 10% of subjects with no evidence of arterial disease (Ludbrook et al 1962; Nuzzaci et al 1984) and may be congenitally absent in this proportion of the population (Bamhorst & Barner 1968). Arteriographic information contributes greatly to knowledge of the location and distribution of lesions. This is dealt with more fully in the next chapter.

Natural history and therapeutic options
Intermittent claudication is essentially a benign condition from the point of view of the leg but has serious implications as to the state of the whole arterial tree. Bloor (1961) followed 1,476 claudicants for between 4 and 10 years. 673 (45.6%) died during this time, 60% and 17% of these deaths resulted from coronary and cerebrovascular disease respectively. Only 16% of deaths were not related to occlusive vascular disease. Amputation was necessary in 121 patients (8.2%) i.e. only 20% of the number who died. Claudication improved in 60% of the survivors and some improvement was seen up to 3 years after the onset of symptoms.
Thus it would seem that the prognosis for the patient's life is much worse than that for his limb as a result largely of associated coronary artery disease. These findings have been confirmed by other groups. Imparato (1975) found a 5.8% amputation rate among 104 claudicants followed for an average of 2.5 years. The Framingham study (Peabody et al 1974) showed that claudication underwent spontaneous remission in 59% of cases but frequently recurred. In 2.5% progression of disease resulted in major amputation while at 10 years 24% of men and 41% of women had died, mostly of cardiovascular disease.

Consequently treatment of claudication is usually conservative. Patients are advised to stop smoking and to exercise (Clyne 1980). Cessation of smoking has been shown to improve exercise tolerance and possibly to increase ankle pressure (Quick & Cotton 1982). Similarly exercise results in improved walking distance (Larsen & Lassen 1966; FitzGerald et al 1971a; Ekroth et al 1978). Two of these groups showed that these changes were not associated with an increase in blood flow measured either by plethysmography or Xenon-133 clearance (Larsen & Lassen 1966; Ekroth et al 1978) while FitzGerald and his colleagues (1971) found a significant increase in maximal calf flow as measured by Xenon-133 clearance following an exercise programme. Similarly Wilson and his co-workers (1980) showed an improvement in the walking distance of 26 of 53 claudicants but only 12 had an increase in ankle pressure index.

Some of this improvement, particularly early after the onset of symptoms, probably relates to the development of collaterals which
appears to occur in response to a pressure gradient across an arterial obstruction (Winblad et al 1959; John & Warren 1961). There is probably also an increase in muscle efficiency which is as yet poorly understood (Holm et al 1973).

**Surgical Reconstruction**

Surgery is only offered in claudication if symptoms are severe and disabling and show no improvement with conservative therapy in a relatively fit patient. The presence of ischaemic rest pain, on the other hand, implies that blood supply to the limb is precarious. There is a high risk of major amputation unless surgical reconstruction is successfully undertaken as a matter of some urgency.

Aorto-iliac disease may be treated by aorto-femoral bypass. This gives good results in terms of graft patency since the graft is of wide bore and the flow rate is high. The standard approach is transperitoneal and this represents a significant operative risk in these patients. In selected patients, however, recent reports show mortality rates of less than 3% (Diehl et al 1983). Less fit patients can be treated by aorto-femoral bypass using the retroperitoneal route (Metz & Mathieson 1978; Kwaan et al 1982) which represents less operative trauma but is technically more difficult. Alternatives in the relatively unfit patient include axillo-bifemoral bypass (Johnson et al 1977; Corbett et al 1984) or if the disease is unilateral, femoro-femoral crossover (Plecha & Pories 1976; Berqvist et al 1984). Percutaneous transluminal angioplasty (Dotter & Judkins 1964; Gruntzig & Kumpe 1979) is a recent innovation which gives good results in the
aorto-iliac segment in selected cases (Waltman et al 1982; Zeitler et al 1983).

Femoro-popliteal bypass represents less of an operative risk but results, in terms of graft patency, depend both on run-off and on in-flow. Several groups have shown that patency rates fall with decreasing numbers of patent vessels distal to the popliteal artery (DeWeese & Rob 1977). Aorto-iliac disease resulting in reduced in-flow has a similar effect (Charlesworth et al 1975). Failure of a femoro-popliteal graft results in a higher incidence of limb loss than failure of aorto-iliac reconstruction. In addition there is some evidence that distal disease may progress more rapidly after bypass of a "haemodynamically protective" superficial femoral occlusion (Warren et al 1964; Mozersky et al 1972b). Femoro-popliteal bypass is therefore performed less often for claudication and tends to be reserved for the treatment of ischaemic rest pain. Bypass grafts to arteries distal to the popliteal give less good results (Barry et al 1985) which depend on distal vessel patency to the plantar arch. Their role in the treatment of vascular patients is still under discussion (Bell 1985).

In general the mortality of surgical reconstruction is no greater than that of amputation (Gregg 1985). Reconstruction should not therefore be withheld on the grounds of risk to the patient's life. On the other hand, there is some evidence that failure of surgical reconstruction may result in a higher amputation than would otherwise be necessary (Dardik et al 1982).
While results, in terms of graft patency, depend on the factors outlined above, patency is also adversely affected by continued smoking (Wray et al 1971; Myers et al 1978a; Greenhalgh et al 1981) and some surgeons recommend that surgery should not be undertaken in the claudication group unless it is confirmed that they have stopped smoking (Thomas 1981).

It is also important to emphasise that although graft patency is of obvious importance, it is not the only factor which must be taken into account when assessing the success of surgical reconstructions. Patent grafts may fail to provide haemodynamic improvement (O'Mara et al 1981) and may also fail to relieve symptoms (see Chapter 4). Conversely late occlusion of reconstructions, performed for limb salvage, does not always result in amputation (Myers et al 1978b). Such grafts may have protected a limb during a critical period prior to their occlusion.

Alternatives to Surgical Reconstruction

Not all distributions of peripheral vascular disease are amenable to surgical reconstruction. Patients with advanced disease distal to the popliteal artery are a particularly difficult group to treat. Lumbar sympathectomy, performed either surgically or by injection of phenol, still has a useful role to play in this group. Cotton and Cross (1985) in a recent review state that there is no improvement in haemodynamic indices following this procedure and that if the Ankle Pressure Index is <0.35 it is not likely to be successful in the relief of rest pain. They suggest that it may be acting as an analgesic method rather than improving blood flow to ischaemic tissues. This is not surprising since
ischaemia is a potent vasodilator and methods aimed at producing further vasodilatation in this situation are unlikely to help.

For this reason, vasodilator drugs do not appear to be useful (Coffman 1979). In a recent review of drug therapy in the management of lower limb ischaemia Boobis and Bell (1982) concluded that there is still no drug which can cure or affect the progress of the disease; although they did suggest that drugs affecting the platelet/vessel wall interaction may be the most promising area in which future developments may occur. There have indeed been some encouraging reports of the use of intra-arterial Prostacyclin infusions (Szczechlik et al 1979).

CONCLUSIONS
Atherosclerosis is often a widespread disease. Certain lesions in the arteries supplying the legs are amenable to surgical reconstruction but before embarking on surgery, the state of the rest of the arterial tree and the significance of other lesions for the prognosis of the patient's life and limb must be taken into account. The selection of a particular operation for an individual patient involves weighing many factors in the balance.
Single plane arteriography is the most widely used investigation in patients presenting with peripheral vascular disease. It can be performed by direct needle puncture of the aorta by the translumbar route under general anaesthesia but is now more often achieved by common femoral artery puncture under local anaesthesia. Using this route a catheter can be introduced by the Seldinger technique (Seldinger 1953) and passed upstream so that it lies in the lower abdominal aorta. Using either route, radiographs of the arterial system from the abdomen down to the feet can be produced from a single contrast injection by automatic serial exposures as the contrast travels down the legs. The use of modern non-irritant contrast media has made arteriography much more tolerable to patients under local anaesthesia.

Complications following arteriography, performed by the translumbar or transfemoral route, are infrequent (Hessel et al 1981) but when they do occur they may be serious and necessitate emergency surgery (Bouhoutsos & Morris 1973, Szilagyi 1977). They are associated with: the contrast medium which is nephrotoxic and may also cause drug reactions, mechanical damage to the arterial wall during catheter introduction and manipulation and the anaesthetic techniques. Consequently it is generally recognised that arteriography should not be performed either to confirm the presence of peripheral vascular disease
or as a routine investigation in vascular patients but rather should be reserved for those in whom the severity of symptoms has led to the decision to operate (Christenson et al 1978, Macpherson et al 1980). The information provided is thus used to decide whether operation is feasible and if it is what segment or segments should be reconstructed at operation.

Several other methods of imaging the arterial system have been described which reduce or avoid the risks of intra-arterial contrast injection.

Digital subtraction angiography (Crummy et al 1980, Turnipseed et al 1981) is a computer assisted technique for constructing images of vessels using intravenous administration of low doses of contrast medium although better images are produced by intra-arterial injection. Two fluoroscopic images are digitised and stored; first a bone and soft tissue "mask" image made before contrast injection and secondly the contrast image. These two images are then subtracted so that the bone and soft tissue shadows are cancelled. The technique can resolve faintly opacified vessels and is useful for imaging the arteries distal to the popliteal trifurcation and especially the pedal arch. Its limitations are the small size of the field that can be processed and the effect of patient movement on the quality of the image.

Static isotope angiography (Hurlow et al 1978, Hurlow & Strachan 1978) employs a gamma camera to follow the first transit of an intravenous bolus of radioisotope. The image is enhanced by computer
processing to subtract low counts and double high counts. It is a
technique which can produce quick results but its use is limited by the
small available field and poor resolution particularly in arteries which
are not close to the collimator.

Ultrasound B-mode imaging is an imaging technique using
transcutaneous ultrasound to produce a grey scale picture and is
consequently non-invasive. It has found a useful role in delineating
the outer wall of abdominal aortic aneurysms and thus providing a
measure of their diameter (Leopold et al 1972) but as yet the available
resolution is insufficient for vessel lumen imaging except in vessels
lying close to the skin surface such as the carotid artery (Weinberger &
Robbins 1983).

Although these techniques reduce the risks of arteriography, at
their current stage in development the price is a small image field and
a poorer image quality as compared with standard arteriography. None of
them can therefore replace the standard methods of arteriography at
present.

Arteriography delineates the site, nature and extent of
atherosclerotic lesions. The importance of performing aortography
rather than femoral arteriography in order to reveal clinically
unsuspected proximal disease has been emphasised by several workers
(Weslowski et al 1966, Haimovici 1967). It has however been shown that
single-plane aortography does not reveal all haemodynamically
significant lesions in the aorto-iliac segment (Weslowski et al 1966,
Moore & Hall 1971, Udoff et al 1979, Brewster et al 1979) because of the thick contrast column and foreshortening of the iliac arteries. The origin of profunda femoris is not well shown (Beales et al 1971) and distal vessels may not be filled if there is severe proximal disease (Madejski & Tobik 1964). Bruins Slot (1981) has shown that interobserver agreement on the profunda origin using single plane arteriography is only marginally better than chance. Obtaining exposures using the anterior oblique projection visualises the origin of profunda femoris (McDonald et al 1976). Simultaneous biplane arteriography may reduce the false negative rate in the aorto-iliac segment (Crummy et al 1978) but this requires additional equipment which is not widely available in this country. Even triplane arteriography underestimates aorto-iliac disease (Flanigan et al 1983).

Consequently after arteriography the clinician may not be in possession of sufficient information to make a confident clinical decision. In the presence of femoro-popliteal occlusion there may be clinical suspicion of disease in the aorto-iliac segment which has not been shown on arteriography, while in the presence of combined segment disease (coincident aorto-iliac and femoro-popliteal disease) it is often not possible to estimate which lesion dominates as the cause of the patient's symptoms. Apparently minor lesions on arteriography may result in significant pressure gradients. Conversely, well developed collateral circulation may largely compensate for the haemodynamic effects of a complete occlusion.

For elucidation of the clinical problem of overt or suspected
combined segment disease, functional haemodynamic information is required to complement the anatomical information provided by an image of the vessels. It is possible to perform pressure studies at the time of arteriography by the translumbar route (Castaneda-Zuniga et al 1976, Udoff et al 1979) but the common femoral arteries must also be punctured. Such measurements are simpler to perform if the arteriography itself is performed via the transfemoral route (Moore & Hall 1971, Brewster et al 1979).

CONCLUSIONS

Arteriography provides an essential anatomical map of the patient's arteries and this contains a wealth of information which neither non-invasive nor invasive haemodynamic tests are ever likely to duplicate. In the presence of combined segment disease, however, this may still be insufficient information for a confident clinical decision as to which segment or segments to reconstruct. Haemodynamic studies should complement arteriography by providing a functional interpretation of the anatomical lesions and allow more confident decisions in such situations.
As blood flows through a narrowed arterial segment, energy is lost in contraction and expansion as the blood enters and leaves the narrowed region. There are also increased viscous energy losses associated with the increased flow velocity through the narrowed region. These energy losses are expressed as a reduction in distal pressure and volume flow, the magnitude of which is dependent on the geometry of the stenosis and also the viscosity of the blood. The relationship between pressure and flow of Newtonian liquids at steady flow rates in rigid tubes is relatively well understood and expressed by Poiseuille's law:

\[ Q = \frac{K \cdot P \cdot r^4}{l} \]

where \( Q \) = volume flow

\( K \) = constant dependent on viscosity

\( P \) = pressure drop along the tube

\( r \) = internal tube radius

\( l \) = tube length

The human arterial system is a good deal more complex, however, in that blood is a non-Newtonian fluid, flow is pulsatile and arteries are elastic.

The first experimental work to have a bearing on the haemodynamic effects of arterial stenosis was that of Mann and his co-workers in 1938. They had found that in order to measure blood flow successfully,
their probe must slightly compress the artery and they were concerned that this slight narrowing may have some influence on flow through the vessel. In order to study this, they performed experiments on canine carotid arteries and found that the artery could be constricted to a point where its internal diameter was reduced by 55% and its luminal area by 80% before there was much reduction in the flow. If the artery was constricted further than this, there was a marked reduction in flow. They referred to this as the "critical point in the degree of constriction" (Figure 1). The concept of "critical stenosis" has subsequently become popular among vascular surgeons.

Figure 1. The Effect on Blood Flow of Reducing the Lumen of a Blood Vessel (From Mann et al. 1938).
Shipley and Gregg in 1944 performed similar experiments on the carotid arteries of dogs but found a wide scatter of results and were unable to show any fixed relationship between narrowing of the lumen and reduction in flow. They realised that this was largely a result of the varying peripheral resistance of the distal vascular bed in response to ischaemia.

Crawford and his colleagues, in 1962, also studied canine carotid arteries and showed that there was an inverse relationship between pressure drop across a stenosis and the flow through it.

Figure 2. Flow and Pressure Changes with Increasing Stenosis

(From Berguer & Hwang 1974).
This has since been confirmed by several other groups such as Berguer & Hwang (1974) (Figure 2). They also showed that the length of the stenosis as well as its diameter are important. For a narrowing 0.5mm long a 50% diameter reduction produced a critical stenosis while for a length of 12mm, 35% diameter reduction was sufficient.

May and his co-workers (1963a), in a study on the canine aorto-iliac segment, confirmed the effect of reduction in diameter and increase in length of stenosis and showed that the pressure drop across a stenosis and the flow through it are linearly and inversely related (Figure 3).

![Graph showing relationship between flow and pressure drop across an increasingly tight stenosis.](image)

**Figure 3. Relationship Between Flow and Pressure Drop across an Increasingly Tight Stenosis (From May et al 1963a).**
They made an attempt to quantify the energy losses involved using a mathematical model which gave a curve closely corresponding to their experimental results. They concluded that pressure drop across the stenosis could be explained entirely as a result of the properties of fluid flow through the stenosis and there was no need to invoke a fall in peripheral resistance to explain the fall in distal pressure as had been suggested by Shipley and Gregg. They were later able to study the effect of flow increases caused by sympathectomy and exercise, mimicked by electrical stimulation of the sciatic nerve (May et al 1963b). Elevation of flow resulted in reduction of the value of the critical stenosis (a fact confirmed by Van de Berg and his colleagues in 1964) and also the slope of the curve after the critical point became less steep.

![Figure 4. The Effect of Increasing Flow on "Critical Stenosis"
(From Berguer & Hwang 1974)](image_url)
This has subsequently been confirmed by Berguer and Hwang (1974) (Figure 4). May and his colleagues, using their mathematical model, went on to calculate theoretical values of critical stenosis for various human arteries.

Fiddian and his co-workers in 1964 used an extra-corporeal circulation with a dog as a source of pulsatile blood flow. This enabled them to control peripheral resistance accurately and confirm the predictions of May's mathematical model, in particular the relatively small contribution of stenosis length as opposed to its diameter.

Figure 5. The Effect of Lengthening a Stricture on Blood Flow

(From Kindt & Youmans 1969).
Kindt and Youmans (1969) have since demonstrated the critical lengths of various degrees of stenosis in the canine aorta and shown that length has a more marked effect with increasingly tight stenosis (Figure 5).

Lee and his colleagues in 1978 using both in vitro and in vivo models showed that as the degree of stenosis increases, the pulsatile components of flow and distal pressure decrease earlier and to a greater degree than changes in mean values (Figure 6).

![Figure 6. The Effect of Stenosis on Pulsatile and Mean Flow](From Lee et al 1978).
Young's group has studied the characteristics of fluid flow through models of arterial stenoses in great depth. Initial studies were in vitro using steady flow (Young & Tsai 1973a) and showed that the resistance due to a constriction as shown by the pressure drop was much greater than would be predicted from Poissuille's law. This is probably the result of extra energy losses due to disturbed flow. They went on to study unsteady oscillatory flow in their in vitro model (Young & Tsai 1973b) and produced a much more complex mathematical model than that of May. They were able to validate this model experimentally in vitro and subsequently in vivo in canine femoral arteries (Young et al 1975). They have also studied the effect of stenoses at elevated flow rates in canine carotid and femoral arteries (Young et al 1977) and suggested that critical stenosis should be defined in terms of its effect on maximal flow rather than resting flow.

Studies more closely relating to the situation found in human arterial occlusive disease have been performed by Schultz and his colleagues in 1967. They excised human aorto-femoral segments post mortem and studied them in a pulsatile flow rig. The predicted pressure-flow relationships held true and only at very high flow rates was there a measurable pressure drop across the normal aorto-femoral segment. Brice and his co-workers (1964) performed successful in vivo experiments on 8 conscious human subjects at the time of common carotid ligation for berry aneurysm and found that a stenosis corresponding to 84-93% area reduction was critical.

It would appear then that for a given stenosis, three variables are
important in determining its effect on flow and distal pressure:

1. stenosis diameter
2. stenosis length
3. peripheral resistance

The importance of peripheral resistance depends on its magnitude relative to the resistance of a proximal stenosis. If the peripheral resistance is high then it will dominate as the determining factor in restricting volume flow down the limb. In this case there will be little pressure drop across the proximal stenosis. If, on the other hand, the peripheral resistance is low relative to the resistance of the proximal stenosis, it is the latter which will dominate and there will be a pressure drop across the stenosis. Peripheral resistance may be manipulated by peripheral vasodilatation so that the proximal stenosis becomes relatively dominant. In this way a stenosis which previously caused no fall in distal pressure will now cause a pressure drop and thus be "revealed". Such manipulation of peripheral resistance forms the basis of hyperaemic clinical tests such as the papaverine test (see below).

Effect of multiple stenoses

Vonruden and his co-workers in 1964 studied two stenoses in series in canine carotid arteries with no collaterals between them. The total effect was not additive but was essentially the effect of the tighter stenosis alone. Seeley and Young (1976) also studied two stenoses in series in their in vitro steady flow model. They also showed that the effect was not additive and suggested that the two stenoses may "interfere" with each other unless the spacing between them exceeded
some critical distance. Flanigan and his colleagues in 1977 studied multiple subcritical stenoses, up to 8 in series, in vitro under conditions of steady flow and also in vivo in canine femoral arteries. They found that the resulting pressure changes were additive but not in a linear fashion and the total effect is less than would be predicted.

Figure 7. The Effect of Multiple Stenoses on Distal Pressure
(From Flanigan et al 1977).
They suggested each added stenosis gave less of a pressure drop than the previously placed one because after each one the flow was reduced and consequently the pressure drop across each of the previously placed stenoses was also reduced. Karayannacos and his co-workers (1977) found only a slightly lower rate of increase of pressure drop when stenoses were close together than when they were far apart. Studying multiple non-critical stenoses both in vitro and in a canine model, they concluded that the total effect of such a series of non-critical stenoses may become critical and produce symptoms of arterial insufficiency.

The effect of collateral flow
Two groups have performed animal studies designed to investigate the effect of collateral flow on critical stenosis. The first of these was in the carotid circulation of monkeys (Youmans & Kindt 1968) and the second in dogs (Eklof & Schwartz 1970). Both showed that with collaterals (i.e. the contralateral carotid and both vertebrais) patent the value of critical stenosis was higher than when these collaterals were ligated. The reason for this is again related to flow. With the collaterals ligated flow in the remaining vessel is much higher.

Clinical Implications
It has long been realised that peripheral pulses which are easily palpable at rest may disappear during exercise induced claudication. This phenomenon was initially attributed to arterial spasm but it is now clear that it is the direct result of the fall in pulse pressure distal to a stenosis that is consequent upon the increase in flow associated
with exercise (Strandness & Bell 1964; Keitzer et al 1965; Barner et al 1968). Similarly the effect of multiple stenoses on an intervening pulse can be explained. In the presence of simultaneous aorto-iliac and femoro-popliteal disease, the femoral pulse may feel strong if the distal disease predominates (Blaisdell & Gauder 1961). The presence of a good femoral pulse does not therefore by itself rule out significant aorto-iliac disease.

Limb blood flow in patients with intermittent claudication is often normal at rest (Myers 1964). This is because the peripheral resistance dominates over the proximal stenosis and controls limb blood flow. Peripheral resistance may be reduced by exercise (Moore & Hall 1971), by drugs such as papaverine (Sako 1966) or by a period of ischaemia leading to reactive hyperaemia (Lorentsen et al 1972). Flow is thus increased and a proximal stenosis may now be revealed by a pressure drop associated with this augmented flow. These methods are mainly applied to assessment of the aorto-iliac segment (see below).

CONCLUSIONS

Arterial stenoses do not have a measurable effect on flow and distal pressure until the lumen is considerably reduced. The degree of reduction which is critical depends on flow and therefore on peripheral resistance. The first measurable effect occurs on the pulsatile components of pressure and flow. If peripheral resistance is artificially reduced, a stenosis which had no measurable haemodynamic effect at rest may now be revealed by its effect on distal pressure.
Chapter 4

COMBINED SEGMENT DISEASE

The term "combined segment disease" may properly be applied to any distribution of peripheral vascular disease involving more than one of the three segments of the leg. Until relatively recently, however, only the two proximal segments i.e. aorto-femoral and femoro-popliteal, were readily amenable to surgical reconstruction and the term "combined segment disease" has come to mean disease involving both of these two segments.

Between 20% and 60% of patients coming to reconstructive surgery for aorto-iliac disease also have femoro-popliteal lesions (Table 1). Patients with combined segment disease are in general older than those presenting with lesions confined to a single segment (Leeds & Gilfillian 1961; Royster et al 1976; Mulcare et al 1978; Cronenwett et al 1980). Diabetes is twice as common (Royster et al 1976; Mulcare et al 1978). There is a higher incidence of coronary and cerebral vascular disease (Kouchoukos et al 1968; Cronenwett et al 1980) and life expectancy is less (Crawford et al 1981). It is reduced approximately 10 years by associated coronary disease and diabetes. If neither of these is present however, then life expectancy may be normal (Malone et al 1977).
TABLE 1 INCIDENCE OF COMBINED SEGMENT DISEASE

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kouchoukos et al (1968)</td>
<td>35%</td>
</tr>
<tr>
<td>Moore et al (1968)</td>
<td>50%</td>
</tr>
<tr>
<td>Haimovici &amp; Steinman (1969)</td>
<td>21%</td>
</tr>
<tr>
<td>Suy et al (1969)</td>
<td>69%</td>
</tr>
<tr>
<td>Imparato et al (1970)</td>
<td>63%</td>
</tr>
<tr>
<td>Perdue et al (1971)</td>
<td>53%</td>
</tr>
<tr>
<td>Irvine et al (1972)</td>
<td>51%</td>
</tr>
<tr>
<td>Edwards &amp; Wright (1974)</td>
<td>45%</td>
</tr>
<tr>
<td>Vanttinen &amp; Inberg (1975)</td>
<td>36%</td>
</tr>
<tr>
<td>Royster et al (1976)</td>
<td>58%</td>
</tr>
<tr>
<td>Brewster &amp; Darling (1978)</td>
<td>66%</td>
</tr>
<tr>
<td>MacGowan &amp; Johnston (1978)</td>
<td>30%</td>
</tr>
<tr>
<td>Mulcare et al (1978)</td>
<td>58%</td>
</tr>
<tr>
<td>Cronenwett et al (1980)</td>
<td>42%</td>
</tr>
<tr>
<td>Hill et al (1980)</td>
<td>35%</td>
</tr>
<tr>
<td>Martinez et al (1980)</td>
<td>66%</td>
</tr>
<tr>
<td>Nevelsteen et al (1980)</td>
<td>65%</td>
</tr>
<tr>
<td>Crawford et al (1981)</td>
<td>43%</td>
</tr>
<tr>
<td>O'Donnell et al (1981)</td>
<td>57%</td>
</tr>
</tbody>
</table>
Patients with combined segment disease have a greater tendency to develop progressive distal disease (Mozersky et al 1972). This occurs in 38% compared with 14% of those with isolated aorto-iliac disease. Although patients with combined disease may present with claudication, they often present with ischaemic rest pain and gangrene (Kouchoukos et al 1968; Royster et al 1976; Mulcare et al 1978; Crawford et al 1981). A long history of intermittent claudication with a gradually decreasing claudication distance culminating in rest pain implies initially localised disease which has become more widespread (Samson et al 1985). The prognosis for a limb affected by combined segment disease is considerably worse than for limbs affected by single segment disease (MacGowan & Johnston 1978; Crawford et al 1981).

Arteriography may confirm the presence of combined segment involvement but does little to indicate which of the two lesions is dominant as the cause of the presenting symptoms (Perdue et al 1971; Edwards & Wright 1974; Malone et al 1975; Bone et al 1976). Not all cases of combined segment disease will be recognised after arteriography since the aorto-iliac segment may appear normal in some patients with haemodynamically significant disease (Moore & Hall 1971; Quin et al 1975; Bone et al 1976; Udoeff et al 1979).

The profunda femoris artery and its network of branches lie in parallel with the superficial femoral artery. It tends to remain patent even in the presence of extensive atheroma involving aorta, iliac, superficial femoral and popliteal arteries. When the profunda is involved by atheroma, this is usually confined to its orifice and the
proximal few centimetres (Martin et al 1968). Significant lesions of the deep and superficial femoral arteries occurring together are uncommon in patients with combined segment disease (Haimovici 1967). In the presence of superficial femoral occlusion the distal branches of the profunda system develop and take over the function of blood supply to the distal limb. The collateral flow provided in this way is of prime importance in the leg affected by combined segment disease. Morris and his colleagues in 1961 showed the value of restoring the inflow to the profunda in combined segment disease by performing aorto-femoral bypass or endarterectomy. They reported that 40% of 102 patients so treated had return of palpable pedal pulses in spite of uncorrected superficial femoral occlusion. They emphasised that patients with combined segment disease are not good candidates for lengthy total correction operations by virtue of their age and high incidence of coronary artery disease. They also suggested that total repair was not always the best approach since some of these patients also have tibio-peroneal disease which would significantly impair the run-off of the femoro-popliteal component. Other groups quickly confirmed the importance of profunda femoris revascularisation in patients with combined segment disease (Leeds & Gilfillian 1961; Weslowski et al 1966; Martin et al 1968; Moore et al 1968). Techniques have varied but more recently it has been suggested that the normal profunda orifice represents a haemodynamically significant obstruction to the outflow of an aorto-femoral bypass graft in the presence of superficial femoral occlusion (Berguer et al 1975). The undiseased profunda orifice represents a stenosis of 50% in this situation. Intimal thickening of 0.5mm or 1mm may raise this to 64% or 76% respectively. It would therefore seem that a long profundaplasty
should always be performed in conjunction with proximal reconstruction when this is performed in the presence of superficial femoral occlusion. Following these early encouraging results it has become generally accepted that the most appropriate surgical treatment of patients presenting with combined segment disease was to restore inflow to the profunda femoris artery. This is usually performed using a Dacron onlay aorto-femoral bypass with the addition of profundaplasty provided by placing the distal anastomosis over the profunda origin.

It has gradually been realised, however, that proximal reconstruction alone may fail to provide symptomatic relief in a proportion of patients. This proportion has been variously estimated by different groups to be between 20% and 50% of cases (Table 2). Some groups have shown a higher incidence of failure in patients presenting with claudication (Strandness 1970; Sumner & Strandness 1978; Mulcare et al 1978) while others have reported a higher incidence in the limb salvage group, with ischaemic ulceration (Imparato et al 1970). Approximately 25% of such patients may require subsequent distal reconstruction either to provide symptomatic relief or to achieve limb salvage (Perdue et al 1971; Edwards & Wright 1974; Welsh & Repetto 1975; Martinez et al 1980; Crawford et al 1981; Jones & Kempczinski 1981; Brewster et al 1982; MacGowan & Johnston 1978; Mulcare et al 1978; Benson et al 1966; Satiani et al 1980).

It is well known that haemodynamically significant aorto-iliac disease may result in occlusion of a femoro-popliteal bypass graft (Charlesworth et al 1975; Baird et al 1977). It is perhaps less well
appreciated that femoro-popliteal disease may prejudice the long-term patency of aorto-femoral bypass (Kouchoukos et al 1968; Mozersky et al 1972; Malone et al 1975; Vanttinen & Inberg 1975; Harris et al 1985).

Table 2  INCIDENCE OF FAILURE OF SYMPTOMATIC RELIEF WITH PROXIMAL RECONSTRUCTION ALONE IN COMBINED SEGMENT DISEASE

<table>
<thead>
<tr>
<th>Study</th>
<th>Failure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suy et al (1969)</td>
<td>24%</td>
</tr>
<tr>
<td>Imparato et al (1970)</td>
<td>32%</td>
</tr>
<tr>
<td>Perdue et al (1971)</td>
<td>24%</td>
</tr>
<tr>
<td>Edwards &amp; Wright (1974)</td>
<td>57%</td>
</tr>
<tr>
<td>Bone et al (1976)</td>
<td>34%</td>
</tr>
<tr>
<td>Mulcare et al (1978)</td>
<td>29%</td>
</tr>
<tr>
<td>Martinez et al (1980)</td>
<td>35%</td>
</tr>
<tr>
<td>Jones &amp; Kempczinski (1981)</td>
<td>17%</td>
</tr>
<tr>
<td>Brewster et al (1982)</td>
<td>26%</td>
</tr>
</tbody>
</table>

Because of these results, both in terms of symptomatic relief and also graft patency, reconstruction of both aorto-iliac and femoro-popliteal segments has been recommended (Harris et al 1985;
Collins et al 1978; Dardik et al 1979). This may be performed at a single sitting or alternatively as a staged procedure to avoid a single long operation. Recently Harris has shown that synchronous proximal and distal reconstruction results in no increase in mortality over proximal reconstruction alone in combined segment disease (Harris et al 1985). This has not however been the universal experience and several groups have reported unacceptable increases in morbidity and mortality with combined reconstructive procedures (Benson et al 1966; Suy et al 1969; Provan et al 1960; Heyden et al 1980). Even if this were not the case, combined proximal and distal reconstruction in all cases would involve unnecessary procedures in a large proportion of patients since in most series at least 50% of patients gain symptomatic relief with proximal reconstruction alone.

Identification of the group in whom proximal reconstruction alone will be inadequate would allow selection of this group alone for combined proximal and distal reconstruction. Arteriography may show the technical errors of proximal reconstruction (Plecha et al 1972) but is not helpful in predicting symptomatic relief (Perdue et al 1971; Edwards & Wright 1974; Malone et al 1975; Bone et al 1976). Excluding operative technical errors, early failures must represent either imprecise diagnosis of the severity of aorto-iliac disease or of the significance of residual uncorrected distal disease. Various haemodynamic methods have been described which may have some use in this context but none has gained widespread acceptance. The ideal time for selection of this group would be pre-operatively when reconstructive surgery is being planned. An alternative would be to assess the
haemodynamic status of the patient after proximal reconstruction while still under general anaesthesia and to perform distal reconstruction if proximal reconstruction alone appeared to be inadequate at that stage.

CONCLUSIONS

Patients with combined aorto-iliac and femoro-popliteal disease present difficult clinical problems. They tend to have more generalised atheroma and therefore operation is a greater risk. Total repair in all cases is both unnecessary and unwise but it is not possible to tell from arteriography which patients will not benefit from proximal reconstruction alone. It was therefore decided to study both aorto-iliac and femoro-popliteal haemodynamics in an attempt to provide information which may be of use in the pre-operative assessment of these patients.
Chapter 5
HAEMODYNAMIC ASSESSMENT OF THE AORTO-ILIAC SEGMENT

Assessment of the haemodynamic significance of an arterial stenosis necessitates measurement of the pressure gradient across the stenosis or the flow through it and ideally both.

**Pressure Measurement**

Measurement of pressure in vivo is considerably easier than measurement of flow. The haemodynamic effect of arterial stenosis is therefore often assessed by measurement of distal pressure and comparison of this with a proximal pressure to estimate the pressure gradient across the stenosis. As applied to the aorto-iliac segment, this involves measurement of thigh pressure and division by the brachial pressure to produce a thigh/brachial pressure index which should not be less than unity since blood pressure in the brachial and femoral arteries is normally the same (Pascarelli & Bertrand 1964).

Both thigh and brachial systolic pressures can be measured non-invasively using occlusion cuffs and some method of sensing the return of pulsatile flow distal to the cuff. The accuracy of pressure measurements made using occlusion cuffs depends primarily on the size of the cuff relative to the size of the limb to which it is applied. The American Heart Association has recommended that the inflatable bag should be 20% wider than the diameter of the limb. For the average
adult it is recommended that a cuff 12-14 cms wide should be used for brachial pressure and one 18-20 cms wide for thigh pressure (Kirkendall et al 1967). Too wide a cuff underestimates while too narrow a cuff overestimates pressure (Geddes & Whistler 1978). Cuff length also appears to be important. Random error is less with a longer bag although measured systolic values are low compared with intra-arterial pressure measurements (Karvonen et al 1964).

The use of a wide cuff for the measurement of thigh pressure is prone to errors directly related to the width of the cuff. An 18 cm wide cuff necessarily overlies a large part of the upper superficial femoral artery and therefore a low recorded pressure may in fact represent the effect of superficial femoral disease rather than an aorto-iliac lesion (Paris & Jamieson 1974; Flanigan et al 1981). The use of a narrow cuff undoubtedly results in high measured values but this disadvantage may be outweighed by the higher specificity for aorto-iliac disease and better discrimination from superficial femoral lesions. Gutajar and his co-workers (1973) showed that results using a narrow (10 cm wide) cuff correlated well with arteriography. Heintz and his colleagues (1978) compared a single wide cuff with two narrow cuffs, one in the proximal and the other in the distal thigh and showed that the narrow cuffs correctly localised aorto-iliac, femoro-popliteal and combined disease in 78% of cases. This compared with only 19% correct localisation using a single wide thigh cuff. Flanigan and his colleagues (1982) compared wide (17 cm) and narrow (10 cm) cuffs with intra-arterial common femoral pressure measurement. They found that the narrow cuff gave a 73% accuracy compared with 52% for the wide cuff.
False positives occurred in 75% using the wide and 65% using the narrow cuff. All but one of these false positives occurred in the presence of superficial femoral obstruction. The false negative rate was 3% using the wide and 8% with the narrow cuff. They concluded that thigh pressure measurement using a wide cuff may have a role in screening for aorto-iliac disease. Interpretation of the significance of an abnormal thigh pressure measurement, even using a narrow cuff, requires knowledge of the patency of the superficial femoral artery.

Another source of error in occlusion cuff measurements results from lesions between the cuff and the sensing site. Bernstein and his colleagues (1981b), in a canine model, showed that adding a stenosis distal to a thigh cuff resulted in underestimation of thigh pressure and a false implication of a proximal lesion. This has been confirmed in man by Franzeck and his co-workers (1981) who found that, using either a mercury strain gauge or Doppler as a sensing method, lower pressures are recorded in the thigh in patients with multi-level disease if the sensing site is at the ankle rather than the knee. No difference was found in normal individuals.

Occlusion cuffs may also lead to false negative readings due to the incompressibility of stiff diseased arterial walls and indeed Flanigan and his colleagues (1981) excluded obviously artefactual falsely high thigh pressures (thigh/brachial index > 1.5) before calculating the sensitivity and specificity of their measurements. False negatives may also result from a tourniquet effect of the cuff reducing blood flow through the stenosis and consequently the pressure gradient across it.

Because of all these sources or error, it has been recommended that high thigh pressure should be measured intra-arterially by direct needle puncture of the common femoral artery (Faris & Jamieson 1974). In addition to avoiding the above mentioned errors, this method has the advantage that pressure can be measured at various flow rates. Flow can be increased by exercise, reactive hyperaemia or by pharmacological agents such as papaverine or tolazoline. The effects of a stenosis on pressure can be studied under conditions of elevated flow more closely mimicking the situation in the claudicating extremity during exercise.

Weismann and Upson (1963) measured pressure in the common femoral or external iliac artery under conditions of resting flow. They measured brachial pressure at the same time by an oscillometric method and found that while clinical recognition of a normal or an absent femoral pulse was in general accurate, clinical suspicion of a diminished femoral pulse was inaccurate in 69% of cases. In 12 of 13 patients with a femoral pressure 20% or more below the brachial pressure, aorto-iliac reconstruction gave good results. Weslowski and his colleagues in 1966 made direct pressure measurements in both femoral and brachial arteries, again at resting flow. They showed that with a pressure gradient of 10 mm Hg or more, proximal reconstruction gave good results.

Moore and Hall (1971) studied 40 patients with intermittent claudication but apparently normal arteriography. They made bilateral
simultaneous direct common femoral pressure measurements and exercised each calf individually to produce claudication, using a pedal ergometer. The difference between the mean pressures of the exercising and resting limb was measured as an index of iliac occlusive disease. Several groups have used reactive hyperaemia following the application of a thigh cuff as a means of increasing blood flow (Lorentsen et al 1972; Brener et al 1974; Brewster et al 1979; Verhagen & van Vroonhoven 1984a & b). Lorentsen and his colleagues combined this with indirect brachial pressure measurement and also calf flow measured plethysmographically to produce a "stenosis index". Brener and his co-workers suggested that a fall in femoral arterial pressure of 15% with hyperaemia was indicative of haemodynamically significant aorto-iliac disease. In 10 of 26 patients with such abnormal pressure studies, the common femoral pulse had been felt to be normal. Brewster and his colleagues used a pull-through method for pressure measurement at the time of Seldinger transfemoral arteriography and combined this with reactive hyperaemia in 150 patients. They found that 36% of cases with diminished femoral pulses had normal inflow haemodynamics while 31% of patients with angiographically revealed aorto-iliac disease had a normal pressure study. Similarly 28% of limbs with an abnormal pressure study had a normal femoral pulse and 24% of patients with no significant lesion on angiography had an abnormal pressure study. They noted a better correlation between haemodynamic studies and the results of operation than between haemodynamic studies and clinical assessment including arteriography. Verhagen and van Vroonhoven (1984a & b) have used femoral artery puncture together with radial or brachial artery puncture and reactive hyperaemia to assess the aorto-iliac segment.
They suggested that if the femoro/brachial index falls >20% with hyperaemia, then significant proximal disease is present. In contrast to most previous studies, however, they concluded that single plane arteriography tends to overestimate aorto-iliac disease.

The first use of papaverine to induce peripheral vasodilatation for haemodynamic studies is often attributed to Sako (1966). It was, however, reported in the femoro-popliteal segment by Hall and Cappelen in 1964 (Hall 1964; Cappelen & Hall 1964). Sako measured aortic and common femoral pressure by needle puncture at operation and also monitored common femoral arterial flow with an E-M flowmeter. The effect of papaverine was shown by Quin and his colleagues (1976) to be reproducible and dose-dependent as well as being dependent on the degree of arterial stenosis. The papaverine test is now widely used in the pre-operative assessment of the aorto-iliac segment (Quin et al 1975; Barber et al 1980; Flanigan et al 1983). It has also been used at the time of translumbar aortography (Castañeda-Zuniga et al 1976) with bilateral femoral artery puncture for measurement of distal pressure. Papaverine testing is also used as an adjunct to pull-through pressure studies, principally during Seldinger transfemoral arteriography (Udoff et al 1979) but also at the time of vascular reconstruction (Bliss 1973; Baird 1977) and more recently at percutaneous transluminal angioplasty (Gunn et al 1981). It is now often used as the "gold standard" for the aorto-iliac segment against which other investigations are compared (Demorais & Johnston 1981; Archie & Feldtman 1982; Macpherson et al 1984). Various cut-off points have been recommended for the interpretation of the test. Sako (1966) suggested a 30% fall in the
femoral pressure with vasodilatation indicated significant disease. Quin and his colleagues (1975) and Barber's group (1980) recommended 18% while Flanigan and his co-workers (1983) used receiver operating characteristic curve analysis (see below) to show that 15% gave the best discrimination of disease as shown on triplane arteriography. When absolute pressure in mm Hg is used, Udoff and his co-workers (1979) recommended a 20mm Hg aorto-femoral gradient and Macpherson and his colleagues (1984) a 25 mm Hg difference between the two common femoral arteries as indicative of significant disease. The technique used to make the measurements may affect the optimum cut-off levels. The pull-through technique tends to produce higher pressure drops across the aorto-iliac segment, at resting flow, than does a technique involving radial and femoral arterial puncture (Baker et al 1985).

In addition to systolic pressure measurements, the pulse pressure wave has also been analysed for various characteristics which are altered by proximal stenosis. Weismann and Upson, in 1963, stated that a decreased rate of systolic rise of the pulse wave confirmed the presence of proximal stenosis as suggested by a reduced absolute systolic pressure. Leveson and his co-workers (1978) put this on a more formal basis by showing that the systolic slope index (femoral systolic slope/aortic systolic slope) is normally greater than unity reflecting the increase in pulsatility of the pressure wave as it passes distally. More recently Murie and his colleagues (1983) studied the maximal gradient of the pulse pressure wave at rest and following papaverine and showed that, in addition to absolute pressure values, the maximum gradient is reduced with increased flow. Pulse pressure waves can be
obtained non-invasively using a pulse volume recorder (Darling et al 1972) and can be used as an adjunct to absolute pressure measurements (Francfort et al 1984).

Flow Measurement

Limb blood flow can be estimated using venous occlusion plethysmography (Strandness and Bell 1965). This is performed by briefly occluding the venous outflow from the limb while allowing arterial inflow to continue unimpeded and measuring the volume change in the limb. It gives a measure of whole limb blood flow but segmental information is difficult to obtain. Impedance plethysmography (Porter et al 1985) does not involve venous occlusion and may therefore be more physiological. Unfortunately, however, it can only be applied in a healthy circulation because of difficulties in calibration in the presence of monophasic flow.

The electromagnetic (E-M) flowmeter is the most reliable method of volume flow measurement in man but can only be used at the time of operation when the artery is exposed and the probe can be applied directly to it. Golding and Cannon reported such a method in 1966 and used papaverine to augment flow. They concluded that, if such a test was performed before and after reconstruction, an immediate assessment of the technical result could be obtained. Baron and his colleagues (1981) have more recently used an E-M flowmeter to quantify the immediate haemodynamic result of profundaplasty but although they measured flow, they did not make simultaneous pressure measurements.
In the pre-operative assessment of the vascular patient, volume flow measurement is very difficult although some attempts have been made to use a modified electromagnetic technique without exposing the artery (Kolin et al 1978). Most groups have attempted to measure flow related indices rather than flow itself.

The time taken for an injected dose of radioactive tracer to be cleared from the quadriceps muscle is related to flow (Grimby et al 1967) and has been shown to correlate with arteriography (Angelides & Nicolaides 1980). The Birmingham group, which pioneered the use of static isotope angiography, have also developed a technique for dynamic isotope angiography (Hurlow et al 1978). The time taken for an intravenously injected isotope bolus to travel from the aortic bifurcation to the common femoral artery was measured and this was more accurate than thigh/brachial index.

Probably the most commonly used flow related measurements are various indices derived from the Doppler waveform recorded at the common femoral artery. The alterations in the Doppler waveform as a result of proximal and distal stenoses are complex and visual interpretation has been used with some success (Walton et al 1984). Various methods of objective waveform analysis have also been developed. The earliest of these was Pulsatility Index (PI) (FitzGerald et al 1971; Gosling et al 1971), which remains the easiest to calculate. Laplace Transform Damping (LTD) (Skidmore & Woodcock 1980) and Principal Component Analysis (PCA) (Martin et al 1980; Evans et al 1981) are two more complex methods of waveform analysis.
Johnston's group (Demorais & Johnston 1981; Johnston et al 1983) found that PI correlated well with pull-through intra-arterial pressure measurements but they did not use hyperaemia at the time of pressure studies. They also did not mention whether any of their patients had co-existing femoro-popliteal lesions. In a study, involving pressure measurements during papaverine-induced hyperaemia and including patients with combined segment disease, PI was much less closely related to pressure measurements (Macpherson et al 1984). Johnston (1978) has also confirmed that PI correlates well with the results of proximal reconstructive surgery but here again, he only studied patients with isolated aorto-iliac disease.

Femoro-popliteal lesions certainly affect the common femoral Doppler waveform (Nicolaides et al 1976). Although common femoral PI correlates with aorto-iliac arteriography if the superficial femoral artery is patent, if it is occluded there is no such correlation (Baird et al 1980). Auckland and Hurlow (1982) found that the mean value of common femoral PI, distal to <50% aorto-iliac stenosis, fell from 6.6 with a patent superficial femoral artery to 5.1 when this artery was occluded but the difference was not statistically significant. A common femoral PI value of <4 is highly predictive of a haemodynamically significant aorto-iliac lesion (89%) when the superficial femoral artery is patent. When it is occluded, however, only 60% of aorto-iliac segments with a PI of <4 are significantly diseased (Thiele et al 1983). Junger and his colleagues (1984), using receiver operating characteristic curve analysis (see chapter 7), found that a common femoral PI value of 7.6 gave the best accuracy in isolated aorto-iliac
disease but a value of 5.0 was best in combined segment disease. There is considerable evidence, therefore, that superficial femoral disease affects common femoral PI and tends to reduce the measured values. In spite of this, Charlesworth and his colleagues (1975) found that the results of common femoral PI, in showing covert aorto-iliac disease, correlated well with the early failure rate of femoro-popliteal bypass. Baird's group (1980) found that LTD (δ) was better than PI at every level of stenosis and was not affected by distal disease. Johnston and his co-workers (1984) however, failed to show any superiority for LTD and favoured PI since it is easier to calculate. Campbell and his co-workers (1984a) found that, while PI was superior in the detection of severe stenoses, LTD was better in the less severe group. Evans and his colleagues (1980) showed that PI was affected by peripheral resistance in a canine model and in 1981, using a similar canine model, they showed that LTD (δ) was also affected by peripheral resistance. When comparing all three methods they concluded that PCA was better than LTD or PI, particularly in the less severe stenoses (65%-77% area reduction). The superiority of PCA was subsequently confirmed in vascular patients with and without superficial femoral disease (Macpherson et al 1984).

Almost all the Doppler waveform analysis reported has been performed on the Doppler waveform at resting flow rate. Some attempt has, however, been made to provide a hyperaemia index using waveforms recorded at rest and during post-occlusive reactive hyperaemia (Fronek et al 1973b). The half recovery time of the mean flow velocity, following reactive hyperaemia, has also been advocated as a sensitive
indicator of aorto-iliac disease (Ward & Martin 1980). In addition, occasional attempts have been made to estimate volume flow using Doppler methods. In this latter application, errors are introduced because of the difficulty in measuring the cross-sectional area at the point of insonation (Reagan et al 1971). These errors may be reduced by B-mode imaging (Gill 1979) but Duplex scanners are still liable to several sources of error in estimation of volume flow (Gill 1985; Evans 1986).

Relevance of Simultaneous Pressure and Flow Measurement

Sako (1966) in initial evaluation of the papaverine test measured aortic and common femoral pressure together with common femoral flow. He appreciated the relevance of flow to the pressure measurements and stated that a "pressure fall of 10% to 20% in the face of increased flow" implied that there was no significant aorto-iliac disease. Golding and Cannon (1966) reported a case in which a normal pulsatile pressure was recorded in a saphenous vein graft associated with oscillatory movement of blood but no mean flow. Lorentsen and his colleagues, in 1972, found that the addition of plethysmographic flow measurements to provide a "stenosis index" was more informative than pressure alone. They stated that even a pressure fall of 5-10 mm Hg during reactive hyperaemia may indicate significant disease if this occurred in association with a low reactive hyperaemia flow. Bliss (1973) used papaverine at the time of femoro-popliteal reconstruction and measured pressure and flow to calculate run-off resistance. More recently Archie and Feldtman (1981) have emphasised the importance of knowing the flow rate as well as the pressure drop in order to be able
to compare results between patients. They expressed their results as the iliac artery pressure gradient at twice resting flow (Archie & Feldtman 1982).

CONCLUSIONS
Pressure is simpler to measure than flow. Intra-arterial pressure is more reliable than occlusion cuff pressure, particularly at the upper thigh level. Pressure measurements at elevated flow rates will reveal stenoses which have no measurable effect on pressure at resting flow. Simultaneous measurement of pressure and flow should increase the accuracy of assessment and allow better comparison of results between patients.

For these reasons a study of aorto-iliac pressure gradient, at resting and elevated flow, was initiated. The study involved intra-arterial pressure measurement above and below the stenosis together with Doppler monitoring of hyperaemia. Initial studies were performed in a canine model (Chapter 6) and the refined technique was then evaluated in a group of patients with peripheral vascular disease (Chapter 7).
A canine model was chosen for initial studies of this test since several haemodynamic methods have been evaluated in the past, in this department, using dogs under general anaesthesia (Evans et al 1980; Evans et al 1981; Evans et al 1982; Prytherch et al 1982). The model was, therefore, already well developed and there was considerable local expertise available in the anaesthesia and maintenance of stability of such a preparation.

MATERIALS AND METHODS

Five adult dogs weighing between 25 kg and 29 kg (Table 3) were anaesthetised using Thiopentone. Intermittent positive pressure ventilation was instituted using 67% nitrous oxide and 33% oxygen together with 1/4-1/2% Halothane. Anaesthesia was supplemented with a continuous infusion of Fentanyl/Fluanisone (Hypnorm - Janssen) plus bolus injections of Etorphine/Methotrimeprazine (Small Animal Immobilon - C.Vet).

Each animal was placed supine on a warming blanket. Pulse rate, blood pressure, central venous pressure, urine output and rectal temperature were all monitored continuously. Frequent estimations were made of haematocrit, blood sugar and arterial blood gases.
Table 3. Dogs studied in the aorto-iliac experiment

<table>
<thead>
<tr>
<th>Dog No</th>
<th>Sex</th>
<th>Wt (kgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>F</td>
<td>25</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>27.5</td>
</tr>
<tr>
<td>44</td>
<td>M</td>
<td>29</td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>26.5</td>
</tr>
<tr>
<td>46</td>
<td>F</td>
<td>27</td>
</tr>
</tbody>
</table>

The abdomen was opened through a midline incision extended across the right rectus abdominis muscle, through the right inguinal ligament and down the right leg along the line of the femoral artery. The iliac and femoral arteries were dissected from the aortic trifurcation to the point at which the femoral artery passes deep into the muscles of the leg and all branches were tied off.

The animal was heparinised and a stenosis assembly (Evans et al 1980) tied into the proximal iliac artery. This assembly had an interchangeable middle section (Figure 8) allowing different stenoses, with diameter reductions from 0 to 78% (Table 4), to be rapidly inserted without damage to the arterial wall. Dog 44 was a larger animal than the other four (Table 3) and in this animal a larger series of stenoses (C Series) was used than in the others (B series - see Table 4). The pressure proximal to the stenosis was measured using an 18 gauge medicut cannula, modified to have a side hole rather than an end hole, tied into the median sacral artery.
Table 4. Stenosis dimensions

<table>
<thead>
<tr>
<th>Stenosis number</th>
<th>B Series</th>
<th>C Series</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diam (mm)</td>
<td>% Diam reduction</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>2.95</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>2.38</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>1.95</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>1.7</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>78</td>
</tr>
</tbody>
</table>

Adaptor
PTFE tubing

Stenotic insert
Suture groove

1 cm.

Figure 8. Stenosis assembly.
Figure 9. The canine aorto-iliac experiment.
The distal pressure was measured using an 18 gauge Abbocath cannula, with a 3-way tap for arterial blood gas sampling, tied into a side branch so that its tip lay flush with the femoral arterial wall.

A cannulating E-M flow probe was tied into the artery distal to the stenosis. This had a 4mm lumen in each case except Dog 44 where a 5mm probe was used because of its generally larger arteries. Doppler recordings were made distal to both the stenosis and the flow probe using an 8MHz Sonicaid probe held rigidly in a clamp at 45 degrees to the longitudinal axis of the vessel (Figure 9).

After a period of stabilisation, stenoses were inserted in random order. The vessel was clamped for one minute. When the clamp was removed a hyperaemic Doppler recording was made together with simultaneous E-M flow and pressure recordings. When the reactive hyperaemia had settled, a further set of recordings was made at resting flow. Figure 10 shows examples of Doppler recordings at resting flow and during hyperaemia. These are directly comparable to the recordings made in the patient study (Figure 19).

**Pressure monitoring equipment**

The arterial cannulae were connected to calibrated Elcomatic EM751 pressure transducers by 1.5 metres of manometer line (Type 200/495/150 Portex). Similar systems have been shown to have a flat frequency response up to 20Hz (Yeomanson & Evans 1983). Each transducer was connected to a Gould (130-4615-50) pressure pre-amplifier and pressure
traces were recorded simultaneously on two channels of a Gould Pressure Ink Chart Recorder (Series 2000). The two pressures were also electronically meaned and subtracted to allow simultaneous display of pressure drop on a third channel.

The subtracted mean pressure was used to show when pressure drop across the stenosis had reached a maximum during hyperaemia, so that Doppler recordings could be made at this time. For the calculation of pressure drop, however, the systolic pressures at the peak of the respiratory cycle were used.

**Doppler equipment**

The ultrasound transducer was driven by a Sonicaid "Vasoflo" Doppler unit, which was interfaced to a "Unigon Angioscan 1" spectrum analyser via a "Unigon TRA-1" heterodyne unit. The audio Doppler frequencies analysed by the spectrum analyser consisted of signals corresponding to forward and reverse blood flow, separated about a heterodyne frequency (equivalent to zero flow). The spectrum analyser was also interfaced to a "Vector Graphics 3100" microcomputer which received the results of the spectrum analysis in real time (see Appendix 1).
Figure 10. Sonograms from the canine femoral artery
(a) at resting flow rate and (b) during hyperaemia.
For convenience the spectrum analysed data produced by the spectrum analyser, corresponding to one cardiac cycle, will be referred to as a "sonogram" here (Figure 10). On command the microcomputer captured and stored on mini-floppy disk 3.2 seconds of spectrum analysed data (typically 3 to 4 complete sonograms) at each data acquisition. However, so as to record respiratory variations in blood flow, the microcomputer was programmed to acquire the data from alternate heartbeats and therefore the acquisition of 3.2 seconds of sonogram data took typically 6 seconds.

In the work described in this chapter, the stored sonograms were analysed in two different ways:

1. The complete sonograms within the 3.2 seconds of spectrum analysed data were processed to find the mean Doppler shift frequency over one cardiac cycle, D.

2. The frequencies corresponding to maximum forward and maximum reverse flow at each instant were found and then processed to form the maximum frequency envelope, which was then meanted over each complete sonogram (within the 3.2 seconds of data) to give the mean of the maximum Doppler shift frequency over one cardiac cycle, Dmax. Since this process involves the manipulation of far less data than the first, it is simpler and faster to perform. The processes involved in the formation of the maximum frequency envelope are described in detail elsewhere (See Appendix 1).
Figure 11. DOGS: Mean Doppler shift frequency plotted against electromagnetic flow.

Circles represent Dog 44.
Figure 12. DOGS: Mean of the maximum Doppler shift plotted against electromagnetic flow.

Circles represent Dog 44.
E-M flow recording equipment

In addition, volume blood flow (EM) was monitored using the Statham cannulating electromagnetic flow probe connected to a Statham SP2201 flowmeter. The output from this was recorded on the chart recorder together with the pressure information.

RESULTS

The detailed results from the experiment described in this chapter can be found in Appendix 3. It can be seen that both mean Doppler frequency shift, \( D \) (Figure 11) and mean maximum Doppler shift, \( D_{\text{max}} \) (Figure 12) are approximately linearly related to E-M flow, \( EM \), as would be expected from the Doppler equation:

\[
V = \frac{\Delta f \cdot c}{2 \cdot ft \cdot \cos \theta}
\]

where: 
- \( V \) = flow velocity
- \( \Delta f \) = Doppler frequency shift
- \( c \) = velocity of ultrasound in tissues
- \( ft \) = transmitted frequency
- \( \theta \) = angle between the ultrasound beam and the blood vessel

The points plotted in Figures 11 and 12 are derived from sonograms recorded at resting and hyperaemic flow. It would appear from these results that Doppler frequency shift monitoring can be used to give a
reliable estimate of proportional changes in blood flow during a hyperaemic test, provided that the angle of insonation is constant or known.

Table 5. Symbols used in Chapters 6 and 7

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>D</td>
<td>kHz</td>
<td>Mean Doppler shift frequency over the cardiac cycle.</td>
</tr>
<tr>
<td>Dmax</td>
<td>kHz</td>
<td>Mean of the maximum Doppler shift frequency over the cardiac cycle.</td>
</tr>
<tr>
<td>EM</td>
<td>l/min</td>
<td>Volume blood flow measured using an electromagnetic flowmeter</td>
</tr>
<tr>
<td>P</td>
<td>mm Hg</td>
<td>Pressure drop across the stenosis or vessel segment.</td>
</tr>
<tr>
<td>ΔP</td>
<td>mm Hg</td>
<td>Increase in the pressure drop across the stenosis, or vessel segment, which occurs between resting and maximal flow.</td>
</tr>
<tr>
<td>ΔVmax</td>
<td>m/s</td>
<td>Increase in the mean maximum flow velocity between resting and maximum flow.</td>
</tr>
<tr>
<td>Gpf</td>
<td>mm Hg/m/s</td>
<td>P/Vmax</td>
</tr>
<tr>
<td>ΔGpf</td>
<td>mm Hg/m/s</td>
<td>ΔP/ΔVmax</td>
</tr>
</tbody>
</table>
Figure 13. DOGS: Pressure drop across the stenoses during peak hyperaemia plotted against % diameter reduction.

Circles represent Dog 44.
Figure 14. DOGS: Electromagnetic flow through the stenoses during peak hyperaemia plotted against % diameter reduction.

Circles represent Dog 44.
Figure 15. DOGS: Pressure drop across the stenoses during peak hyperaemia divided by the electromagnetic flow at that time, plotted against % diameter reduction.

Circles represent Dog 44.
The pressure drop across the stenosis during hyperaemia, $\Pi$, is plotted against percentage diameter stenosis in Figure 13. The value of $\Pi$ rises as the degree of stenosis increases. There is considerable variation in pressure drop recorded for each stenosis, which is particularly marked for the tighter stenoses. As a result there is considerable overlap of values recorded for different stenoses and this increases with increasing degree of stenosis. None of the pressure drops, $\Pi$, recorded for the tightest stenosis (78%) exceed the highest drop for the previous stenosis (72%). The results for Dog 44 are widely scattered among those for the rest of the animals. Figure 14 shows the corresponding results for flow during hyperaemia. Again there is considerable scatter but this gets less with increasing stenosis.

If the pressure drop at hyperaemia, $\Pi$, is divided by the volume flow, $EM_i$, an estimate of stenosis resistance at incremented flow is found. This is plotted against percentage diameter stenosis in Figure 15. The degree of scatter is reduced and the results for Dog 44 now lie in a separate curve from those of the other animals. Considering all animals except Dog 44 there is no overlap of values for stenoses $>50\%$. Now that flow is known, values for the 78% stenosis are widely separated from those recorded for the 72% stenosis. Thus the reason that the pressure drops recorded for the 78% stenosis were not greater than those for the 72% stenosis is that flow is limited by increasingly severe stenosis and is in fact less for the 78% than for the 72% stenosis. Consequently to achieve good separation and characterisation of stenoses, both pressure drop and flow must be taken into account.
Figure 16. DOGS: Pressure drop across the stenoses during peak hyperaemia divided by the mean of the maximum Doppler shift at that time plotted against % diameter reduction.

Circles represent Dog 44.
Figure 17. DOGS: The increase in pressure drop across the stenoses caused by hyperaemia, divided by the increase in the mean of the maximum velocity plotted against % diameter reduction. Circles represent Dog 44.
In the pre-operative study of the vascular patient, the artery is not exposed and E-M flow measurement cannot be used. Instead it is necessary to rely on transcutaneous Doppler signals. Figures 16 and 17 show the results, in the canine model, when Doppler blood flow information was combined with pressure information. Figure 16 shows pressure drop $P_i$ divided by the mean maximum flow velocity at hyperaemia $V_{\text{maxi}}$ plotted against percentage diameter stenosis. The values of $V_{\text{maxi}}$ are obtained simply from $D_{\text{maxi}}$ by inserting the insonation angle (held constant at 45 degrees) into the Doppler equation (see page 77). The values of $P_i/V_{\text{maxi}}$ provide a measure of the stenosis resistance or gradient of the pressure-flow curve, which we shall refer to as $C_{pf}$. The degree of overlap and scatter are again reduced compared with pressure drop alone (Figure 16 cf Figure 15) but the improvement is somewhat less than using E-M flow information. Nonetheless there is an increase in the accuracy of classification of stenoses.

Flow velocity information can be combined with pressure drop information in other ways. The increase in pressure drop across the stenosis, $\Delta P$, caused by incremented flow can be divided by the increase in mean maximum flow velocity, $\Delta V_{\text{max}}$, to give a second measure of the gradient of the pressure-flow curve (stenosis resistance) for the stenosis, which we shall refer to as $\Delta G_{pf}$. Figure 17 shows $\Delta G_{pf}$ plotted against percentage diameter stenosis. Again there is improvement in the scatter of values recorded for individual stenoses compared with using pressure drop information alone (Figure 17 cf Figure 15) but the improvement is not as great as using $G_{pf}$ (Figure 16). Results obtained in Dog 44 appear to lie consistently in the lower range.
of results obtained in the other four animals in the case of Gpf. For \( \Delta \)Gpf however, there is no apparent consistency and the results are widely scattered.

**DISCUSSION**

In the canine model stenoses of known geometry were inserted into the aorto-iliac segment. Accurate measurements of pressure above and below the stenoses were made together with the associated blood flow. In this tightly controlled situation pressure drop information alone did not characterise stenoses with sufficient accuracy to allow the narrower stenoses to be adequately separated; nor did volume flow alone at hyperaemia. Dividing the pressure drop at augmented flow by the volume flow (as measured by the E-M flow probe) gives a value for the resistance of the stenosis. This value gives a more accurate measure of stenosis severity.

Doppler mean frequency shift, D, and mean maximum frequency shift, Dmax are shown to give a reliable indication of changes in flow through an arterial segment. Since Dog 44 was larger than the rest and its arteries were of greater diameter, a lower mean flow velocity should have been required to produce a given volume flow. The mean frequency shift and mean maximum frequency shift might be expected therefore to have been considerably lower in this animal than in the rest at each volume flow. Figures 11 and 12 show that Doppler frequency shifts recorded in Dog 44 generally lie in the lower range of values recorded.
in the other animals. The scatter of values recorded in the other dogs however is such that results in Dog 44 do not lie separately from the rest. This scatter is probably due to the variation in arterial dimensions between the rest of the animals. Of the two Doppler frequencies, Dnax is easiest to calculate since it only involves processing the maximum frequency envelope rather than the complete sonogram. Dnax is also more reliable since it is less susceptible to minor deviations of the probe axis from the vessel axis (see Appendix 2). This is almost certainly because as the Doppler probe is moved transversely away from the longitudinal axis of the vessel the maximum frequency envelope is lost less rapidly than the information under it.

There is no apparent difference between the absolute pressure drops at maximum flow recorded for the larger Dog 44 and the rest of the animals (Figure 13). There is however a lot of scatter in these results. When the scatter is reduced by dividing the pressure drop by the electromagnetic flow, to give the stenosis resistance at maximum flow (Figure 15), the difference is more obvious. Resistances for Dog 44 appear to lie in a separate curve below that for the other animals. Stenosis resistance is not solely a function of \% diameter reduction but is also affected by absolute stenosis dimensions. The energy lost as blood flows through a stenosis (see Chapter 3) is partly due to contraction and expansion which is related to proportional changes in dimensions and partly due to frictional losses of the high velocity flow through the narrow segment which is more closely related to the absolute diameter and length of the stenosis. These considerations are likely to be particularly relevant in human studies where subjects arteries are of
a range of sizes (Callum et al 1983) and where stenoses may sometimes be of considerable length.

Using a measurement of the angle of insonation, mean maximum velocity, $\text{V}_{\text{max}}$, can be derived from $\text{D}_{\text{max}}$. Division of the pressure drop at incremented flow, $\text{P}_i$, by $\text{V}_{\text{maxi}}$ gives $\text{Q}_{\text{pf}}$. Alternatively, using the increase in pressure drop, $\Delta \text{P}$, and the increase in mean maximum velocity, $\Delta \text{V}_{\text{max}}$, caused by incremented flow, $\Delta \text{Q}_{\text{pf}}$ may be derived. In the canine study both $\text{Q}_{\text{pf}}$ and $\Delta \text{Q}_{\text{pf}}$ offered an improvement in the characterisation of stenoses over using pressure drop alone, with $\text{Q}_{\text{pf}}$ being somewhat superior to $\Delta \text{Q}_{\text{pf}}$. When considering these two velocity derived indices, the effect of absolute stenosis dimensions appears more obvious in the case of $\text{Q}_{\text{pf}}$. Here results for the larger Dog 44 are consistently low in the range for the other animals. In the case of $\Delta \text{Q}_{\text{pf}}$ this is not the case but this may be because of the greater scatter of results for this index in the canine model.

It is not claimed that the canine model accurately represents the stenosis of the aorto-iliac segment of the vascular patient. It is recognised that the arterial walls in these two situations differ in their stiffness. Also the number of collaterals in parallel with the stenosis being studied may be dissimilar. In addition, the geometry of the stenoses used in this experiment is very different from that found in vascular disease. The experimental stenoses were symmetrical with sharp corners and a smooth stenosed section.
CONCLUSIONS

The canine model represents a situation where stenosis geometry can be controlled and studied in isolation and provides a sound haemodynamic basis for combining pressure drop and flow velocity information. The velocity derived indices of stenosis resistance appeared to provide an improvement in the characterisation of stenoses and obtaining them does not require any information which is not readily obtainable in the pre-operative study of the vascular patient. It was therefore decided to study these indices in a group of patients with peripheral vascular disease.
Chapter 7

THE FLOW MONITORED HYPERAEMIC TEST IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE

Following initial studies in the canine model, it was decided to assess the flow-monitored hyperaemic test in patients with a wide spectrum of symptomatic peripheral vascular disease.

MATERIALS AND METHODS

Thirty six patients (67 limbs) with various patterns of arterial occlusive disease affecting the legs were studied, usually before but always without knowledge of the results of arteriography. The patients were rested supine for at least 20 minutes in a warm room while a clinical history was taken and an examination performed including palpation of the peripheral pulses. Allen's test (Allen 1929) was performed on the non-dominant hand. If a functionally adequate ulnar artery was demonstrated, the radial artery was cannulated under local anaesthesia using a 20 gauge Teflon cannula (Abbocath). Those patients in whom the radial artery was not considered functional had simultaneous puncture of both femoral arteries so that contralateral femoral pressure could be used to monitor systemic pressure during the papaverine test. They are not included in the data presented in this chapter.
Figure 18. The patient aorto-iliac study.
Figure 19. Sonograms from the patient aorto-iliac study
(a) at resting flow and (b) during hyperaemia induced by papaverine.
Following radial arterial cannulation (P1), a 21 gauge needle was inserted into one common femoral artery (P2) again under local anaesthesia. The external iliac artery was insonated using a hand-held 4MHz Sonicaid Doppler probe and the angle of insonation (between probe and skin) was measured using a protractor.

Doppler sonogram recordings were made at the resting flow rate together with simultaneous radial and common femoral pressure measurements. 20mg papaverine hydrochloride (McCarthy's) was injected via the common femoral needle and at the moment of maximum pressure drop a further series of recordings was made. This procedure was repeated for the contralateral aorto-iliac segment. In general the femoral needles were each in situ less than five minutes and the radial cannula for less than half an hour. No complications have been noted during or following this procedure in any of the patients studied. Figure 18 shows a schematic diagram of the layout of this patient study and Figure 19 shows Doppler recordings made at resting flow and during papaverine induced hyperaemia.

ARTERIOGRAPHY

All the patients underwent single plane arteriography usually using the Seldinger transfemoral route under local anaesthesia. A small number of patients had translumbar aortography under general anaesthesia because their femoral arteries were not suitable for the Seldinger technique.
Measurements were taken from the radiographs. The diameter of the narrowest portion of the aorto-iliac segment was measured together with that of the nearest portion of artery judged to be normal. From these two measurements a percentage reduction of luminal diameter was calculated for the aorto-iliac segment supplying each leg. The arteriographs were evaluated by two observers and a consensus agreement was reached.

RESULTS

Two patients were excluded because air bubbles in the manometer line rendered the radial pressure measurements invalid and two more patients were excluded because their Doppler waveforms were recorded in such a fashion that meaningful analysis was precluded. There were 59 limbs remaining for analysis. The detailed results of the patient studies described in this chapter are given in Appendix 4.
Figure 20. PATIENTS: The % increase in pressure drop at the femoral artery during hyperaemia, plotted against % diameter reduction.
Figure 21. PATIENTS: The pressure difference between radial and femoral arteries at resting flow, plotted against % diameter reduction.
Figure 22. PATIENTS: The pressure difference between radial and femoral arteries at maximal flow, plotted against % diameter reduction.
Figure 20 shows the increase in pressure drop during hyperaemia corrected for variations in systemic pressure and expressed as a percentage of the femoral pressure at resting flow, plotted against stenosis severity. This represents the standard method of interpretation of the papaverine test with the addition of the radial line to eliminate variations in systemic pressure. If a value of 18% is taken to indicate significant disease (Quin et al 1975) there are four limbs out of 17 (23.5%) with radiographic stenosis of >50% diameter classified as not significantly stenosed.

Figure 21 shows the pressure drop between radial and femoral arteries at resting flow, Pr, plotted against percentage diameter stenosis on arteriography and Figure 22 shows the pressure drop between these two arteries following the administration of papaverine, Pi, similarly plotted. If a resting drop of 10 mm Hg or a hyperaemic drop of 25 mm Hg is taken to indicate significant disease (Macpherson et al 1984), there are 5 limbs (29.4%) which have >50% stenosis on arteriography which are classified as having insignificant disease.
Figure 23. PATIENTS: Pressure drop between radial and femoral arteries during hyperaemia divided by the mean maximum flow velocity, plotted against % diameter reduction.
Figure 24. PATIENTS: Increase in pressure drop between radial and femoral arteries during hyperaemia, divided by the increase in mean maximum flow velocity, plotted against % diameter reduction.
These apparent false negatives of the standard papaverine test give cause for concern for they represent lesions which are clearly visible on the radiographs as obscuring at least half the vessel lumen. It is hard to imagine that such lesions are not haemodynamically significant. Less worrying are the apparent false positives of the test (lesions which appear insignificant on arteriography but which are haemodynamically significant). These are easier to explain as false negatives of single plane arteriography and may represent narrowings at right angles to the plane of the radiograph plate (Berne et al 1970).

Doppler flow information can be added as in the canine experimental model. \( Q_pf \) is plotted against percentage diameter stenosis in Figure 23. If a value of 30 mm Hg/m.s\(^{-1}\) is chosen to indicate significant disease, there are two limbs (11.8%) misclassified as insignificantly stenosed when arteriography shows >50% stenosis. Figure 24 shows \( \Delta Q_{pf} \) plotted against percentage diameter stenosis. If a value of 40 mm Hg/m.s\(^{-1}\) is chosen, there is only one limb (5.9%) which has >50% stenosis on arteriography and is classified as not being significantly stenosed. The false negative rate for arteriography as compared with \( \Delta Q_{pf} \) is 15.5% (n=9).
Figure 25. Receiver operating characteristic curves used to compare the diagnostic accuracy of different tests.
Figure 26. PATIENTS: Receiver operating characteristic curves for the standard papaverine test and for $\Delta G_{pf}$. 

- % papaverine drop
- $\Delta G_{pf}$

(4.4-6.5 mm Hg/m-s$^{-1}$)

(20 mm Hg)
Any test which gives a continuous scale of values poses the question of where to choose the cut-off value. To help determine the best cut-off point we may plot the true positives against the false positives of the test using different cut-off values. The resulting curve is known as the Receiver Operating Characteristic (ROC) curve (McNeil et al 1975; O'Donnell et al 1980). From the curve we can find the cut-off point that makes the test as sensitive as possible (ie picks up the most true positives) before the specificity falls (ie the number of false positives rises). The comparison of such curves for different tests (Figure 25) can be used to determine which of the tests is most valuable (ie has the curve lying nearest to the ordinate).

Figure 26 shows a comparison of the ROC curves for the standard papaverine test (where fall in femoral pressure is expressed as a percentage of the femoral pressure at resting flow) and for the values of ΔQpf derived from the pressure drop and Doppler flow data. The curve for ΔQpf lies to the left of that for the standard papaverine test suggesting that it is a better test in the evaluation of aorto-iliac stenoses. At the optimum cut-off points ΔQpf gives a statistically greater sensitivity (p=0.029 Fisher's exact test).

DISCUSSION

In the patient studies the angle of insonation of the vessel by the Doppler probe was estimated using a hand-held protractor to measure the angle between the insonating probe and the skin and the probe itself was
held by hand. This must have introduced considerable errors into the velocity calculations.

In the patients with vascular disease the combination of pressure and flow information improves the characterisation of arterial stenoses as predicted from the canine model. Gpf, when calculated for the patient results, considerably reduces the scatter of the points and the distribution of the points exhibits the same general characteristics (Figure 23) as that of the comparable results in the canine model (Figure 16). The use of $\Delta$Gpf also allows a similar reduction of scatter and in the group of patients studied gives the best results in terms of misclassifying least of the patients with significant stenoses on arteriography.

In the canine model Gpf gave better results than $\Delta$Gpf while the converse is true in the patient studies. The probable reason for this lies in the sources of error in pressure measurement present in the two situations. In the canine model the pressure drops across the stenoses are accurately known, and combining two pressures and two flow velocities to derive $\Delta$Gpf is likely to increase the proportional errors. In the patient study the pressure drops themselves are not as accurately known since measurement of the systemic pressure is taken at the radial artery. However, if the error in the systemic pressure remains relatively constant at incremented flow, then subtraction of $P_r$ from $P_i$ will give a reasonably accurate value of $\Delta P$ and consequently it is likely that $\Delta$Gpf will give a more accurate indication of stenosis severity than Gpf.
Given that Vmax, which is derived from Dmax, is linearly related to volume blood flow, then the parameters Gpf and ΔGpf are both estimates of, or rather related to, the gradient of the pressure-flow curve (stenosis resistance). The pressure-flow curve is non-linear (though the degree of non-linearity need not necessarily be striking) and since Gpf and ΔGpf are each calculated using different portions of this curve, they represent estimates of the gradient averaged over different flow ranges. In the patient results the mean increase in Vmax following the administration of papaverine was 204% (range 23% to 547%). On average, Gpf extends over an extent of the flow curve greater by a factor of 1.49 \((\frac{1+2.04}{2.04})\) than does ΔGpf. As explained above, the superiority of ΔGpf in the patient results is believed to be due to the smaller error in ΔP.

The use of the radial artery cannula to monitor pressure above the stenosis allows quantification of the pressure drop across the stenosis in mm Hg and also provides a continuous record of the systemic pressure. It has been shown to be a simple and safe procedure for diagnostic studies (Barr 1961). In a study of the complications of needle puncture and cannulation of various arteries, there were no major complications after puncture of the radial artery for pulse pressure studies in 120 patients (Mortensen 1967). More recently Bishop and Payne (1983) found among 50 patients studied, only 5 with small areas of bruising and one patient with transient pain in the thumb and forefinger. Approval was obtained from the hospital ethical committee for this procedure before the beginning of the study.
The patients' arteriographs were measured in a single plane. No attempt was made to estimate the additive effect of stenoses in series or the contribution of collateral vessels to limb blood flow. Consequently the geometry of the stenosis being studied in the patients is much less accurately known than in the canine model.

It must be emphasised that throughout the interpretation of the patient studies single plane arteriography had to be used as a "gold standard". The aim of the work presented in this chapter was to improve on the papaverine test which itself has been instrumental in showing the inadequacy of single plane arteriography and perhaps should be considered the "gold standard" for the aorto-iliac segment. The aim therefore was to improve on the reigning gold standard and show an improvement by comparing the relative efficacy of two haemodynamic tests against a third investigation (ie arteriography) which is known to be worse than either. It is difficult to show that improvements have been made but ROC curve analysis is useful in this respect. The curves show the most useful cut off points for both the standard papaverine test and $\Delta G_{pf}$ in the group of patients studied (Figure 24). At the optimum cut-off points $\Delta G_{pf}$ gives a statistically greater sensitivity.

The accuracy of stenosis grading using pressure drop and maximum flow velocity could probably be improved by the use of a Duplex scanner to monitor volume flow. These machines have the advantage of providing accurate measurement of the angle of insonation and an estimate of the cross-sectional area of the vessel at the point of insonation so that volume flow can be calculated. Such a machine was not locally available.
at the time of this study.

CONCLUSIONS

Monitoring flow increases during the papaverine test together with intra-arterial pressure measurement above and below the stenosis allows the estimation of stenosis resistance. Indices of resistance provide a useful estimation of stenosis severity and improve the characterisation of aorto-iliac arterial stenoses. The improved papaverine test employing both flow monitoring and radial artery pressure measurement confirms that single plane arteriography does not show all haemodynamically significant lesions in the aorto-iliac segment.
In the presence of combined segment disease, proximal reconstruction alone may provide symptomatic relief if the aorto-iliac disease is significant and the distal disease is relatively insignificant.

Bone and his colleagues (1976) showed that if pre-operative thigh pressure index (TPI) was <0.85, all patients were improved by proximal reconstruction regardless of the run-off. If TPI was >0.85 only 63% were improved. This would seem to be reasonable as one would not expect good results to follow proximal reconstruction if the proximal component of the disease is not haemodynamically significant. O'Donnell's group (1979), however, found that thigh pressure had no predictive value. Verhagen and van Vroonhoven (1984a & b) measured common femoral artery pressure by direct needle puncture at resting flow and also during reactive hyperaemia. They defined haemodynamically significant disease as a femoral/brachial index of <70% at rest or a fall of >20% with hyperaemia. Proximal reconstruction was successful in all patients with positive femoral artery pressure studies but 5 of 8 patients with negative studies were not improved by proximal reconstruction.

In the preceding three chapters the assessment of the aorto-iliac segment has been discussed and a haemodynamic test has been described
for determining its severity. Such a test should prevent proximal reconstruction being performed for disease which is not haemodynamically significant. Where the aorto-iliac component is significant, however, the success in terms of symptomatic relief that may be expected following proximal reconstruction depends on the severity of the distal disease which will remain. To predict the chance of success or failure therefore, it is necessary to assess both aorto-iliac and femoro-popliteal haemodynamics.

Although less work has been reported on femoro-popliteal than aorto-iliac haemodynamics, several methods have been described. They may be conveniently divided into those depending primarily on pressure measurement and those related to flow.

**Pressure methods**

As long ago as 1950, Winsor used a pneumoplethysmographic technique to measure systolic blood pressures in the lower limb and he emphasised the significance of resting systolic pressure gradients in the presence of peripheral arterial disease. Hocken, in 1967, attempted to measure occlusion cuff pressure at the ankle by auscultation over the pedal pulses in a manner similar to the standard method for measuring brachial pressure. He reported a failure rate of 10% in obtaining Korotkoff sounds in normal individuals. Yao and his colleagues, in 1969, popularised the Doppler method for measuring resting ankle systolic pressure. In this technique, an occlusion cuff is applied immediately above the ankle and inflated to a pressure greater than systolic. The
cuff is then slowly deflated and systolic pressure is signalled by the return of pulsatile flow in the pedal artery monitored by the Doppler probe. They divided the ankle pressure by the brachial pressure, measured in the same way, to provide an ankle systolic pressure index (API). In normal individuals, this index is greater than or equal to unity while in patients with arterial disease it is generally less than one. In patients undergoing reconstructive arterial surgery an increase in the ankle pressure index indicates a successful operation.

In 1970 Yao described the effect of treadmill exercise on the ankle pressure. In the presence of arterial disease, the ankle pressure falls with exercise and the length of the recovery time is related to the severity of the disease. Ankle pressure measurements, therefore, provide useful information for the diagnosis of arterial disease and subsequently it has been shown that the absolute values relate to the patients' symptoms. Eikhoff and Engell (1980) have shown that a blood pressure gradient of more than 20 mm Hg from arm to ankle has a high diagnostic accuracy as a screening procedure for arterial disease. A toe blood pressure of <30 mm Hg has a high diagnostic accuracy in deciding whether constant pain is in fact ischaemic rest pain.

Dean and his colleagues (1975) reported that the results of femoro-popliteal reconstruction are related to the pre-operative ankle pressure index in that if the index is less than 0.20, 91% underwent early thrombosis. Corson and his co-workers (1978), however, found that neither early or late graft failure was related to pre-operative ankle pressure in their hands. Some authors have reported differing results
in the presence of aorto-iliac and femoro-popliteal lesions (Chamberlain et al 1975). Pre-operative measurements of ankle pressure, however, do not have any predictive value for assessing the likelihood of symptomatic relief after proximal reconstruction in the presence of combined segment disease (O'Donnell et al 1978). Satiani and his colleagues (1980) showed that the pre-operative ankle pressure index of a group in whom subsequent distal bypass was necessary, following proximal reconstruction, was not significantly different from that of a group who did not require additional distal surgery.

Several groups have measured the change in ankle pressure following proximal reconstruction. Garrett and his co-workers (1977) showed that in 47 of 52 successful proximal reconstructions API increased by >0.1. In 8 patients, who showed some improvement, API increase ranged from 0 to 0.1, while in 11 with no improvement there was no API increase and in fact API often decreased. They recommended, on the basis of these results, that if the intra-operative increase in API is <0.1 following proximal reconstruction, then distal bypass should also be performed. O'Donnell and his colleagues (1978) also concluded that intra-operative ankle pressure is helpful in predicting the results of proximal reconstruction. They point out that the change in API that can be expected depends on the presence or absence of superficial femoral disease. This is however, usually known pre-operatively from arteriography. Bone et al (1976) found that if the API is increased by <0.1 following aorto-femoral bypass in combined segment disease this implies that symptoms will not be relieved. This conclusion was supported by Satiani et al (1980). Sumner and Strandness (1978) on the
other hand found that measurement of API in the recovery room was no help in predicting the results of proximal reconstruction. They criticised Garrett's group (1977) and pointed out that 54% of Garrett's cases, showing an increase in API <0.1, did in fact gain some symptomatic improvement following proximal reconstruction. Kozloff and his colleagues (1980) showed a prompt increase in API post-operatively in patients with a patent superficial femoral artery and stated that if such a prompt increase does not occur in such patients then this implies technical failure and is an indication for re-exploration. In patients with occluded superficial femoral arteries, however, the situation is more complex since the expected rise in API takes at least 3 hours. Other groups have also noted this delay in the API rise (Yao et al 1969; Bone et al 1976; O'Donnell et al 1978). Baird and his colleagues (1977) showed that API may continue to rise for 2 to 3 days and more recently Hesselfeldt and his co-workers (1983) have shown that API may not reach its final level till more than 10 days post-operatively.

Although ankle pressure measurement gives some idea of the extent and severity of disease, it represents the fall in pressure across all segments of the limb and therefore does not provide any information on the location of disease responsible for a low measured pressure. Some idea of the site of the disease can be provided by the measurement of systolic pressures at several levels down the limb so that segmental pressure gradients can be calculated. Winsor (1950) in his original report had measured pressure at four levels using a plethysmograph. Strandness and his colleagues (1961) reported the use of a simplified plethysmograph to provide segmental pressure information.
Several methods of measuring segmental pressure are now practised. These differ mainly in the method used to detect the onset of flow on deflation of the occlusion cuff. The majority of groups use the Doppler method (Allan & Terry 1969; Cutajar et al. 1973) or a mercury in rubber strain gauge applied to the big toe (Strandness & Bell 1965) and Carter has reported the use of capacitance pulse pickups applied over the pedal arteries (Carter 1968; Carter & Lezack 1971). However they are obtained, segmental occlusion cuff pressures at rest provide useful localising information. Allan and Terry (1969) used a Doppler flow detector to obtain segmental pressures in 50 patients in a manner directly comparable to the method used by Yao to measure ankle pressure. They used a 12 cm cuff at the ankle, calf, above-knee and high-thigh levels and compared the results in 66 limbs with the appearance on arteriography. All the segmental pressures were expressed as differences from the brachial pressure and they found total agreement in 57 of the limbs. They stated that in every limb a reliable indication of the blood supply was obtained. Cutajar and his colleagues (1973) used a narrow (10 cm) thigh cuff and also measured calf and ankle pressure using the Doppler technique. They expressed all their results as brachial indices and found good correlation with arteriography even for the thigh cuff values (see Chapter 5). Bell and his colleagues (1973) used the strain gauge technique and measured thigh, calf and ankle pressure with an 18 cm cuff. They only studied 30 limbs in 16 patients but found good correlation between pressure measurements and arteriography including the thigh cuff measurements. They plotted their results as graphs, producing one line for each limb, as Winsor had done. This allows easy and rapid interpretation of the results in each
Colt (1978) also advocated plotting the results as curves, though the curves he proposed are more complex and interpretation less simple.

Leaving aside the potential inaccuracies of the thigh cuff, which are discussed more fully in Chapter 5, errors may still occur using occlusion cuffs at more distal levels. Siggaard-Andersen and his colleagues (1972) showed that the above knee to ankle pressure gradient correlates well with the state of the crural arteries on arteriography. They discussed possible errors due to incompressibility of arteries particularly in diabetic patients but they did not encounter the problem in the 34 patients they studied. Colt (1978) encountered calcified incompressible arteries in the groin and also incompressible tibial arteries in diabetics. In both instances he had no difficulty in recognising the problem since unphysiological pressures (300 mm Hg) were applied without cessation of flow. Nonetheless it is conceivable that lesser degrees of wall stiffening might lead to falsely high occlusion pressures being recorded without the contribution of the wall stiffness being recognised (Fronek et al 1978). This would result in underestimation of the disease present and is particularly likely to produce unreliable results in diabetic patients.

Bollinger and his co-workers (1976) performed intra-arterial pressure measurements in foot arteries of normal individuals and patients with arterial occlusive disease. They used steel micro-needles with a lumen diameter of 76 microns together with a micro-manometer technique. When they compared the results with those obtained
non-invasively using an ankle occlusion cuff and the Doppler method, they found good overall correlation. Although none of the patients was reported to be diabetic, one of the 13 with arterial disease had diffuse "pipe-stem" vascular calcification on radiography and in this patient's case and also in one other the Doppler method greatly overestimated the systolic pressure.

Recently there has been controversy over the general reliability of segmental pressure measurements. Kiekara and his co-workers (1985) have correlated lower limb systolic pressure ratios in a series of 62 patients with intermittent claudication with the angiographically determined reduction of vascular lumen. They found a statistically highly significant, though not particularly close, correlation for ankle/brachial and thigh/brachial pressure ratios using 12 cm cuffs. In 1978 Heintz and his co-workers reported the use of proximal and distal narrow thigh cuffs to differentiate aorto-iliac and superficial femoral disease. They only studied 7 patients with each disease pattern but showed that disease localisation was improved in spite of the artificially high pressure readings. In 1981 Reidy and her colleagues, using a 3-cuff system, were able to diagnose superficial femoral disease in 90% of cases overall. All the cases with aorto-iliac but no superficial femoral disease were correctly diagnosed but only 67% were diagnosed in the presence of combined disease. Lynch and his co-workers (1984), correlated Doppler segmental pressure results and arteriography in 345 aorto-iliac and 326 femoro-popliteal segments using proximal and distal narrow (8 cm) thigh cuffs as well as calf and brachial cuffs. They stressed the problems of diagnosing aorto-iliac or superficial
femoral disease in the combined situation. Their results showed a 97% sensitivity for aorto-iliac and 67% sensitivity for femoro-popliteal disease. The accuracy in each instance was affected by associated disease in the other segment. The sensitivity to haemodynamically significant femoro-popliteal disease was 89% without associated aorto-iliac disease but only 55% if significant proximal disease was present. In the presence of significant superficial femoral disease, the specificity for the absence of aorto-iliac disease fell from 70% to 41%. In spite of the possible inaccuracies, a recent survey of "vascular technologists" revealed that ankle pressure and segmental pressure measurements were the most common methods used to assess patients in the vascular laboratories of the USA (Beach et al 1982).

Bone and his colleagues in 1976 assessed the haemodynamic significance of distal lesions using segmental pressures. He found that segmental pressures were more predictive than radiography alone. All patients with no abnormal distal pressure gradients were improved after proximal reconstruction including 5 who had lesions visible on arteriography. Of 25 with one abnormal gradient 19 were improved and of 7 with two abnormal gradients only 2 were improved. Boren and his co-workers (1980) derived a profundapopliteal collateral index by subtracting the below-knee from the above-knee systolic pressure and dividing the result by the above-knee pressure. They showed that, in patients with superficial femoral occlusion, if this index was low profundaplasty gave good results, while when it was high, a successful result was less likely.
Segmental systolic pressures using direct femoral artery pressure measurements can be used predictively by assuming that the proximal gradient to the level of the common femoral artery will be completely corrected by proximal reconstruction and that the distal pressures will rise in proportion to the rise in femoral artery pressure (Noer et al 1978; Paris et al 1982). In this way the final expected distal pressures can be calculated and if these values reach the necessary levels distal reconstruction should not be necessary. This group, working in Copenhagen, has advocated the use of direct pressure measurement in the popliteal as well as the femoral artery (Agerskov et al 1983; Tonnesen et al 1983) to improve accuracy in this technique and overcome the problem of stiff arteries in diabetics. Although direct pressure measurement has been widely adopted at the groin, it seems to have been less widely accepted at the knee. This may be because it is technically more difficult in the popliteal artery and the risks may be greater in this smaller diameter vessel.

In addition to the absolute values of systolic pressure at various levels down the leg, the pulse wave contour can also be studied using a plethysmograph or pulse volume recorder (Strandness & Bell 1961; Darling et al 1972). Carter (1968) was also able to perform similar studies with capacitance pulse pickups. Pulse volume measurements are particularly useful when taken together with segmental occlusion pressures (Raines et al 1976). O'Donnell in 1979 derived a pulse volume recorder index which had a predictive value for failure of 100% (in 6 cases) and a 66% chance of predicting success of proximal reconstruction (11 of 16 cases). Rutherford and his colleagues (1979) combined the
4-cuff segmental pressure technique with pulse volume recordings in 69 limbs and showed a 97% accuracy in the diagnosis of aorto-iliac and superficial femoral artery disease compared with arteriography. This represented an improvement on 86% accuracy using segmental pressure or pulse volume recorder alone. Francfort and his co-workers (1984) used 4 cuffs and achieved a sensitivity for aorto-iliac disease of 96% when no superficial femoral disease was present. In this situation 4 cuffs gave no better results than three. In combined disease however 4 cuffs gave a sensitivity for aorto-iliac disease of 100% and a specificity for a normal aorto-iliac segment of 76% which was significantly better than using three cuffs. Plethysmography alone was the most sensitive method for superficial femoral disease in this study and gave a sensitivity of 90% even in the presence of aorto-iliac disease and was not improved by the addition of segmental pressure information.

**Flow Measurement**

As in the aorto-iliac segment, it is relatively simple to measure flow at operation using an electromagnetic flowmeter applied directly to the exposed artery. Mundth and his colleagues in 1969 reported intra-operative flow and pressure measurement at the time of femoro-popliteal bypass. They calculated peripheral resistance but did not find that this correlated with graft patency. Terry and his co-workers (1972) measured post-reconstruction flow and found that this correlated with patency at twelve months. Bliss (1971) measured both pressure and flow at operation and calculated peripheral resistance. In 1973 he showed that low flow was associated with marked tibio-peroneal
disease and that such measurements could be used to detect technical errors at the end of the bypass procedure. Dedichen and his colleagues (1973) also advocated peroperative measurements for this purpose.

In 1975 Dean and his co-workers confirmed that electromagnetic flow at operation provides a prognostic indicator of graft failure. Corson and his colleagues (1978) showed that a flow of <70 mls/min implied a high chance of graft failure. More recently Parvin and his colleagues (1985), in Leicester, have shown that peripheral resistance measurements are related to disease severity, angiographic assessment of run-off and also graft patency.

Cave and his co-workers (1976) used intra-operative pressure and flow measurements to calculate hydraulic impedance. They found that it was not possible to predict the result of femoro-popliteal bypass using these measurements. Law and his colleagues (1983) showed that hydraulic impedance measurements post-bypass were a useful method of assessing the success of aorto-iliac reconstructions. There was a similar trend for femoro-popliteal reconstructions but the results were equivocal.

Preoperative measurement of flow, however, is more difficult. As mentioned in chapter 5, plethysmography provides a measurement of limb blood flow but does not give segmental information. Some segmental information may be obtained with radiolabel clearance studies. Mannick and his co-workers (1966) measured calf muscle blood flow using sodium 131-I clearance. Measurements made before and after femoro-popliteal bypass (in 6 patients) correlated with intra-operative pressure and flow
measurements. Lewis and his colleagues (1972) used a similar method (133-Xe clearance) to measure flow in patients with intermittent claudication. They found that the method gave a good objective assessment of the extent of disease. Angelides and Nicolaides (1980) used 99-Tc clearance in the thigh and the calf muscles simultaneously and reported good correlation with arteriography even in patients with combined segment disease.

A good deal of work has been reported using Doppler waveforms at the common femoral and popliteal arteries. Yao and his colleagues, in 1968, examined Doppler waveforms at the ankle in patients with arterial disease. They noted that when the superficial femoral artery was occluded the waveform was damped; there was a slower acceleration to a lower peak and reverse flow was absent. Allan and Terry (1969) used auditory assessment together with visual interpretation of the Doppler waveforms to complement Doppler segmental pressures.

In 1971 Gosling's group at Guy's Hospital produced an objective method of interpreting the change in Doppler waveforms between the common femoral and popliteal arteries (FitzGerald et al 1971). This involved the use of two Doppler probes simultaneously, one at the groin and the other behind the knee. They measured the transit time (TT) from the onset of flow in the femoral artery to the onset of flow in the popliteal artery (Figure 29). They also calculated the pulsatility index (PI) at each site. This was defined as the peak to peak excursion of the waveform divided by the mean (Figure 30). Pulatility index damping factor (DF) was then calculated by dividing the common femoral
PI by the popliteal PI. They showed that these two indices increased as limb perfusion, measured by strain gauge plethysmography, decreased (Woodcock et al 1972). Fronek and his co-workers (1973a) derived several indices, including rise time (RT-see Figure 29) from Doppler waveforms recorded at the groin and the ankle but did not examine popliteal waveforms. Harris and his colleagues (1974) recorded Doppler waveforms from the femoral and popliteal arteries and simultaneously recorded the electrocardiogram. They compared the pulsatility index and the pulse wave velocity at the popliteal artery with arteriography. They related popliteal PI to the angiographic appearance but before doing this excluded limbs with a low femoral PI so that patients with combined disease were not considered. The femoro-popliteal pulse wave velocity was significantly lower than normal in limbs with an occluded superficial femoral artery. Angelides and his co-workers (1977) reported that pulsatility index damping factor for the femoro-popliteal segment is not affected by aorto-iliac disease. Craxford and Chamberlain (1977) attempted to increase the usefulness of transit time measurements by eliminating the effects of age and vessel wall compliance. They suggested the use of the transit time ratio between the time from the ECG R-wave to a point half way up the upslope of the waveform at the ankle to the corresponding time for the waveform at the groin (Figure 29). Waters and his colleagues (1977) proposed an even more complex index which they called the proximal damping quotient (PDQ). This was defined as the interval between the ECG R-wave and the peak of the maximum frequency waveform divided by the interval between the ECG R-wave and a point halfway up the upslope of the waveform (Figure 29). They examined this index for the common femoral waveform
only.

Subsequent reports have largely concentrated on transit time and pulsatility index damping factor. Johnston and his co-workers (1978) studied transit time and inverse damping factor and showed that severe disease could be localised and quantified. Gosling and King (1974) recommended that transit time should be normalised according to systemic arterial blood pressure which gave increased accuracy. They plotted results for transit time on the abscissa and damping factor on the ordinate and showed clustering of normal results near the origin with increasingly diseased vessel segments tending to lie increasingly further away. Humphries and his colleagues (1980) confirmed these findings and also studied rise time ratios. The rise time ratio was defined as the ratio between the rise time at the popliteal artery divided by the equivalent time at the common femoral artery. They concluded that rise time ratios were simpler to measure than the more commonly used parameters and were at least as sensitive in distinguishing between severe disease and mild disease or normal. None of them, however, was sensitive enough to distinguish between mild to moderate disease and normal.
Figure 29. Definition of Transit Time, Transit Time Ratio, Rise Time Ratio and Proximal Damping Quotient.

Transit Time = BE

Transit Time Ratio = AC/AF

Rise Time Ratio = EG/BD

Proximal Damping Quotient

Femoral = AD/AC

(Popliteal = AG/AF)
Figure 30. The definition of Pulsatility Index (a) in the presence and (b) in the absence of reverse flow.

\[ PI = \frac{\text{Maximum excursion}}{\text{Mean}} \]
Aukland and Hurlow (1982) studied transit time and damping factor and found significant differences in damping factor for three categories of disease: <50% stenosis or normal, >50% stenosis, and occlusion. Transit times were not significantly different for the two grades of stenosis but were significantly longer in the presence of superficial femoral occlusion. They did not normalise the transit times according to systemic blood pressure. When they excluded significant aorto-iliac disease, however (thus removing patients with combined segment disease from the analysis), there was a significant difference between patients with the two grades of stenosis.

More involved methods of interpreting Doppler waveforms have been described. These are based on complex mathematical models of the arterial system. Morris and his colleagues (1975) described the impulse response of a vessel segment, which depends on transfer function modelling of the arterial system. The input and output waveforms are considered for the vessel segment and the mathematical operation "performed" by the segment on the input waveform to obtain the output waveform is derived and the resulting curve analysed. They reported initial results in five patients with arterial disease using visual interpretation of the impulse response waveform (Woodcock et al 1975). The results in six normals, six patients with vascular disease and six patients with "early vascular disease" were reported in 1978 (Brown et al 1978). This involved Doppler recordings at the common femoral and popliteal arteries.

Laplace transform damping was developed from the impulse response
The blood velocity/time waveform is transformed into the frequency domain and then described in terms of a third order equation. The coefficients of the equation are related to lumen size (δ), arterial elasticity (ω₀) and peripheral impedance (γ). The δ coefficient has been applied with some success in the aorto-iliac segment (see Chapter 5). In 1980 Skidmore and Woodcock described a Laplace transform based method for analysing waveforms recorded at the posterior tibial artery. They showed that at this site in normal individuals the equation has two complex and one real pole. In occlusion of the superficial femoral artery, however, all three poles are real. In 1983 Campbell and his colleagues reported the use of ω₀ gradient between the common femoral and ankle vessel waveforms in diagnosing femoro-distal disease. The calculation of ω₀ requires a pair of complex poles in the solution to the Laplace transform equation. They found that ω₀ gradient was superior to pulsatility index damping factor in the diagnosis of femoro-distal disease, including both stenosed and occluded vessels.

However both Evans and his colleagues (1981) and more recently, Law and his co-workers (1984) have called into question the validity of the transfer function model in the lower limb, largely on the grounds that it is greatly affected by peripheral resistance.

Relevance of Simultaneous Pressure and Flow Measurement

Pressure and flow have been measured together in the femoro-popliteal segment at operation as discussed above (Mundth et al 1969; Bliss 1973;
Dedichen et al 1973; Cave et al 1976; Law et al 1983; Parvin et al 1985). These measurements can be used to calculate peripheral resistance (Bliss 1973; Parvin et al 1985) or hydraulic impedance (Cave et al 1976; Law et al 1983). Preoperatively, however, simultaneous measurement of both pressure and flow is not usually possible. This is because the method usually used to measure pressure, i.e. the occlusion cuff, necessarily results in cessation of flow during the measurement. The Copenhagen group, using femoral and popliteal artery puncture, could do this but have not reported such studies to date.

There have been, however, several attempts to relate pressure and flow measurements. Sumner and Strandness (1969) measured resting ankle pressure and calf flow. They found that resting flows were usually normal in the presence of arterial disease and consequently resting pressure drop gave a better index of disease severity than resting plethysmographic flow. Post-exercise pressure/flow patterns, however, correlated well with the severity and extent of disease. Lewis and his colleagues (1972) obtained similar results. Fronek and his co-workers in 1978 combined segmental pressures and Doppler derived flow indices. They concluded that the addition of quantitative flow indices improves the reliability of diagnostic decision making. Breslau and his colleagues in 1981 combined strain gauge plethysmography and ankle systolic pressure measurement. They found that the combination was not helpful in predicting the level and degree of disease. Only superficial femoral disease was more correctly identified by adding flow to pressure. This disappointing result may well have occurred because they only measured pressure at the ankle.
Pre-operative toe pulse reappearance time is an indicator of the overall severity of the vascular disease affecting the limb. Bernstein and his co-workers (1981) have shown that it may have some predictive value. This is contrary to what one would expect since ankle pressure provides the same information, i.e., an indication of overall disease affecting the leg (Fronek et al. 1977).

**Conclusions**

Many different haemodynamic methods have been applied to the femoro-popliteal segment. The simultaneous measurement of pressure and flow pre-operatively is technically difficult and likely to be associated with unjustifiable risks. No agreement exists on the most useful method in this segment. For these reasons a comparison of the various methods described was thought to be useful. This was performed initially in a canine model and further studies were then undertaken in a group of patients with peripheral vascular disease.
Chapter 9
A CANINE MODEL OF THE FEMORO-POPLITEAL SEGMENT IN COMBINED SEGMENT DISEASE

It was decided to assess both pressure and Doppler methods in an animal model of the femoro-popliteal segment in combined segment disease. The aims of these experiments were to compare different methods of quantifying changes in Doppler waveforms, to relate these to changes in pressure and flow and to study pressure drops in the presence of two stenoses in series.

MATERIALS AND METHODS

Four adult dogs weighing between 23 and 31 kgs (Table 6) were anaesthetised and ventilated in the same way as for the experiment described in Chapter 6. Anaesthesia was supplemented with a continuous infusion of Fentanyl/Fluanisone (Hypnorm - Janssen) plus bolus injections of Etorphine/Methotrimeprazine (Small Animal Immobilon - C.Vet) as previously. The animals were monitored as in the earlier experiment. The abdomen was opened using a midline incision which was extended across the right inguinal ligament and down the right leg. The abdominal aorta, the right iliac and femoral arteries were dissected and displayed. The left femoral artery was also exposed through a separate incision immediately
below the inguinal ligament.

Table 6. Dogs used in the femoro-popliteal experiment

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Sex</th>
<th>Weight (kgs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>F</td>
<td>29</td>
</tr>
<tr>
<td>49</td>
<td>M</td>
<td>30</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>23</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>31</td>
</tr>
</tbody>
</table>

The small branches from the back of the abdominal aorta were dissected and tied off. A snare stenosis was passed around the abdominal aorta and proximal to this a Carolina 8mm diameter cuff electromagnetic flow probe (Q1) was applied to the aorta to measure flow through this stenosis. A small proximal branch was cannulated with a 20 gauge Medicut cannula to allow measurement of proximal (systemic) pressure (P1). The animal was then heparinised and a stenosis assembly (Figure 8) was tied into the right femoral artery. In this series of experiments, B-series stenoses were used throughout, in spite of the size range of the animals, in order to avoid scatter of results due to absolute stenosis dimensions (see Chapter 6). Pressure was measured proximal (P2) and distal (P3) to this stenosis using cannulae tied into small branches as previously. Flow through this distal stenosis was measured using a Statham 4mm
Diameter cannulating electromagnetic flow probe (Q2) tied into the femoral artery distal to the stenosis assembly. The left iliac and femoral arteries remained uncannulated and unstensonized. All the branches between the aortic snare stenosis and the cannulating E-M flow probe were tied off with the exception of one moderate sized deep femoral branch between the aortic and femoral stenoses. This was left patent to simulate the profunda femoris artery. It was intermittently clamped in order to show the effects of collateral flow on femoro-popliteal haemodynamic studies.

Doppler recordings were made using an 8MHz probe at three sites:

A. right femoral artery distal to the aortic but proximal to the femoral stenosis
B. right femoral artery distal to both stenoses
C. left femoral artery distal to the aortic stenosis but with no distal stenosis.

At each site, the probe was held rigidly in a clamp at 45 degrees to the longitudinal axis of the vessel. Recordings were made at site A both with and without the collateral vessel clamped.
Figure 31. The canine femoro-popliteal experiment.
Figure 31 shows the general layout of this experimental model. Once the surgical manoeuvres had been completed, the preparation was allowed to stabilise for a period of half an hour. Stenoses were then inserted into the distal stenosis assembly in random order, first without an aortic stenosis and subsequently with varying degrees of aortic snare applied. All recordings were made at resting flow rate after any hyperaemia due to clamping had settled.

**Pressure monitoring equipment**
The three arterial cannulae were connected to Elcomatic EM 751 pressure transducers as before. Each transducer output was fed through a Gould (130-4615-50) pressure pre-amplifier and the pressure traces were recorded simultaneously on three channels of a Gould Pressure Ink Chart Recorder (Series 2000). For this experiment, mean pressures were used throughout to calculate pressure drops across both stenoses and also stenosis resistances.

**E-M flow recording equipment**
Volume flow was measured using the 8mm non-cannulating EM flow probe (Q1) around the aorta and the 4mm cannulating probe (Q2) tied into the right femoral artery. The aortic probe was connected to a Carolina 601D flowmeter and the femoral probe to a Statham SP 2201 flowmeter. The outputs from these were meaned and recorded on the chart recorder together with the pressure recordings.
Doppler methods

The same hardware was used as in the aorto-iliac experiment (see Appendix 1). In this experiment however, the outline capture program was used rather than the sonogram capture program. At each insonation site, 32 consecutive maximum frequency envelopes were acquired and stored on mini-floppy disk. The two variable time delays (see Appendix 1) were used as timing markers. The first was set to lie immediately before the onset of flow and the second at the point of maximum forward flow. These markers were used to calculate the transit and rise times. Transit Time was defined as the interval from the onset of flow at site A to the onset of flow at site B. Transit Time Ratio was defined as the ratio of the time between the ECG R-wave and the half-upstroke time at site A to the equivalent time at site B. Rise Time Ratio was defined as the ratio of the time between the onset of flow and the maximum forward flow at site B to the corresponding time at site A. Figure 29 shows the definitions of the time indices.

Damping factor was calculated as the ratio of the Pulsatility Index at site A to that at site B. Figure 30 shows the definition of Pulsatility Index in the presence and absence of reverse flow. \( \omega_0 \) was calculated at each site by transforming an ensemble average waveform into the frequency domain and fitting a third order equation to it (Laplace transform equation). The roots of this equation were then found (Skidmore & Woodcock 1980). The calculation of \( \omega_0 \) demands a pair of complex poles in the solution to the Laplace Transform equation. If there were two complex poles for
the waveform recorded at site A and all three poles at site B were real, it was not possible to calculate \( \omega_c \) gradient but this was taken to indicate significant stenosis (Skidmore & Woodcock 1980).

True Transfer function analysis was performed by transforming both proximal and distal waveforms into the frequency domain. Beats of identical length were first selected by the microcomputer. An ensemble average at each site was calculated from these beats and these were transformed into the frequency domain. The transfer function waveform was calculated from this and principal component analysis (Martin et al 1980) was applied to the transfer function waveform as a pattern recognition technique. This method then was different from the Laplace transform method. It was closely related to the impulse response method described in chapter 8 but was improved by the addition of an objective feature recognition technique (principal component analysis) rather than relying on visual interpretation of the resulting transfer function waveforms.
Figure 32. Maximum frequency envelopes from the canine femoro-popliteal experiment

(a) distal to no aortic stenosis
(b) distal to severe aortic stenosis.
Figure 33. Maximum frequency envelopes from the canine femoro-popliteal experiment

(a) distal to no femoral stenosis

(b) distal to severe femoral stenosis
Median values at each site were used for all the various types of waveform analysis except $\omega_0$, gradient and True Transfer Function Analysis. Because of the excessive computation time necessary to calculate $\omega_0$ and derive the transfer function waveform for each of 32 waveforms, both these were calculated using the ensemble average waveform calculated from the selected beats of identical length at each site.

Figure 32 shows maximum frequency envelopes recorded at site A, with and without aortic snare stenosis. Figure 33 shows similar maximum frequency envelopes recorded at site B, with and without a severe femoral stenosis (and no aortic stenosis). These waveforms are comparable to the corresponding waveforms recorded in the patient study (Figures 51 and 52).
Figure 34. Pressure/flow relationships for the aortic snare stenoses. The stenoses are divided into three groups according to their resistances 

(R<7mRU= None, 7<R<38mRU=Mild, R>38mRU=Severe).

Solid squares = No snare applied
Open squares = Snare applied
RESULTS

The detailed results of the experiments described in this chapter are tabulated in Appendix 5. It was not possible to measure the geometry of the aortic stenoses accurately; they were therefore characterised haemodynamically. Figure 34 shows pressure drops across the aortic snare stenosis (P1-P2) plotted against aortic flow as measured by the non-cannulating EM flow probe (Q1). Using this measurement of stenosis resistance, the aortic stenoses have been characterised and divided into three groups according to their severity (No effective stenosis = R<7mRU, Mild stenosis = 7<R<38mRU, Severe stenosis = R>38mRU). There are eight instances where the snare had been tightened around the aorta but resistance measurements show no effective stenosis. These represent occasions where the snare had slipped and become loose. There are also three instances where the snare had not been tightened but resistance measurements show a mild effective aortic stenosis. These may represent some unintentional traction on the snare or possibly some local thrombus formation at the site of the snare application. All the graphs depicting the results of haemodynamic tests of the femoral stenosis have three different symbols which correspond to these three grades of effective aortic stenosis (None, Mild, Severe).
Figure 35. DOGS: Transit Time between sites A and B plotted against % diameter reduction of the femoral stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 36: DOGS: Transit Ratio (site A : site B) plotted against % diameter reduction of the femoral stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 37. DOGS: Rise Time Ratio (site B : site A) plotted against % diameter reduction of the femoral stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figures 35 and 36 show Transit Time and Transit Time Ratio for the femoral stenosis plotted against the percentage luminal diameter reduction of that stenosis. Figure 35 shows that results for Transit Time fall into three groups (0, 12.5, 25 msec) for all of the stenoses regardless of their severity. This was a consequence of the limitations of the time resolution of the equipment as described below. For similar reasons Transit Time Ratio is almost always unity for all the stenoses studied (Figure 36). Neither of these methods involving transit times showed any tendency to separate the stenoses in this animal model either with or without an aortic snare stenosis being present. Figure 37 shows the results for Rise Time Ratio plotted against percentage diameter reduction of the femoral stenosis. In this instance there is a tendency for higher results to be recorded in the presence of tighter femoral stenoses but results for stenoses >50% completely overlap those recorded when there was no stenosis present. The three grades of aortic stenosis do not appear to affect the results.

Pulsatility Index Damping Factor is plotted against percentage diameter reduction for the femoral stenosis in Figure 38. Again higher results are recorded with tighter stenoses. There is less overlap of results for the tightest stenosis with results for zero stenosis. Nonetheless, the scatter of results is large for all stenoses and the overlap is considerable so that Damping Factor does not accurately characterise the femoral stenoses or separate even the two ends of the spectrum of stenoses studied. Again aortic stenosis does not seem to affect the usefulness of this method.
Figure 38. DOGS: Damping Factor (PI at site A/PI at site B) plotted against % diameter reduction of femoral stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 39. DOGS: $\omega_o$ gradient ($\omega_o$ at site A/$\omega_o$ at site B) plotted against % diameter reduction of femoral stenosis.

- Solid squares = No aortic stenosis
- Open squares = Mild aortic stenosis
- Circles = Severe aortic stenosis
- Stars = Calculation of $\omega_o$ gradient impossible.
Figure 40. DOGS: Coefficient of 1st Principal Component of the True Transfer Function waveform plotted against % diameter reduction of femoral stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 41. DOGS: Coefficients of 1st and 2nd Principal Components of the True Transfer Function waveform.

Solid squares = Femoral stenosis of 41% or less
Open squares = Femoral stenosis of 52% or more.
Figure 39 shows $\omega_0$ gradient for the femoral stenosis plotted against its percentage diameter reduction. The scatter of results is again wide and there is no discernable tendency to separate any of the stenoses. There were 10 instances in which there was a pair of complex poles at site A but all three poles were real at site B. These are indicated by stars in the figure. Of these, 4 occurred with 78% femoral stenosis, 3 with 72% and one with each of 66%, 61% and no femoral stenosis. Thus in every case except the last one, this occurred in the presence of femoral stenoses of >50% diameter reduction. It is interesting to note that there is only one point plotted in the group with the most severe aortic stenoses. This was the only instance in this group in which it was possible to calculate $\omega_0$ gradient. In all the other 11 cases with the tightest aortic stenosis and also in 22 cases with moderate and 4 with no aortic stenosis it was not possible to calculate $\omega_0$ gradient. It was therefore not possible to gain any information using $\omega_0$ gradient in 37 (39%) of the 94 segmental observations made.
Figure 40 shows the coefficient of the first principal component of the true transfer function waveform plotted against the percentage diameter reduction of the femoral stenosis. There is a tendency for this coefficient to fall with increasing stenosis severity but again the scatter is wide. To get the most out of the principal component analysis technique, it is necessary to consider the coefficients of at least the first two principal components (Macpherson et al 1984). Figure 41 shows the coefficients of these two components. The dimensions of the femoral stenoses are now represented by the two different symbols. There is almost total overlap of the areas covered by results recorded with stenoses of 41% or less and the area occupied by stenoses of 52% or more; though there may be a tendency for the two groups to cluster in different areas. It is also important to note that the transfer function analysis technique failed to provide any information in a total of 5 out of 94 (5%) instances. This occurred because of variability in the animals' heart rate between the observations made at sites A and B. The failures occurred when there were no beats of identical length at the two sites for analysis.
Figure 42. DOGS: Pressure drop (P2-P3) plotted against
% diameter reduction of the femoral stenosis.
Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 43. DOGS: Stenosis resistance, \((P_2-P_3)/Q_2\), plotted against % diameter reduction of the femoral stenosis

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 44. DOGS: Stenosis resistance (P2-P3)/Q2, plotted against % diameter reduction of the femoral stenosis for the three separate grades of aortic stenosis.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 42 shows the pressure drop (at resting flow) across the femoral stenosis (P2-P3) plotted against percentage diameter reduction. There is an increasing scatter of results with increasingly tight stenosis. This method gives the best separation of stenoses in this experiment although the scatter of results does cause considerable overlap between stenoses. All the measurements plotted in Figure 42 were made at resting flow. The effect of variations in flow can be eliminated by division of each pressure drop by its associated volume flow to give a measure of stenosis resistance at resting flow. Figure 43 shows stenosis resistance plotted against percentage diameter reduction. The degree of scatter is reduced and now the effect of aortic stenosis can be seen more clearly (Figure 44). The degree of scatter for each femoral stenosis increases with increasingly tight aortic stenosis and the degree of overlap between tight femoral stenoses increases with increasing severity of the aortic stenosis.

In order to examine the failings of Damping Factor more closely, it is interesting to consider Pulsatility Index at the three sites. Figure 45 shows Pulsatility Index at site C plotted against aortic stenosis resistance (P1-P2/Q1). This is recorded distal to the aortic snare stenosis with no femoral stenosis distal to the site of recording. PI falls with increasingly tight stenosis (p<0.0005 Spearman Rank Correlation). The decrease is initially rapid and then levels off. There appears to be increasing scatter of results with lesser degrees of stenosis although there are fewer points recorded for the highest aortic resistances. Figure 46 shows
PI at site A plotted in the same way against aortic stenosis resistance. PI is now recorded distal to the aortic stenosis but there is a variable femoral stenosis distal to the insonation site. The range of recorded PI's is now approximately half of that for site C. This may imply that there was a partial sympathetic in the right limb as a result of the greater dissection performed. Nonetheless PI falls with increasingly tight stenosis (p<0.0005). The relationship between PI and aortic resistance, therefore, is similar to that at site C but is now less clear.
Figure 45. DOGS: Pulsatility Index at site C plotted against aortic stenosis resistance.

Solid squares = femoral stenosis of 41% or less
Open squares = femoral stenosis of 52% or more.
Figure 46. DOGS: Pulsatility Index at site A plotted against aortic stenosis resistance.

Solid squares = femoral stenosis of 41% or less
Open squares = femoral stenosis of 52% or more.
Figure 47. DOGS: Pulsatility Index at site B plotted against femoral stenosis resistance.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figure 48. DGS: Pulsatality Index at site A plotted against femoral stenosis resistance.

- Solid squares = No aortic stenosis
- Open squares = Mild aortic stenosis
- Circles = Severe aortic stenosis.
Figure 49. DOGS: PI at site A with collateral patent, divided by PI with collateral clamped, plotted against femoral stenosis resistance.

Solid squares = No aortic stenosis
Open squares = Mild aortic stenosis
Circles = Severe aortic stenosis.
Figures 47 and 48 show the Pulsatility Index distal and proximal to the femoral stenosis, that is the PI’s which are divided to give the Damping Factor, plotted against the resistance of the distal stenosis \((P_2 - P_3/Q_2)\). First Figure 47 shows the PI at position B, that is distal to both stenoses, plotted against femoral stenosis resistance. PI decreases with increasingly tight stenosis \((p<0.0005\) Spearman Rank Correlation), as would be expected, and there is a marked reduction in scatter for increasingly tight stenosis. At low femoral resistances PI falls with increasing aortic stenosis. Thus PI distal to both stenoses is affected by both the femoral and the aortic stenosis resistances. Figure 48 shows the PI at position A, that is between the two stenoses, again plotted against femoral stenosis resistance. PI falls with increasingly severe femoral stenosis \((p<0.01\) Spearman Rank Correlation) but there is greater scatter of results for tighter femoral stenoses. Again at low femoral resistances, PI is reduced by increasing aortic resistance. Thus the same general characteristics are exhibited by the PI between the two stenoses as by PI distal to both.

To examine the effect of the collateral flow on the proximal PI, it is useful to compare the PI at this site with and without the collateral clamped. Figure 49 shows the PI at site A with the collateral patent, divided by the PI with the collateral clamped, plotted against aortic stenosis resistance. Each pair of measurements was made without altering proximal or distal stenosis or moving the Doppler probe position. Values for mild degrees of aortic stenosis tend to lie close to unity implying that collateral
flow does not affect PI greatly in this situation. For tighter aortic stenoses, however, lower values tend to be recorded \((p<0.01\) Spearman Rank Correlation). This implies that for these stenoses the PI with the collateral clamped tends to be larger than with it patent.

DISCUSSION

Both Transit Time and Transit Time Ratio gave very poor results in this canine model. There are two probable reasons for this. Firstly, the length of the arterial segment between the two insonation sites A and B in the animal was short (mean = 13.7cms; range = 13.2-15.1) compared with the length of the femoro-popliteal segment in man. Secondly, the time resolution for recordings at each site depends on the characteristics of the Doppler acquisition system. For the system used, this was 12.5 msec (see Appendix 1) for each site giving a time resolution for each test (TT and TTR) of 25 msec. For these reasons, it might have been expected that transit times would not give good results in this model. These results were, therefore, not considered a valid reason to exclude these indices from a patient study and efforts were made to improve their accuracy in the subsequent patient study (see Chapter 10). Rise Time Ratio gave better results but may also have been affected by the time resolution of the Doppler acquisition system.

The results for Damping Factor might have been expected to have
been the best of the Doppler methods examined in the canine model. The results were however disappointing. The reason for this appears to be that proximal PI (at site A) as well as distal PI (at site B) is reduced by femoral stenosis. Thus while Damping Factor would be expected to increase with increasingly severe femoral stenosis, the magnitude of the increase is reduced by the fall in proximal PI. In a rigid pipe such a relationship would be expected. Any stenosis in a rigid pipe will reduce flow and the characteristics of the volumetric flow waveform above and below the stenosis must be identical. This situation is modified in vivo and the degree of similarity in flow waveforms, proximal and distal to an arterial stenosis, may be affected by two main variables: arterial wall elasticity and collateral flow. The stiffer the walls of the arterial segment under study, the more closely the segment resembles a rigid tube. With increasing wall stiffness, therefore, proximal and distal flow characteristics become more nearly identical. Collateral vessels which bypass the segment under study result in part of the flow observed proximally not being present at the distal observation site and therefore, with increasing collateral flow, proximal and distal flow characteristics become less similar.

It may seem paradoxical that PI falls proximal to a stenosis when it is well documented that increasing peripheral resistance results in a rise in PI (Evans et al 1980). In the latter case, however, there is a large compliant chamber (due to arterial elasticity) between the measurement site and the distal resistance. The effect of increasing this distal resistance is to reduce damping
and decrease the time constant of the oscillatory component of blood flow.

The effect of the collateral flow on proximal PI is demonstrated in Figure 49. This confirms that clamping the collateral (i.e., increasing the distal resistance) raised the proximal PI at least in the presence of a severe aortic stenosis when it might be expected to be particularly low.

\[ \omega_0 \] gradient gave poor results in this model and in addition it was not possible to calculate it in a total of 37 (39%) of cases. Failure was more common with severe aortic stenosis. This may have considerable implications for the clinical application of this method particularly in the presence of combined segment disease. True transfer function analysis is a much more complex and time-consuming technique. In this experiment, it also failed to provide any information in 5% of cases. When the coefficients of the first two principal components were considered together, stenoses of <50% were not separated from those of >50% diameter reduction.

Pressure drop gives the best results in terms of characterising the stenoses in this canine model. There was a considerable degree of scatter in the results obtained. This may have been related partly to the variation in size of the animals. Variation in the resting flow rates between measurements has been shown to have some effect. When this is eliminated an effect of aortic stenosis is
revealed. With increasing aortic stenosis, the scatter of the effective resistance of the tightest distal stenosis is increased. It might have been anticipated that with increasingly severe proximal stenosis, the effective resistance of a distal stenosis should have been reduced since the flow will be restricted by the proximal stenosis (see Chapter 3). This was not the case in this animal model. The increased scatter with tighter aortic stenoses, however, means that characterisation of distal stenoses is more difficult and may have implications for the use of this method in patients with combined segment disease.

CONCLUSIONS

Of the haemodynamic methods examined, pressure drop gives the best characterisation of distal stenosis in this animal model of combined segment disease. The results for Pulsatility Index Damping Factor were particularly disappointing. This occurred because both proximal and distal Pulsatility Index fall with increasing femoral stenosis, reflecting the similarity of flow characteristics above and below a stenosis. In view of the effect of arterial stenosis on proximal Pulsatility Index, it is unlikely that Damping Factor could be clinically useful on its own, particularly in the presence of combined segment disease. \( \omega_p \) gradient failed in the assessment of the femoral stenosis in 39% of cases, most often in the presence of severe aortic stenosis. If this failure rate occurred in patient assessment, its use would be severely limited particularly in the
assessment of combined segment disease.
Chapter 10

COMPARISON OF HAEMODYNAMIC METHODS IN THE FEMORO-POPLITEAL SEGMENT IN VASCULAR PATIENTS

The haemodynamic methods studied in the canine model were also evaluated in a group of patients with peripheral vascular disease. The pressure method had given the most encouraging results in the animal model and therefore seemed most promising. Of the Doppler methods, those dependent on the time intervals had given the worst results in the animal model. These were nonetheless included in the patient study since the femoro-popliteal segment in man is several times longer than the segment studied in the dogs. In addition, to attempt to increase the accuracy of the time interval methods, the timing markers were not used to calculate the time intervals, rather the analysis software was modified to find the appropriate times directly from the waveforms.

MATERIALS AND METHODS

72 limbs of 38 patients with various distributions of peripheral vascular disease were studied in a warm room after a period of approximately 20 minutes supine rest. The mean age of this group was 63 years (range 47-75). 82% were male and 79% presented with intermittent claudication, the remaining 21% complained of rest pain. Two patients (5%) were diabetic.
Pressure measurements

The radial artery was cannulated with a 20-gauge Teflon cannula (Abbocath) and each femoral artery punctured with a 21-gauge needle, all under local anaesthesia, to allow pressure monitoring. The radial and femoral cannulae were primarily inserted for the purpose of papaverine testing of the aorto-iliac segment (see Chapter 7). A fall of 18% or more was taken to indicate a haemodynamically significant aorto-iliac lesion (Quin et al. 1975). After the papaverine test the femoral needle was removed but the radial cannula was left in situ to provide a continuous record of systemic pressure while the distal pressure was measured. This was accomplished using an occlusion cuff (23x12.5cms) applied immediately below the knee (Quin et al. 1975; Evans et al. 1980). The pedal artery with the strongest Doppler signal was insonated using a hand-held 8MHz probe. Systolic pressure was indicated by the return of the flow signal on deflation of the cuff and the observed value written on the pressure chart against the corresponding radial pulse. The mean of three readings was taken as the radial to below-knee drop. The radial to femoral drop was subtracted from this to give the femoro-popliteal segmental pressure drop. Figure 50 shows the general layout of this patient study.
Figure 50. The patient femoro-popliteal study.
**Doppler equipment**

Doppler waveforms were acquired and analysed using the same microcomputer based system as in the work described in the previous experimental chapters (see Appendix 1). An 8MHz ultrasound transducer was used in this study and the Vector Graphics microcomputer recorded the spectrum analysed data in real time and stored it on mini floppy disc. The ECG R-wave was also recorded together with a variable time interval marker which was set, by the operator, at the onset of flow. The system stored the maximum forward and reverse flow envelopes together with the information necessary to calculate the time delay from the R-wave or the onset of flow to various points on the waveform. On command the microcomputer recorded this information for 65 consecutive heartbeats at each common femoral and popliteal artery.

The same three methods employing the timing markers were evaluated:

1. Transit Time (Normalised)
2. Transit Time Ratio
3. Rise Time Ratio

(see Figure 29)

Normalised transit time was calculated using mean radial arterial pressure and the table published by Gosling (1976). Damping factor was calculated as the ratio of the Pulsatility Index at the common femoral to that at the popliteal artery (FitzGerald et al 1971). \( \omega_0 \) was calculated at each site as described by Skidmore and Woodcock (1980). If there were two complex poles for the common femoral waveform and all three poles were real for the popliteal waveform, this was taken to
indicate superficial femoral occlusion (Skidmore & Woodcock 1980). True Transfer Function Analysis was performed as described in the previous chapter.

Median values at each site were used for the various types of waveform analysis since the median is less prone than the mean to errors introduced by the occasional ectopic beat commonly found in these patients. $\omega_o$ gradient and True Transfer Function Analysis were performed using the ensemble average waveform as described in the previous chapter because of the excessive computation time involved in applying these methods to 65 individual waveforms.

Figure 51 shows common femoral waveforms recorded from patients with and without significant aorto-iliac disease and no femoro-popliteal lesions. Figure 52 shows popliteal artery waveforms recorded in the presence and absence of isolated femoro-popliteal disease.
Figure 51. Common femoral artery waveforms from patients:

(a) with no significant aorto-iliac disease

(b) with significant aorto-iliac stenosis.
Figure 52. Popliteal artery waveforms from patients:

(a) with no significant superficial femoral disease
(b) with significant superficial femoral stenosis.
Arteriography

All patients underwent single plane arteriography and measurements were taken from the radiographs. The diameter of the narrowest portion of the superficial femoral and popliteal arteries was measured together with the nearest portion of artery judged to be normal. A percentage reduction in luminal diameter was then calculated. The radiographs were all assessed by two observers and agreement was reached over their assessment. Arteriography was used as the "gold standard" against which the haemodynamic methods were compared. A stenosis of more than 50% of the femoro-popliteal luminal diameter was considered to be significant.

RESULTS

The detailed results of the patient studies described in this chapter can be found in Appendix 6. In all the data graphs limbs with and without significant proximal aorto-iliac disease, as judged by papaverine testing, are distinguished by different symbols. Figures 53-55 show the results of Normalised transit time, Transit time ratios and Rise time ratios plotted against percentage diameter stenosis on arteriography. In all three cases there is a large spread of results which is particularly marked for the tighter stenoses. There is almost complete overlap of results for normal segments by those for segments which are completely occluded. It is therefore not possible to separate even these two ends of the spectrum using any of these tests. Comparison of the receiver operating characteristic (ROC) curves for
these three methods (Figure 56) shows that there is little to choose between them although the curve for Normalised Transit Time lies to the left of those for the other two methods, suggesting that it is the best of these three time interval methods. In constructing the ROC curves a stenosis of more than 50% of the femoro-popliteal luminal diameter was taken to be haemodynamically significant. Although the median values were used to calculate these results, a summary of the statistics of the sample standard deviations is given in Table 7.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>5th Centile</th>
<th>Median</th>
<th>95th Centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalised Transit Time</td>
<td>0.021</td>
<td>0.008</td>
<td>0.012</td>
<td>0.067</td>
</tr>
<tr>
<td>Transit Time Ratios</td>
<td>0.119</td>
<td>0.057</td>
<td>0.091</td>
<td>0.212</td>
</tr>
<tr>
<td>Rise Time Ratios</td>
<td>0.51</td>
<td>0.13</td>
<td>0.35</td>
<td>1.21</td>
</tr>
<tr>
<td>Damping Factor</td>
<td>0.29</td>
<td>0.06</td>
<td>0.21</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Figure 53. PATIENTS: Normalised Transit Time between the common femoral and popliteal arteries plotted against % diameter reduction.

Solid squares = limbs with aorto-iliac disease.
Open squares = limbs with no significant proximal disease.
Figure 54. PATIENTS: Transit Time Ratio (common femoral : popliteal)
plotted against % diameter reduction
Solid squares = limbs with aorto-iliac disease
Open squares = limbs with no significant proximal disease.
Figure 55. PATIENTS: Rise Time Ratio (popliteal : common femoral) plotted against % diameter reduction

Solid squares = limbs with aorto-iliac disease
Open squares = limbs with no significant proximal disease.
Figure 56. PATIENTS: Receiver operating characteristic curves for Normalised Transit Time, Transit Time Ratio and Rise Time Ratio.

A stenosis >50% was considered to be significant.
Figure 57 shows Damping factor plotted against stenosis severity. Even though the values for totally occluded segments do not completely overlap those for apparently normal ones, there is considerable scatter of results. Figure 58 shows the $\omega_\theta$ gradient similarly plotted. For this method, there were 6 limbs in which two poles were complex for the common femoral waveform and all three poles were real for the popliteal waveform, making calculation of $\omega_\theta$ impossible at this site. In all 6 cases the superficial femoral artery was occluded. These limbs are indicated by a star on the graph and they are included as true positives in the ROC curve analysis. In addition there were 9 limbs in which all three poles were real at the common femoral. Of these, 8 cases had a pair of complex poles for the popliteal waveform and in the ninth all three poles were real at this site also. These 9 limbs (12.5%) were considered failures of the technique since $\omega_\theta$ gradient could not be calculated and thus no information on the state of the femoro-popliteal segment was provided. Examination of the angiographic status of these 9 limbs showed that one was occluded, 6 were >50% stenosed and 2 had <50% stenoses. For the limbs in which calculation of $\omega_\theta$ was possible (Figure 58), there is complete overlap between normal and occluded segments.

Figure 59 shows the coefficient of the first principal component of the true transfer function waveform plotted against stenosis severity. Again there is wide scatter of the results particularly for the less severe stenoses. As stated previously, to get the most out of the principal component method as a pattern recognition technique, it is necessary to consider the coefficients of at least the first two principal components. Figure 60 shows these two components. There is a
tendency for values recorded for occluded vessels to cluster in one area but results for those with >50% and those with <50% stenoses overlap widely. The true transfer function technique failed to provide any information in 5 (7%) of the 72 limbs. This occurred for the same reason as in the animal study. There were, in each instance, no beats of identical length in the samples recorded at the common femoral and popliteal insonation sites.
Figure 57. PATIENTS: Damping Factor (common femoral PI/popliteal PI) plotted against % diameter reduction.

Solid squares = limbs with aorto-iliac disease
Open squares = limbs with no significant proximal disease.
Figure 58. PATIENTS: $\omega_{o}$ gradient (common femoral $\omega_{o}$/popliteal $\omega_{o}$) plotted against % diameter reduction.

Solid squares = limbs with aorto-iliac disease

Open squares = limbs with no significant proximal disease

Star = 6 limbs where calculation of $\omega_{o}$ gradient impossible.
Figure 59. PATIENTS: 1st principal component of the True Transfer Function waveform plotted against % diameter reduction.

Solid squares = limbs with aorto-iliac disease
Open squares = limbs with no significant proximal disease.
Figure 60. PATIENTS: Coefficients of 1st and 2nd principal components of the True Transfer Function waveform.

Circles = No significant femoro-popliteal disease
Open squares = significant femoro-popliteal disease
Solid squares = femoro-popliteal occlusion.
Figure 61. PATIENTS: Receiver operating characteristic curves for Damping Factor, $\omega_0$ gradient and Transfer Function analysis. A stenosis >50% was considered to be significant.
Comparison of the ROC curves for these three methods (Figure 61) shows that the curves cross. $\omega_0$ gradient appears marginally more sensitive at high specificities, while Damping Factor is more sensitive at lower specificities. The curve for True Transfer Function Analysis is close to that for Damping Factor. Damping Factor is considerably easier to calculate than $\omega_0$ gradient and in addition it was possible to assess all the limbs using Damping Factor. This was not possible using $\omega_0$ gradient. The same criticism is true for the True Transfer Function Analysis method.

The results for all the individual methods were analysed to determine whether the accuracy of any of them varied with the degree of stenosis used as a break figure. None of them showed any marked change in accuracy except for $\omega_0$ gradient. Figures 62-67 show ROC curves for the various methods in detecting different degrees of stenosis as shown on radiography. Only the accuracy of $\omega_0$ gradient (Figure 66) increases with increasing degree of stenosis. The statistics of the sample standard deviations for Damping Factor are given in Table 7. This is not possible for $\omega_0$ gradient or True Transfer Function Analysis as these were both calculated from ensemble average waveforms at each site.
Figure 62. PATIENTS: Receiver operating characteristic curves for Normalised Transit Time in the detection of different degrees of stenosis.

Solid squares: >25%  Open squares: >50%
Solid circles: >75%  Open circles: 100%
Figure 63. PATIENTS: Receiver operating characteristic curves for Transit Time Ratio in the detection of different degrees of stenosis.

Solid squares : >25%  Open squares : >50%
Solid circles : >75%  Open circles : 100%
Figure 64. PATIENTS: Receiver operating characteristic curves for Rise Time Ratio in the detection of different degrees of stenosis.

Solid squares : >25%  Open squares : >50%
Solid circles : >75%  Open circles : 100%
Figure 65. PATIENTS: Receiver operating characteristic curves for Damping Factor in the detection of different degrees of stenosis.

Solid squares : >25%  Open squares : >50%
Solid circles : >75%  Open circles : 100%
Figure 66. PATIENTS: Receiver operating characteristic curves for \( \omega \) gradient in the detection of different degrees of stenosis.

- Solid squares: >25%
- Open squares: >50%
- Solid circles: >75%
- Open circles: 100%
Figure 67. PATIENTS: Receiver operating characteristic curves for True Transfer Function Analysis in the detection of different degrees of stenosis.

Solid squares: >25%  Open squares: >50%
Solid circles: >75%  Open circles: 100%
To gain the maximum diagnostic information from continuous wave Doppler recordings, the combination of transit time and damping factor has been recommended (Gosling 1976; Johnston et al 1978; Humphries et al 1980). Figure 68 shows Damping Factor plotted against Normalised Transit Time. The arteriographic appearance of the femoro-popliteal pathway is indicated by different symbols. This figure is directly comparable to figures published by others (Gosling 1976; Humphries et al 1980) and shows clustering of values recorded for segments without significant stenosis near the origin. Figure 69 shows a comparison of the ROC curves for each of the two individual methods used alone and also in combination. At a specificity of 95%, the sensitivity of Normalised Transit Time is significantly greater than that of Damping Factor ($p<0.01$ $\chi^2$ analysis with Yates' correction). The addition of Damping Factor to Normalised Transit Time tends to improve the accuracy though this is not statistically significant.

Figure 70 shows the segmental pressure drop between the common femoral needle and the below-knee occlusion cuff plotted against stenosis severity. Although the spread in results is wide in the case of occlusion, it is possible to separate not only occluded from normal segments but also those with less than 50% stenosis from those with greater than 50% stenosis with considerable accuracy. Figure 71 shows ROC curves for segmental pressure drop in the detection of different degrees of femoro-popliteal stenosis. The accuracy of this method does not markedly change.
Figure 68. PATIENTS: Damping Factor plotted against Normalised Transit Time for the femoro-popliteal segment.

Circles = No significant femoro-popliteal disease
Open squares = Significant femoro-popliteal disease
Solid squares = femoro-popliteal occlusion.
Figure 69. PATIENTS: Receiver operating characteristic curves for the combination of Normalised Transit Time and Damping Factor and for the two individual methods.
Figure 70. PATIENTS: Segmental Pressure Drop, between the common femoral needle and the below-knee occlusion cuff, plotted against % diameter reduction.

Solid squares = limbs with aorto-iliac disease
Open squares = limbs with no significant proximal disease.
FIGURE 71. PATIENTS: Receiver operating characteristic curves for Segmental Pressure Drop in the detection of different degrees of stenosis.

Solid squares : >25%  Open squares : >50%
Solid circles : >75%  Open circles : 100%
Figure 72. PATIENTS: Receiver operating characteristic curves for Normalised Transit Time with Damping Factor and for Segmental Pressure Drop
Figure 72, a comparison of the ROC curves for segmental pressure drop and for the plot of Damping factor and Normalised transit time, clearly shows the superiority of segmental pressure over the Doppler techniques in the assessment of the femoro-popliteal segment. Values for segmental pressure drop = 13 mm Hg, Normalised transit Time = 1.9 and Damping Factor = 1.9 give specificities of 95% for each of the two tests. At this specificity level, the sensitivity of segmental pressure drop is 89% which is significantly better than the 70% for the Doppler method on $\chi^2$ analysis ($p<0.05$).

DISCUSSION

The spread of the Doppler results obtained is due partly to errors inherent in the recording of Doppler waveforms. These errors have been shown to be greater at the common femoral than at the posterior tibial (Campbell et al. 1984b). In this study, 65 consecutive waveforms were collected at each site to ensure capture of truly representative waveforms for later analysis and minimise any errors due to collection of a small number of waveforms. Some of the methods of assessment of the femoro-distal segment involve recording Doppler waveforms at the common femoral artery and at the ankle, usually from the posterior tibial artery (Crawford & Chamberlain 1977; Campbell et al. 1983). These methods therefore study both the femoro-popliteal and tibio-peroneal segments. Disease of the tibial vessels undoubtedly contributes to the measured transit times and also to alterations in waveform indices. In order to relate the Doppler studies as closely and
simply as possible to the patients' arteriography, this study used common femoral and popliteal artery recordings, as have some others (Harris et al 1974; Gosling 1976; Humphries et al 1984; Aukland & Hurlow 1982). The level of the popliteal trifurcation varies to some extent and in patients with peripheral vascular disease there are often several well developed collateral vessels around the knee. In the presence of superficial femoral occlusion there may be reverse flow in the upper popliteal artery. There may, therefore, be several waveforms to choose from in the popliteal fossa and insonation of vessels other than the popliteal artery is probably the main source of error in this study. The B-mode image of a Duplex scanner would aid recognition of the popliteal artery and thus help reduce this error. The spread of results obtained may also, to some extent, reflect the development of collateral flow via the profunda femoris artery as is shown by the particularly marked spread found in the presence of superficial femoral occlusion.

Of the individual Doppler methods, when used alone, Normalised transit time gives the best results. Craxford and Chamberlain suggested that Transit time ratios for groin and ankle waveforms were better than absolute transit time measurements but they did not normalise these for variations in systemic blood pressure. This is not true for our results. However, our absolute transit times have been normalised and our ratios are between groin and knee. The combination of two Doppler methods ie. Normalised Transit Time and Damping Factor tends to give greater accuracy, as shown by ROC curve analysis, and represents the most useful method studied. This method was proposed by Gosling in 1976
and makes use of both the time taken for the blood velocity waveform to traverse the arterial segment under study and also the alteration in waveform shape imposed by that segment. Prior to this Gosling and his colleagues had combined both types of information but had not normalised the transit time for the subjects' arterial blood pressure (Gosling and King 1974) which improves its accuracy.

Considering the two individual methods, ROC curve analysis (Figure 69) clearly shows the superiority of Normalised transit time over Damping factor in the detection of femoro-popliteal stenoses as shown by arteriography (p<0.01). The disappointing results for Damping factor may result from the effect of superficial femoral lesions on common femoral Pulsatility Index (Baird et al 1980; Aukland & Hurlow 1982; Thiele et al 1983; Junger et al 1984; See chapter 5). Figure 69 also shows that the ROC curve for the combined method lies to the left of those for each of the individual methods. Close inspection of these ROC curves shows that the improvement on the curve for Normalised transit time alone, provided by the addition of Damping factor, occurs at the upper end of the curve. The most useful part of the curve, however, in determining the cut-off value for a test and in comparing tests in a clinical setting is that part lying close to the ordinate i.e. the true positive ratio (sensitivity) when the false positive ratio is low (high specificity) which gives the strict threshold (Metz 1978). In the population studied, the addition of Damping factor provides little improvement in this part of the curve (not statistically significant). This implies that the combined method may not provide a clinically useful improvement over Normalised transit time alone. The addition of
Damping factor to the Normalised transit time tends to give improved accuracy but this remains to be proven by further studies involving greater numbers of patients.

Since the combined method was proposed other methods have been recommended for interpreting the changes between the input and output Doppler waveforms for an arterial segment (Craxford and Chamberlain 1977; Humphries et al. 1980; Aukland and Hurlow 1982; Campbell et al. 1983). These have all been compared by ROC curve analysis in this study. The most recent method is $\omega_0$ gradient (Campbell et al. 1983). This is similar in principle but considerably more difficult to calculate than Pulsatility Index Damping Factor. In addition $\omega_0$, at any site, can only be calculated if there are a pair of complex poles in the solution of the Laplace transform equation. It can be assumed that there is significant disease if there is a pair of complex poles at the common femoral and all three poles are real at the popliteal (Skidmore & Woodcock 1980). If all three poles at the common femoral are real, then the technique gives no information on the femoro-popliteal segment. It should be emphasised that Campbell and his colleagues, in their initial investigation of this method, used Doppler waveforms recorded from the common femoral artery and the ankle. They related the $\omega_0$ gradient, thus derived, to the angiographic appearance of the femoro-popliteal segment and did not attempt angiographic assessment of the tibio-peroneal segment which was also spanned by their Doppler $\omega_0$ gradient. They did not mention any patients in whom it was not possible to calculate this gradient because all three common femoral poles were real. In this study Doppler waveforms from the common femoral and popliteal arteries
were used to calculate $\omega_0$ gradient and this was related to the angiographic appearance of the superficial femoral and popliteal arteries. It might have been expected that this would have produced better results for $\omega_0$ gradient than those achieved by Campbell and his colleagues. The ROC curve comparison shows that $\omega_0$ gradient, where its calculation was possible, tends to give higher sensitivity than Damping factor at high specificity levels, but there were 9 limbs which could not be assessed. It seems, therefore, that $\omega_0$ gradient may be less useful than Damping factor in the evaluation of patients with peripheral vascular disease.

Gosling and his colleagues (1976) used brachial cuff occlusion pressures to normalise the measured transit times. In this study we have been able to avoid the errors of occlusion cuffs in this process by using the radial artery pressure. This has been useful for the purposes of investigation of this method. For the practical application of Normalised Transit Time, however, the occlusion cuff is probably adequate. Femoro-popliteal haemodynamic methods are most likely to find a role in the assessment of combined segment disease. It is our belief that a flow-monitored papaverine test, with radial and femoral artery puncture, is the best method for haemodynamic assessment of the aorto-iliac segment (See chapters 6 & 7). In the patients studied, therefore, the radial artery was cannulated primarily for the haemodynamic assessment of the aorto-iliac segment and the accurate systemic pressure measurement provided was also used to normalise the transit times. The intra-arterial radial and femoral pressures were also used in calculating the femoro-popliteal segmental pressure drop.
The segmental pressure results show good discrimination of stenosis severity as measured from the radiographs. The radial cannula provides reliable systemic pressure monitoring and direct needle puncture of the common femoral artery avoids the error of a proximal thigh cuff. The below-knee occlusion cuff is the greatest source of error. It might have been expected that some patients with peripheral vascular disease would have such hard popliteal arteries as to be incompressible. This would result in falsely high below-knee pressures as recorded by the occlusion cuff technique and false negatives of segmental pressure drop in detecting significant femoro-popliteal stenosis. This probably occurred in the one limb in which, in spite of superficial femoral occlusion, a higher pressure was recorded with the below-knee occlusion cuff than was recorded by direct puncture of the common femoral artery. Radiography in this case showed calcified arteries extending down to the ankle. Unacceptable errors have however not been introduced in the group of patients overall and ROC curve analysis confirms the superiority of the segmental pressure method over the Doppler techniques.

Radial arterial cannulation using a Teflon cannula is a simple and safe procedure for diagnostic studies (Barr 1961; Mortensen 1967; Bishop and Payne 1983). Ethical committee approval was gained before this study was undertaken and no complications have been encountered in any of our patients.
CONCLUSIONS

Accurate haemodynamic assessment of the femoro-popliteal segment can be provided by measurement of the segmental pressure drop between a common femoral needle and a below-knee occlusion cuff. This pressure method is invasive in that it requires needle puncture of at least the common femoral artery. However it is only likely to be used in the assessment of combined segment disease and in these patients needle puncture of the femoral (and ideally the radial) artery is necessary to perform papaverine testing of the aorto-iliac segment. Of the individual Doppler methods studied, Normalised Transit Time gives the best results. There was a tendency for the accuracy of this technique to be improved by the addition of Damping Factor but this was not statistically significant.
Assessment of combined aorto-iliac and femoro-popliteal vascular disease requires the application of haemodynamic tests to both these segments. Aorto-iliac haemodynamic methods aim to fulfil two roles. First they should ensure that arteriography has not failed to show a haemodynamically significant inflow lesion. Secondly they confirm that the disease, which is shown on the radiographs, truly has adverse haemodynamic effects. In this way the clinician can avoid prejudicing the success of a femoro-popliteal bypass by leaving significant inflow disease uncorrected. He is also able to prevent proximal reconstruction being performed for disease which is not actually haemodynamically significant.

Pressure and flow distal to an arterial stenosis are closely related and a stenosis can be studied using either. However measurement of both these variables together defines a stenosis as accurately as possible. It is now well established that reliable pressure measurement at the upper thigh level necessitates invasive direct measurement of pressure within the common femoral artery. Reduction of peripheral resistance during such a pressure measurement is clearly valuable since a "borderline critical stenosis" which does not limit flow at the resting flow rate, may dominate as the flow limiting resistance when peripheral resistance is reduced. Such a stenosis may, therefore, be
revealed by causing a pressure drop at an elevated flow rate. Such hyperaemic tests mimic the situation found in the patient with intermittent claudication. Flow and delivery pressure to the periphery are adequate at rest but during exercise the increased demands can not be met.

The best available haemodynamic test for the aorto-iliac segment is a hyperaemic test such as the papaverine test. The animal experiment described in chapter 6 shows that the combination of pressure and flow information in a hyperaemic test provides more accurate characterisation of stenoses than the use of either pressure or flow alone. It was also shown that continuous wave Doppler recordings provide a feasible method of monitoring flow increases during a hyperaemic test. Using this tightly controlled animal model, indices were derived from the pressure and Doppler readings and these were related to the experimental stenosis dimensions.

The patient study described in chapter 7 investigated the use of these indices in the assessment of patients with peripheral vascular disease. This study confirmed that the addition of flow velocity information gave increased accuracy in the use of the papaverine test to assess the aorto-iliac segment. This was the first time that flow monitoring had been used to increase the accuracy of a pre-operative hyperaemic test.

The success, in terms of symptomatic relief, of proximal reconstruction performed for haemodynamically significant aorto-iliac
disease depends on what distal disease remains uncorrected. The assessment of this distal disease demands femoro-popliteal haemodynamic studies. Many different methods have been advocated for the haemodynamic assessment of this segment including several Doppler methods and also the use of segmental pressures. There was no clear indication of which of these methods was the best.

In an animal model, described in chapter 9, all these methods were compared. This was the first time that True Transfer Function Analysis had been studied in an animal model and the first attempt to construct an animal model of combined segment disease. This experiment showed that pressure measurement, albeit invasive, was superior to any of the Doppler methods in characterising distal disease. Of the Doppler techniques, those involving the time intervals gave particularly poor results and Pulsatility Index Damping Factor, although better, was also disappointing. The reason for the poor results using Damping Factor was found to be that arterial stenosis results in reduction of Pulsatility Index both distally and also proximally. \( \omega_g \) gradient failed to provide any information in 39% of the observations.

For the patient study, described in chapter 10, efforts were made to improve the accuracy of the Doppler methods involving the time intervals. This study represents the first investigation of True Transfer Function Analysis in a group of patients with peripheral vascular disease greater than 6 in number. The best results, using a Doppler method, were obtained with Normalised Transit Time. Damping Factor produced disappointing results and although its addition to
Normalised Transit Time tended to give an improvement in accuracy, this improvement was not statistically significant in the area of clinical relevance. $\omega_0$ gradient failed to provide any information in 12.5% of the limbs.

Segmental pressure measurement provided the most accurate haemodynamic assessment of the femoro-popliteal segment in the patients as it had in the animal model. In the patient study, some of the accuracy of the method was sacrificed by the use of an occlusion cuff rather than arterial puncture for the measurement of the most distal pressure. The Copenhagen group has used direct intra-arterial pressure measurement at this level as well as more proximally but this technique has not yet gained widespread acceptance. The popliteal artery is both small and deep compared with the common femoral and its direct puncture may well carry higher risks. The avoidance of needle puncture at this level and the use of an occlusion cuff means that pressure measurements at this level involved cessation of flow. This technique precluded the evaluation of a hyperaemic test in this segment.

In spite of the use of the distal occlusion cuff, the segmental pressure method was invasive. The technique is, however, only likely to find a clinical role in the assessment of patients with combined segment disease. Haemodynamic assessment of the aorto-iliac segment in such patients is best performed using the papaverine test and this necessitates femoral arterial puncture and ideally radial arterial puncture as well. Consequently only the addition of the below knee occlusion cuff is necessary for assessment of the femoro-popliteal
segment in these patients.

The conclusion that must be drawn from these studies is that in both the aorto-iliac and femoro-popliteal segments, invasive pressure measurements are required for accurate haemodynamic assessment. Where possible hyperaemia should be induced and Doppler flow monitoring performed to increase accuracy. If it could be arranged, these invasive tests would be best performed at the time of arteriography to reduce the number of invasive investigations performed and so that both haemodynamic and anatomical information would be available at the same time.

The inevitable question that follows this conclusion is: "Does the non-invasive vascular laboratory have any role in the management of arterial occlusive disease?" Certainly non-invasive tests have a role in detecting whether or not there is vascular disease present at all in an individual patient. Measurement of the ankle systolic pressure and the ankle/brachial pressure index with and without exercise and estimation of the recovery time provide useful information for answering this question. Non-invasive measurements before and after reconstruction and sequentially thereafter can be used to monitor the success of the procedure and the duration of this success. A role for non-invasive tests in localising disease and in estimation of segmental dominance in the presence of multisegmental involvement is more questionable. Except for rare instances where ankle pressure measurements can distinguish between rest pain due to occlusive disease and that due to small vessel embolism from a proximal lesion, non-invasive tests do not have the
accuracy required for such localisation.

The work described in the above chapters suggests several areas for future research. The combination of ultrasonic B-mode imaging and pulsed Doppler in the Duplex scanner offers several possibilities. Such a machine was not locally available when this work was undertaken. The Duplex scanner offers knowledge of the precise site from which the Doppler signal is recorded. From the B-mode image provided, dimensions can be measured. This provides the possibility of making volume flow measurements non-invasively. Volume flow estimations may provide an even greater increase in the accuracy of papaverine testing than the use of flow velocity described in chapters 6 and 7.

The Duplex scanner may also improve the accuracy of Doppler methods in the femoro-popliteal segment by allowing more accurate identification of the popliteal artery. Indeed, as the B-mode image quality improves, a time may be envisaged when images of selected sites such as the infra-renal aorta, the common femoral bifurcation and the popliteal artery together with Doppler flow information at these sites might enable operative planning without the need to perform arteriography, at least in selected cases.

From the point of view of the haemodynamic assessment of combined segment disease, the obvious gold standard for assessment is the results in a large population of patients who are treated on the basis of the haemodynamic test results. This would involve a large prospective study which is the next stage in evaluating the methods studied above.
Although some authors report a high incidence of combined aorto-iliac and femoro-popliteal disease, clinical problems in terms of deciding between proximal reconstruction alone and simultaneous proximal and distal reconstruction, are relatively uncommon. In order to give a definite answer to this problem, it would be necessary to collect a large number of such patients, perform pre-operative haemodynamic studies and reconstruct the proximal segment alone. It should then be apparent whether or not those in whom proximal reconstruction failed could be identified pre-operatively.

The main problem with any haemodynamic investigation performed in combined segment disease is that the division between proximal inflow and distal run-off disease on testing is the common femoral measurement site. Proximal reconstruction, however, usually includes some form of profundaplasty which in addition to correcting the proximal disease also modifies what testing defines as distal disease. Thus the inflow test does not test all the disease which can be improved by proximal reconstruction and the distal test reflects more than what will remain after proximal reconstruction. This difference in the separation between proximal and distal on testing and at operation makes the use of haemodynamic tests, performed in this way, difficult to assess on the basis of operative results.

At present the clinician's dilemma in choosing one particular operative procedure for his patient with combined segment disease can be summed up in the words of Immanuel Kant: "a decision must often be made on the basis of knowledge, sufficient for action but insufficient to
satisfy the intellect". 
APPENDIX 1
DOPPLER ACQUISITION AND ANALYSIS SYSTEM

The system, used for the acquisition and analysis of Doppler waveforms, is described more fully elsewhere (Prytherch & Evans 1985). The following short description serves to explain the methods used for the work described in this thesis and also makes several points which are relevant to the interpretation of the results.

The ultrasound transducer (either 4 or 8 MHz) was driven by a Sonicaid "Vasoflo" Doppler unit. This unit produces two separate outputs, one corresponding to forward and the other to reverse flow. These two signals are combined by the Unigon TRA-1 heterodyne unit. The result is a single signal consisting of the forward and reverse flow signals separated about a heterodyne frequency equivalent to zero flow. The heterodyne frequency can be set by the operator to 1, 2, 4 or 8 kHz. The combined signal is then fed to the Unigon "Angioscan" I spectrum analyser. The frequency range of this can similarly be set by the operator to 5, 10 or 20 kHz.

The spectrum analyser performs one analysis sweep every 6.25 msec and the digital spectrum analysed data from each sweep is put out in 128 sequential frequency bins. The frequency resolution is therefore 40, 80 or 160 Hz depending on the frequency range setting. The spectrum analyser, as normally supplied, outputs the information from adjacent
pairs of frequency bins combined and therefore puts out 64 bytes of information for each sweep. The unit used in this system however was modified to output adjacent frequency bins in parallel and therefore puts out 64 byte pairs for each sweep. The onset of each sweep is signalled by a "Sweep Start" signal and each pair of bytes by a "Data Ready" signal. The interval between sweep start signals is fixed at 6.25 msec. This information is fed via the interface unit to the Vector Graphics microcomputer. The frequency settings of the heterodyne unit and the spectrum analyser together with the time delay cursor information (see below) all pass through this interface unit to be recorded by the microcomputer.

The time delay equipment consists of an isolated ECG amplifier, an R-wave detector and two variable time delays in series which can be set by the operator. Each variable time delay generates a signal which together with the R-wave signal are used by the software for synchronisation and control purposes as described below. Additional control signals are provided by the operator, using a hand-held control unit. This allows alteration of the discrimination level (see below) and initiation of data acquisition. Figure 73 shows a schematic diagram of the hardware.
Figure 73. The Doppler acquisition and analysis system.
SOFTWARE

Data acquisition

As already described, the spectrum analyser produces 128 bytes of data every 6.25 msec. Before displaying or storing data, the microcomputer averages pairs of analyser sweeps to give one averaged sweep every 12.5 msec. All data displayed, stored and used for calculations is based on averaged sweeps. Thus the time resolution of the analyser is reduced from 6.25 to 12.5 msec.

Two different acquisition programs were used for the work described in this thesis.

1. Sonogram Capture

When initiated this program acquires alternate complete sonograms until it has filled the data buffer (32 kBytes of data). This data consists of the averaged sweeps described above. Usually three or four complete beats are captured together with a further incomplete beat. Alternate beats are captured in order to increase the time over which acquisition occurs. Normally 3.2 sec of data is captured over approximately 6 sec. In this way respiratory changes in the blood flow waveform are recorded.

The program has two phases. During the display phase, the operator adjusts the frequency range of the spectrum analyser and sets the heterodyne frequency. Then, using the hand held control unit, he adjusts the discrimination level so that the maximum forward and reverse flow envelopes sit on the edge of the displayed sonogram. The operator then adjusts the first variable delay to position the trigger just before the onset of systolic flow. A complete beat is then defined as
including the sweep following the trigger and all subsequent sweeps up to and including the next occurrence of the trigger. Having made the above adjustments and checking that the signal is satisfactory, the operator initiates the acquisition phase of the program and the program acquires 32 kBytes of data.

Then follows a question and answer session. The operator supplies a code for the insonation site and the number of the particular run captured from that site. These are combined with the patient code, which was entered when the program was initiated, to provide the file name for the file as recorded on disk. The operator is also asked to supply the frequency of the Doppler probe, the angle between the probe and the skin and also his opinion as to whether or not true arterial reverse flow was present.

If the captured data was thought not to be optimum it can be rejected before the question and answer session and a further sample captured.

Outline Capture
This program stores the maximum forward and reverse flow envelopes for up to 65 complete consecutive beats (which again is the capacity of the buffer). The definition of a beat is the same as for the sonogram capture program. The major difference between the two programs is that the bulk of each frequency/amplitude spectrum (sweep) is discarded.
Figure 74. The use of the discrimination level to find the maximum and minimum arrays.
Figure 75. Stages in the construction of the maximum frequency envelope.
The use of the operator-set discrimination level is fundamental to the detection of the maximum forward and reverse flow envelopes and the subsequent combination of these to form a single smooth sonogram outline. During the data acquisition phase, the microcomputer finds for each sweep the first and last bins to equal the discrimination level (Figure 74). These are brightened up on the display to allow the operator to correctly set the discrimination level. As the discrimination level rises out of the noise, the edge of the sonogram is found. The discrimination level can then be considerably increased before the maximum forward and reverse flow envelopes encroach upon the sonogram.

This results in a maximum and minimum array (Figure 75). In combining these to form the maximum frequency envelope, the software performs several artefact rejection operations:

1. If the bin number of the minimum significant frequency is greater than the bin number corresponding to zero flow, then this is set to zero.

2. If the bin number of the maximum frequency is less than the zero flow bin, this is set to zero (Figure 75).

This results in two stored arrays corresponding to maximum forward and reverse flow. Once these are complete, the software sets to zero:

3. Any reverse flow component occurring before maximum forward flow.

4. Any reverse flow component occurring during a period of high forward flow.

Experience has shown that any reverse signal occurring during these
periods must be due to venous flow.

The processor then adds the maximum and minimum arrays to produce a single array representing maximum flow (Figure 75). This process is described more fully elsewhere (Gibbons et al 1981; Prytherch et al 1982). For the purpose of outline capture, as well as setting the first variable time delay to the onset of forward flow, the operator also sets the second delay to the point of maximum forward flow.

Data Analysis
The aorto-iliac canine and human studies involved analysis of the whole sonogram to provide mean Doppler frequency shift. For these studies, therefore, waveforms captured using the sonogram acquisition program were analysed. For each acquired sample the complete sonograms were analysed to give mean Doppler frequency shift and the maximum frequency envelopes were also analysed alone to provide mean maximum frequency shift.

The femoro-popliteal studies, on the other hand, involved various methods which were applied to the maximum frequency envelope. For these studies, the outline acquisition program was used, since this gave many more waveforms for analysis.

The data was analysed off-line in the manner described in the relevant chapters above. As well as analysis to provide numerical waveform indices, the system is also capable of recreating complete
sonograms using a pseudo-grey scale both for inspection and also to provide illustrations as shown.
APPENDIX 2

IN VITRO EXPERIMENTS

Chapters 6 and 7 describe the use of Doppler frequency shift monitoring to calculate flow velocity and provide indices of stenosis resistance. It was thought important to determine in what ways the relationships between probe and vessel may affect these indices. A series of experiments was therefore conducted with a pulsatile flow rig to investigate the effects of:

1. rotation of the probe around its long axis
2. distance between the probe and the vessel
3. incomplete vessel insonation

on mean Doppler frequency shift and mean maximum frequency shift.

MATERIALS AND METHODS

Vessel The vessel was simulated using a length of silastic tubing whose lumen was 5.9mm in diameter with a wall thickness of 2.6mm. This was placed in a water bath to allow insonation with a Doppler probe at different distances.

Fluid Blood was simulated by dissolving 400gms of sucrose and 18gms of sodium chloride in 2l of water. 1gm of Sephadex G-25-40 (Sigma Chemical Company) which has a particle size of between 10 and 40 microns was
suspended in this. The sucrose provided viscosity, the sodium chloride provided ions essential for the function of the electromagnetic flowmeter and the Sephadex provided microspheres which backscattered the ultrasound.

**Pulsatile flow** was obtained with a Harvard pulsatile pump (Model 1405A). The output non-return valve was removed from this to allow some reverse flow at the onset of "diastole".

Flow was monitored using a 3mm Statham cannulating flow probe. This was calibrated at the beginning of each experiment using a time-clock and a measuring cylinder. The EM flow measurements were used to eliminate the effects of variations in the output of the pump.

**Doppler recordings** were made with a 4MHz Sonicaid probe held rigidly at 45 degrees to the longitudinal axis of the silastic tube and moved with a travelling microscope vernier scale.

Doppler sonograms were acquired and analysed using the microcomputer based system used in the rest of the experimental work described in this thesis (Prytherch & Evans 1985). The sonograms were analysed in two ways to produce the mean Doppler frequency shift and also the mean maximum frequency shift as described in Chapter 6. Figure 76 shows a sonogram from this experiment. Its general form is comparable to sonograms recorded in both canine models (Figures 10, 32 & 33) and the patient studies (Figures 19, 51 & 52).
Figure 76. Sonogram from the in vitro experiment.
Figure 77. Mean frequency shift and mean maximum frequency shift both divided by EM flow and plotted against probe rotation.
Figure 78. Mean frequency shift and mean maximum frequency shift both divided by EM flow and plotted against probe height.
Figure 79. Mean frequency shift and mean maximum frequency shift both divided by EM flow and plotted against distance traversed across the longitudinal axis of the tube.
RESULTS

1. The first experiment studied the effect of rotating the probe around its longitudinal axis. Measurements of mean frequency and mean maximum frequency shift were made every 10 degrees during full 360 degrees rotation. Figure 77 shows both frequency shifts, divided by electromagnetic flow, plotted against degrees of rotation. There is very little variation in either frequency shift.

2. The second experiment studied the effect of increasing distance between the probe and the vessel being insonated. Measurements of mean frequency shift and mean maximum frequency shift were made as the distance was increased in millimetre steps up to 5cms. Figure 78 shows the results for both frequency shifts, divided by electromagnetic flow, plotted against height above the vessel. There is little variation in either frequency shift.

3. The third experiment investigated the effect of incomplete vessel insonation due to misalignment of the longitudinal axes of the probe and the vessel. Measurements of the two frequency shifts were made as the probe was traversed across the vessel in half millimetre steps. Figure 79 shows both frequencies, divided by the electromagnetic flow, plotted against distance. Mean frequency shift falls as the probe is moved away from the centre of the vessel. Mean maximum frequency shift, however, is much less affected.

CONCLUSIONS

Neither mean frequency shift or mean maximum frequency shift is much affected by probe rotation or distance between the probe and the
vessel. Incomplete insonation, however, reduces the mean frequency while mean maximum frequency shift is relatively spared. This provides an advantage for mean maximum frequency in velocity calculations which reinforces the advantage of the relative simplicity of its calculation. The use of these measurements in vivo is described in Chapters 6 and 7.
APPENDIX 3

RESULTS FROM EXPERIMENTS DESCRIBED IN CHAPTER 6.

COLUMN HEADINGS

Dog = Dog Number
DR% = Percentage diameter reduction
MdPi = Difference between mean pressures (P1-P2) at maximum hyperaemia
PP1i = Systolic pressure at the peak of the respiratory cycle for P1 at maximum hyperaemia
PP2i = Systolic pressure at the peak of the respiratory cycle for P2 at maximum hyperaemia
Mean BMi = Mean electromagnetic flow at maximum hyperaemia
Mean Fi = Mean Doppler frequency shift at maximum hyperaemia
Freq2i = Mean maximum frequency shift at maximum hyperaemia
MdPr = Difference between mean pressures (P1-P2) at resting flow
PP1r = Systolic pressure at the peak of the respiratory cycle for P1 at resting flow
PP2r = Systolic pressure at the peak of the respiratory cycle for P2 at resting flow
Mean EMr = Mean electromagnetic flow at resting flow rate
Mean Fr = Mean Doppler frequency shift at resting flow
Freq2r = Mean maximum frequency shift at resting flow
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APPENDIX 4

RESULTS FROM EXPERIMENTS DESCRIBED IN CHAPTER 7.

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<td>DR%</td>
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APPENDIX 5

RESULTS FROM EXPERIMENTS DESCRIBED IN CHAPTER 9.

COLUMN HEADINGS

Dog = Dog Number
run = 1st character - 0 No aortic snare applied
1-3 Degrees of aortic snare applied
2nd character - Femoral stenosis number
3rd character - Doppler recording site
4th character - recording run number
PI = Pulsatility Index
Wo = $\omega_0$ coefficient of the Laplace Transform
PC1 = Coefficient of the first Principal component of the
True Transfer Function waveform
PC2 = Coefficient of the second Principal component of the
True Transfer Function waveform
P1 = Mean pressure proximal to both stenoses
P2 = Mean pressure between aortic and femoral stenoses
P3 = Mean pressure distal to both stenoses
Q1 = Aortic flow
Q2 = Right femoral flow
Ta = Time interval between ECG R-wave and the onset of flow
Tb = Time interval between ECG R-wave and a point half way
up the upslope of the waveform
Tc = Time interval between the ECG R-wave and maximum
forward flow
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APPENDIX 6

RESULTS FROM EXPERIMENTS DESCRIBED IN CHAPTER 10.

COLUMN HEADINGS

Pat = Patient number

DR% = Percentage diameter reduction (superficial femoral 
and popliteal arteries)

dP = Difference between systolic pressures at common 
femoral needle and below-knee occlusion cuff

AIX = % diameter reduction of aorto-iliac segment as 
measured from the patients' radiographs.

AIP = % fall in common femoral pressure on papaverine 
testing

wf = ωo for the common femoral waveform

wp = ωo for the popliteal waveform

avTT = Normalisation factor from Gosling's data (1976)

PIf = Pulsatility Index for the common femoral waveform

PIP = Pulsatility Index for the popliteal waveform

TTf = Transit time for the common femoral waveform

TTp = Transit time for the popliteal waveform

Tf = Time from the ECG R-wave to a point half way up 
the systolic upslope for the common femoral waveform

Tp = Time from the ECG R-wave to a point half way up 
the systolic upslope for the popliteal waveform

RTf = Rise time for the common femoral waveform

RTp = Rise time for the popliteal waveform
PCI = Coefficient of 1st principal component of the True Transfer Function waveform

PC2 = Coefficient of 2nd principal component of the True Transfer Function waveform
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APPROACHES TO THE ASSESSMENT OF COMBINED SEGMENT VASCULAR DISEASE

Antony Richard Baker

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Co-existing aorto-iliac and femoro-popliteal disease is difficult to manage. Arteriography does not show the relative importance of the two components. Proximal reconstruction alone fails to relieve symptoms in 20-50% of cases. Total repair in all cases may increase mortality and morbidity and would involve unnecessary procedures in many patients. Haemodynamic information may allow pre-operative identification of the group in whom total repair is necessary.

A canine model of aorto-iliac disease showed that Doppler recordings are reliable in monitoring flow increases during a hyperaemic test. Indices were derived from the pressure and Doppler readings. These were shown to provide more accurate characterisation of stenoses than either pressure or flow alone. These indices were then investigated in patients with peripheral vascular disease where they gave increased accuracy in the assessment of the aorto-iliac segment.

The success of proximal reconstruction depends on what distal disease remains uncorrected. Many haemodynamic methods have been advocated for the assessment of the femoro-popliteal segment. In a canine model of combined segment disease segmental pressure gradient and several Doppler methods were compared. Pressure measurement was superior to the Doppler methods in characterising distal disease. Of the Doppler techniques Pulsatility Index Damping Factor was particularly disappointing. The reason for this was that arterial stenosis results in reduction of Pulsatility Index both distally and also proximally. The methods were then investigated in vascular patients. The best Doppler results were obtained with Normalised Transit Time. Damping Factor again produced disappointing results and its addition to Normalised Transit Time did not produce a statistically significant improvement in the area of clinical relevance. Segmental pressure measurement provided the most accurate assessment of the femoro-popliteal segment. None of the Doppler methods was sufficiently accurate for reliable clinical use.

Pressure measurements are required for accurate haemodynamic assessment in both the aorto-iliac and femoro-popliteal segments.