MEASUREMENT AND MONITORING OF ATHEROMATOUS LESIONS OF THE FEMORAL ARTERY BY DUPLEX ULTRASOUND

VALIDATION STUDIES AND CLINICAL APPLICATION

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Thesis presented to the University of London for the degree of Master of Surgery 1992

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Abstract

In Western Societies atheromatous stenosis and occlusion of the superficial femoral artery cause intermittent claudication in up to 5% of the population over 55 years of age, and the associated morbidity and disability are considerable. A foreknowledge of impending lesion progression might allow prevention of clinical deterioration by early intervention. However, the natural history of these lesions needs to be more fully evaluated.

Critical to the monitoring of early lesions is the need for accurate, repeatable and non-invasive investigations. The role of duplex ultrasound in this area is largely unexplored. In this thesis clinical and laboratory data demonstrate the accuracy and repeatability of duplex ultrasound in the measurement of femoral stenoses. A prospective study was carried out to determine the incidence of progression from stenosis to occlusion.

There has been an enormous increase in the use of percutaneous transluminal angioplasty (PTA) in the treatment of patients with claudication. However, the relative benefits of PTA over conventional treatment have not been established. A study to determine the role of duplex in screening patients with claudication prior to PTA was carried out. The results demonstrate its accuracy and the consequent clinical benefits. A randomised controlled trial of PTA for patients with intermittent claudication has been established and the early patient data at trial entry are presented.

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Declaration

The research in this thesis was conducted while I held the post of Clinical Research Fellow in the Wolfson Unit for Prevention of Peripheral Vascular Diseases, in the University of Edinburgh, and was conducted in the Royal Infirmary of Edinburgh. My employment was funded by the Wolfson Foundation. I obtained a grant of £51,942 from the Scottish Home and Health Department to fund the angioplasty trial described in chapter 6, and recently obtained a grant of £52,900 from the same source to update to High Definition Imaging technology the colour duplex machine used in the studies described in this thesis.

My personal contribution to the work in the thesis is as follows:- I have been involved in the conception and organisation of all the studies. I have carried out all duplex scans. Drs GC Leng and PL Allan performed those scans necessary for the repeatability studies. Dr P Hoskins was responsible for the construction and maintenance of the laboratory flow phantom described in chapter 2. I am responsible for the data analysis and interpretation throughout, except for the analysis of variance in chapter 2 which was done by Mr P Donnan using the SSPSX programme on the University mainframe computer, and the analysis of data in chapter 3 which was done by Dr GC Leng. My own data analysis was done with the assistance of the computer

programmes "Slidewrite" and "Lotus123".

The source of information is the Erskine Medical Library of the University of Edinburgh, where references were obtained by a search of Index Medicus, and by computer access to published literature (CD-ROM - Medline). Approval for the clinical studies was granted by the local ethics committee and details are given under the appropriate chapter.

At the time of writing the publications which have arisen from work done towards this thesis are:-

Whyman MR, Ruckley CV, Fowkes FGR. Angioplasty for mild intermittent claudication. Br J Surg 1991;78:643-645 (Leading Article)

Whyman MR. The Natural History of Femoral lesions. In: The Epidemiology of Peripheral Vascular Disease Ed:Fowkes FGR, Springer-Verlag, London 1991, p 301-313

Whyman MR, Leng GC, Hoskins PR, Allan PL, Donnan P, Ruckley CV, Fowkes FGR. Accuracy and reproducibility of duplex ultrasound in a phantom model of femoral artery stenosis. J Vasc Surg (in press).

Leng GC, Whyman MR, Donnan PT, Ruckley CV, Gillespie I, Fowkes FGR, Allan PL. Accuracy and reproducibility of duplex ultrasound in grading femoropopliteal stenoses. J Vasc Surg (in press).

Whyman MR, Gillespie I, Ruckley CV, Allan PL, Fowkes FGR. Screening patients with claudication due to femoropopliteal disease before angioplasty using Doppler Colour Flow Imaging. Br J Surg (in press).

Claims to originality of the thesis

The reproducibility of duplex ultrasound velocity measurements of femoral artery stenoses has not been previously reported, and there has been no previous account of the natural history of femoral stenosis using duplex ultrasound. The results presented in chapters 2-4 of this thesis indicate that duplex can be used to study the natural history of femoral stenoses. There has been no previous account of the true value of screening patients with claudication before angioplasty using duplex. The study in chapter 5 demonstrates the clinical benefits consequent on screening. The randomised controlled trial of angioplasty described in chapter 6 differs fundamentally from the only other similar trial. The results will demonstrate the role of angioplasty in the management of patients with intermittent claudication.

Acknowledgements

First and foremost I owe a debt of gratitude to Mr CV Ruckley and Dr FGR Fowkes for their guidance and patience during these studies. Their experience, and in particular their ability to define the essence of a problem have saved me countless hours of fruitless labour. I am grateful to Mr JA Murie, Mr AMcL Jenkins and Dr E Housley for their advice and help in many areas, particularly the angioplasty trial, and for allowing me to see and manage their patients. I must thank Dr P Allan for introducing me to duplex ultrasound, for his continued support and advice, and his help with the phantom study. Dr Gill Leng patiently listened to my academic problems during the last two years. Without her expertise the validation studies would have been arduous if not impossible. My understanding of Doppler principles would have been even poorer had Dr Peter Hoskins not devoted much of his time to explanation. His careful management of the technical aspects of the flow phantom made a study which might otherwise have been fraught with methodological hazards seem deceptively simple. Dr Ian Gillespie has offered sound advice on many radiological matters, and I am grateful for his enthusiasm and help in ensuring the angioplasty trial will be a success. I thank Mr Peter Donnan and Dr R Prescott for their advice on the use of statistical tests, and Peter for his time in performing some of the analysis. Special thanks go to Eileen Kerracher for her hard work as physiological measurement technician, and for her thoughtfulness towards the patients in the trial. Without a multitude of small and large favours, day to day activities would have become onerous, so I would like to thank Margaret Dunn in the Wolfson Unit, Vie, Celia

and Ellen from the PVC, and the nurses on wards 13,14 and 28. Finally, a word of thanks to Meedox for their financial support of the trial, and ATL and Vascutek for making my travel to various conferences possible.

Preface

In the United Kingdom approximately 50,000 Hospital admissions per year are for Peripheral Arterial Disease (PAD). Around 15,000 major operations are performed annually (DHSS 1986) in an attempt to redress the disabling and often devastating effects of lower limb ischaemia. Intermittent claudication is usually the earliest symptom of lower limb atherosclerosis. In Scotland, where this research is based, claudication affects approximately 5% of the population over 55 years of age, and it is estimated that the prevalence of asymptomatic significant occlusive disease is around three times higher than this (Fowkes et al 1991).

Until recently claudication was treated conservatively by most vascular specialists. This situation arose for a number of reasons:

1. Bypass surgery carries a significant risk of complications and is associated with limited patency rates.
2. Claudication often remains stable for long periods and may run a relatively benign course.
3. Many clinicians believe that aggressive treatment of claudication is not warranted in the face of a high mortality from associated vascular diseases.

However, the lifestyle of some patients with claudication is seriously affected by claudication. There may in turn be a detrimental affect on other cardiovascular risk factors, eg. exercise, smoking, diet and psyche. In addition, many patients run the risk of progression of disease. This not infrequently results in more severe ischaemia which requires

reconstructive surgery or interventional radiology to relieve rest pain and prevent or limit tissue loss.

The typical lesion in early claudication is a stenosis or short segment occlusion in the femoral artery and this lesion is potentially reversible by percutaneous transluminal angioplasty. When the disease progresses the difficulty of the procedure increases and the risks are higher. Thus, a "window of opportunity" may be present early in the disease which is lost as the disease progresses. **It is not known how rapidly progression of early and potentially reversible lesions occurs nor how inevitable are the consequences in terms of clinical deterioration. Such information might be fundamental to improving management strategies which include angioplasty in patients with early lesions.**

A number of circumstances combine to suggest the need for re-appraisal of the pros and cons of early intervention. These are:

1. Minimally invasive treatment is now available (angioplasty).

2. There are new non-invasive screening techniques (duplex ultrasound).

3. A more active approach is now being taken to coronary artery disease and stroke prevention (Hertzer 1991, European Carotid Surgery Trialists Collaborative Group 1991).

The first step in defining the place of early intervention is to evaluate the tools available for measuring the disease. Duplex ultrasound is safe, can be used repeatedly, and in trained hands gives important haemodynamic and morphological information. It therefore lends itself to the study of peripheral arterial disease and its natural history. **However, most studies comparing duplex with other diagnostic methods have been done on the carotid circulation and much of the validation of duplex in lower limb disease, particularly in measurement of stenosis, has gone unchallenged.** Validation studies are therefore presented in this thesis which demonstrate the potential of duplex to monitor early lesions of the femoral artery.

The next step is to evaluate the treatment to be used in early intervention. Randomised controlled trials are necessary to assess the relative benefits of early intervention. The setting up and initial data from a new clinical trial of percutaneous transluminal angioplasty for the treatment of intermittent claudication are described.

Chapter 1

Background information on atherosclerosis and peripheral arterial disease is given. The relevant history of the subject is described, the natural history of femoral atheromatous lesions is reviewed, and the basis of early intervention is discussed in the context of the natural history. The principles of Doppler and duplex ultrasound are explained, in order to understand the role of duplex in monitoring femoral lesions, and simple aspects of flow dynamics relevant to the subject are described.

Chapter 2

A laboratory flow model of the femoral artery is used to study 14 concentric and eccentric stenoses using duplex ultrasound. The aim is to correlate relative increase in velocity within the stenosis (Velocity Ratio, VR) with the degree of narrowing, and to determine the variability of VR measurements. VR showed good correlation with degree of stenosis. Intra-observer variability was low, but inter-observer variability was significant with more severe stenosis. It is concluded that duplex ultrasound can accurately grade arterial stenosis and the potential exists for non-invasive monitoring of progression of pre-occlusive femoral atherosclerosis and its response to treatment.

Chapter 3

Thirty patients with isolated areas of stenosis on arteriography were evaluated using colour duplex ultrasound,

with the aim of establishing the accuracy and variability of the latter. Patients were scanned by two observers on two separate occasions. Each observer was blind to the results of the other. An increase in peak systolic velocity of more than 200% accurately predicted a ≥50% reduction in luminal diameter on arteriography. Spectral broadening and an abnormal waveform shape were found to correlate poorly with the degree of stenosis. Analysis of variance showed no significant difference between observers in velocity measurements. It is concluded that stenoses of greater than 50% can be accurately distinguished from minor stenoses, but more precise definition of the degree of narrowing could not be demonstrated. This might be partly due to the difficulty in precise measuring of arteriographic stenosis. The repeatability of velocity ratio measurements make it a suitable index to use in monitoring major changes in the progression of disease.

Chapter 4

The aims of this study were to determine:-

1. the change in degree of femoral stenosis over time according to duplex ultrasound velocity ratio measurements.
2. the incidence of progression from stenosis to occlusion.

Forty-three stenoses in 38 patients were studied using duplex ultrasound to quantify the degree of stenosis. Repeat duplex examinations of the same stenoses were performed after a median of 28 weeks. None of the stenoses with a velocity ratio (VR) less than 3 progressed to occlusion. One half (6/12) of those in the VR range 3-6 and one third (3/9) of

those in the VR range >6 occluded. It is concluded that occlusion is liable to occur in any stenosis with a VR of >3 as a sudden event.

Chapter 5

Thirty patients underwent duplex scanning prior to arteriography with the aim of ascertaining whether duplex could be used to screen patients prior to angioplasty. Agreement between the two methods over presence of significant lesions was excellent and the predictive accuracy of duplex for lesions amenable to PTA was good; sensitivity = 94%, specificity = 85%, positive predictive value = 83%, negative predictive value = 94%, overall accuracy = 89%. It is concluded that duplex ultrasound is a valid screening tool before arteriography, and affords clinical benefits.

Chapter 6

This chapter describes a randomised controlled trial of percutaneous transluminal angioplasty (PTA) for the treatment of intermittent claudication. The rationale of the trial is discussed, the aims and methods are described, and early patient data at trial entry are given.

Abbreviations

The meaning of the abbreviations in common use in this thesis is as follows:

PAD	Peripheral arterial disease
PSV	Peak systolic velocity
PTA	Percutaneous transluminal angioplasty
PVC	Peripheral vascular clinic
RIE	Royal Infirmary Edinburgh
SB	Spectral broadening
SD	Standard Deviation
SFA	Superficial femoral artery
VR	Velocity ratio

MRW	Mark Roy Whyman
GCL	Gillian C Leng
PLA	Paul L Allan
IG	Ian Gillespie
CVR	C Vaughan Ruckley

CHAPTER 1

This chapter provides the background information necessary for an understanding of the studies presented in chapters 2-6. The literature is reviewed and gaps in present knowledge are highlighted. The chapter is divided into two sections: Section one deals with peripheral arterial disease and its natural history. Section two covers the principles of haemodynamics and Doppler ultrasound.

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SECTION 1

SECTION 1

1.1. ATHEROSCLEROSIS

Although atherosclerosis is a contempory problem, it is by no means a modern disease. In fact, it has probably affected the human race for thousands of years. Atherosclerosis was found in the mummy of the Ancient Egyptian Pharaoh Menephthah (Shattock 1909), and also in pre-Hispanic Peruvian mummies (Henshen 1962). The terms "atheroma", "arteriosclerosis" and "atherosclerosis", often used interchangeably, were coined respectively, by Albrecht Von Haller in 1755, J.F.Lobstein in 1833 and Felix Marchand in 1904, and some of the histological features recognised today were described in the mid 19th Century by Von Rokitansky. The unravelling of the mysteries of atherosclerosis has, however, been left largely to this century. The natural history of human disease is difficult to study and animals have been used extensively as models for research. Rabbits were the first to be used (Ignatovski 1908) and since then many varieties (Show Racer and White Carneau pidgeons, swine, chicks, dogs, Rhesus and African Green Monkeys, baboons and Cynomolgus macaques) have been shown to have qualities suitable, though not perfect, for mimicking various aspects of human disease (Clarkson et al 1987, Blankenhorn and Kramsch 1989).

Despite extensive research, the precise nature of plaque development is still far from clear, but a picture is emerging which suggests that a multiplicity of factors contribute to initiation and maturation of the lesion.

1.1.1. Initiation of atheroma

There is considerable controversy over how atherosclerosis begins. The very earliest lesion is, arguably, the gelatinous (mucoid) streak. This consists of an area of focal intimal thickening, with intimal oedema which contains fibrinogen, glycosaminoglycans and collagen, and only rarely encroaches significantly on the arterial lumen (Gresham 1987). If this is the progenitor for more advanced lesions, then the ability to measure arterial wall thickness (Beach et al 1989), intimal/medial thickness (Poli and Paoletti 1987), and change in thickness over time (Salonen and Salonen 1990) using ultrasound imaging has important implications for epidemiological research. The same method might also prove useful in future intervention studies in very early disease. At the stage of intimal thickening there is increased permeability of the endothelium to blood constituents. This is not a new concept since Virchow considered an "infiltrative theory" of imbibition of blood constituents (Virchow 1856). Areas exposed to an unstable stress pattern may have a predilection for lipid deposition, although the permeability of endothelium is sensitive to a large number of chemical and physical factors in addition to mechanical stress (Fry 1973). There may be a synergy between mechanical and infiltrative influences on development of the atherosclerotic lesion. Some of the haemodynamic mechanisms canvassed have been summarised by Woolf (1982), and include changes in lateral wall pressure, changes in wall shear stress, flow separation and turbulence.

1.1.2. The advanced lesion

Plaque, stenosis and "critical stenosis"

I have deliberately avoided defining each of these terms. What is a plaque to the histopathologist may be a stenosis to the radiologist and a critical stenosis to the vascular surgeon. However, the terms are used in order to convey the idea that an atheromatous lesion can go through a series of changes (Table 1.1), progressively encroaching on the arterial lumen until a fall in distal pressure occurs and the patient develops symptoms.

In the superficial femoral artery (SFA) most primary stenoses have been shown to consist of mature atheromatous plaque (Figure 1.1) (Johnson et al 1990). Atheroma, (derivation - the Greek for "porridge") describes the gross appearance of one of the important morphological features. Full development of the lesion may occur gradually or in a series of step-like increments, but in any case a number of well recognised events first occur: There is proliferation of smooth muscle cells and macrophages which secrete a connective tissue matrix, and an accumulation of intra- and extra-cellular lipid most of which is cholesterol derived from plasma. Further complex events allow development of a fibrous connective tissue cap which overlies a pool of necrotic lipid-rich debris, cholesterol crystals and foci of calcification (Ross et al 1984), and the whole sits atop the internal elastic lamina. Advanced plaques also frequently involve the arterial media. Exactly how and why such a mature

plaque liable to cause the symptoms of peripheral arterial disease (PAD) which are so prevalent in Western Society develops from its precursors is not well understood.

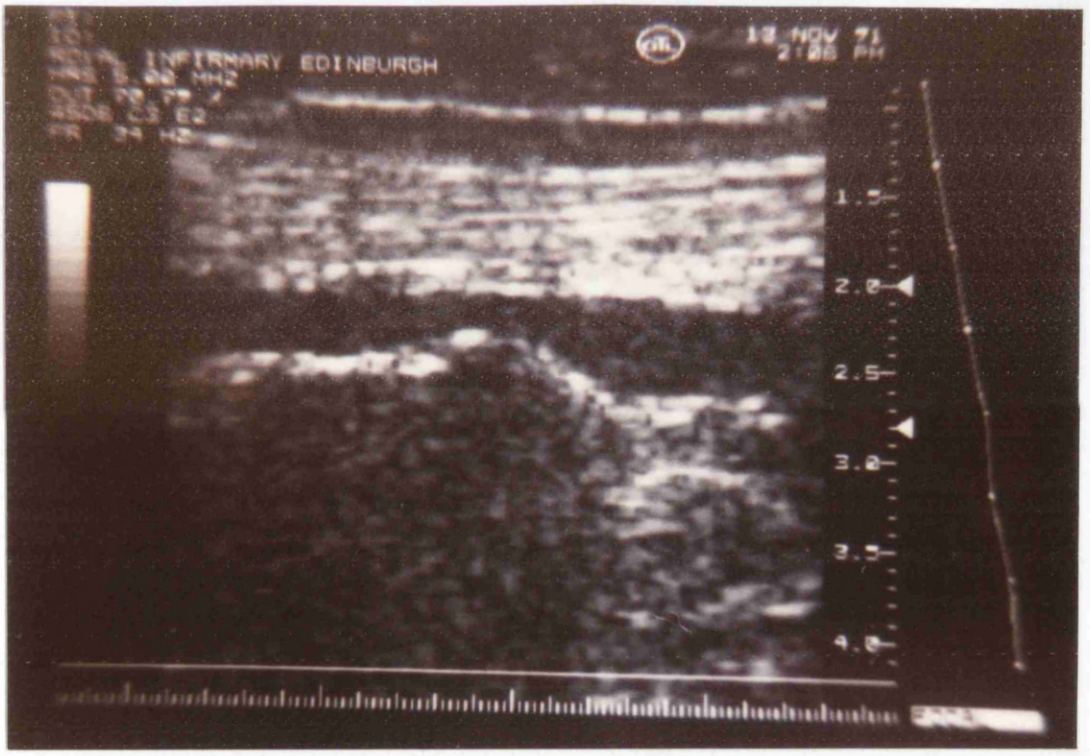
Table 1.1

Pathological events in stenosis progression

Intra-plaque events	- incorporation of thrombus/lipid
	- medial necrosis
	- haemorrhage
	- dissection
Extra-plaque events	- platelet accumulation
	- intravascular thrombosis
	- vessel spasm
Haemodynamic events	- turbulence
	- haemodynamic "stress"
	- reduction in distal pressure
	- reduction in volume flow
	- flow separation
	- change in lateral wall pressure

Figure 1.1

Ultrasound image of an atheromatous plaque in the SFA



1.1.3. Intra-plaque events

A number of well recognised pathological events might, alone or in combination, be responsible for plaque progression:

i) Incorporation of thrombus into the plaque: The thrombogenic theory of atherogenesis is not new (Von Rokitansky 1852). Thrombus may directly promote growth of the lesion (Duguid 1946, 1948), or it may effect growth indirectly by increasing the proliferative response of the arterial wall (Woolf 1982). One third of plaques of the SFA excised by atherectomy were covered by thrombus (Johnson et al 1990), and this surface thrombus might therefore be both an integral component of a plaque in evolution and at the same time an external element which aggravates the haemodynamic effect of the lesion, and promotes lesion progression.

ii) Medial necrosis: The early plaque which barely protrudes into the lumen and offers minimal obstruction to flow may eventually thicken sufficiently to cause impaired oxygen diffusion to the inner media deeper than 1 mm. The outer media is supplied by the vasa vasorum. A vascular watershed therefore exists, with the vulnerable cental media potentially at risk of necrosis due to ischaemia. In addition, there may be a cytotoxic effect of medial oxysterols (Adams 1987) which cause further necrosis. The medial necrosis and oedema which results can add to the size of the lesion.

iii) Intra-plaque haemorrhage: This is common (Woolf 1982) and may be important in the sudden transformation from plaque to significant stenosis. Atherogenesis is associated with thin-walled vasa vasorum (Heistad and Armstrong 1986) which can rupture (Paterson 1938). If a connection develops between the site of haemorrhage and the lumen then an innocent plaque may become clinically important, more so in the carotid territory than the lower limb (Persson et al 1983).

iv) Plaque dissection: This is of potential importance during plaque growth and as the final (pre-) occlusive event (Friedman and Van Den Borenkamp 1966), but very little is known about the extent to which it contributes to disease progression in the lower limb.

1.1.4. Platelets

The role of platelets in the formation of advanced lesions may be important, particularly in relation to thrombus formation. At the site of stenosis, where flow is altered sufficiently to cause turbulence and points of stagnation, platelets can accumulate (Fox and Hugh 1966). There may be increased platelet/vessel wall interactions which then mediate the formation of intimal microthrombi (Murphy et al 1962, Muller-Mohnssen et al 1978) and further stimulation of smooth muscle cell proliferation (Robertson 1960, Wesolowski et al 1965). However, there is divergence of opinion on the exact site of platelet interaction since animal experiments have indicated that platelets accumulate mostly on the apex

of a stenosis and not in the flow recirculation zone (Badimon and Badimon 1989). In any case, the process of mural thrombus formation might effect progression of an atherosclerotic narrowing (Haust 1971).

1.1.5. Haemodynamic influences on the lesion

Complex flow patterns can exist even in the healthy artery and there is much evidence suggesting that haemodynamic factors are of paramount importance not only in initiating atherogenesis but also in localising disease (Stehbens 1974). Haemodynamic stress can produce intimal tears, ulceration and mural thrombosis (Stehbens 1974), and it may therefore be responsible for some of the pathological events involved in evolution of a plaque and its transformation to a haemodynamically significant stenosis.

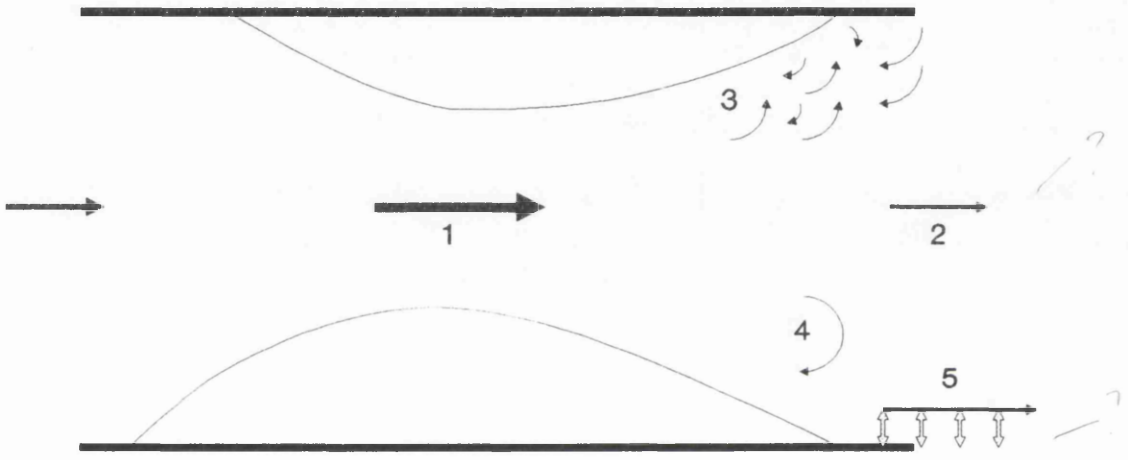
1.1.6. Effects of the lesion

i) Haemodynamics

In the case of severe stenosis there may be a dramatic alteration in the flow patterns, with high and low flow states, turbulence, reverse flow and flow separation (Figure 1.2). Conditions of increased flow velocity, eg. within a stenosis (Barnes 1980), may exert a protective effect on atherogenesis, whereas flow separation and instability might favour atherogenesis (Zarins et al 1981). A vortex distal to a stenosis may lead to an increase in size of the latter (Fox and Hugh 1966), thereby establishing a vicious cycle of accelerated plaque progression and further flow disturbances.

Figure 1.2

Flow abnormalities within a hypothetical stenosis



1 ▪ High velocity

2 ▪ Low flow

3 ▪ Turbulence

4 ▪ Reverse flow

5 ▪ Flow separation

Recently, it has been suggested that endothelial loss which occurs in the central region of a fibrous plaque may alter vascular reactivity (Kolodgie et al 1990), and this in turn might accentuate a stenosis and the haemodynamic disturbances associated with it.

ii) Velocity changes

As blood flows through an area of narrowing there is an increase in velocity (Barnes 1980). It may therefore be possible to document a progressive reduction in luminal diameter by measuring increases in blood velocity within a stenosis over the course of time. It is possible to imagine a self-perpetuating cycle of deranged flow and acceleration of disease, which could be monitored over a relatively short period before an occlusive event occurs. This might be achieved by a reliable instrument capable of measuring blood velocity such as duplex ultrasound.

iii) Progression of disease

The effect of the lesion itself on blood flow may affect progression of disease but the direction in which it does so is unclear. Clinical deterioration is more frequent in the presence of occlusion than stenosis (Selvaag et al 1960), possibly because the slow flow distal to an occlusion leads to the development of other occlusions via a mechanism of "thrombosis-in-situ" of stenotic segments (Humphries 1971). On the other hand, it has been shown in animal experiments that disease distal to a stenosis advances more rapidly if

there is subcritical (reduction in luminal diameter of up to 65%), rather than haemodynamically critical narrowing (Bomberger et al 1981). In fact, it has even been suggested (light-heartedly) that a stenosis be deliberately constructed when performing a surgical bypass, in order to minimise distal disease progression (Warren et al 1961). One explanation is that hypotension inhibits development of atherosclerosis (Bomberger et al 1980).

iv) Embolism

An atheromatous plaque is a potential source of embolic material which can cause digital ischaemia and gangrene (Hoye et al 1959). However, the frequency with which this occurs and the extent to which it can be prevented by early intervention is not known.

There are, therefore, numerous potentially important mechanisms involved in plaque formation and subsequent development into the lesion which causes complete luminal obliteration. It is important to appreciate these possible mechanisms when looking at new means of investigating stenosis progression and when considering new types of treatment, and further reference will be made to them in chapter 4.

1.2. OCCLUSION

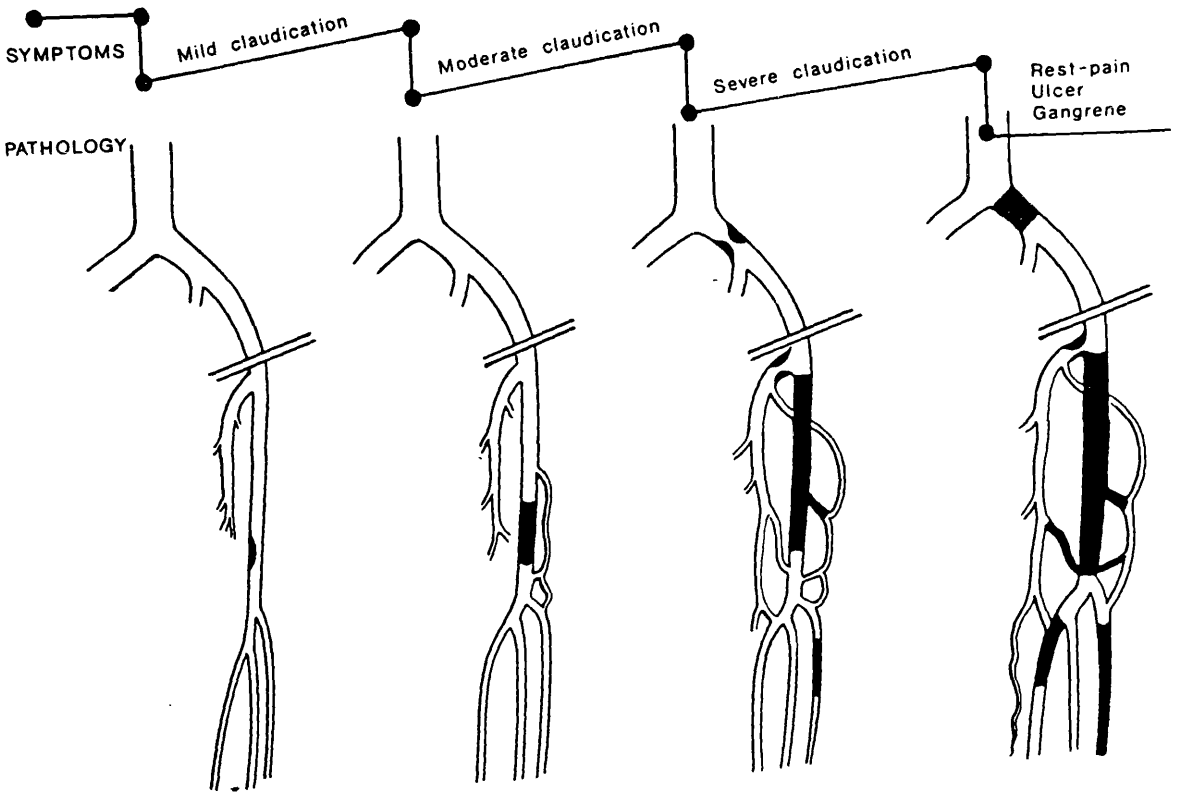
It is likely that one or more of the aforementioned processes precipitates thrombotic occlusion, but **how severe a stenosis has to become before it is a significant risk of producing occlusion is not clear.** In a series of coronary angiograms the only morphological feature of plaque which predicted total occlusion after a mean of 29 months was narrowing of greater than 75% of the luminal diameter (Halon et al 1985). If the same could be said of femoral stenoses, degree of narrowing might be the most important measurement to make when monitoring stenosis progression. When the stenotic process is so advanced as to cause severely deranged flow then occlusion occurs, and there is traditionally thought to be complete cessation of flow through the affected arterial segment. However, it is possible that early after thrombosis there is still minimal flow through the thrombus for some time until organisation occurs and a solid obstruction to flow is present (personal observation using duplex sonography). This suggests that the site of the stenosis might still be patent, and that atheroma alone might not always be responsible for luminal obliteration. In some cases, of course, there may be an intra-plaque event such as haemorrhage, necrosis, dissection or thrombosis which precipitates sudden growth of the plaque to a degree sufficient to completely occlude the lumen. In this case the supervening thrombosis would not allow any flow at all, and the situation might be distinguishable from that mentioned above.

It is thought that thrombotic occlusion is usually limited to a short length of artery in the first instance, but that after a variable period of time the thrombus propagates to the next collateral vessel, usually in a proximal direction (Lindbom 1950). When the mouth of the collateral is occluded by further thrombus or atherosclerosis, the process continues until the entire length of the vessel is occluded (Figure 1.3). Proximally this is generally not beyond the common femoral artery bifurcation since the main collateral supply in SFA occlusion is the large profunda femoris artery, and the medial and lateral circumflex arteries where flow is high. Distally the supreme geniculate artery provides the major distal source of re-entry into the SFA (Humphries 1971).

After occlusion the distal circulation is dependent upon collateral vessels, and where these allow good volume flow ischaemia is minimised. Thus the prognosis for a limb is better in SFA than popliteal artery occlusion (Mavor 1956). On a historical note, it is interesting that Hunter himself initiated the experimental investigation of collateral circulation in 1785, but this was in the stag antler, not the femoral artery. His understanding of the collateral circulation led to the treatment of popliteal aneurysm by proximal ligation of the superficial femoral artery (Dobson 1969).

Figure 1.3

Progression of Peripheral arterial disease



The accurate detection of an "at risk" lesion might allow timely intervention by, for example, percutaneous transluminal angioplasty (PTA), which would pre-empt the worsening of symptoms. The stenosis and "early" short length occlusion are readily amenable to PTA. Long occlusions (>10cm) are technically more difficult to treat and long term patency is poorer. The "window of opportunity" thus presented at an early stage in the disease might be the appropriate time for intervention by a relatively low risk treatment. This, in turn, might prevent further progression and need for reconstructive surgery. However, many of the patients with SFA occlusion deteriorate as a result of progression of disease in the profunda femoris or iliac arteries (Wilson et al 1980) and lengthening of occlusion might, in many instances, confer no disadvantage. The paucity of knowledge of the natural history of specific femoral lesions and the relative lack of long term results of PTA mean that it is still not clear whether early intervention is of benefit to patients. The concept of early intervention is discussed further in chapter 6.

1.3. REGRESSION OF ATHEROSCLEROSIS

Regression might occur not only as the result of therapeutic intervention but also as part of the natural history of atherosclerosis. It is important, therefore, that new instruments are sufficiently sensitive to record change in disease in both directions.

Professor Neville Woolf (1982) conveys well the divergence of opinion regarding possibilities for intervention:

"Attitudes range from:

> 'a growing body of evidence indicates that the process of atherosclerosis is almost completely preventable and that it is substantially reversible' (Wissler and Vesselinovitch 1976)
>
> to
>
> 'to think of preventing atherosclerosis itself is to shut ones eyes to the nature of the condition. It is a product of ageing and, as Aschoff (1938) remarked "there is no remedy for old age"' (Duguid 1976)".

Regression is more likely to occur in an uncomplicated plaque or in early atherosclerosis than in the mature stenosis (Blankenhorn and Kramsch 1989). The potential for individual plaque components to contribute to regression in experimental models has been summarised well in a recent review (Armstrong et al 1990):

Endothelium can regenerate to provide renewed cover of a denuded subendothelium and it can regain normal permeability. Intimal cells and foam cells can decrease and lipid diminish. From a functional aspect the altered vascular reactivity of atherosclerosis can be reversed during regression. The extent to which fibrous connective tissue, calcification, elements of necrosis, thrombus and intra-plaque haemorrhage can change is more controversial, and although it is possible that they might be altered in an experimental setting, there is little evidence to suggest they change substantially in humans.

Historically, Aschoff is credited with being the first to offer indirect evidence of regression when he noticed a reduction in aortic atherosclerosis as the first World War progressed (Aschoff 1924). This has been attributed to the imposed dietary restrictions at that time. More recently there have been studies of human femoral disease where arteriography was used to measure atherosclerotic encroachment on the lumen. This method has a number of significant limitations, not least of which is the risk and discomfort for the patient. In addition, most of the work was conducted in patients with hyperlipidaemia after intensive drug treatment and risk factor management. Nevertheless, regression was reported in between 10% and 75% of patients (Ost and Stenson 1967, Barndt et al 1977, Erikson et al 1983), and in one case a femoral occlusion was reported to have actually disappeared (Ost and Stenson 1967). Individual cases of regression have also been reported (DePalma et al 1970, Crawford et al 1979), and one randomised trial of drug versus standard therapy in hyperlipidaemic patients showed that lesion progression was reduced by one third in the drug treated compared to the control group (Duffield et al 1983).

It is apparent that meticulous long term studies would be required to show significant improvement in lesion size or extent in the "normolipidaemic" patient with claudication, and that the role of regression in this situation is far from clear.

1.4. THE NATURAL HISTORY AND MANAGEMENT OF PERIPHERAL ARTERIAL DISEASE

Clinical manifestations of peripheral arterial disease (PAD) occur at a relatively late stage in the evolution of atheroma. However, this is a stage which can be readily recognised and measured with reference to its clinical, radiological and haemodynamic effects. Chronic lower limb ischaemia caused by advanced PAD has a tremendous impact on Western Society. A perspective of the problem is given in the following summary of the epidemiology and natural history of, and risk factors for PAD. The need to approach the problem as much from a preventive standpoint as a palliative one thus becomes apparent.

1.4.1. Epidemiology

The prevalence of PAD has been assessed in a number of population surveys. The earliest estimate was in Switzerland, where claudication was identified in 1.1% of pharmaceutical employees aged 15-64 (Widmer et al 1964), and the highest prevalence reported is 10% in East Finland in men aged 55-74 (Heliovaara 1978). Figures from the Edinburgh Artery Study show local prevalence to be 4.6% in those aged over 55 years (Fowkes et al 1991). Men are more frequently affected than women (Schroll and Munck 1981, Criqui et al 1985), and the prevalence rises with age (Widmer et al 1964, DeBacker et al 1979).

Asymptomatic disease is more common than this. In a post mortem study 15% of men and 5% of women had severe disease (at least 50% stenosis) in at least one lower limb artery, and very few were completely free of disease (Mitchell and Schwartz 1965). Main vessel occlusion is silent in two-thirds of cases (Widmer et al 1964, Schroll and Munck 1981).

The cumulative incidence of claudication in a normal population is around 3% after 14 years (Kannel and McGee 1986). In one study it was shown to vary between 2.5% and 33% after 11 years, depending on whether patients had clinical evidence of asymptomatic disease (confirmed on arteriography) at the outset of the study (Widmer 1985).

1.4.2. Natural history

1) Mortality

Patients with PAD have a higher mortality than that of the general population (Reunanen et al 1982, Widmer 1985). In patients who initially present to hospital with claudication or more severe ischaemia, the 5 year mortality is around 10-30% (Spaulding 1956, Richards 1957, Singer 1960, Bloor 1961, Begg and Richards 1962, Coran and Warren 1966, Jelnes et al 1986). Lassila et al (1986) reported a 69 % mortality with follow up beyond 9 years. In general the mortality of patients with chronic leg ischaemia can be stated to be around 30, 50, and 70% after 5, 10, and 15 years of follow up (Dormandy et al 1989a). Ischaemic heart disease is the cause of death in 35-60% of patients (Fowkes 1988), and all

vascular causes together account for 50-85% of deaths (Spaulding 1956, Schadt et al 1961, Bloor 1961, Begg and Richards 1962, Mathieson et al 1970, Kallero 1981, Cronenwett et al 1984). Thus intermittent claudication is a "marker" of substantially increased mortality from cardiovascular disease. Since it is "not so benign" (Coffman 1986) where survival is concerned, attempts to improve mortality are to be welcomed. One way would be to take an aggressive approach to coronary artery disease and stroke prevention. Similarly, it is also possible to intervene at an early stage in the natural history of the arterial lesion which causes claudication. By effecting a change in lifestyle through improved walking and better motivation in carefully selected patients it might be possible to bring about beneficial changes in risk factors and alter the otherwise unfavourable outlook of many individuals. However, whereas it might be true that regular exercise improves health and longevity for the majority, patients with claudication might not achieve the same benefits.

2) Morbidity (Table 1.2)

There is considerable variation in the literature in the definition of deterioration of claudication. Most studies refer to a classification of ischaemia akin to the Fontaine system (Fontaine 1947), and deterioration means progression to the next stage. By this definition the rate of deterioration of hospital-referred patients with claudication is around 25-35% after 3-5 years (Richards 1957, Bloor 1961,

Begg and Richards 1962). Kallero (1981) found that of those who needed surgery for deterioration, 60% did so within one year of presentation. Alternatively, the rate of deterioration has been calculated as 7.5% in the first year after presentation then 2.2% per year thereafter (Jelnes et al 1986). This would give a lower cumulative figure than that quoted above but the lower rate is supported by data from other recent studies (Kallero 1981, Dormandy 1991). Table 1.2 shows data from primarily non-surgical series. It can be seen that in approximately 1/4 of patients there is significant deterioration some time after presentation.

A simple worsening of claudication distance is a more frequent event. In one series 60% of patients were worse after 2.5 years (Cronenwett et al 1984). Where the population includes patients with more severe ischaemia at presentation, then the figures for deterioration are worse: 43-65% progress after 3-4 years (Strandness and Stahler 1966, Selvaag et al 1960, Humphries et al 1963). Estimates of the number of patients with claudication requiring reconstructive surgery vary between 3 and 22% (Dormandy et al 1989a).

Symmetry is a notable feature of the disease. In a study of 100 patients with claudication not needing surgery, 39% of those with femoropopliteal occlusion developed a contralateral occlusion during 2-6 years of follow up (McAllister 1976).

Table 1.2

Natural history of intermittent claudication

Author	Number of patients	Follow up (years)	% Stable or improved	% Worse
Silbert & Zazeela 1958	1115	3-25	56.5	43.5
LeFevre et al 1959	185	5	74.6	25.4
Bloor 1961	1476	4-10	71	29
Schadt et al 1961	362	9	93.3*	6.7*
Taylor & Calo 1962	412	3-12	82.7	17.3
Begg & Richards1962	198	5-13	68.8	31.2
Ulrich et al 1973	304	0.6-6.4	75	25
Imparato et al 1975	104	0.5-8	79	21
McAllister 1976	100	1-18	78	22
Kallero 1981	193	8-11.5	78.8	21.1
Cronenwett et al 1984	91	0.5-6	40	60
Jelnes et al 1986	257	6.5	84	16

Reproduced with permission (Dormandy et al 1989a)

* = survivors only

The incidence of amputation is used as a definitive outcome measure, and although several factors affect the incidence, it serves as another means of describing natural history. The incidence of amputation in patients with claudication who did not have the benefit of reconstructive surgery was around 1.4% per year (Bloor 1961) or, cumulatively, around 7% after 5 years (Bloor 1961, Begg and Richards 1962). The amputation rate is lower in patients presenting only with claudication, as opposed to a population of patients with PAD including more severe ischaemia (Juergens et al 1960), and is higher in diabetics (Silbert and Zazeela 1958). In two major community surveys the incidence of amputation after more than 14 years and after 7-15 years was 1.6% (Kannel and McGee 1986) and 1.8% (Widmer 1985) respectively.

1.4.3. Clinical studies of Progression of the disease process (Table 1.3)

There have been a number of studies of the true natural history of femoral disease in patients with symptoms of PAD, where arteriography was performed in a scheduled manner rather than after deterioration of symptoms. Coran and Warren (1966), in updating earlier results (Warren et al 1964), performed annual femoral arteriography for more than five years in 15 patients with claudication. All patients had at least 90% reduction in luminal diameter of the femoropopliteal segment. It was not stated what proportion of the 19 limbs had occlusion as opposed to stenosis. Five limbs showed no progression of disease at all. Fourteen showed

Table 1.3

Progression of the disease process - clinical studies

Study	Investigation	Follow up	Progression*
Coran and Warren 1966	Scheduled angiography	5 years	74% of limbs
Kuthan et al 1971	Scheduled angiography	2.5	52% of limbs
Chilvers et al 1974	Angiogram for symptoms	1-4 years	↑ SFA narrowing in 27-46%
Dawson and Raphael 1968	Angiogram for symptoms	23 months	59% of limbs
Murphy et al 1990	Angiogram for symptoms	2 years	1/3 stenoses
Tillgren et al 1963	Angiogram for symptoms	5 years	1/4 patients
Ulrich and Siggaard-Andersen1975	Venous Occlusion Plethysmography	3 years	35% patients
Strandness & Stahler 1966	Segmental limb blood pressure	3 years	45% of limbs

* see text (1.4.3) for definition

progression (increase in length or degree of narrowing or presence of new lesion), and in all instances the progression occurred proximal to the original lesion. Only one patient experienced worsening of symptoms. Two patients also had disease progression distal to the original lesion and one of these deteriorated symptomatically, thus lending support to the theory of Mavor (1956) that a distal extension of occlusion confers a worse prognosis than proximal. Kuthan et al (1971) examined 1196 limbs by scheduled arteriography, in 705 patients with PAD, excluding cases needing surgery. With a mean follow up of two and a half years, 31% of limbs had evidence of new occlusion or lengthening of an old, and 21% had worsening of a stenosis, or development of stenosis where there was none before. Again, progression rate was found to be higher proximal to the original lesion.

A small number of studies have described disease progression in patients in whom arteriography was done for symptomatic deterioration:

Chilvers et al (1974) reported a series of patients who had more than one good quality arteriogram at intervals of between one and four years. Measuring at a fixed point in the SFA, the average increase in narrowing (when this occurred) varied between 27-46%, and at some points there was even widening of the lumen. Another study examined disease progression in 29 limbs where the mean observation period (time between arteriograms) was 23 months (Dawson and Raphael

1968). Nineteen sets of observations involving progression in 17 limbs were made. These observations comprised:- 8 extensions of occlusion, 7 new occlusions, 3 new stenoses and one increase in vessel wall irregularity. In the SFA, six short occlusions remained unchanged in length. Again, patients requiring surgery were excluded from analysis. In a similar retrospective analysis of repeated arteriograms it was concluded that one third of asymptomatic stenoses became symptomatic within 2 years (Murphy et al 1990).

Where progression of stenosis is defined as development of collateral circulation, one quarter of patients show evidence of progression within 5 years (Tillgren et al 1963).

Other methods for determining disease progression rates have been used but the diagnostic specificity of the methods is open to question. Ulrich and Siggaard-Andersen (1975) found that of 156 claudicants demonstrated by Venous Occlusion Plethysmography to have non-occlusive atherosclerosis, 35% developed an occlusion during mean follow up of 3 years. In a study using segmental limb blood pressures (where only 60% of patients had confirmatory arteriography) to determine extent of peripheral arterial disease, Strandness and Stahler (1966) followed up 99 limbs. Of the 80 which initially were judged to have occlusions, 34 (43%) progressed (developed further disease) in the same or other segments. The nature of this progression was not clearly defined. Of the 19 with no occlusion initially, nine (47%) developed an occlusion during

a mean follow up of three years.

1.4.4. Risk factors for progression of PAD (Table 1.4)

In order to appreciate the rationale behind treatment of patients with PAD and the possibilities for intervention in the future, a summary of the known factors associated with *development* of PAD is given. These factors are broadly the same as those responsible for *progression* of disease, namely:

i) Age

Clinical deterioration is generally more rapid with increasing age (Kuthan et al 1971, Taylor and Calo 1962, Hughson et al 1978), although in one series propagation of occlusive thrombus was more common in patients under 50 years of age (Tillgren et al 1963).

ii) Smoking

This appears to be a stronger risk factor for developing PAD than coronary artery disease (Gordon and Kannel 1972). It is associated with a poor outlook (Cronenwett et al 1984), particularly if the habit continues (Silbert and Zazeela 1958, Juergens et al 1960, Mathieson et al 1970, Hughson et al 1978, Jonason and Ringquist 1985a).

Table 1.4

Risk Factors for Progression of PAD

General	- Advancing age
	- Smoking
	- Diabetes
	- Hyperlipidaemia
	- Hypertension
	- Duration of symptoms
	- Elevated fibrinogen
	- ? Lack of exercise
	- ? Obesity
	- ? Type A behaviour
	- Others eg. homocystinuria
Local	- Calf vessel patency
	- Multiple stenoses
	- Severity of stenosis

iii) Diabetes

Interestingly, PAD was negatively associated with elevated glucose levels in one risk factor survey (DaSilva et al 1979). Indeed, there is conflicting evidence that diabetes is a risk factor for developing PAD, but it does appear to be associated with higher limb morbidity (Reunanen et al 1982, Schadt et al 1961), and disease progression (Strandness and Stahler 1966, Kuthan 1971). Early and aggressive treatment has been proposed in view of the poor outlook (Bendick et al 1983).

iv) Lipids

There is still controversy as to whether hypercholesterolaemia is an independent cause of atherosclerosis progression, but there is little doubt about its association with the presence of atherosclerosis (Roberts 1984). Regression and retardation of progression of femoral lesions have been documented after treatment of hypercholesterolaemic patients (Erikson et al 1988, Duffield et al 1983).

v) Blood Pressure

Hypertension may be a risk factor for progression of PAD. It has been described both as conferring a good prognosis for the limb (Taylor and Calo 1962), and having no effect (Cronenwett et al 1984).

vi) Symptoms

The prognosis for the limb is better if claudication is the only symptom of PAD (Juergens et al 1960, Taylor and Calo 1962). Some have found that prognosis is poorer the longer the duration of symptoms (Selvaag 1960), but this is not universally accepted (Humphries 1971).

vii) Fibrinogen

To date, there is no proven link between haemostatic factors and progression of PAD. However, elevated blood fibrinogen levels are increasingly being incriminated as important risk factors for development of PAD (DePalma 1992, p23).

vii) Other

Rarer entities have been associated with accelerated disease. Aronson found a 13% prevalence of heterozygous homocystinuria in 37 young arteriopaths (Aronson et al 1989). The role of obesity, exercise and personality are not well defined.

In addition to the traditional risk factors, there are a number of characteristics of local disease which determine rate of deterioration of symptoms:

a) The number of patent calf vessels ("run-off") correlates positively with a better limb prognosis (Imparato et al 1975).

b) Multiple as opposed to single stenoses were found significantly associated with the development of rest pain in claudicants, and with a higher mortality (Jonason and Ringquist 1985a and 1985b).

c) Although not confirmed for lower limb disease, it is possible that the severity of stenosis affects the risk of progression to occlusion. This proposal is explored further in chapter 6.

A low ABPI on presentation might also predict a worse outcome, as might the location of the disease. However, there is disagreement as to the importance of these factors (McDaniel and Cronenwett 1989).

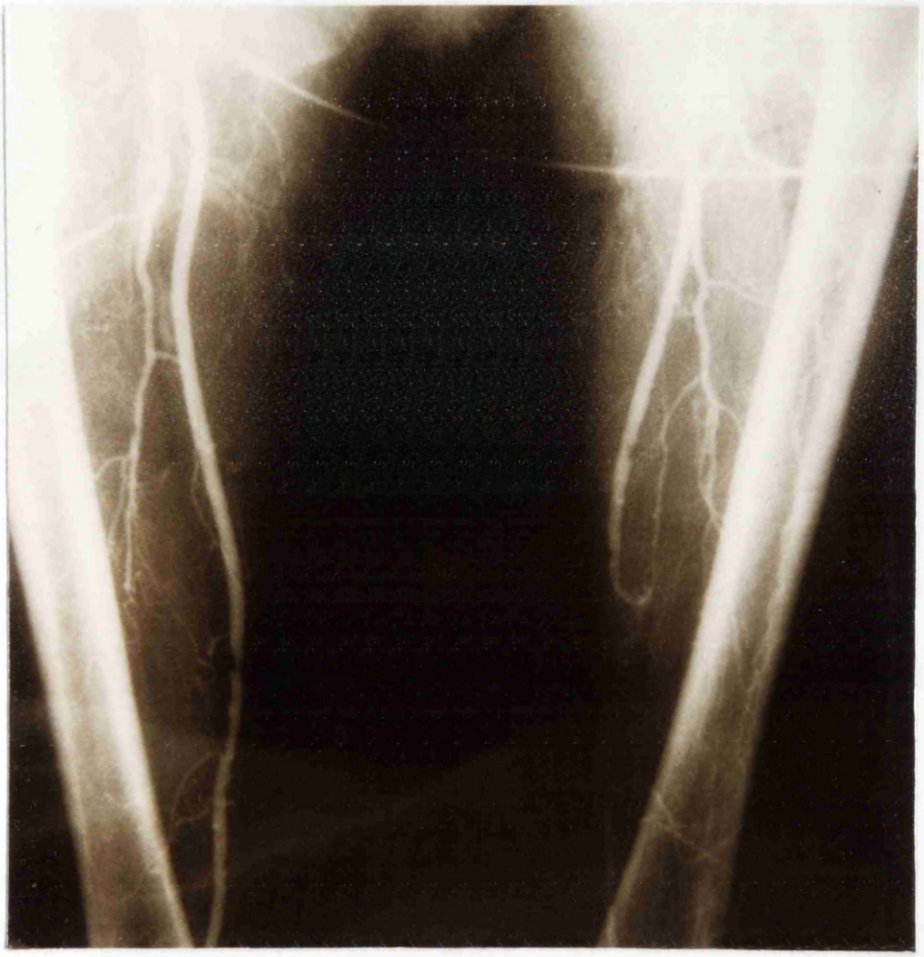
1.4.5. Relationship between symptoms and extent of disease

The earliest symptom of lower limb atherosclerosis is usually calf claudication. When symptoms are confined to this site the causal lesion is most often in the superficial femoral artery (SFA), frequently the adductor (Hunter's) canal (Lindbom 1950, Mavor 1956). The typical lesion at this early stage is an atheromatous plaque which narrows the lumen sufficiently to cause a fall in pressure across the stenosis. This in turn is responsible for encouraging collateral vessel formation (John and Warren 1961).

Many patients initially experience partial, or occasionally complete relief of symptoms. This might be a result of metabolic changes (Lundgren 1989a) and other physical adaptations as well as development of collateral vessels since clinical improvement is often not matched by any improvement in Doppler ankle pressures or radiological appearances. However, over a period of time, the stenosis progresses and complete occlusion occurs (figure 1.4). As mentioned previously, one of several final pathological events might precipitate occlusion, but in any case once flow has ceased in the segment, thrombosis is certain to supervene and propagation of clot along a variable distance of artery occurs. This much is not new. What is poorly understood, however, is how rapidly a stenosis progresses to occlusion,

Figure 1.4

Transfemoral arteriogram. In the left leg there is a short complete occlusion of the SFA, and in the right leg a stenosis symmetrically opposite the occlusion.



what features of the stenosis predispose to rapid progression, and how the severity of stenosis or length of occlusion relates to symptoms. For an individual patient this information could be obtained by regular and accurate "lesion-specific" investigations, but this goal has not yet been achieved.

Within populations there is a poor correlation between severity of lesion and symptoms (Baker 1978). Two-thirds of patients with complete femoral artery occlusion have no symptoms at all (Widmer et al 1964), whilst some patients with moderate severity stenoses are disabled by claudication. This is one reason why despite there being no shortage of data on the natural history of claudication, there is still a paucity of information on the natural history of the underlying lesion. Although the natural history of the clinical manifestations of PAD and that of the underlying lesions are inextricably linked, the two are not the same.

Claudication can cause great disability for an otherwise active person, compromising employment and making leisure pursuits unpleasant or impossible. These factors alone make it desirable to treat patients at this stage in the disease. When, in addition, there is a risk that the disease might progress to the point where reconstructive surgery or even amputation becomes necessary, it is even more important to know which patient to manage actively in the early stages.

1.4.6. Management of patients with PAD

1.4.6.1. Severe symptoms

A variety of treatments is available to patients with intermittent claudication (IC). Patients with severe IC, often arbitrarily defined as a maximum walking distance of less than 50 metres, and those with more severe ischaemia, ie. rest pain, ulceration or gangrene, are generally investigated by conventional arteriography and treated by Percutaneous Transluminal Angioplasty (PTA) and/or reconstructive surgery as appropriate. A small number of patients have non-reconstructible disease at the outset and require primary amputation. Where technically possible, PTA is performed as the first line treatment, followed by reconstruction if this fails, and this appears to be the most cost-effective means of management (Doubilet and Abrams 1984).

1.4.6.2. Very early disease

General measures to prevent atherosclerosis or its progression to haemodynamically significant narrowing, such as exercise and modification of diet may be of some benefit but this is difficult to prove since either very large numbers of compliant individuals or very sensitive tests of outcome are needed. Neither of these requirements has been fulfilled in the case of PAD. However, the 36% reduction in mortality from coronary heart disease in the U.S.A. in the two decades before 1983 (Kannel and Thom 1984) may have come about partly because of preventive measures and one might

expect the same to be true for PAD. The same comments apply to interventions such as anti-thrombotic agents, fish oils etc. in primary or early secondary prevention. There is therefore no reason for complacency but it must be borne in mind that intervention would have to be on an enormous scale, since in Western Society atherosclerosis is present, sooner or later, in nearly all individuals.

1.4.6.3. Treatment of disease of intermediate severity

Patients not disabled by symptoms are conventionally advised to "stop smoking and keep walking" (Housley 1988). However, there is controversy over what constitutes the optimum treatment of the mildly symptomatic or asymptomatic patient who often has either a short occlusion or relatively localised and significant stenosis. It is worthy of note that many patients who have such a lesion and remain asymptomatic probably do so because they do not attain levels of exertion comparable to symptomatic patients. However, adaptations to ischaemia in the lower limb are highly efficient (Larsen and Lassen 1966, Ekroth et al 1978), and these adaptations may be responsible in part for the relative or absolute lack of symptoms in some patients. The measurement of these lesions and the application of the information acquired to treatment of mild and moderate severity disease is addressed in chapters 2-6.

Summary of main points in Section 1

1. Peripheral arterial disease is a common condition. It causes considerable morbidity and is associated with high mortality. The cost to the Health Service is substantial.

2. The natural history of the clinical manifestations of PAD is well documented but that of the pathological lesion is not. This is partly because the disease is heterogeneous, with a spectrum from diffuse to isolated lesions, but also because current diagnostic tools are either not lesion - specific or involve discomfort and risk to the patient.

3. Newer methods of examining lower limb disease such as duplex ultrasound offer an opportunity to obtain information on specific lesions of the femoral artery with the aim of improving management strategies.

4. It is not known whether treatment of isolated femoral lesions at an early stage by angioplasty would confer benefit in terms of symptomatic relief, limb morbidity or survival.

SECTION 2

In this section an account is given of the physical principles governing normal and abnormal lower limb blood flow, in order to explain how duplex ultrasound enables interpretation of commonly found haemodynamic abnormalities. The principles of Doppler and duplex ultrasound, and waveform analysis are described, the purpose being to explain how and why duplex is used to measure femoral artery stenosis and occlusion. Lastly, a short description of the normal anatomy of the lower limb arterial tree is given.

1.5. PHYSICAL PRINCIPLES GOVERNING LOWER LIMB BLOOD FLOW

The principles governing fluid dynamics are complex, and it is not correct to strictly apply these principles to arterial blood flow, even in relatively straight, non-branching arteries such as the superficial femoral. To date, it has not been possible to accurately reproduce in the laboratory the precise physiological characteristics of normal vessels, and in peripheral arterial disease a complete understanding of abnormal haemodynamics is therefore even less tenable at present. Nevertheless, certain physical principles are commonly applied to the investigation and treatment of PAD, and these are outlined below.

1.5.1. Volume Flow

Jean Leonard Poisseuille (1799-1869), a French physician and physiologist defined the relationship between flow and other measurable parameters, for fluid in a tube (Poisseuille 1846).

$$Q = \frac{\pi\ (P1-P2)\ R^4}{8\ \cap\ L}$$

where, Q = rate of volume flow,

P1-P2 = fall in pressure,

$\cap$ = viscosity,

L = vessel length,

R = vessel radius.

The equation applies only to non-pulsatile, laminar, irrotational flow of a Newtonian fluid in a straight, non-branching rigid cylinder. Nevertheless, the formula gives an indication of the variables capable of altering flow in any system including lower limb arteries.

In practice, a significant fall in flow does not occur until an artery is markedly narrowed to the point which is often termed "critical" stenosis (Rutherford et al 1982). However, rather than measuring volume flow, duplex ultrasound might enable measurement of lesser degrees of narrowing by detecting small changes in peak systolic and/or mean velocities.

1.5.2. Pressure.

Daniel Bernouilli (1700-1782), a Swiss Physicist and mathematician, described the relationship between pressure and energy during flow. Essentially, the Law is one of conservation of energy (Burns and Jaffe 1985) :-

Pressure drop = kinetic energy gain (from acceleration) + viscous energy loss + inertial energy gain (from changing flow rate).

The viscous and inertial changes which occur with changing vessel diameter mean that the relationship between flow and pressure is not as perfect as Poisseuille's Law predicts. In addition, the Law does not hold for a non-Newtonian fluid,

nor for conditions of turbulent flow. Also, the R^4 function refers specifically to the entire conduit, not just an interspersed stenosis (Byar et al 1965). Despite this, it is still useful to refer to the equation: If flow is constant, and vessel diameter changes eg. in a stenosis, there is a pressure drop. Thus potential is converted to kinetic energy (figure 1.6).

Since kinetic energy = $1/2\ m\ v^2$,

it follows that velocity of blood increases through a stenosis. A simple way of restating this is to say that since $Q = v\ A$, if Q remains constant, then as A decreases (within a stenosis) so v must increase. This increase in velocity is one of the most important means by which duplex detects an area of stenosis. In the laboratory, where arterial stenoses can be made and constant flow maintained (as described in chapter 2), an increase in velocity can be demonstrated within the stenosis. However, in severe atheromatous narrowing limb blood flow is reduced and the absolute velocity within a stenosis might be less marked than expected.

1.5.3. Laminar Flow

Blood can be thought of as consisting of longitudinal layers of cells, each sliding across each other during flow, with the central layer travelling fastest and the layers nearest the intima being retarded by frictional forces. These

"concentric cylindric laminae" take a parabolic shape, with the velocity at the axis being twice the mean velocity (Figure 1.5), although with wider diameter vessels the shape is flattened, eg. aortic "plug" flow. If a small sample volume is used during Doppler measurement, velocity must be recorded away from the edge of the vessel, or erroneous readings may be acquired.

1.5.4. Turbulence

Sir Osborne Reynolds (1842-1912), an English engineer, described in mathematical terms the factors which determine the development of turbulence which occurs when laminar flow is disrupted (Reynolds 1883). The Reynold's number, a dimensionless value, represents the ratio of inertial to viscous forces and is given by the formula :-

$$N = \frac{v\ D\ \Omega}{\cap}$$

where, N = Reynolds number

v = mean velocity,

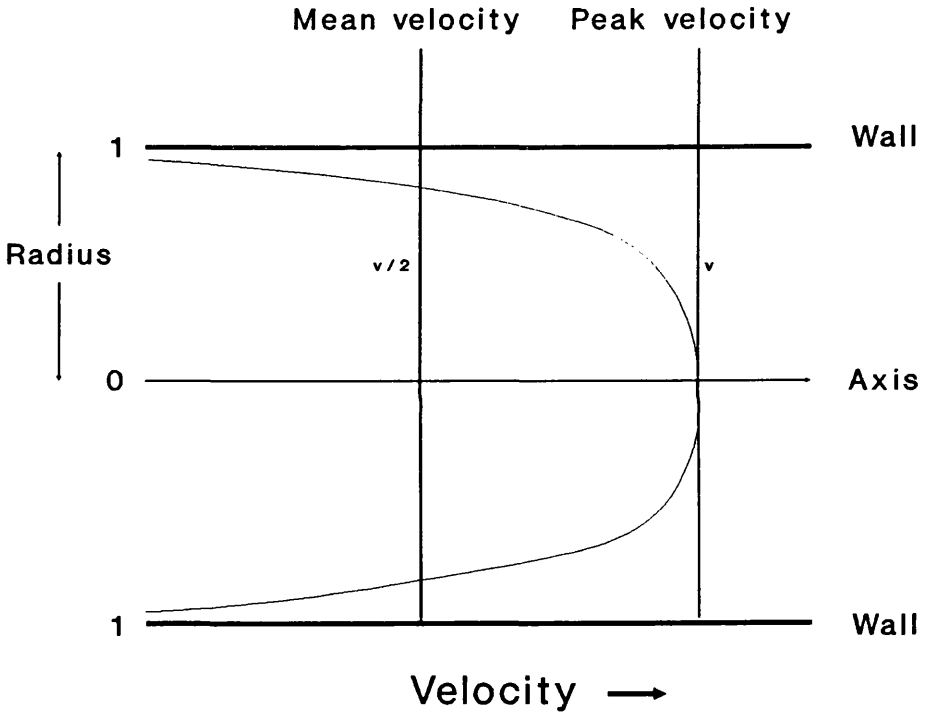
D = vessel diameter,

Ω = blood density,

$\cap$ = blood viscosity.

Figure 1.5

Diagram to show the parabolic velocity profile of blood during laminar flow



Generally, when N exceeds 2000, turbulence will occur. This depends on the geometry of the vessel and is smaller with greater vascular complexity (Nelson and Pretorius 1988), and in the presence of pulsations (McDonald 1974). Turbulence is easily visualised with the colour duplex scanner and may contribute to the bruit heard in clinical practice. However, high velocity intra-stenotic jets and vessel wall vibration near areas of turbulence may also be significant noise producers.

1.5.5. Vascular Resistance

A form of Ohm's Law can be used in fluid dynamics:-

$$\text{Resistance, } k = \frac{P1-P2}{Q}$$

$$\text{ie. } k = \frac{8 \cap L}{\pi R^4} \qquad \text{(from Poisseuille's Law)}$$

This equation demonstrates resistance as a function of the factors retarding flow. It follows that, provided other variables remain constant, reducing vessel radius profoundly affects vascular resistance. An example of the importance of high resistance is arterial bypass graft failure due to poor "run-off" into diseased calf vessels.

For vessels running in parallel :-

$$1/Rt = 1/R1 + 1/R2 + \ldots + 1/Rn$$

where, Rt = Total Resistance,

n = number of vessels.

This situation arises wherever collateral vessels are found. It implies that many collaterals are required to provide the same resistance as a large occluded artery. If each collateral were as much as one quarter the diameter of the main vessel, 256 would still be required to provide a resistance equal to that in the main vessel. Thus, a patent main vessel (eg. after angioplasty), is associated with lower resistance and higher distal pressures than found with collaterals around an occlusion.

1.5.6. Viscosity

This was defined by Sir Isaac Newton as the ratio of stress to velocity gradient. Stress is the accelerating force per unit area, and velocity gradient is the change in velocity from one layer of fluid to the next. A Newtonian fluid is one whose viscosity does not alter with velocity. Blood is non-Newtonian because viscosity rises with fall in flow rate. In addition (although the effect is small in vessels of >0.5mm diameter), viscosity increases with increasing haematocrit and falling temperature of blood (Milnor 1980). This is important in hypothermia and in individuals with polycythaemia, particularly those with PAD.

1.5.7. Other Factors

a) Another reason that the relationship between flow and pressure is not linear is that the arterial tree is distensible and as pressure rises, cross-sectional area increases.

b) Robert Hooke (1635-1703) described the law which relates distending force to deformation. The elasticity of a substance is given by Young's Modulus (stress / strain), and is usually constant within certain limits of deformation. In the vascular wall, however, Young's Modulus increases with increasing radius, ie. the wall becomes stiffer. This may be because the stress becomes transferred from elastin to collagen with increasing radius.

c) Flow in a vessel has a periodic waveform, ie. is pulsatile. The complex mathematics of a Fourier series describe pulsatile flow as a function of time and mean flow. The situation is even more complex where oscillatory pressure and flow are concerned.

d) Arteries taper. In the superficial femoral artery this is no more than 2.3 % per cm (Barndt et al 1974).

e) Arterial geometry affects the velocity profile. Curvature causes acceleration towards the outer wall producing helical flow and a skewed velocity profile (Zierler 1990a).

f) The arterial tree has variable peripheral resistance.

g) Reflection of waves can occur at branch points.

Many of these factors may be responsible for the changing shape of the waveform as it propagates distally.

1.6. HAEMODYNAMICS RELATING TO ARTERIAL STENOSIS

The characteristics of flowing blood can change markedly in the immediate vicinity of an arterial stenosis. The increase in velocity which occurs within a stenosis and the fall in pressure and flow distal to it have already been mentioned. Other changes include turbulence, reverse flow and flow separation (figure 1.2) and the effect these might have on progression of a stenosis has already been discussed. However, a more detailed mention of haemodynamic changes near a stenosis is worthwhile.

According to the Bernouilli principle there should not be a pressure gradient across a stenosis, merely transfer of energy from potential (pre-stenosis) to kinetic (within stenosis) and back again to potential (post-stenosis) (Berguer and Hwang 1974). However, when blood flows in an artery, energy is lost in a number of ways. The main (exit) loss arises in the creation of post-stenotic turbulence. Other losses occur at the entrance to (contraction) and within the stenosis (viscous) (Figure 1.6). The total fall in energy equals the fall in potential energy ie. pressure drop across the stenosis. In theory, halving vessel diameter ought to reduce flow by 1/16, but in practice there is usually no measurable effect on flow or pressure at this stage. There are several ways of defining "critical stenosis" (Berguer and Hwang 1974), but in practical terms it amounts to the degree of narrowing which causes a measurable fall in blood pressure, or clinical symptoms and signs of circulatory

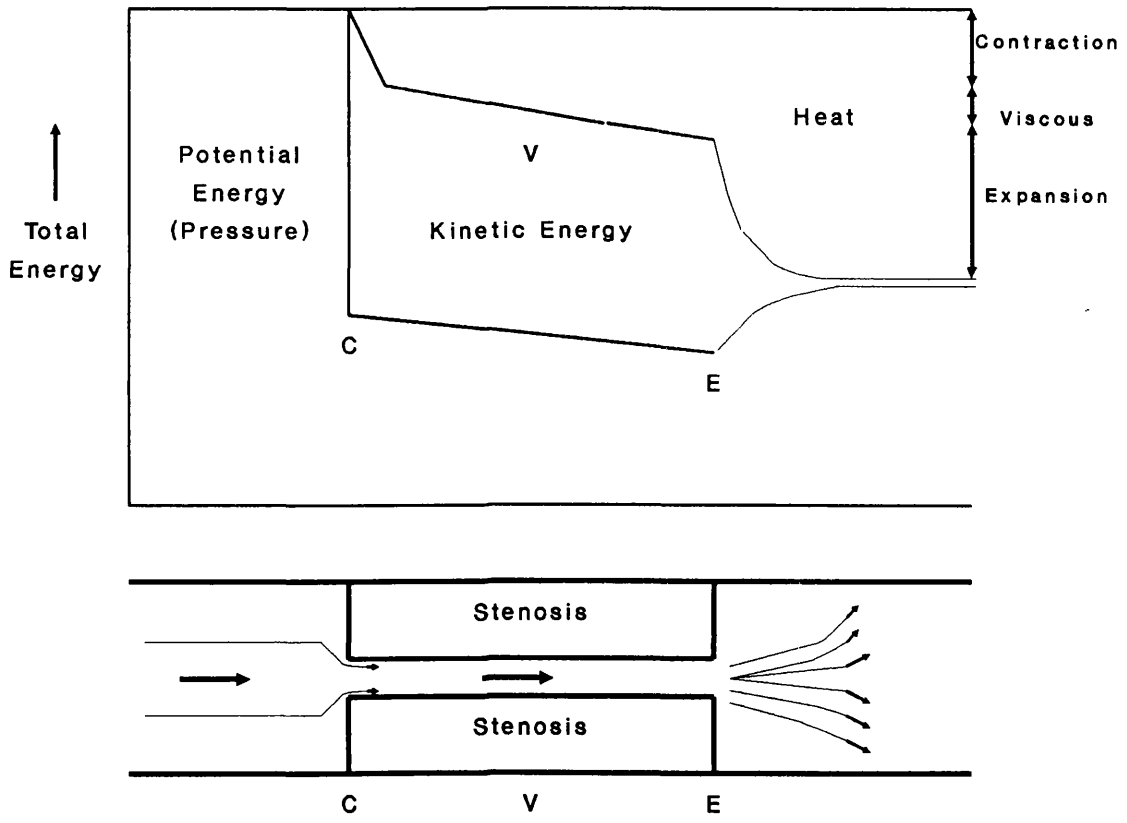
insufficiency. It cannot be ascribed an absolute value but depends on velocity of flow, and to a lesser extent on length of stenosis and blood viscosity. Because length of a stenosis is less important than the magnitude of reduction in vessel diameter (Byar et al 1965), sequential stenoses have a greater effect on fall in blood pressure than a single one covering the same length. Duplex ultrasound might therefore have a role in assessing which of several stenoses has the most important effect on flow and, therefore, which should be treated.

1.6.1. Limb Blood Flow in peripheral arterial disease

In the normal femoral artery resistance to flow is low and there is only a small pressure drop across it. With exercise, resistance in calf vessels falls and flow increases, still with little pressure drop. Where there is occlusive disease of the femoral artery, segmental resistance is high but total flow is normal because of a compensatory fall in peripheral

Figure 1.6

The energy losses within a stenosis



vascular resistance (PVR). With exercise, little further reduction in PVR is possible, and an increase in calf flow is limited by high resistance in the femoral artery and its collaterals. The significantly reduced perfusion pressure in the calf causes ischaemia and symptoms of claudication (Barnes 1980). This explains why exercise precipitates a fall in ABPI, a phenomenon which is used in practice to confirm the diagnosis of claudication, and it explains the pulse changes seen in occlusive vascular disease (Keitzer et al 1965). Despite a number of drawbacks to the method, it also gives the basis for measuring the severity of lesions by blood pressure measurements.

1.7. ANATOMY OF THE LOWER LIMB ARTERIAL TREE

A brief description of the normal anatomical arrangement of lower limb arteries (Last 1984) is given as far as it is relevant to duplex scanning and studies in this thesis.

The common femoral artery arises as a direct continuation of the external iliac artery as it passes beneath the mid point of the inguinal ligament. It bifurcates into two large arteries. The profunda femoris normally arises from the posterolateral aspect of the common femoral artery, spiralling deep to it and separated from it by the adductor longus. The profunda has medial and lateral circumflex arteries which supply the thigh and can form important collateral channels with geniculate arteries in the presence of occlusion of the superficial femoral artery.

The other main branch, the superficial femoral artery occupies the adductor (Hunter's) canal. Passing through the hiatus between the two parts of the adductor magnus, it enters the popliteal fossa one hand's breadth above the knee. This is one of the most difficult areas to scan, the artery being at least 3-4 cm deep to the skin at this point. There are rarely major branches before this level but the descending genicular (anastomotica magna) leaves the femoral artery just above the hiatus and descending, divides into vessels which contribute to the anastomosis around the knee. It therefore contributes to collateral formation in cases of popliteal artery occlusion.

The artery continues beyond the adductor hiatus as the popliteal for approximately 20 cm, deep in the popliteal fossa, to the fibrous arch in soleus. Five genicular arteries and muscular branches are given off in the fossa before the first calf vessel, the anterior tibial artery branches off laterally at the lower border of popliteus. This acts as a useful landmark when imaging the popliteal artery. It leaves the tibioperoneal trunk which continues a short distance before dividing into the two remaining main calf vessels, the posterior tibial and the peroneal arteries. These are not frequently studied by duplex.

1.8. DOPPLER ULTRASOUND

1.8.1. The Doppler Effect

This physical phenomenon was first described in 1842 by Christian Johan Andreas Doppler (1805-1853), Professor of mathematics in Prague, and was first demonstrated in public in 1845 by a trumpet being played continuously from a passing train.

The Doppler effect is the change in frequency of a wave such as sound or light produced by movement of the source (transducer) or observer with respect to the other. For insonation of blood vessels by ultrasound this Doppler frequency "shift", δf, is in the audible range (which is <20Hz-20KHz), but needs graphic display to allow quantification (Burns and Jaffe 1985). In can be described in mathematical terms by:-

$$\delta f = \frac{2 f_t \, v(\cos\theta)}{c}$$ The Doppler Equation

alternatively,

$$v = \frac{\delta f \; c}{2 f_t \; (\cos\theta)}$$

where (Figure 1.7), f_t= transducer frequency

v = velocity (eg. of blood)

c = velocity of sound (around 1540m/s in tissue)

θ = angle between ultrasound beam and direction of flow

From the Doppler equation follow several important principles:-

i. Doppler shift depends on transducer frequency
ii. Doppler shift depends on direction of blood flow
iii. Blood velocity can be calculated knowing Doppler shift and angle.

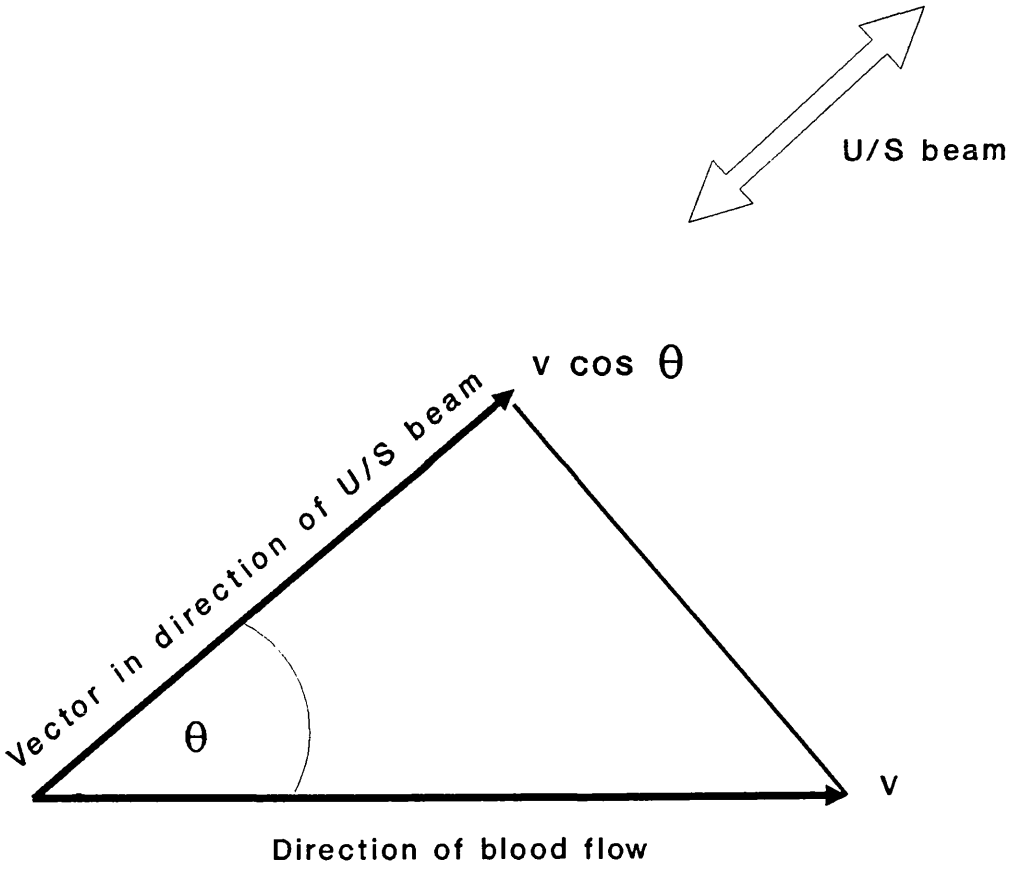
The frequencies used in medical diagnosis are usually in the range 2-10 MHz, and the range of velocities encountered in clinical practice is up to around 10 m/s.

1.8.2. Imaging

Ultrasound waves are altered in amplitude as a result of reflection at the interface between different tissues, and the sum of these changes is represented in real time by a 2-dimensional image displayed on a screen, B-mode imaging.

Figure 1.7

Diagram to show that blood flow has a velocity vector in the direction of the ultrasound beam



It is known that:- $c = f \lambda$ (where λ = wavelength)

Resolution increases as λ becomes smaller, and an attempt is therefore made to scan at the highest transducer frequency possible. However, attenuation of sound waves, ie. reduced penetration, occurs with increasing frequency. Thus there is a pay-off between improved resolution and poorer penetration (Nelson and Pretorius 1988).

It is possible to image a large number of soft tissues in the body, including certain components of atherosclerotic plaque. Calcification, which is seen as a brightness with corresponding acoustic shadows, is readily detected. It is difficult to visualise thrombus since it has nearly the same echogenicity as blood. This important participant in the natural history of atheroma is therefore not readily amenable to study by imaging alone. However, as mentioned in Section 1.1.1., measurement of femoral arterial wall thickness (Beach et al 1989) and intimal-medial thickness (Poli and Paoletti 1987) can be made and might be of use in epidemiological studies of early atherosclerosis (Salonen and Salonen 1990).

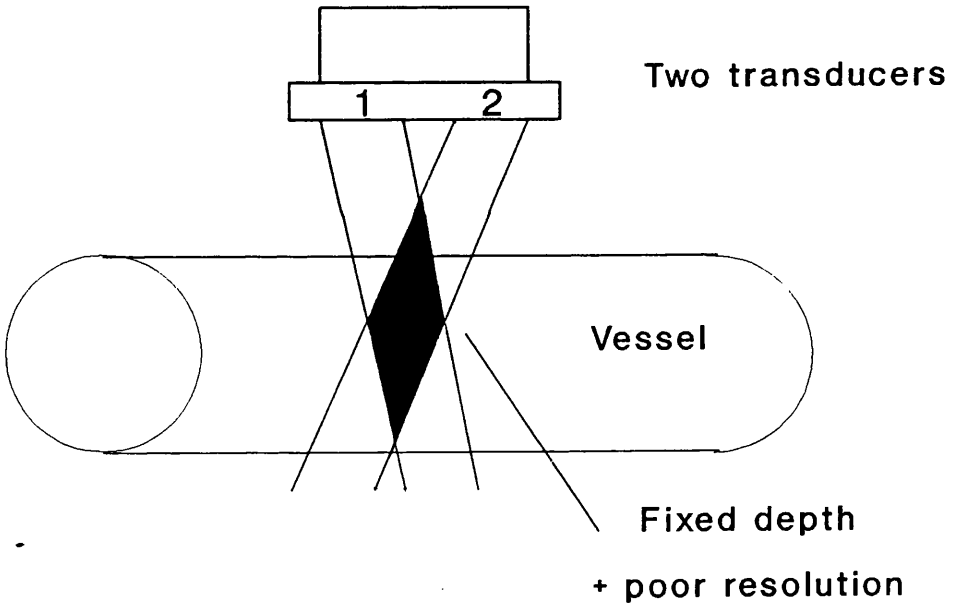
1.8.3. Continuous Wave Doppler (Figure 1.8)

These simple and inexpensive devices use two transducers, one for transmission and one for reception of reflected signals. The Doppler shift signal can be presented in real time as a spectral display, or as an audible signal,

eg. when measuring ankle pressure. High velocities can be detected but there is no range resolution and the devices are therefore best reserved for known superficial vessels.

Figure 1.8

Continuous wave Doppler

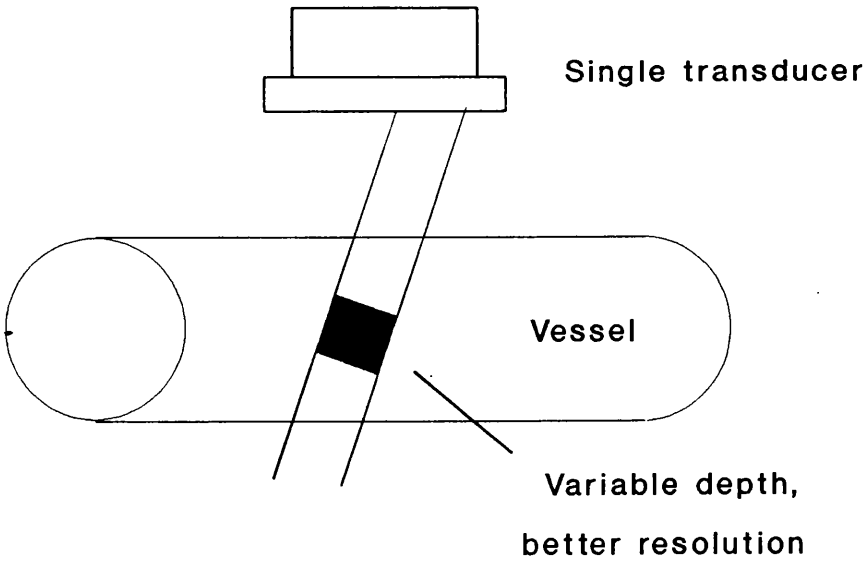


1.8.4. Pulsed Wave Doppler (Figure 1.9)

This type of transducer is used in transcranial Doppler ultrasound (Aaslid et al 1982), as well as in duplex ultrasound. The same crystal is used for both transmission and reception, as in imaging. Since the signal is pulsed, reception can be gated for time and therefore for depth. This means information from flowing blood, for example, can be selected from the vessel at any site or depth (ie. known location along the beam) for determination of frequency shift and therefore velocity.

Figure 1.9

Pulsed wave Doppler



1.8.5. Signal Analysis

In pulsed mode the Doppler signal is sampled once per pulse transmission, and a signal is generated from the samples. In practice, the system computer uses an algorithm, most commonly Fast Fourier Transform analysis (FFT) to display short periods of the Doppler signal as series of spectra (Figure 1.10). The display shows the relative power and magnitude of each of the frequency components in the signal and expresses this in grey scale. The resulting waveform can then be analysed.

1.9. WAVEFORM ANALYSIS

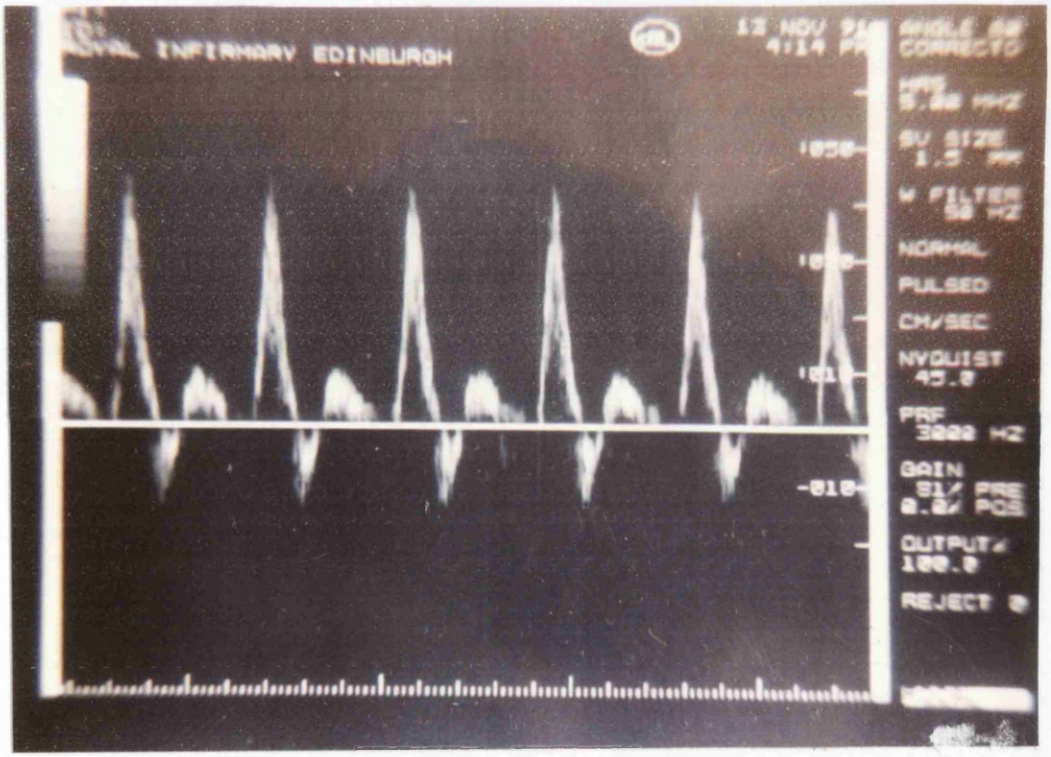
There are numerous ways of interpreting the waveform obtained after signal analysis. Those described below concentrate on analysis of waveform shape rather than quality, eg. spectral broadening indices, which will not be discussed here. Some allow inference about disease proximal and distal to the site where the waveform was obtained (indirect, non lesion-specific measurements), and some about disease at the site itself (direct, lesion-specific measurements).

1.9.1. Indirect measurements

- Laplace Transform Damping (LTD), (Skidmore and Woodcock 1980). This method is used to fit an equation to the FFT of the waveform. It relates distal impedance, vessel elasticity and proximal arterial luminal diameter. It has

Figure 1.10

Spectral waveform after FFT signal analysis



a number of significant faults which make its use in clinical practice questionable. It assumes that the waveform starts at zero (which is not the case in significant proximal disease), it is a simplistic model of the arterial system which does not account for some of the features seen in practice such as the presence of a "shoulder" on the waveform when there is distal occlusion, and it requires complex analysis of the Doppler waveform.

- Principal Component Analysis (PCA), (Martin et al 1980). This technique reduces data from a waveform to a minimum number of base components of varying shape. It has been shown to be useful in distinguishing disease at different sites (Walton et al 1983, McPherson et al 1984).

- Pulsatility Index (PI), (Gosling and King 1974) (Figure 1.11). There is controversy over whether this can separate mild from severe disease (Harris et al 1974, Johnston et al 1978, Baird et al 1980, Ward and Martin 1980, Archie and Feldtman 1981, DeMorais and Johnston 1981, Auckland and Hurlow 1982, McPherson et al 1984), because it is strongly dependent on distal resistance and disease (Barrie et al 1979, Evans et al 1980). Advantages are that it needs no external calibration and it is independent of beam-vessel angle (Bone and Ammons 1978). In the absence of significant femoropopliteal disease, PI of the common femoral artery waveform might prove most useful in evaluating aortoiliac disease when this is difficult to

assess by direct visualisation.

PI, PCA and LTD have been used primarily for research purposes and have not been widely accepted in clinical practice. The three have been compared, with varying degrees of agreement as to which is best (McPherson et al 1984, Campbell et al 1984).

- Aortofemoral Transfer Function.

This involves digital processing of the Doppler signal to derive the mean power frequency index, and comparing values obtained from aorta and femoral artery. The method may be useful for distinguishing critical from sub-critical narrowing of the iliac artery (Sawchuk et al 1990), although this has yet to be validated by other groups.

- Damping Factor, (Figure 1.11)

This can distinguish occluded from non-occluded vessels but not critical from subcritical stenosis (Auckland and Hurlow 1982)

- Other Methods.

A number of other ways of interpreting the waveform have met with varying degrees of success, including systolic acceleration and deceleration time (Nicolaides et al 1976), pulse propagation time and change in shape of velocity/time waveform (Woodcock et al 1972), and spectral

broadening (SB) and waveform shape such as loss of reverse flow (Jager et al 1985a, Kohler et al 1987a). Although attempts have been made to quantify SB objectively, the severity of change occurs at a variable distance beyond a stenosis and is highly dependent on the Doppler sample volume, both of which make standardisation very difficult. The study in chapter 3 aims to determine the accuracy and reproducibility of several waveform features including SB.

Attempts to estimate volume flow by combining area and Doppler measurements have been made, but the errors can be large (Hoskins 1990).

1.9.2. Direct measurements

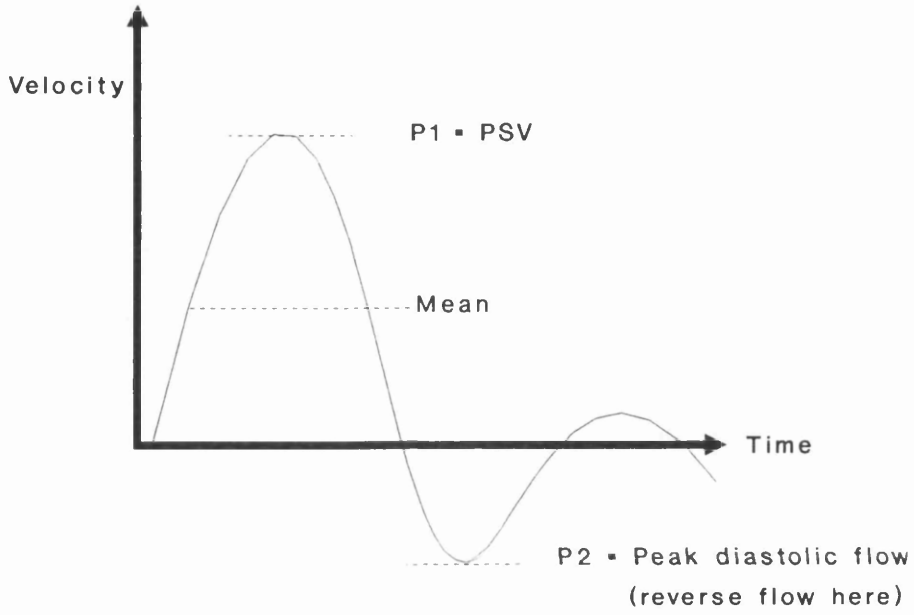
Using a duplex system, velocity of blood can be calculated by measurements taken from the Maximum Frequency Envelope (Figure 1.11).

- Diastolic Flow

Of several variables tested one group found that only diastolic velocity had a consistent relationship with degree of angiographic stenosis (Nicholls et al 1986). This has been supported by the finding of an end-diastolic velocity of >40cm/s distinguishing a >75% stenosis from 50-74% stenosis (Legemate et al 1988).

Figure 1.11

Maximum frequency envelope of Doppler waveform



PSV = Peak systolic velocity

$$\text{Pulsatility Index (PI)} = \frac{P1 - P2}{\text{Mean}}$$

$$\text{Resistive (Pourcelot) Index} = \frac{P1 - P2}{P1}$$

$$\text{Damping Factor} = \frac{\text{PI of proximal waveform}}{\text{PI of distal waveform}}$$

- Peak Systolic Velocity (PSV) (Cossman et al 1989)

The maximum value for velocity within an artery can be assumed to be within the area of maximum stenosis, but because of the relatively large range of normal velocities (Table 1.5) accurate quantification of individual stenoses might not be possible using this value alone. Also, absolute velocity might change from day to day (biological variability), so monitoring of stenosis over time could involve large variability. However, PSV appears to correlate well with pressure gradient measured during arteriography (using $\delta p=4[V_{max}]^2$), and because of this its use has been advocated in non-invasive follow up of stenoses (Langsfeld et al 1988).

A single PSV measurement can also be useful for other purposes. Low absolute velocity (<45cm/s) is a reliable predictor of impending graft failure (Bandyk et al 1985).

- Velocity Ratio

Here the PSV within the stenosis is compared to that proximal to it and expressed as a ratio (Figure 1.12). This means, in principle, that irrespective of the within-stenosis velocity the ratio should reflect change in luminal area within a stenosis and represent the degree of narrowing. A ratio of 2 (Jager et al 1985a) or 2.5 (Legemate et al 1988) has previously been thought to approximate to a 50% reduction in luminal diameter. Velocity ratio therefore allows direct measurement of

discrete stenoses with an element of built-in standardisation. By this is meant that because the velocity within the stenosis is compared with the velocity proximal to it, variations in the latter are mirrored by those in the former. It is, therefore, a potentially useful index for grading stenoses and studying their natural history, and its validity is tested in the studies described in chapters 2 and 3.

1.9.3. Interpretation of the waveform in practice

A normal waveform is triphasic, with the main component of forward flow in systole, a short period of reverse flow in diastole resulting from high peripheral vascular resistance, and a further period of forward flow at the end of diastole (Figure 1.11). In normal subjects the waveform may even have four phases. After exercise, during reactive hyperaemia or in chronic ischaemia, all of which cause peripheral vasodilatation, there is a loss of the reverse diastolic flow component (Kohler et al 1987b). Although not always present the typical waveform changes associated with distal occlusion are: loss of reverse flow, low velocity, a "shoulder" on the downstroke of systole and a pre-occlusive "thump". When the occlusion is reached, these changes often become more marked. One or more collateral vessels can usually be seen arising from the patent segment proximal to the occlusion, and they are often the first indication that flow has become re-established in the main vessel distal to an occlusion.

Table 1.5

Duplex values in normal lower limb arteries

- Diameter and velocity

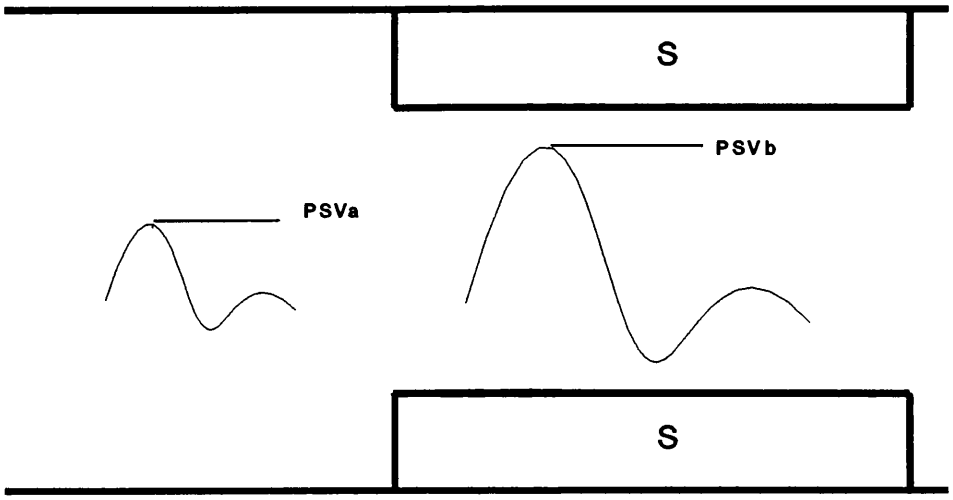
ARTERY	DIAMETER cm ± SD	VELOCITY cm/s ± SD
External iliac	0.79 ± 0.13	119.3 ± 21.7
Common Femoral	0.82 ± 0.14	114.1 ± 24.9
S.F.A. (proximal)	0.60 ± 0.12	90.8 ± 13.6
S.F.A. (distal)	0.54 ± 0.11	93.6 ± 14.1
Popliteal	0.52 ± 0.11	68.6 ± 13.5

Reproduced with permission (Jager et al 1985b)

These changes apply to the mature occlusion. The findings in acute thrombotic occlusion have not been described in the literature, but personal observations suggest that minimal flow may still be present in the apparently occluded segment for many weeks after the initial "occlusive" event. The ability to distinguish between new and established occlusion is not only of academic interest, but might also be of practical significance. Patients with recent thrombotic occlusion might be candidates for thrombolysis followed by angioplasty of the diseased segment. Those shown to have a mature occlusion might be spared the risk and expense of this additional treatment.

Figure 1.12

Representation in longitudinal section of a stenosis



PSV increases within the stenosis

$$\text{Velocity Ratio} = \frac{\text{PSVb}}{\text{PSVa}}$$

1.10. DUPLEX

Alternatively known as Doppler Colour Flow Imaging - a term recommended by Merritt (1987), duplex ultrasound combines the modalities of conventional B-mode ultrasound imaging with range-gated, pulsed-wave Doppler signal analysis. After identifying a particular vessel from the image, a representative velocity "sample" can be taken from within the vessel at a chosen depth. The angle between vessel and beam is determined after steering the beam in the appropriate direction.

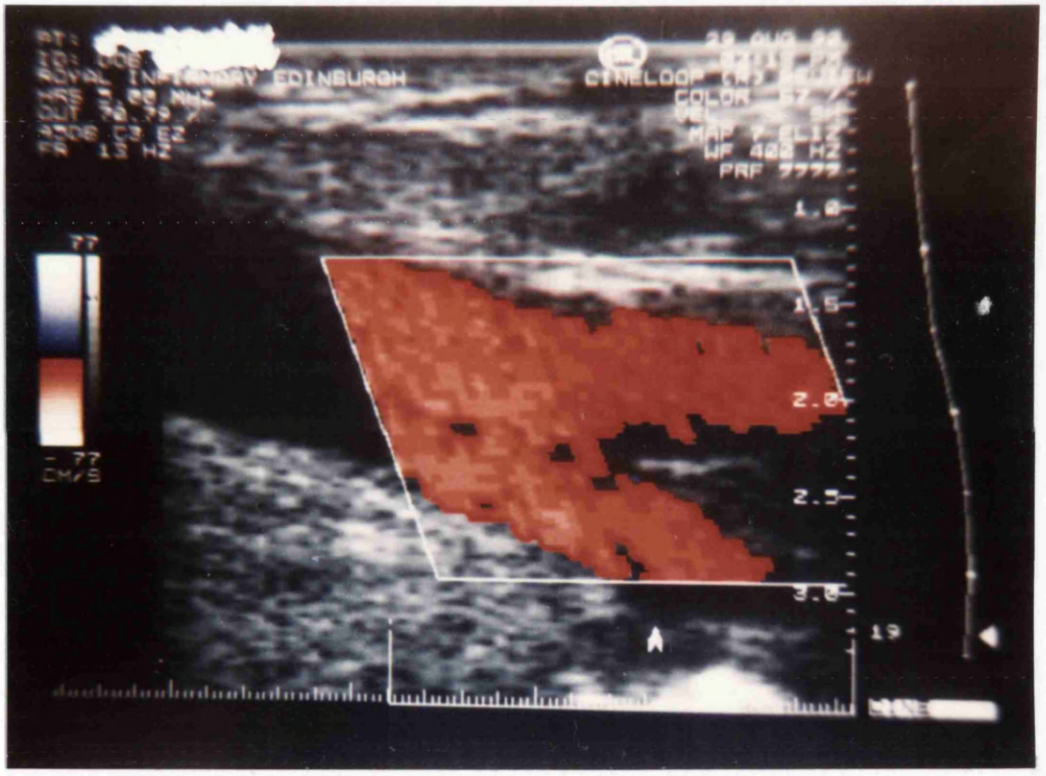
Red blood cells cause Rayleigh-Tindall backscattering of the signal, the amount of which is proportional to the sixth power of the radius of the scatterer (Burns and Jaffe 1985). The Doppler signal thus comprises a set of frequency shifts. Calibration in units of velocity (expressed in cm/s) can be performed after correction of the frequency axis by the beam-vessel angle (Figure 1.7). Since Doppler frequencies are dependent on the transmit frequency, comparison of results obtained by different observers is best done using velocity measurements. Thus the presence, direction and velocity of flow can be determined.

1.10.1. Colour duplex

Duplex has been in use for nearly 20 years (Barber et al 1974), but only relatively recently (1982) has displaying flow information in colour been possible (Figure 1.13).

Figure 1.13

Normal colour flow at the common femoral bifurcation



The mean velocity and direction of flow are converted to a colour code which is superimposed on the image. By convention, the forward component of arterial flow is designated red, and flow in the reverse direction is blue. A lighter shade represents increased velocity. An increase in the mean velocity such as that associated with stenosis is therefore readily detected visually (Figure 1.14) without the need for frequent "random" samples of velocity which are necessary with non-colour equipment. The potential to measure stenosis using colour flow information alone is currently being evaluated (Landwehr 1991). In addition, post-stenotic turbulence, otherwise seen as a broadening of the spectral display, can be visualised.

Potential advantages of colour over non-colour duplex include:-

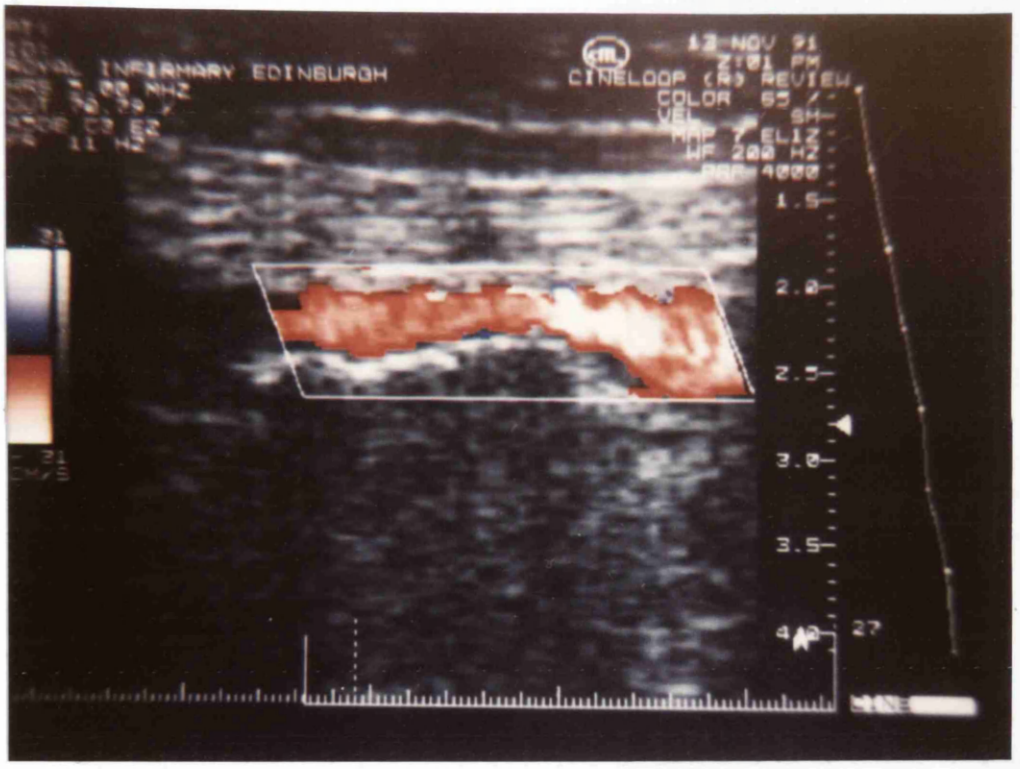
i) Improvement in lesion detection sensitivity by better visualisation of plaque

ii) More rapid scanning

iii) Potential for colour-map detection and quantification of stenosis (Landwehr et al 1991)

Figure 1.14

Increase in velocity within a stenosis (cf. fig 1.1)



1.10.2. The use of duplex in lower limb arteries

a. **General**

i) Identification of site of disease

ii) Determination of degree of stenosis and presence of occlusion (Jager et al 1985a)

iii) Distinction of single from multiple lesions, and isolated from diffuse disease

b. **Specific**

i) Natural History studies (Lewis et al 1989)

ii) Screening before angiography (Collier et al 1990)

iii) Follow up after angioplasty (Landwehr and Lackner 1990)

iv) Graft surveillance (Taylor et al 1990)

v) Diagnosis of pseudoaneurysm and arterial dissection (Coughlin and Paushter 1988)

vi) Detection of A-V fistula after in-situ vein grafting (Cullen et al 1986)

1.10.3. Scanning a patient

The patient is initially examined supine after a period of rest. The transducer is placed over the artery of interest, often starting at the aorta. Ultrasonic coupling gel is placed between scanhead and skin surface and with the transducer approximately perpendicular to the skin and usually orientated to obtain a longitudinal image of the vessel, Doppler information is acquired. The iliac, superficial and deep femoral arteries are examined. When the popliteal artery is reached the patient is turned to the lateral or supine position to make scanning easier. Under ideal conditions it is possible to view arteries only 1-2 mm in diameter including collaterals and calf vessels.

1.10.4. Problems with duplex

Duplex is generally non-invasive and safe, causes little discomfort, requires few staff, is inexpensive to perform, and provides information complementary to arteriography. However, there are certain potential and real problems.

1. It is technically difficult, often requiring several months of training.
2. Even using colour, a full examination may take more than one hour.
3. Some areas are difficult to visualise, particularly in the obese: The adductor canal, where advanced disease is most common, and the proximal iliac segment lying

deep in the pelvis. Attempts have been made to increase the echogenicity of blood during scanning to improve visualisation of the adductor canal (Hendrickx et al 1989). Patients are often asked to fast for up to 12 hours before iliac scanning in order to minimise the obscuring of vascular detail by bowel gas.

4. Vessel calcification may obscure both image and flow information.
5. There may be discomfort near a recent incision.
6. The equipment is expensive to purchase and maintain.
7. There may be unrecognised side effects (Rosario et al 1987).
8. There is a large element of operator dependence, and as a rule surgeons cannot "read for themselves" the results in the same way as arteriograms.

1.11. A PILOT STUDY OF THE NATURAL HISTORY OF EARLY LESIONS OF THE SUPERFICIAL FEMORAL ARTERY

In view of the lack of data regarding the natural history of stenoses and short occlusions of the superficial femoral artery (SFA) a retrospective pilot study was carried out. The aim was to determine the rate and extent of progression of untreated early lesions of the SFA.

Five hundred lower limb angiograms performed during the previous 8 years were randomly selected from the film store of the Royal Infirmary of Edinburgh and assessed by one individual (MRW). Angiograms which showed a localised area of stenosis (reduction in luminal diameter of >50%), or occlusion measuring 10 cm or less in length in one or both superficial femoral arteries were selected as cases of "early" disease. Cases where iliac disease was more severe than femoral were excluded. Hospital notes of the selected patients were obtained from the Medical Records Department. Those who had undergone surgery, angioplasty or amputation of the limb in question were not followed up, but the event was recorded. Surviving patients were sent a letter inviting them to attend the Vascular Studies Unit for a duplex ultrasound scan of the leg. Non-attenders were sent a second letter. Thus the severity of stenosis and presence and extent of occlusion could be determined at follow up.

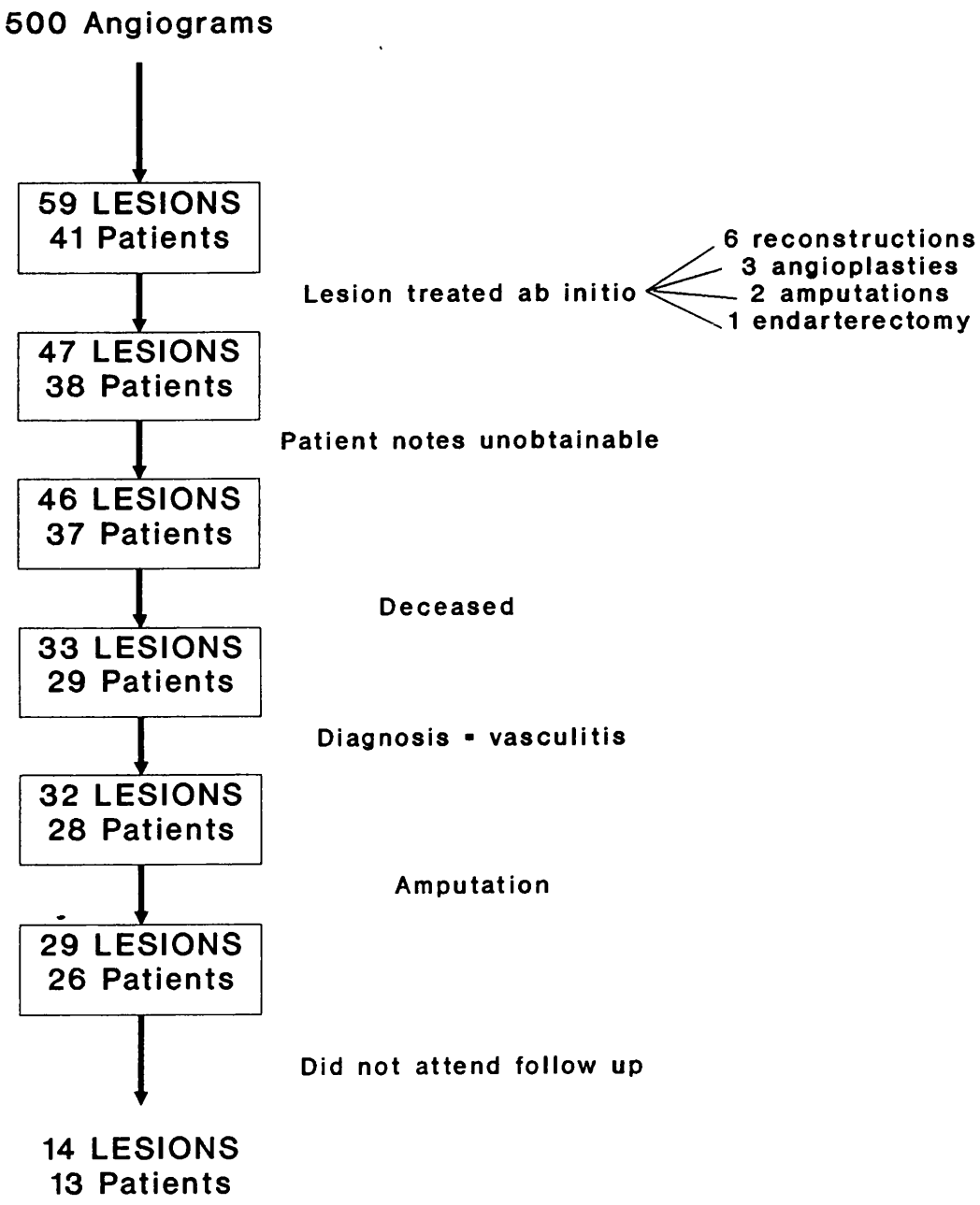
Results

From the 500 angiograms there were 59 early, isolated femoropopliteal lesions in 41 patients. The median age of the patients at the time of angiography was 68 years (range 48-91 years). The interval between angiography and completion of this study ranged from 1-8 years (median 6 years). Twenty-six of the 41 patients were apparently alive and suitable for follow-up. The basis on which patients were excluded from follow-up is summarised in Figure 1.15. Of the 26 patients suitable for follow-up, only 13 attended. Of the 14 lesions (in 13 patients) ultimately re-evaluated, 9 were originally stenoses and 5 were originally short occlusions. In the stenosis group 7 arteries were still patent and 2 had occluded (median follow up = 5.3 years). In the occlusion group 3 had extended to the full length of the SFA, and 2 were unchanged in length (median follow up = 4.0 years). None of the recalled patients was suffering rest pain or had tissue necrosis or ulceration.

There are, therefore, insufficient data on which to base any firm conclusions about the natural history of early femoral artery lesions. On the basis of this study it was deemed necessary to obtain prospective data. The studies described in the following chapters of this thesis are the result.

Figure 1.15

The basis on which patients were excluded from follow up from the pilot study



Summary of main points in Section 2

1. Velocity of blood increases within a stenosis.

2. When a critical level of stenosis is reached, flow and pressure distal to the stenosis are reduced.

3. Duplex ultrasound has the potential to provide important haemodynamic information on femoral artery stenosis.

4. The velocity ratio might be the most useful index of severity of femoral artery stenosis, but validation studies are required before it can be used to monitor the natural history of the lesions.

5. Prospective studies of the natural history of femoral artery lesions are necessary.

CHAPTER 2

ACCURACY AND REPRODUCIBILITY OF DUPLEX ULTRASOUND IN A PHANTOM MODEL OF FEMORAL ARTERY STENOSIS

Contents of chapter

2.1. INTRODUCTION

Since its introduction nearly twenty years ago (Barber et al 1974), duplex ultrasound has been applied to a wide variety of vascular problems (Nicolaides and Renton 1990, Evens 1991, Leng and Fowkes 1991). In lower limb arteries its accuracy in distinguishing haemodynamically significant from non-significant stenosis, and stenosis from occlusion is high (Jager et al 1985, Kohler et al 1987c, Langsfeld et al 1988). However, whether it can accurately distinguish finer grades of stenosis has not been ascertained. In addition, the reproducibility of measurements in the femoral artery is not known. **The ability reliably to detect a change in disease in an individual patient is critically dependent on the reproducibility of measurements.** If improvements in understanding natural history could be brought about by accurate monitoring of femoral artery stenosis, appropriate management strategies in patients with intermittent claudication could be developed. It might, for example, be possible to use angioplasty to dilate stenoses in order to delay progression to occlusion. If a particular grade of stenosis was known to be at high risk of rapid progression to occlusion then these stenoses could be treated before they progressed.

There are problems inherent in the current methods used to study specific lesions. Contrast arteriography is invasive (Hirshberg 1988), its accuracy in measuring stenosis is difficult to ascertain because of a lack of an alternative

and comparable reference standard, variability in interpretation is significant (Bruins-Slot et al 1981), and the anatomical information it gives is sometimes limited compared to the haemodynamic information which can be acquired from duplex ultrasound. Continuous wave (CW) Doppler has been used in previous in-vitro flow models to study waveform characteristics: Douville et al (1983) examined the effect of stenosis on spectral broadening; Morin et al (1987) found that stenoses of less than 30% did not produce significant changes in CW spectra, including peak systolic frequency; Shortland and Cochrane (1989) also found that, in general, the indices tested lacked the sensitivity to detect low levels of disease.

Duplex ultrasound might offer an advance in measurement of atheromatous lesions. It can be used in a number of ways to assess disease:- i) by visualisation of wall thickness or luminal diameter from the real-time image, ii) by the degree of spectral broadening of the Doppler waveform in the post-stenotic region, iii) by the shape of the maximum frequency envelope, iv) by quantifying the increase in blood velocity within a stenosis.

It is generally considered that real-time imaging is not always accurate enough to allow direct measurement of arterial narrowing. It is known that spectral broadening is highly affected by the sample volume size (Knox et al 1982), and by location of sample volume within the vessel. Previous

in-vitro work using flow phantoms suggests that, at best, spectral broadening can distinguish stenoses greater than 40 - 50% by area (Brown et al 1982, Morin et al 1987). Waveform shape is dependent on severity of proximal and distal disease. For these reasons the first 3 methods will not be considered further. By contrast, flow phantom experiments have shown good correlation between degree of stenosis and intrastenotic velocity (Brown et al 1982, Douville et al 1983, Landwehr et al 1991). The increase in velocity can be characterised as an absolute intrastenotic velocity, or as a velocity ratio (equation 1). The velocity ratio should minimise effects due to intra- and inter-patient differences in pre-stenotic velocity.

$$VR = \frac{\text{intrastenotic velocity (V2)}}{\text{pre-stenotic velocity (V1)}} \quad \ldots\ldots \text{ equation 1}$$

A number of studies have examined variability of flow measurements, but in carotid rather than peripheral arteries. Fischer and Alexander (1985) found excellent correlation between repeated peak systolic frequency (PSF) measurements, which was better than peak frequency ratio. Kohler et al (1987b) suggested that PSF was sufficiently precise to warrant its use in classifying disease, and that variability was due mainly to examination technique rather than measurement of waveform parameters or changes in patient haemodynamics. In a small reproducibility study Zbornikova and Lassvik (1986) found that the mean difference in Peak Systolic Velocity (PSV) in patients examined twice within 1-2

weeks was 8.2%. Tessler et al (1990), in examining the factors responsible for measurement variability, concluded that more variability arose from changing transducer or ultrasound machine than from the ultrasonographer. It was noticed that variability increased with increasing PSV, a finding which is investigated in this study. However, little attention has been paid to reproducibility of measurements of femoral artery stenosis, where flow characteristics are very different to those in the carotid circulation.

Variability in measurement of velocity can arise from biological factors, eg. changes in cardiac output and blood pressure, as well as from operator and machine factors. A phantom model of femoral artery stenosis which effectively eliminates biological variability is used in this study. This will allow an estimate of the variability due to machine and operator factors. It also allows multiple observations to be made by several operators, something which is logistically difficult in patients. Lastly, it enables a comparison of VR with a precise measurement of stenosis to be made. Thus, the aims of this study were to determine:-

i) the relationship between the degree of stenosis and the velocity ratio.
ii) the inter- and intra-observer variability, and confidence limits for single measurements of stenosis.
iii) whether accuracy and variability could be improved by standardizing technique.

2.2. MATERIALS AND METHODS

2.2.1. The flow model

A detailed account of the flow model has previously been published (Hoskins et al 1989). It consists of a computer controlled pump which circulates a suspension of Sephadex particles with acoustic properties similar to those of blood (Figure 2.1). When insonated through sponge having similar acoustic properties to human tissue the waveform produced is triphasic and the appearance is similar to that found in femoral arteries (Figure 2.2). A flow phantom which models the physiological circulation in terms of a beating heart, elastic bifurcating tubes and a variable distal resistance is extremely difficult to create. It is more common to use stiff tubing and to produce a desired waveform shape by controlling the speed of the pump. In the flow phantom used in this study preliminary measurements indicated that the waveform shape does not change significantly over the region of interest of the vessel.

In the human a normal waveform is bi- or triphasic, whereas in severe disease or occlusion the distal waveform is damped. The triphasic waveform used in this study was generated at 60 per minute, producing an average flow rate of 80 ml/min. Such a waveform is most appropriate for those stenoses less than 50% (9 out of 14). The same waveform was used for stenoses greater than 50% because it was felt that the effect of using different waveform shapes would constitute an additional source of variability. It is likely that the variability in

this instance represents a worst case because the location of the maximum velocity would be easier to ascertain for a damped waveform. In any case, it is not uncommon in practice for the waveform before stenoses greater than 50% to exhibit reverse flow.

A straight section of non-tapering, non-branching heat-shrink tubing approximately 50 cm in length and with an internal diameter of 5mm was taken as representative of the superficial femoral artery. In a straight tube the flow will become stable at a distance from the entrance known as the inlet length. In this study a peak systolic velocity in the tubing of around 50 cm/s was produced and this required an inlet length of 7 cm. The stenosis was inserted beyond this point, ensuring that flow had stabilised well before the stenosis.

The tubing was immersed in a water bath at room temperature. The temperature of the water was kept within the range 18.3 - 19.0 °C during the measurements.

Stenoses made of perspex were positioned within the heat-shrink tubing and insonated at a depth of 4cm from the 5 MHz linear array transducer of an ATL Ultramark 9 colour flow duplex scanner (Advanced Technology Laboratories, Bothell, WA, USA). Concentric stenoses were made by drilling a cylindric core through solid perspex. Short segments of perspex tubing were used for the eccentric stenoses. These

were heated to plasticity and a metal rod used to compress one side of the tube. After the Doppler data had been acquired the area of the concentric stenoses was measured using a microscope with a calibrated eyepiece. For each eccentric stenosis a short segment which included the narrowest part was cut. A camera and frame grabber was used to transfer an image of this to a computer and appropriate "region of interest" software used to measure the area. These areas were then compared with the area of the heat shrink tubing in the prestenotic region, and a percentage area reduction calculated for each of the 14 stenoses (table 2.1). p123 The length of the stenotic part of the concentric stenosis was 10mm and the end region expanded at an angle of 45 degrees to join the main vessel. The shape of the eccentric stenosis was more difficult to control, but typically this was a smooth projection on one side of the wall whose total length was 10mm. Concentric stenoses have radial symmetry so that the maximum velocity will be exhibited centrally within the vessel, whereas for the eccentric stenoses the flow patterns in the region of the stenosis will also be eccentric. Degree of stenosis is expressed as diameter reduction (concentric) and, for ease of comparison, ***effective*** diameter reduction (eccentric stenoses) in figures 2.5-2.8. The effective diameter reduction is calculated from the area reduction as if the narrowing were concentric.

Peak Systolic Velocity (PSV) was measured before, (V1), and at the centre of, (V2), the stenosis. The velocity ratio, VR,

was calculated as V2/V1 (equation 1). To ensure the ultrasonographer was blind to the PSV values, the velocity scale on the duplex monitor was obscured by opaque tape and the velocity values read from a distant monitor by an independent observer. The flow rate was checked throughout the period during which data were acquired using the measuring cylinder and stopwatch method (McDicken 1986), and the maximum variation in rate with different degrees of stenosis was found to be ± 3.9%.

2.2.2. Doppler data.

Velocity Ratio (VR) measurements were taken in random order by three trained duplex sonographers (PLA, MRW, GCL). Each ultrasonographer obtained five separate values for VR for all 14 stenoses using unstandardised and standardised methods (vide infra). Thus a total of 420 values of velocity ratio was acquired.

Two ways of acquiring the data were tested, an unstandardised and a standardised method. Using the unstandardized method the operator was free to alter machine settings to produce the best signal. This included all parameters normally varied during clinical use of the duplex system - Doppler gain, beam-vessel angle, and aperture position. The sample volume size was set to 1.5mm. Doppler gain and angle were recorded to enable determination of systematic differences between observers.

It is known that the Doppler estimated velocity for the ATL UM9 scanner used in this study is strongly dependent on beam-vessel angle and Doppler aperture position (Hoskins et al 1991). In order to investigate whether these factors contribute to the variability in velocity ratio in practice a "standardised" study was performed where the beam-vessel angle was set to 64^0 and the aperture position to the extreme end of the transducer. The sample volume was again set to 1.5mm. Doppler gain was not fixed, but again its value was recorded to enable determination of systematic differences between observers.

2.2.3. Preliminary measurements

Before the experimental data could be acquired, it was necessary to carry out two preliminary sets of measurements to test the effect of potentially important variables:

a) The effect of altering intra-stenosis sample position

This effect was examined in order to determine where velocity samples should be taken within the stenosis. The choice of sampling position within a stenosis might affect magnitude of PSV and, therefore, might also be important in clinical practice. Constant flow and measurement conditions were established by clamping the transducer in place and fixing Doppler variables, including Doppler gain for each stenosis. The sample volume was placed concurrently within the stenosis: i) At the entrance, ii) in the centre, iii) at the exit. Six values of VR were obtained at each site.

Figure 2.3 shows the effect of altering sample position within the stenosis. The only significant effect was seen at the exit of the stenosis with low pre-stenosis velocity. In figure 2.3 an arbitrary computer generated unit of 0.2 equates to a velocity of around 25 cm/s. The velocity ratio therefore differed from 102/25 (= 4.1) in the centre of the stenosis to 125/25 (= 5.0) at the exit.

b) The effect of altering pre-stenosis velocity

Constant flow and measurement conditions were again established by clamping the transducer in place and fixing Doppler variables, including Doppler gain for each stenosis. For a range of pre-stenosis velocities 6 values of Velocity Ratio were obtained for each of 4 stenoses within the technical limits of recording (until aliasing occurred). Figure 2.4 shows the effect on velocity ratio of altering pre-stenosis velocity. With the exception of the least severe stenosis there are substantial differences in VR which depend on pre-stenosis velocity. For example, in the most severe stenosis the velocity ratio obtained varied from 7.81 (±2SD = 7.72-7.90) to 9.02 (±2SD = 8.87-9.17).

These two preliminary sets of measurements therefore indicate that in order to minimise "biological" variability in this model it was necessary to take Doppler samples from the centre of the stenosis wherever possible and also to use a constant pre-stenosis velocity.

2.2.4. Statistical analysis

Statistical tests were carried out using the SPSS-X programme on the University of Edinburgh mainframe computer. Analysis of variance was used to compare velocity ratio measurements between and within observers. It was necessary to express the data as logarithms to carry out analysis of variance because there was heterogeneity of variance across the range of stenoses. A cubic regression curve was fitted to the data representing the relationship between percent stenosis and velocity ratio. The 95% confidence limits for velocity ratio (table 2.2) were obtained by taking ±2 standard deviations from the mean of 15 VR measurements per stenosis.

2.3. RESULTS

2.3.1. Unstandardised procedure.

a) Relationship between velocity ratio and degree of narrowing.

Figures 2.5 and 2.6 show velocity ratio as a function of percent stenosis for concentric and eccentric stenoses respectively. There are no major differences between the curves for eccentric and concentric stenoses. As a measure of the closeness of fit of the points to the concentric stenosis curve, $R^2 = 0.996$, where $R^2 = 1$ represents a perfect fit of the data to the curve. The cubic regression line from figure 2.5 has been superimposed on the eccentric stenoses data to show the similarities between the two sets of results.

b) Inter- and intra-operator variability

Figures 2.7 and 2.8 show the data for each individual operator for concentric and eccentric stenoses respectively. There is no significant interoperator difference for the eccentric stenoses. For the concentric stenoses there were no significant differences between observers except for the 60% stenosis where a 16% difference between observers 2 and 3 was found, $p=0.002$, analysis of variance. In analysing the reasons for the difference, not one consistent trend was apparent in absolute velocity, in Doppler gain or in beam-vessel angle. Intra-operator variability was found to be insignificant for all stenoses.

c) Confidence limits for stenosis assessment.

The 95% confidence limits for all stenoses are shown in table 2.2. Thus there is a 95% degree of certainty that a single additional VR reading which falls within each of the given limits is measuring the same stenosis. The extremes of velocity ratio for each stenosis range between ±13 and ±22% from the mean.

2.3.2. Standardised procedure.

The relationship between the mean of the velocity ratios and the percent stenosis was nearly identical to that for the unstandardised technique. There was an excellent correlation between velocity ratio and percent stenosis. There was no significant difference in velocity ratio measurements between operators for either concentric or eccentric stenoses. In

particular there was no improvement in the confidence intervals so these results will not be presented in more detail.

2.4. DISCUSSION

Duplex velocity ratio correlates well with degree of stenosis. Although such "accuracy" can be improved by taking the mean of several readings of velocity ratio, this is not necessary since the confidence limits for a single reading are small (within ±22%). It could reasonably be argued on the basis of the results from this study that duplex is accurate enough to be a reference standard for measurement of arterial stenosis.

Variability in measurement of VR is generally low. For both concentric and eccentric stenoses an unstandardised ultrasonography technique proved just as consistent in minimising inter-observer variability as a standardised technique. At first sight this is difficult to explain, but by enforcing rigid measurement conditions in a standardised technique, an operator might find it difficult to align the ultrasound beam with the vessel, resulting in errors due to incorrect angle adjustment. The potential benefits from using a standardised technique might therefore be offset by other factors.

Despite variability being statistically significant for one stenosis, the magnitude of variation in VR is probably of

little importance in practice. No consistent trend in any one observer obtaining high velocities or using high gain or angle was found to account for differences in results. Confidence limits for single values of VR allow a judgement to be made regarding likelihood of change in severity of an individual stenosis from one measurement to the next. The results therefore indicate the potential for duplex to be used in practice to monitor the progression or regression of arterial stenoses. To minimise variability, repeat measurements of velocity ratio in cases of severe stenosis should be made by the same observer.

In clinical practice, a useful way of measuring a stenosis is to allow colour flow to guide the sonographer to the area of narrowing, then to position the Doppler sample where velocity is highest. It was thought inappropriate to do the same in this model since the stenosis could be easily visualised in B-mode, and its centre located accurately. This does not therefore reflect what happens in practice, and a potential source of observer variability may have been ignored. The reason that this method was not chosen is because it was originally thought that a refraction artifact at the stenosis exit would have given rise to artificially high values of VR.

It is not uncommon in the field of Doppler ultrasound to try to derive the % stenosis directly from the velocity ratio (VR) by using this equation:-

% luminal diameter reduction = 100 [1 - (1/√VR)] ..... eq 2

Figure 2.9 shows the correlation (r=0.992) between Doppler derived stenosis and true stenosis (concentric and eccentric stenoses combined). The reduction in diameter is consistently underestimated by the Doppler technique. The basis of the equation is that the velocity profile at peak systole within the stenosis and the profile at peak systole in the pre-stenotic region are identical. It is known that when moving blood encounters a change in vessel geometry a certain distance must elapse before the velocity profile stabilises, the inlet length. This length is typically 10-20 diameters, so that within a short stenosis the profile would not have time to stabilise. The most likely explanation is that the profile becomes blunter which results in a lower intrastenotic peak velocity. This leads to a low velocity ratio with consequent underestimation of the degree of disease. The fact that the relationship between % stenosis and the velocity ratio is the same for both the concentric and the eccentric stenoses suggests that this effect is relatively independent of the detailed geometry of the stenosis, but is mainly related to the degree of stenosis. It is probably more correct, therefore, to obtain a value for stenosis by reading off the velocity ratio correlation curve (eg. figure 2.5), rather than converting the ratio to degree of stenosis using equation 2.

The phenomenon of blunting of the velocity profile might also

explain how low pre-stenosis velocity can give rise to a high velocity ratio (figure 2.3). Such low velocity might allow the intrastenotic profile to stabilise rapidly resulting in higher intrastenotic velocity and velocity ratio. This same explanation could also account for the finding of a higher intrastenotic velocity at the extreme end of the stenosis (figure 2.2). It is unlikely that these findings will be of considerable use to the practising ultrasonographer, but they do explain where some of the variation in velocity ratio which occurs in practice might arise.

This study has shown that moderately precise grading of stenosis with duplex is possible but it has demonstrated only the minimum variability achievable. If accurate measurements of femoral artery stenosis and monitoring natural history are to become feasible, it is also necessary to demonstrate that variability in VR measurement can be kept acceptably low in patients.

Acknowledgements: I am grateful to Mr R Borthwick and Mr M Connel for assistance in the preparation of the stenoses and in the measurement of the stenotic areas.

Conclusions

1. Velocity ratio is an accurate index of severity of simulated and geometrically simple arterial stenoses.

2. In vitro the intra-operator variability in measurement of velocity ratio is small, but inter-observer variability was significant with one of the severe stenoses. Repeat measurements of velocity ratio over time should therefore be made by the same observer.

3. The confidence limits for a single reading of VR for any stenosis are ≤ ±22%

4. Standardisation of beam-vessel angle and aperture position during measurement of Doppler waveforms does not improve variability.

5. The potential exists for non-invasive monitoring of progression of pre-occlusive femoral artery stenoses and their response to treatment.

Table 2.1

Reduction in area and luminal diameter of stenoses

Concentric (C) or Eccentric (E) stenosis	Area reduction (%)	Diameter reduction (%)
C	-8.2*	-4.0*
C	13.7	7.1
C	29.9	16.3
C	49.2	28.7
C	61.4	37.9
C	73.2	48.2
C	84.6	60.8
C	90.5	69.1
E	52.4	31.0
E	62.7	39.0
E	74.8	49.8
E	79.9	55.2
E	83.6	59.5
E	91.0	70.0

* = a negative value was obtained. This can be explained by excessive shrinking of the heat-shrink tubing after modelling to the stenosis, which effectively renders the stenosis dilated compared with the inflow tube.

For eccentric stenoses the "effective" diameter reduction is calculated from the area reduction

Table 2.2

95% confidence limits in velocity ratio measurement.

Diameter reduction (%)	Mean of the Velocity Ratios	95% confidence limits in VR
-4 (C)	0.89	0.76-1.02
7.1 (C)	1.02	0.89-1.15
16.3 (C)	1.15	0.99-1.31
28.7 (C)	1.53	1.33-1.73
31 (E)	1.45	1.21-1.69
37.9 (C)	1.86	1.49-2.23
39 (E)	1.99	1.59-2.39
48.2 (C)	2.45	2.13-2.77
49.8 (E)	2.56	2.18-2.94
55.2 (E)	3.76	2.92-4.60
59.5 (E)	4.20	3.58-4.82
60.8 (C)	3.92	3.29-4.55
69.1 (C)	5.80	4.61-6.99
70 (E)	6.24	5.16-7.32

Values are those from an unstandardised Doppler sampling method.

C = Concentric stenoses

E = Eccentric stenoses

Figure 2.1

Flow phantom set-up

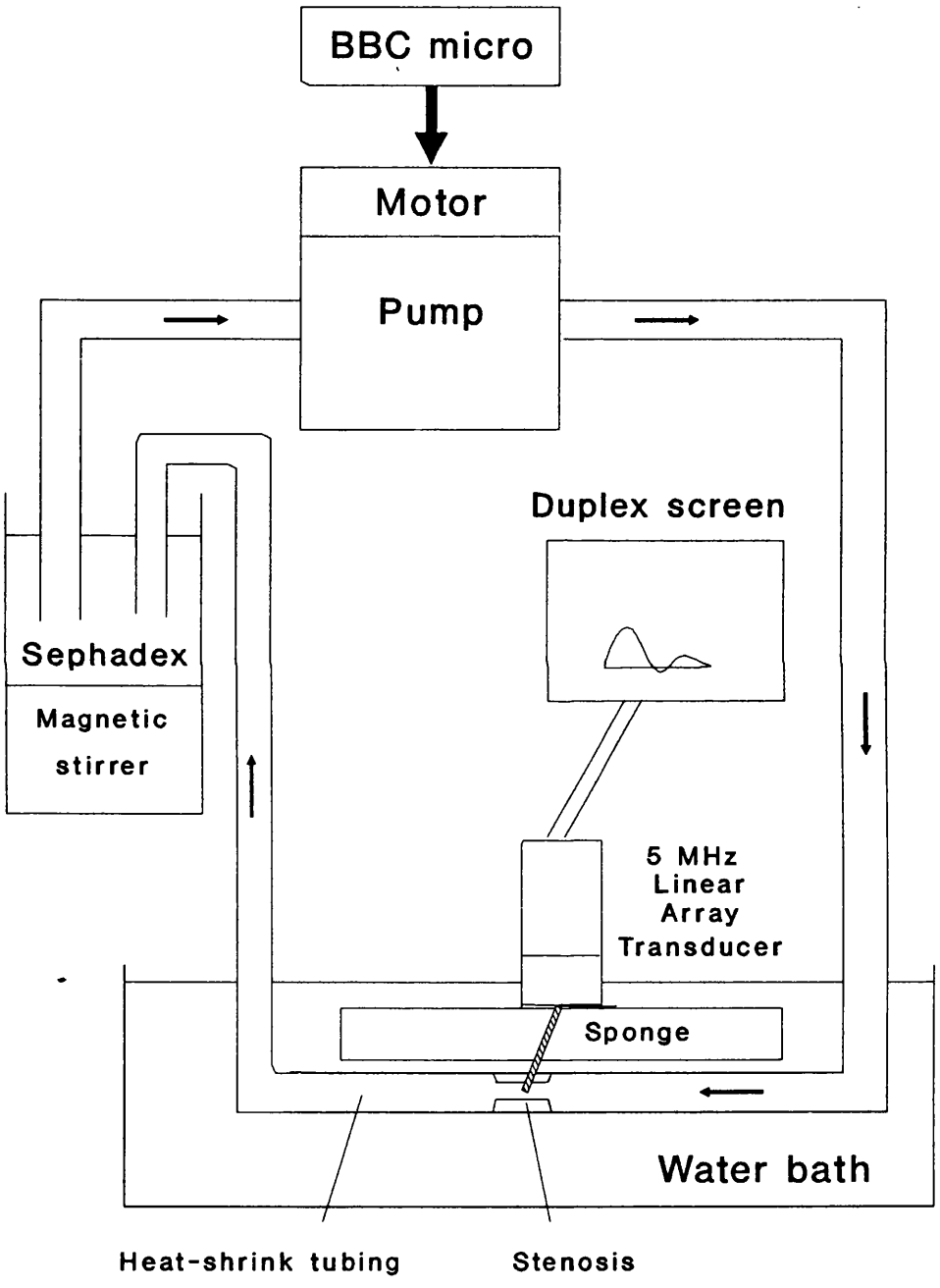


Figure 2.2

A typical waveform produced in the phantom model

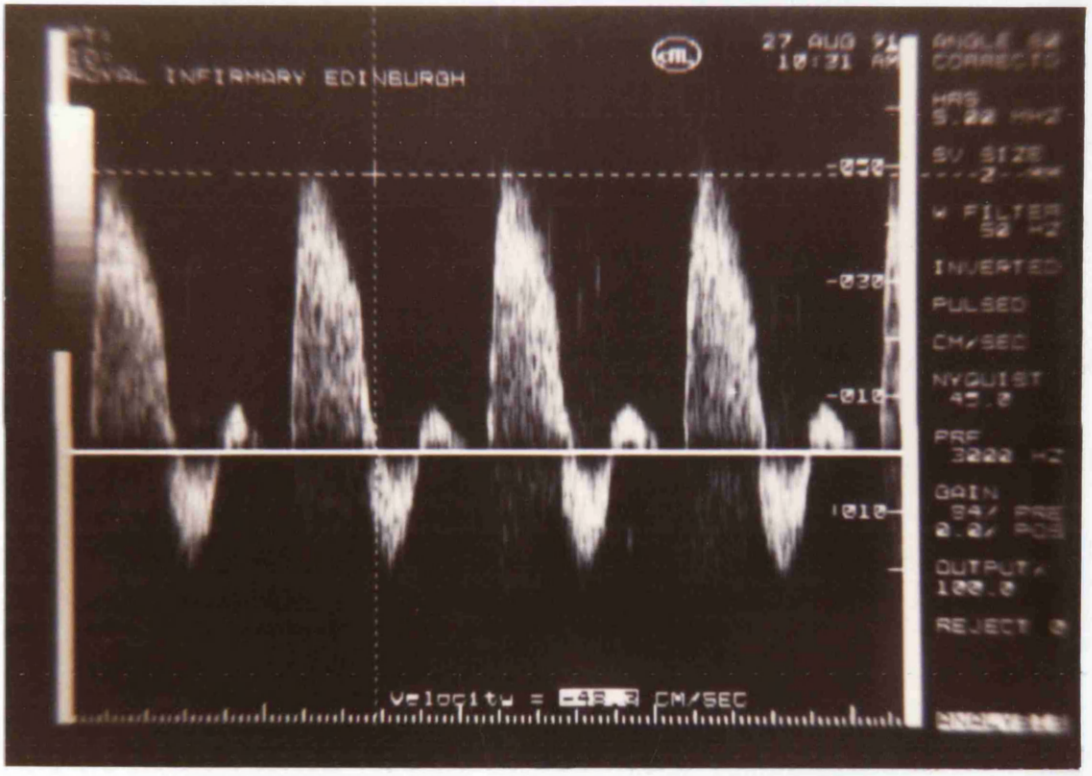
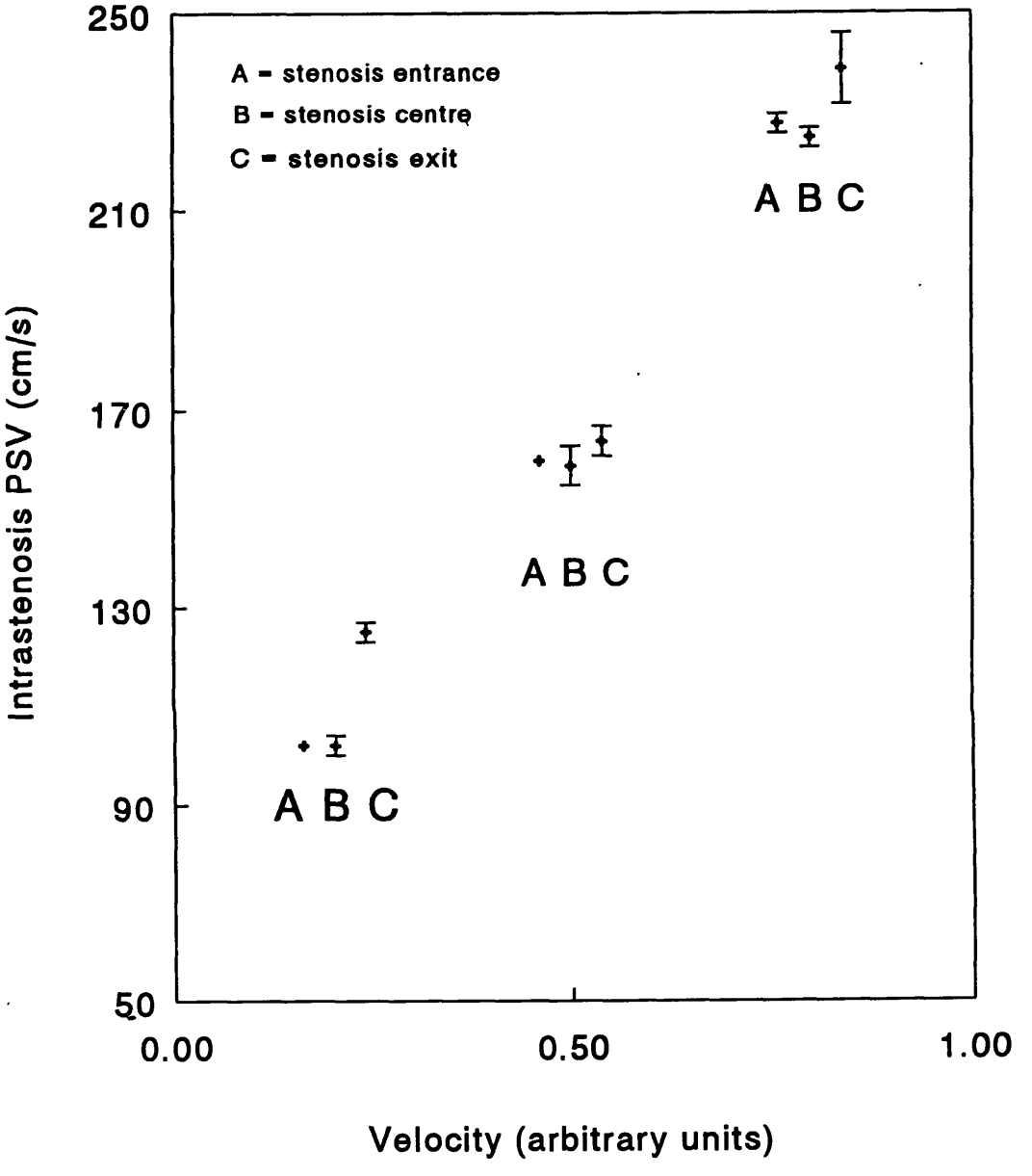


Figure 2.3

The effect on velocity of altering sample position within a stenosis



Error bars represent range of PSV values

Figure 2.4

The effect on velocity ratio of altering pre-stenosis velocity

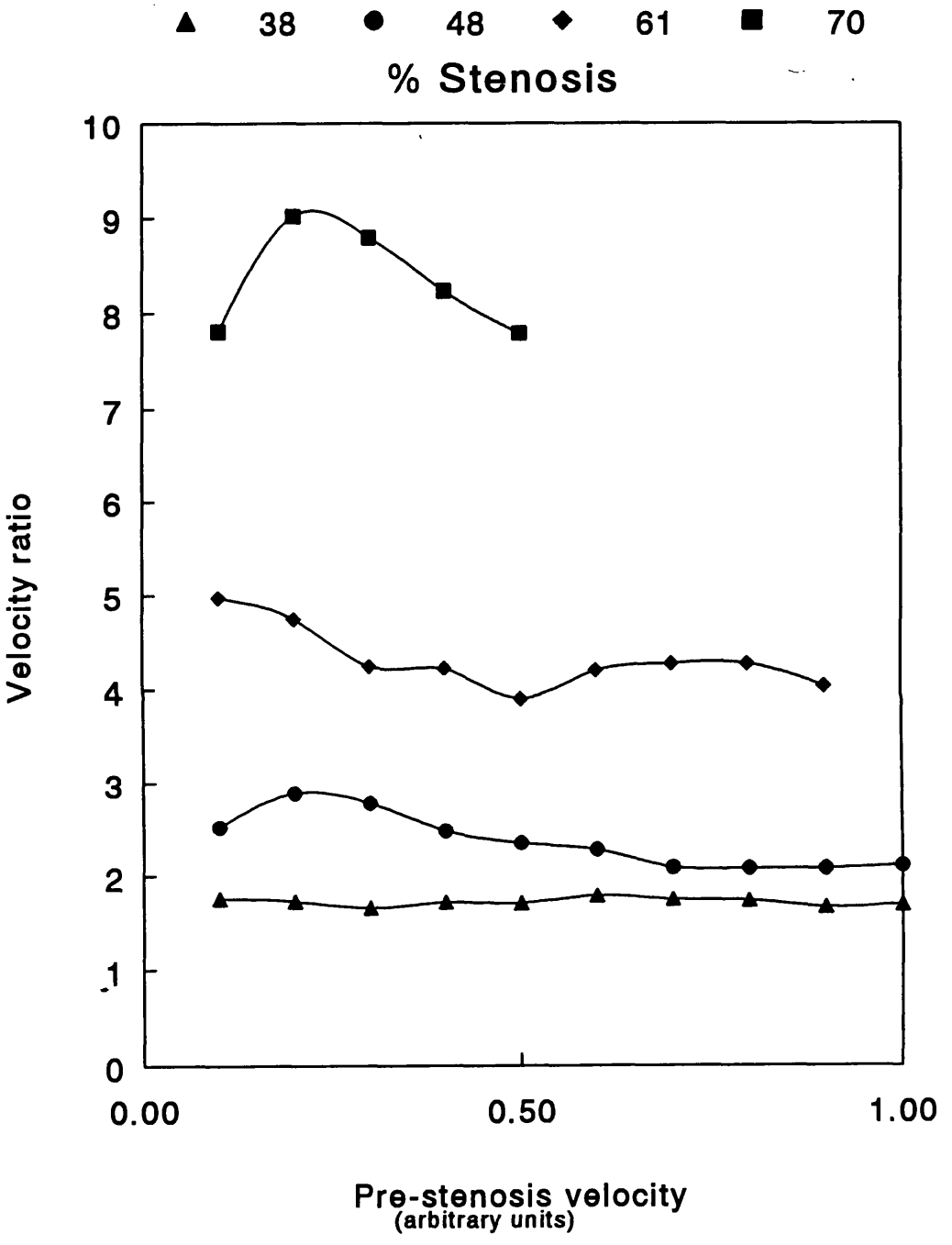


Figure 2.5

Relationship between mean of the velocity ratios (± 2 SD) of 3 observers and % diameter reduction of concentric stenoses.

The regression line is represented by the equation:

$y = 0.964 + 0.027x - 0.001x^2 + 0.000024x^3$.

$R^2 = 0.996$

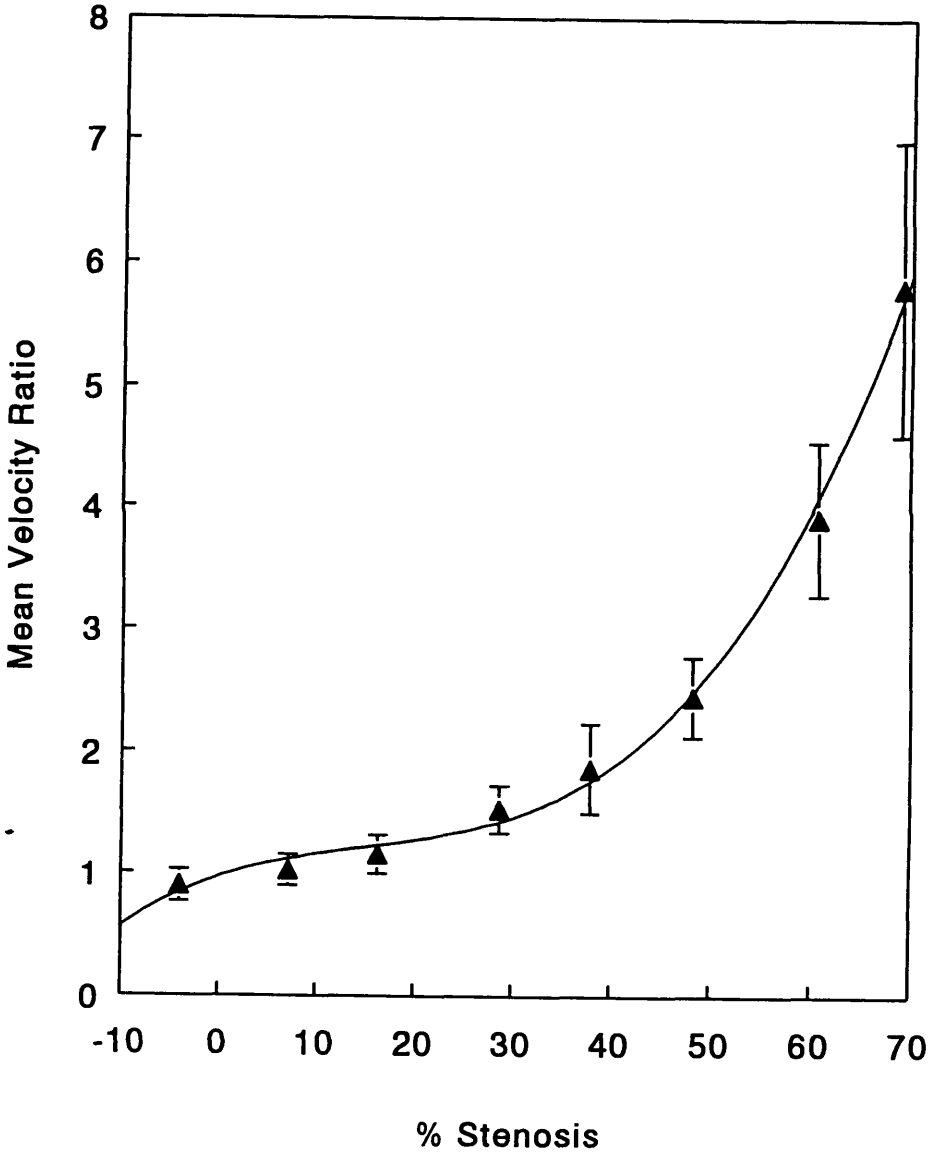


Figure 2.6

Relationship between mean of the velocity ratios (± 2 SD) of 3 observers and effective % diameter reduction of eccentric stenoses.

A regression line of the same equation as that in Figure 2.5 has been superimposed on the data to show the similarities between results from concentric and eccentric stenoses.

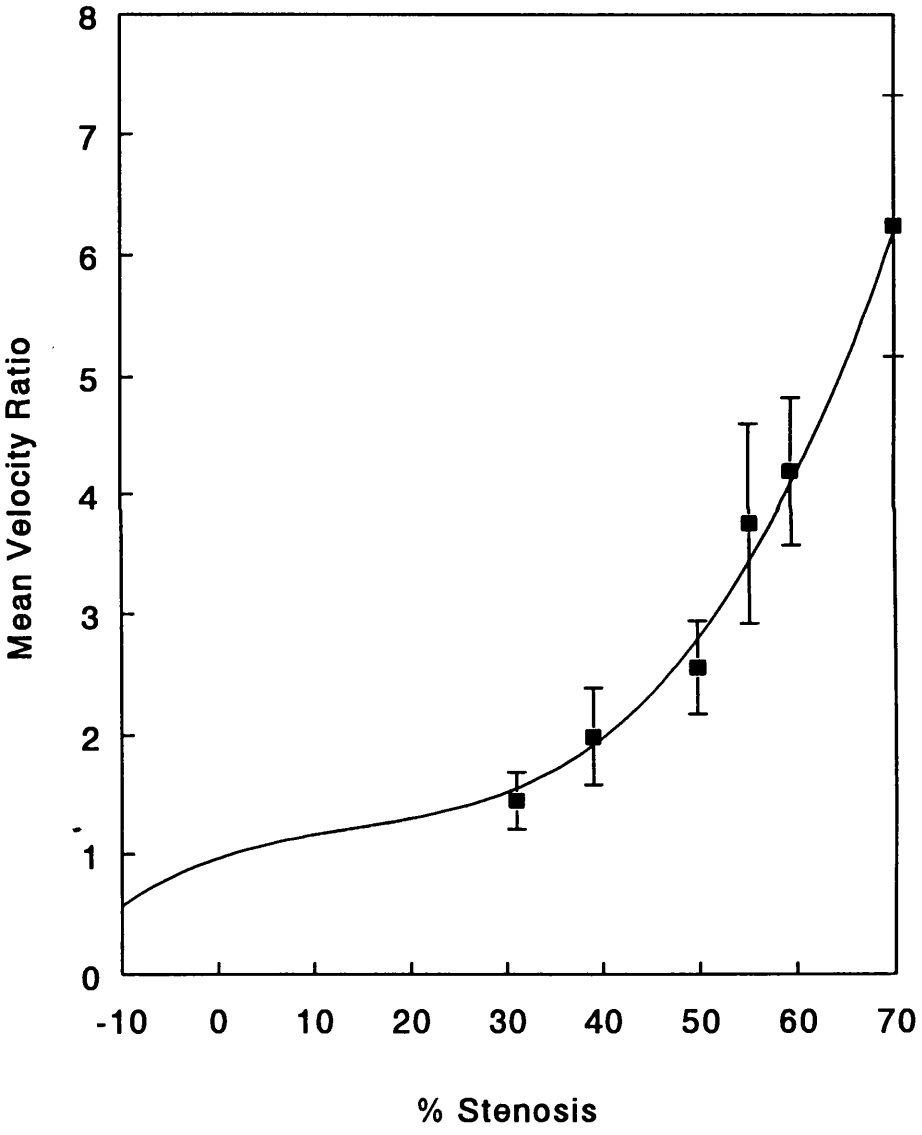


Figure 2.7

Relationship between mean of the velocity ratios of each observer and % reduction in diameter of concentric stenoses.

Legend: + Observer 1 Δ Observer 2 O Observer 3

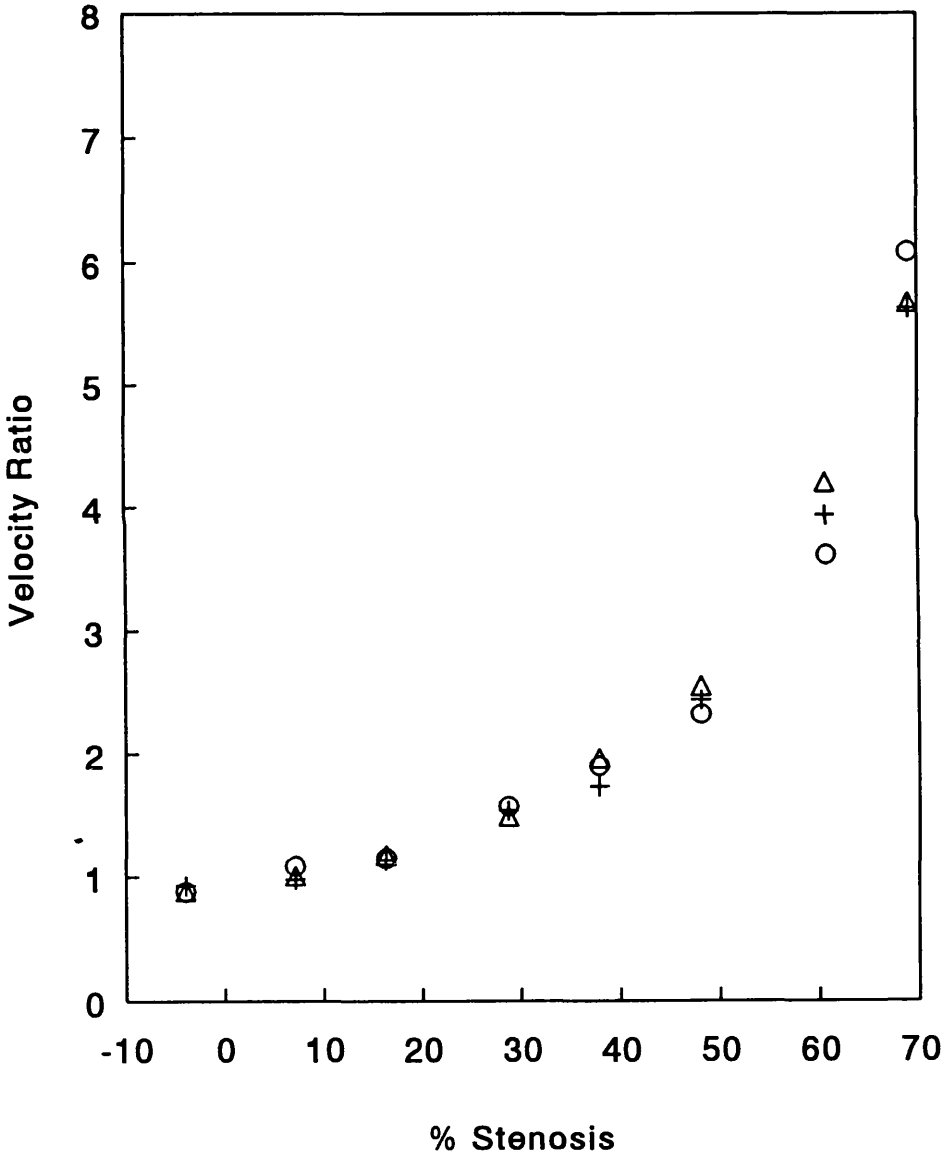


Figure 2.8

Relationship between mean of the velocity ratios of each observer and effective % reduction in diameter of eccentric stenoses.

Legend: + Observer 1 ▵ Observer 2 ○ Observer 3

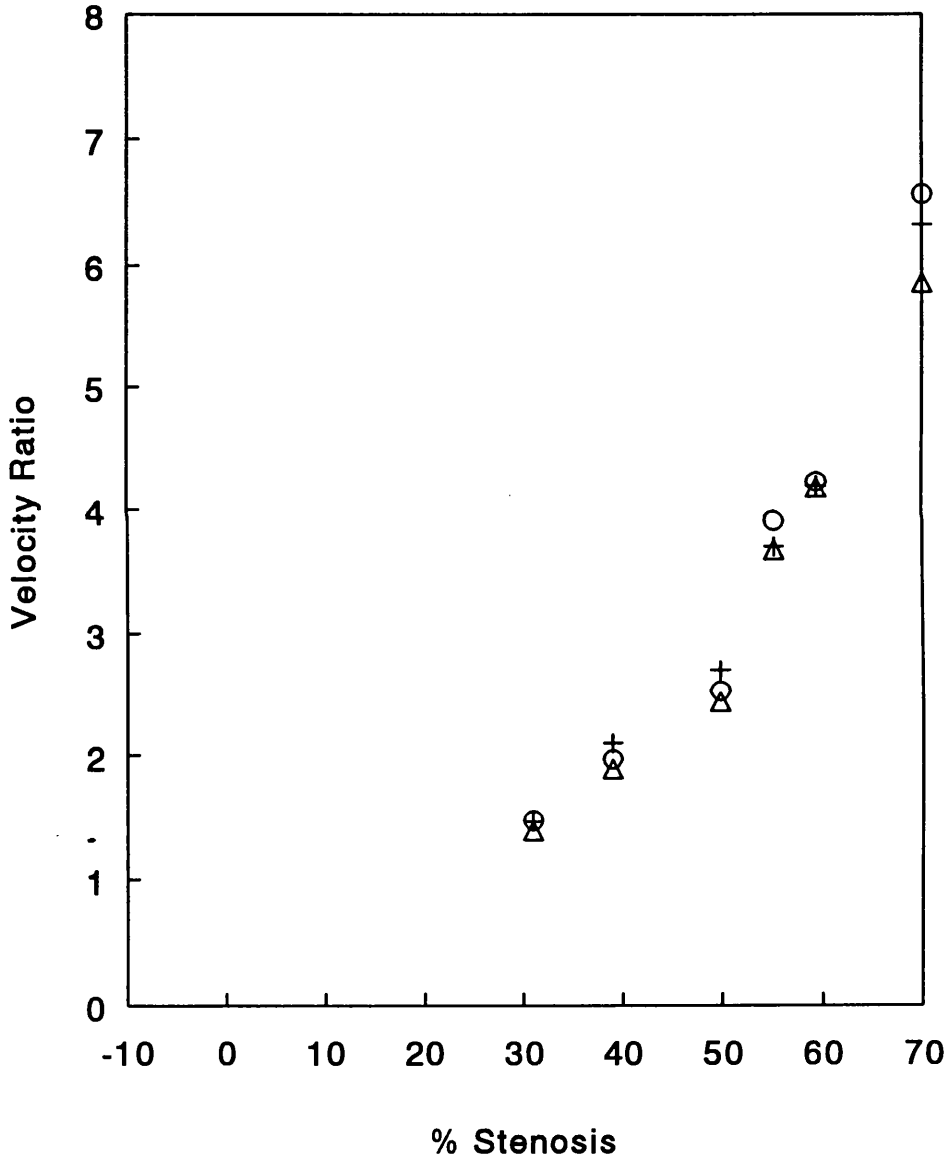
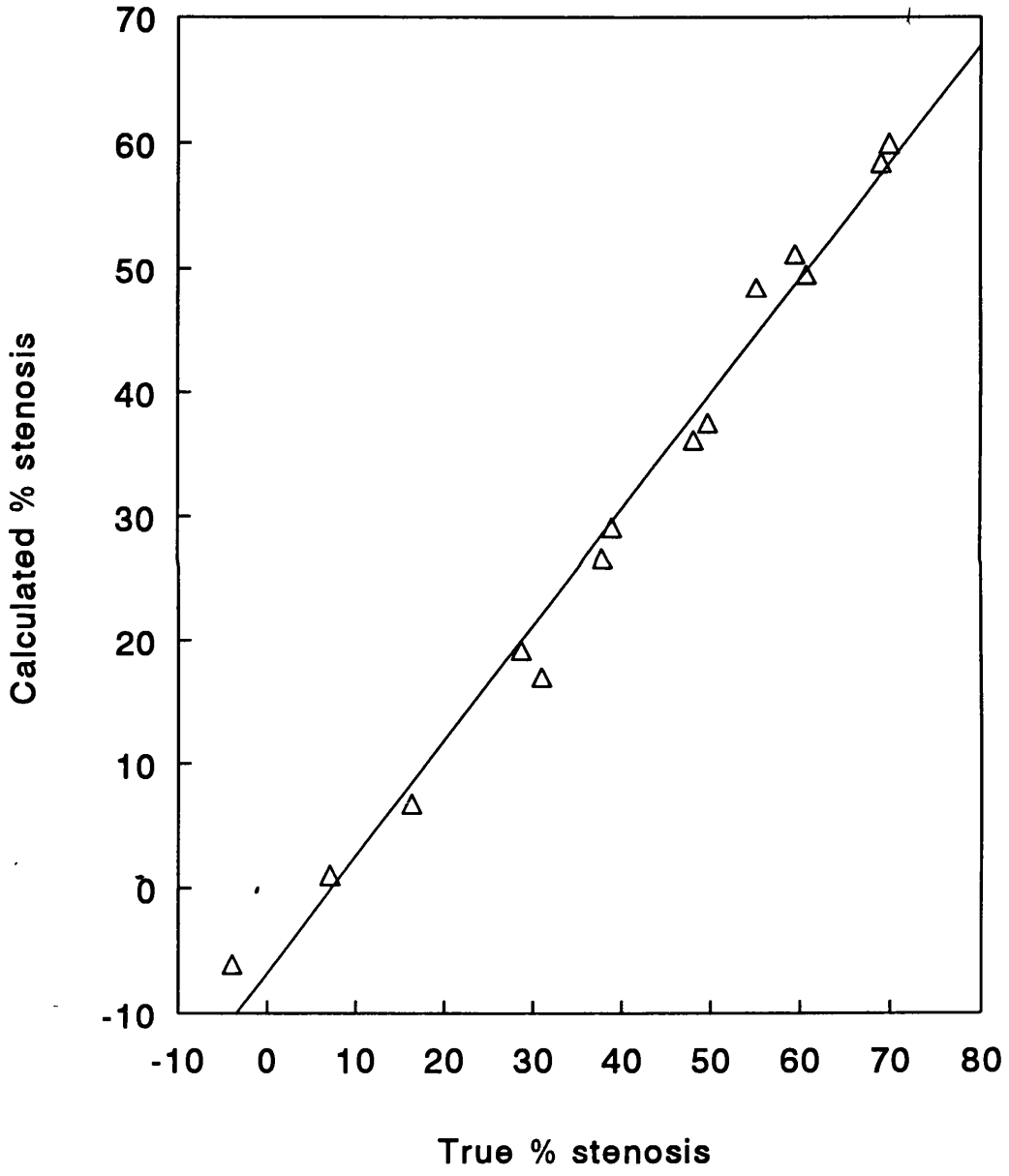


Figure 2.9

Correlation between Doppler derived stenosis and true stenosis (concentric and eccentric stenoses combined)



CHAPTER 3

ACCURACY AND REPRODUCIBILITY OF DUPLEX ULTRASOUND IN THE GRADING OF FEMORAL ARTERY STENOSIS

Contents of Chapter

3.1. INTRODUCTION

An awareness that B-mode ultrasound imaging alone could not accurately measure arterial narrowing prompted the development of duplex ultrasound (Barber et al 1974). Subsequent technological advances enabled the Doppler flow information to be colour-coded, thus allowing areas of high velocity to be easily recognised. This makes scanning quicker, and stenoses more easy to identify.

In 1985, Jager et al. proposed a system for classifying the degree of arterial stenosis in the lower limb based on the Doppler waveform shape, the degree of spectral broadening and the increase in peak systolic velocity within the stenosis. Subsequent classification systems have placed more emphasis on the increase in velocity, and less on the changes in waveform configuration and spectral broadening (Legemate et al 1989, Cossman et al 1989, Polak et al 1990, Mulligan et al 1991). These and other studies (Kohler et al 1987c, Moneta and Strandness 1987, Demes et al 1989) show duplex scanning to have a high specificity and moderate sensitivity in detecting stenoses of greater than 50%, but the results from different studies are not directly comparable because a standard method of classifying disease has not been adopted.

Studies in the carotid system have shown the repeatability of duplex scanning to be good (Kohler et al 1985, Polak et al 1989), but there are no reports of the repeatability of duplex in the lower limb where scanning is recognised to be

more difficult, especially in areas such as the adductor canal of the superficial femoral artery. Good repeatability is particularly important if duplex scanning is to be used for follow-up examinations of lesions, during graft surveillance, or in epidemiological and natural history studies of peripheral arterial disease.

The aims of this study were to determine:

1) the accuracy of Doppler waveform characteristics in identifying femoro-popliteal stenoses, in order to formulate a system for classifying disease

2) the inter- and intra-observer reproducibility of measuring the same Doppler waveform characteristics.

3.2. METHODS

3.2.1. Angiographic measurements

Thirty discrete areas of stenosis in the femoro-popliteal region were identified from the arteriograms of 28 patients with peripheral arterial disease attending the Royal Infirmary of Edinburgh. Biplanar views were taken when lesions were not clear on a uniplanar film. Areas of isolated stenosis were chosen to enable the same area to be easily identified on duplex scanning, thus ensuring that direct comparisons of the same lesions could be made. The degree of stenosis on the arteriogram was measured independently by three experienced observers (MRW, CVR and IG). The diameter of the narrowest region and that of the nearest apparently

normal region were measured with a ruler and the degree of stenosis was expressed as the percentage reduction in luminal diameter. The arteriographic data are summarised here, rather than in the results section because determination of the variability of arteriographic measurements is not one of the principal aims of this study. The intra-class correlation coefficients in each case showed good agreement (r=0.71, CVR/MRW; r=0.77, MRW/IG; and r=0.84, CVR/IG), although individual measurements varied by as much as 30% reduction in diameter. A two-way analysis of variance showed no significant difference between the results of the three observers (p=0.78), which suggests there were not systematic differences. It was therefore considered valid to use the mean of the three measurements as the reference standard against which duplex findings could be compared.

3.2.2. Duplex measurements

Colour duplex scanning was performed by two trained observers (GCL and MRW) using an Ultramark 9 duplex scanner (Advanced Technology Laboratories Inc, Bothell, Washington, USA). The examination was carried out after the patient had rested for 10 minutes, using a 5MHz linear array transducer. The exact position of the stenosis was first identified on the arteriogram. The same area was then identified during duplex scanning by a colour change representing an increase in velocity. Doppler spectra were recorded in the area where colour change suggested the highest velocity, and also at the nearest normal area proximal to this, recognised by an even

colour saturation. A typical Doppler waveform was selected from each site, and from this the following characteristics were measured: peak systolic velocity (PSV); spectral broadening (SB), classified as minimal, moderate or marked; and waveform configuration (triphasic, biphasic or monophasic).

The mean interval between arteriography and duplex scanning was five days. Each observer was blind to the results of the other. In 17 patients the scans were repeated after an interval of two weeks by both observers. The remaining patients underwent bypass surgery or angioplasty before repeat measurements could be made. The stenoses examined on the second occasion ranged from 25-65% (degree of reduction in luminal diameter) compared to 25-71% in those examined on only one occasion.

The study was granted ethical approval by the Lothian Area Ethics of Medical Research Sub-Committee for Surgery.

3.2.3. Statistical Analysis

The data were coded and transferred to the Edinburgh University mainframe computer for analysis using the BMDP statistical package (Dixon et al 1988).

The ratio of PSV within the stenosis to the PSV in the nearest normal proximal segment of artery (velocity ratio, VR) was plotted against the mean arteriographic stenosis.

Sensitivity, specificity and positive and negative predictive values (Fletcher et al 1982) were calculated for the ability of the VR, spectral broadening and waveform configuration to correctly identify stenoses with more than 50% reduction in luminal diameter on the arteriogram. Criteria were then selected using Receiver Operator Curves for the classification of stenosis.

Agreement between the VR of observers was expressed by the intra-class correlation coefficient (r_i). The Kappa statistic was calculated as a measure of agreement for categorical data (Fleiss 1973). Kappa takes into account agreement occurring by chance alone; 1 represents perfect agreement and 0 represents agreement no greater than that expected by chance (see appendix B).

3.1. RESULTS

1) Accuracy of duplex information

Figure 3.1 shows the relationship between velocity ratio and the degree of stenosis according to arteriography. Duplex data repeated on a second occasion have not been included, in case the severity of disease had changed between measurements. The relationship between velocity ratio and percent stenosis is similar to that obtained in the laboratory using the flow phantom in chapter 2. The line of best fit from the phantom study (a cubic regression curve) is superimposed on the data in Figure 3.1, and shows a marked increase in velocity ratio at greater than 50% stenosis. The

linear, quadratic and cubic regressions (R^2=0.32, 0.30, 0.30) for the relationship between the absolute peak systolic velocity within the stenosis and the degree of narrowing were poorer than those for the for the relationship between velocity ratio and degree of narrowing (R^2=0.38, 0.52, 0.52). The data are shown in figure 3.2.

In 68% of cases, the degree of SB identified within the stenosis was the same as in the preceding normal segment. In 18% there was an increase and in 14% there was a decrease in SB within the stenosis. Similarly, in 67% the waveform shape was the same within the stenosis and the preceding segment, and became more abnormal (became biphasic if triphasic before, and monophasic if biphasic before) within the stenosis in only 24%. Table 3.1 shows the agreement between marked SB, a monophasic waveform, and the presence of a greater than 50% stenosis. In both cases kappa was very small which indicates poor agreement. The agreement between VR ≥3 and a >50% stenosis is included in the table for comparison.

Table 3.2 shows the sensitivity, specificity and predictive values of marked spectral broadening and a monophasic waveform in detecting stenoses greater than 50%. A velocity ratio of ≥2 showed excellent sensitivity but poor specificity, whereas a ratio of ≥3 showed moderately good sensitivity and excellent specificity.

2) Variability of duplex measurements

There was good agreement in the measurement of velocity ratio between different observers (r_i=0.88) (Figure 3.3), and moderate agreement for the same observer on two separate occasions (r_i=0.53) (Figure 3.4). In the latter case the second reading was consistently higher than the first. Kappa coefficients have also been calculated to show the inter- and intra-observer agreement in obtaining velocity ratios greater than three (approximately equivalent to greater than 50% stenosis) (Table 3.3).

In classifying waveform shape as either mono-, bi- or triphasic, the kappa statistic was 0.61 for inter-observer agreement, and was 0.37 for intra-observer agreement. In the classification of the degree of SB as either minimal, moderate or marked, the kappa statistic for inter-observer agreement was 0.28, and for intra-observer agreement was 0.18. These results are not tabulated.

3.4. DISCUSSION

1) Accuracy of duplex information

The accuracy of duplex measurements of femoral stenoses has been validated against contrast arteriography, the interpretation of which is known to be subject to substantial variation in interpretation (Bruins-Slot et al 1981). Therefore, some apparent inaccuracies in velocity ratio might be partly due to an inaccurate reference standard.

The velocity ratio showed better correlation with degree of stenosis than did peak systolic velocity. One explanation is that the variation in absolute velocity of blood is considerable, whereas velocity ratio remains relatively constant (Barnes 1980). A velocity ratio of three (200% increase in velocity) showed better overall accuracy in detecting a stenosis of 50% or more than a velocity ratio of two (100% increase). Similar agreement between a 200% increase and a 50% stenosis was also found in the flow phantom study described in chapter 2, but other clinical studies have suggested that a 150% (Legemate et al 1989) or 100% (Jager et al 1985, Cossman et al 1989, Polak et al 1990, Mulligan et al 1991, Kohler et al 1987, Moneta and Strandness 1987) increase in velocity are accurate indicators. The reason for this discrepancy is unclear, but may be due partly to the improved ability of colour duplex to detect the area of highest velocity, or to differences in the reference standard or measurement technique. However, the accuracy of a velocity ratio of ≥ 3 in this study was similar to that of the lower ratios in other studies.

Marked spectral broadening and a monophasic waveform were poor indicators of disease. Both had low sensitivity and moderate specificity in predicting a 50% stenosis (Table 3.2), and in each case the kappa statistic was low, indicating that agreement was little better than expected by chance (Table 3.1). Since the original classification by Jager et al (1985), no other systems have included spectral

broadening. Legemate et al (1989) suggested that it was too subjective, but presented no evidence of its poor correlation with disease. On theoretical grounds, the turbulent flow and therefore abnormal waveform associated with a stenosis would be expected to be most marked some distance distal to (as opposed to within) the narrowing, and also to be affected by the shape of the stenosis in addition to the degree of narrowing (Kassam et al 1985, Morin et al 1987). The waveform shape is also affected by a variety of factors, including cardiac output and rhythm, resistance of the vascular bed, and both proximal and distal disease (Zierler 1990b). These reasons make both the waveform configuration and spectral broadening unlikely to be of use in measuring localised stenoses in the future. It is important to point out that only 5 out of the 17 tri/biphasic waveforms found in stenoses >50% were triphasic and in all of these instances the stenosis was relatively mild. Errors in angiographic estimation of stenosis may therefore have contributed to part of the poor relationship. Previous work has, however, shown that >50% stenoses can be associated with a tri-or biphasic waveform (McPherson et al 1984) although it is often not clear from the literature from precisely where in the artery the Doppler waveform was obtained.

The range of results shown in Figure 3.1, comparing velocity ratio with percent angiographic stenosis, indicates that it was not possible to precisely define the degree of narrowing in each stenosis. Two other recent classification systems

(Polak et al 1990, Mulligan et al 1991) have attempted to distinguish stenoses as less than or greater than 50%. Jager et al (1985) attempted a narrower classification of disease, but showed poor sensitivity in identifying stenoses of 1-19% and 20-49%. These results might, in part, be attributable to the inaccuracies inherent in angiography.

Based on the results presented here, and those from the flow phantom in chapter 2, the following revised system for classifying disease is suggested as the most accurate:

Percentage Reduction in Luminal Diameter	**Peak Systolic Velocity**
0-49%	<200% increase
50-99%	≥200% increase
Complete occlusion	No flow

2) Variability of duplex measurements

There was close agreement between observers in the measurement of velocity ratio (Figure 3.3). Agreement was excellent at ratios less than six, but deteriorated at ratios greater than this. However, there was good inter-observer agreement in obtaining a velocity ratio greater or less than 3 (Table 3.3). This is of practical importance if this cut-off is used to define a 50% stenosis, a level often considered "haemodynamically significant". It is also important if this degree of stenosis is predictive of impending occlusion, a topic addressed in the next chapter.

There was moderately good intra-observer agreement in the estimation of velocity ratio (Figure 3.4) but the second velocity ratio was consistently higher than the first. This is unlikely to reflect a change in observer technique, because the first and second readings were made over a period of several months, with overlap in time. Although there might have been a true worsening in disease, this explanation seems unlikely because there was only two weeks interval between the readings. A third explanation is that hospitalisation had an effect on the resting flow rate, reducing the effective pre-stenosis velocity. It was suggested in the flow phantom studies that pre-stenosis velocity might influence velocity ratio (VR), with very low velocities giving a high VR. However, these very low velocities were by no means always found on the second measurement in this clinical study, and on reviewing the velocity data there was no consistent trend for the pre-stenosis velocity to be lower on the second reading than the first. The explanation for the second VR value of both observers being consistently higher is therefore obscure. However, the ability of an observer to repeatedly classify the velocity ratio as greater than or less than three remained good (Table 3.3).

The agreement both between and within observers in estimating the degree of spectral broadening was poor, probably because quantification of the latter is highly subjective. There was moderately good inter-observer agreement over waveform configuration (measurements done on the same day) but intra-

observer agreement (measurements done two weeks apart) was poor. Since the identification of shape is relatively objective, disagreement here might reflect true differences in the waveform obtained.

There are no previous reports of the repeatability of duplex in the arteries of the lower limb. Kohler et al (1985) examined the inter- and intra-observer variability of classifying stenoses in carotid vessels, based on the original criteria of Jager et al (1985), and found moderate agreement (Kappa=0.48). Variability in the assessment of spectral broadening was not determined independently, but inter-observer agreement in classifying disease from the same spectra was only moderately good (Kappa=0.61). A study of inter-observer repeatability in 60 carotid bifurcations found similar correlation coefficients between velocity ratios to this study, and in accordance with this study the agreement was better at lower velocities (Polak et al 1989).

Conclusions

1. A velocity ratio greater than 3 accurately identifies femoral artery stenoses of greater than 50% diameter reduction. More precise definition of degree of narrowing of individual stenoses was not achieved.

2. Waveform shape and spectral broadening are inaccurate predictors of degree of narrowing.

3. Inter- and intra-observer variability in the measurement of velocity ratio are low. The excellent repeatability of velocity ratio should allow its use in clinical studies.

4. Repeatability of waveform shape and spectral broadening is not sufficiently good to be of practical value.

Table 3.1

Accuracy of waveform parameters (I) in identifying stenoses with more than 50% diameter reduction on arteriography

(i) Spectral broadening:

Kappa = 0.21

		Degree of stenosis	
		<50%	≥50%
Degree of spectral broadening	Narrow /moderate	19	14
	Marked	7	13

ii) Waveform configuration:

Kappa = 0.18

		Degree of stenosis	
		<50%	≥50%
Waveform Configuration	Bi/tri-phasic	21	17
	Monophasic	5	10

iii) Velocity ratio

Kappa = 0.65

		Degree of stenosis	
		<50%	≥50%
Velocity ratio	<3	25	9
	≥3	1	21

Table 3.2

Accuracy of waveform parameters (II) in identifying stenoses of greater than 50% diameter reduction on arteriography

Doppler Parameter	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Kappa
Velocity ratio:					
≥2	93%	62%	74%	89%	0.56
≥2.5	83%	81%	83%	81%	0.64
≥3	70%	96%	95%	74%	0.65
Marked spectral broadening	48%	73%	65%	58%	0.21
Monophasic waveform	37%	81%	67%	55%	0.18

Table 3.3

Agreement between and within observers in obtaining a velocity ratio (VR) greater than and less than 3

(i) Between observers:

Kappa = 0.81

		OBSERVER TWO	
		VR <3	VR ≥3
OBSERVER ONE	VR <3	26	1
	VR ≥3	3	15

(ii) Within observer:

Kappa = 0.70

		SECOND MEASUREMENT	
		VR <3	VR ≥3
FIRST MEASUREMENT	VR <3	22	4
	VR ≥3	0	7

Figure 3.1

Relationship between duplex velocity ratio and the percent reduction in luminal diameter determined by arteriography

The regression curve based on (unstandardised, concentric stenosis) data obtained in the flow phantom study in chapter 2 is superimposed for comparison.

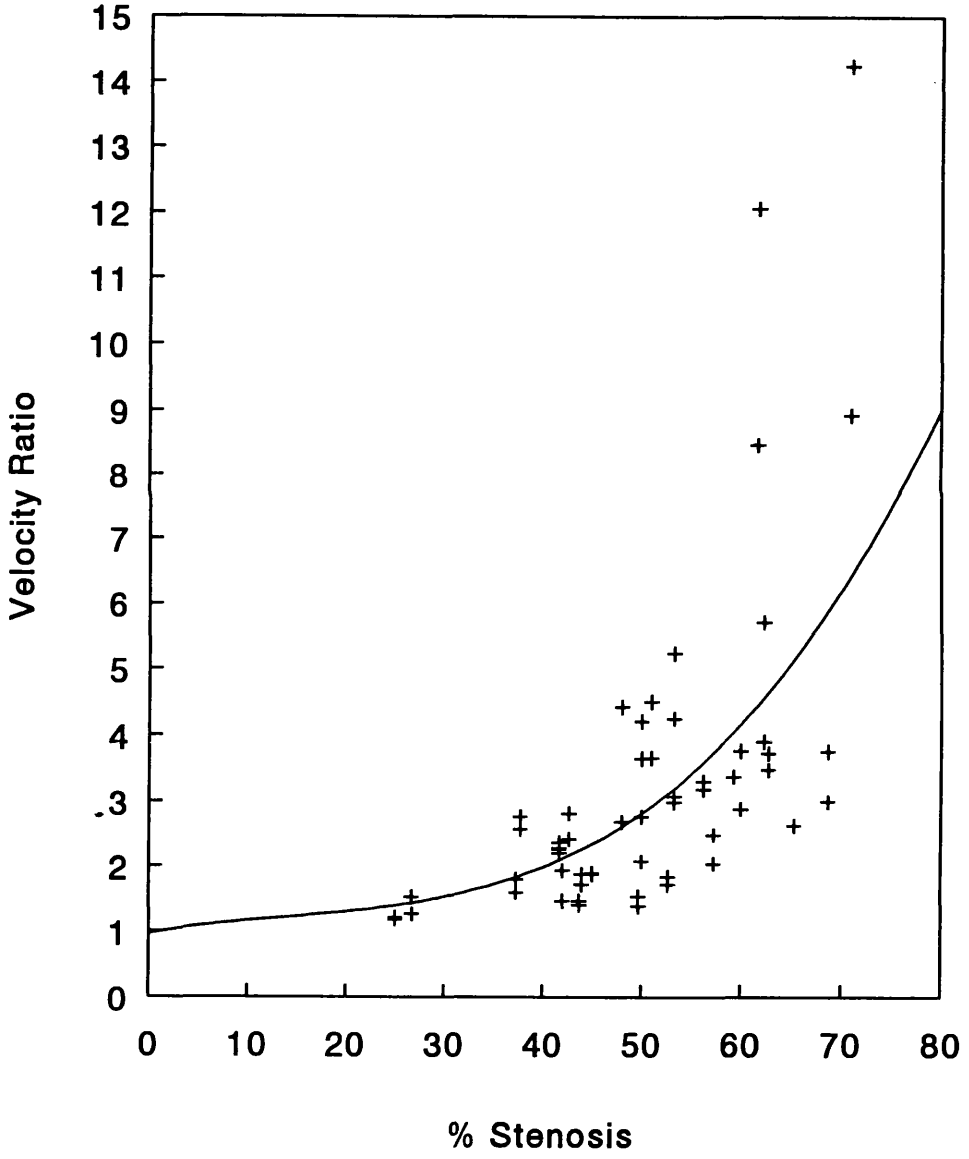


Figure 3.2

Relationship between peak systolic velocity and percent reduction in luminal diameter determined by arteriography

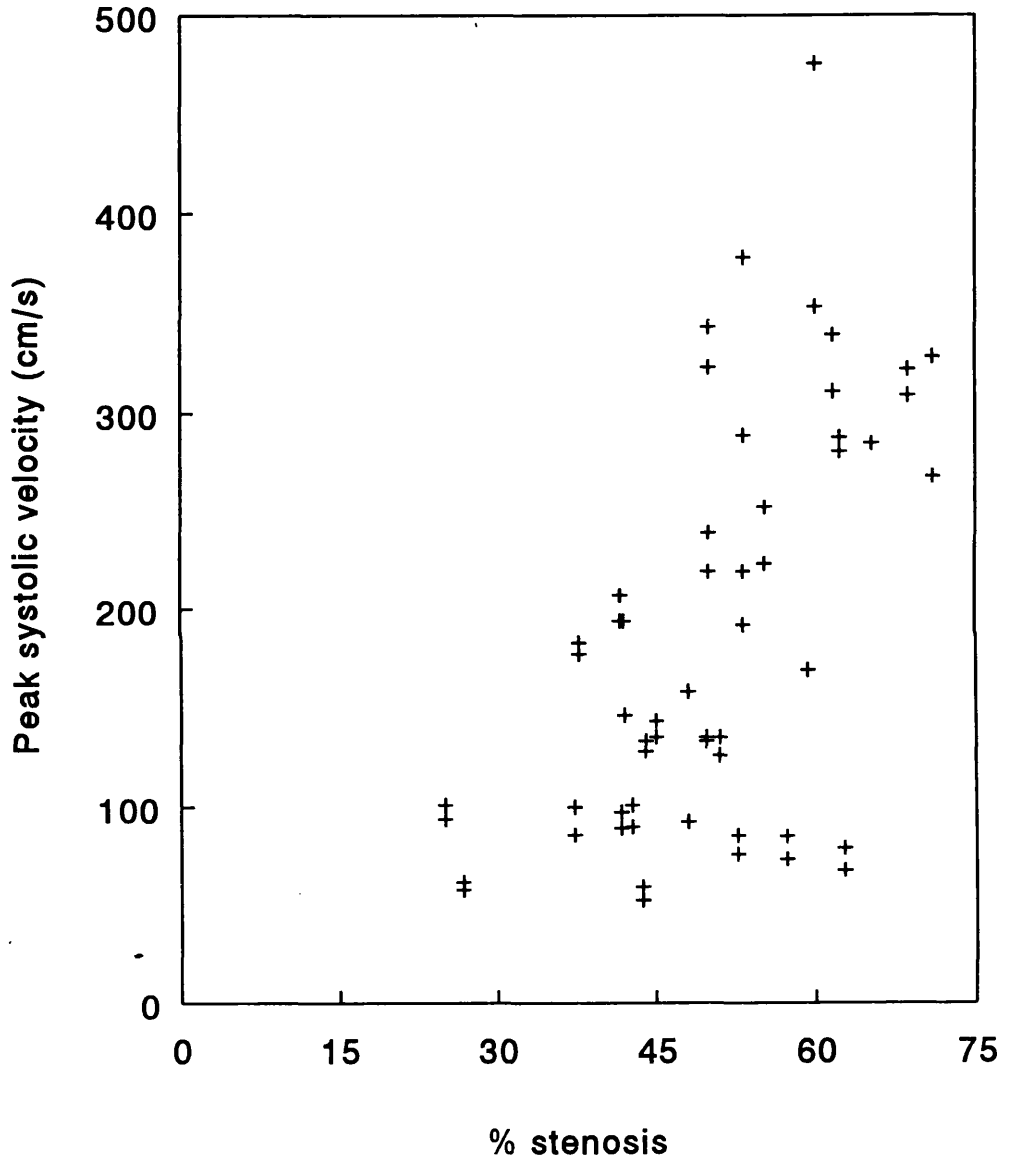


Figure 3.3

Agreement between two observers in the measurement of velocity ratio

The intercept does not differ significantly from zero ($p>0.1$)

$r_i = 0.88$

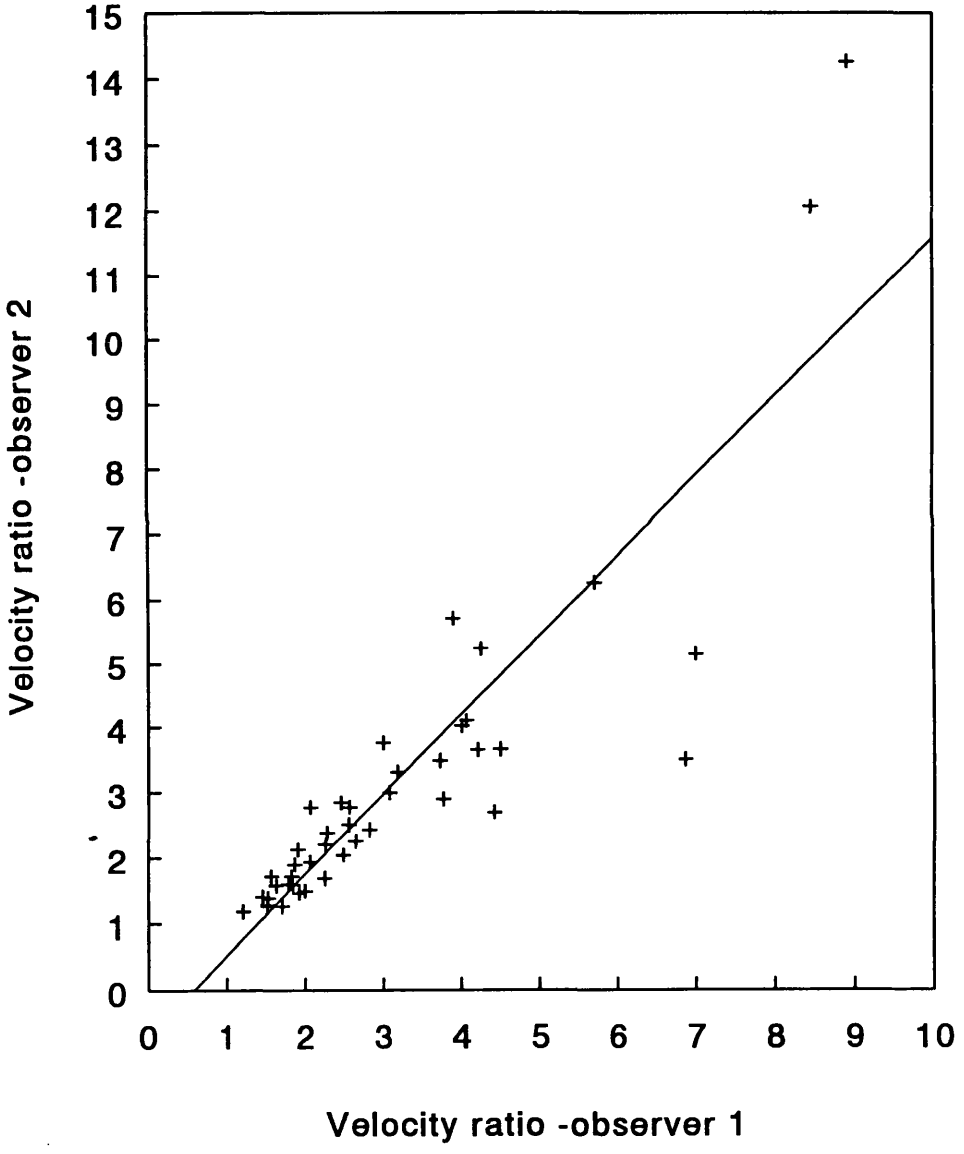
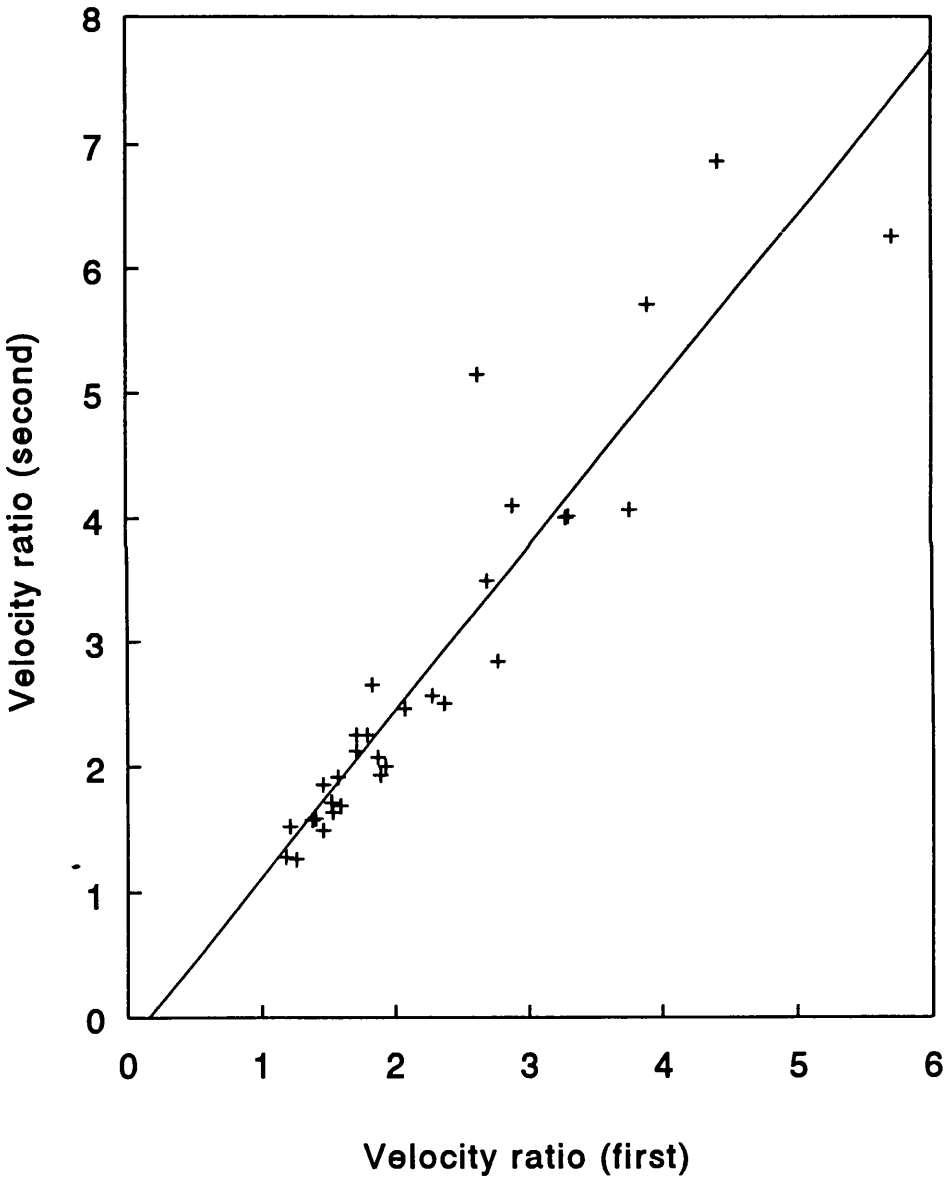


Figure 3.4

Agreement between velocity ratios recorded by the same observer on two separate occasions

$r_i = 0.53$



CHAPTER 4

A PROSPECTIVE STUDY OF THE NATURAL HISTORY OF FEMOROPOPLITEAL ARTERY STENOSIS USING DUPLEX ULTRASOUND

Contents of chapter

4.1. INTRODUCTION

In the lower limb significant atheromatous disease has a predilection for the superficial femoral artery (Walden et al 1985). Symptoms of peripheral arterial disease (PAD) correlate poorly with the nature and extent of disease in the artery (Baker 1978). However, it is generally accepted that if a major progression in the severity of disease occurs in an individual, there is an accompanying deterioration in the severity of ischaemia. A foreknowledge of impending arterial occlusion (and possible deterioration of ischaemia) might allow its prevention by active intervention in the pre-occlusive stage. This could, in principle, be achieved by percutaneous transluminal angioplasty (PTA), which has been shown to have a high primary success in treating femoral stenoses (Wayne-Johnston et al 1987), a low risk (Belli et al 1990), and an acceptable patency (Becker et al 1989, Jeans et al 1990). The procedure is more difficult and associated with lower patency rates when occlusions are recanalised and dilated, particularly when the occlusion is long (Krepel et al 1985). There is, therefore, a "window of opportunity", within which treatment is technically easier and safer. The size of this window has not been ascertained, in other words the length of time between the finding of a stenosis and its progression to occlusion is not known. Many stenoses which cause claudication might progress to occlusion quite soon after the patient first presents to the clinician, and there is therefore a need for a short term prospective study.

The flow phantom study (Chapter 2) demonstrated that there is an excellent agreement between duplex ultrasound velocity ratio (VR) measurements and degree of stenosis. The reproducibility of measurements, particularly with the lesser degrees of stenosis is high, and may be as good as the agreement between two radiologists' readings of the same stenosis shown on conventional arteriography. Duplex has the added advantage of being completely non-invasive. It should, therefore, be an ideal tool for natural history studies but to date there has been no published report of a study of the natural history of femoral artery disease using duplex ultrasound.

The aims of this study were to determine:-

1. the incidence of progression from stenosis to occlusion.

2. the change in severity of stenosis over time.

3. the relationship between severity of stenosis and progression to occlusion.

4.2. PATIENTS AND METHODS

Thirty-eight patients (27 male, 11 female), median age 67 (range 41-78) years with 43 stenoses were studied. In the early part of the study arteriography had already been performed and was used to identify isolated superficial

femoral and popliteal artery stenoses. Duplex ultrasound was then used to quantify the degree of stenosis. Later in the study, duplex ultrasound alone was used to identify and measure stenoses. An "isolated stenosis" was defined as an area of discrete arterial narrowing easily distinguishable from adjacent artery, whether the latter was regarded as diseased or normal. With the exception of one case of a stenosis proximal to an occlusion, all stenoses studied were the most significant lesions in the femoropopliteal segment.

The duplex ultrasound examination was carried out by a single observer (the author) with patients in the supine and prone positions to study femoral and popliteal arteries respectively. A 5 MHz linear array transducer of an ATL UM9 colour duplex scanner was used in all cases. The ratio of intra-stenosis to pre-stenosis peak systolic velocity after correction for Doppler angle was used to estimate the degree of narrowing (velocity ratio). A second duplex examination of the same stenosis was performed by the same observer after a median of 28 (range 5-76) weeks. The range was large because in many cases the second examination had to be organised to coincide with out-patients appointments, and to preempt planned interventions. Four patients were examined for a third time. In these instances if the stenosis had still not progressed to occlusion the follow up period was taken to be the interval between the first and third examinations. If the stenosis had progressed to occlusion the follow up period was taken to be the interval between the second and third

examinations. Significant change of a stenosis was defined as an increase or decrease in the VR of ≥20%. This value is derived from the variability data in the flow phantom study in chapter 2. A comparable figure cannot be derived from the variability study in chapter 3 since too few replicate measurements were obtained for each stenosis. However, only one of the second measurements of VR by the same observer in that study differed from the mean of the two measurements by >20%. It therefore seems reasonable to use this figure for the purposes of data analysis. Occlusion was diagnosed when a complete loss of both colour and Doppler spectral waveform occurred within the vessel lumen as seen on real-time imaging. In this series there were no cases where the diagnosis of occlusion was difficult or equivocal.

For the purposes of data analysis an arbitrary classification of severity of stenosis was drawn up. Stenoses were divided into categories of VR <3, 3-6, and >6.

4.3. RESULTS

The distribution of stenoses within each category is shown in Figure 4.1. None of the stenoses with an initial VR below 3 progressed to occlusion. One half (6/12) of those in the VR range 3-6 and one third (3/9) of those in the VR range >6 occluded. This difference was not significant (P=1.99, Fisher's exact probability test).

The change in severity of stenoses between the first and last duplex examinations is illustrated in figures 4.1 and 4.2. Figure 4.1 shows the data for all stenoses and indicates that when the VR was less than 6 on the first examination the measurement was rarely lower on the second occasion. With an initial VR of more than 6 the second measurement was often lower (if the vessel had not occluded). Figure 4.2 shows the magnitude of change in VR for those stenoses which did not occlude. The mean change was a decrease in VR of 4.6% (range -53 to +96%), $p>0.1$. Essentially, the increase in VR observed in the majority of minor stenoses was balanced by the decrease in VR observed in the more severe stenoses.

For stenoses which progressed to occlusion the relationship between the initial VR and time within which occlusion occurred (the interval between examinations) is shown in Figure 4.3.

4.4. DISCUSSION

An important risk factor for progression from stenosis to occlusion might be the degree of atheromatous narrowing of an artery (Halon et al 1985). One might expect the most advanced pathological and the most disturbed haemodynamic changes to be associated with rapid progression. Although a clear relationship between severity of stenosis and time to occlusion has not been demonstrated in this study, there is a suggestion that severe stenoses progress more rapidly than moderate. A larger study using a life table analysis method

would be necessary to demonstrate the relationship more clearly. However, a velocity ratio of greater than 3 appears to be a significant factor in the progression of femoral artery stenosis. According to the results from the studies in chapters 2 and 3, such stenoses have a reduction in luminal diameter of around 50-55%. Femoral stenoses of this degree might not invariably obliterate the arterial lumen by a gradual process, but in some cases might occlude suddenly due to an intra-plaque event such as haemorrhage, necrosis or dissection. There was no significant difference in the incidence of occlusion between moderate and severe stenoses (arbitrarily defined as VR 3-6 and >6 respectively). However, the follow up interval was not the same for the groups (median 46 and 28 weeks respectively) and therefore a truly valid comparison cannot be made. Nevertheless, if intervention such as PTA is to be undertaken, it should take place as soon as possible after detecting a stenosis whose VR is greater than 3.

For the stenoses which did not occlude there was not a significant overall change in magnitude of VR. However, the VR of the less severe stenoses tended to increase, whereas the VR of the more severe stenoses tended to decrease. One important question is - does this decrease in VR amount to regression? This is exceedingly unlikely. Although it has been suggested from clinical studies that regression of atheroma can occur in femoral arteries (Duffield et al 1983, Ost and Stenson 1967, Barndt et al 1977, Erickson et al

1983), and reversal of atheroma has been demonstrated in-vitro (Armstrong et al 1990), it is unlikely that the pathological features present in a severe atheromatous plaque reverse significantly during its natural history. One explanation is that the variation in velocity ratio estimation by duplex ultrasound in this range of stenoses is more significant than suggested by the validation studies in chapters 2 and 3. The observed decrease in VR of many stenoses might therefore have occurred within the normal range of variation. It is certainly true to say that the measurement of a severe stenosis is not always easy and that peak systolic velocity can vary considerably in a single stenosis from one intra-stenotic region to another. Another possible explanation for the velocity ratio being lower on the second reading is that the pre-stenosis velocity might have increased because of an increase in the severity of disease in this region. This is a largely unavoidable problem when using velocity ratio as an index of stenosis severity.

Conclusions

1. Progression from stenosis to occlusion of the femoral artery occurred in 9/43 cases within the period of study.

3. Only stenoses with a VR >3 progressed to occlusion. There is a suggestion that severe stenoses progress more rapidly than moderate. The window of opportunity for treatment by PTA might be lost if occlusion occurs rapidly in stenoses with a VR >3.

2. Little overall change in VR was demonstrable if occlusion did not occur. Sudden plaque events as opposed to gradual enlargement might precipitate femoral artery occlusion.

Figure 4.1

The severity of stenoses at first duplex scan and their evolution according to a subsequent scan

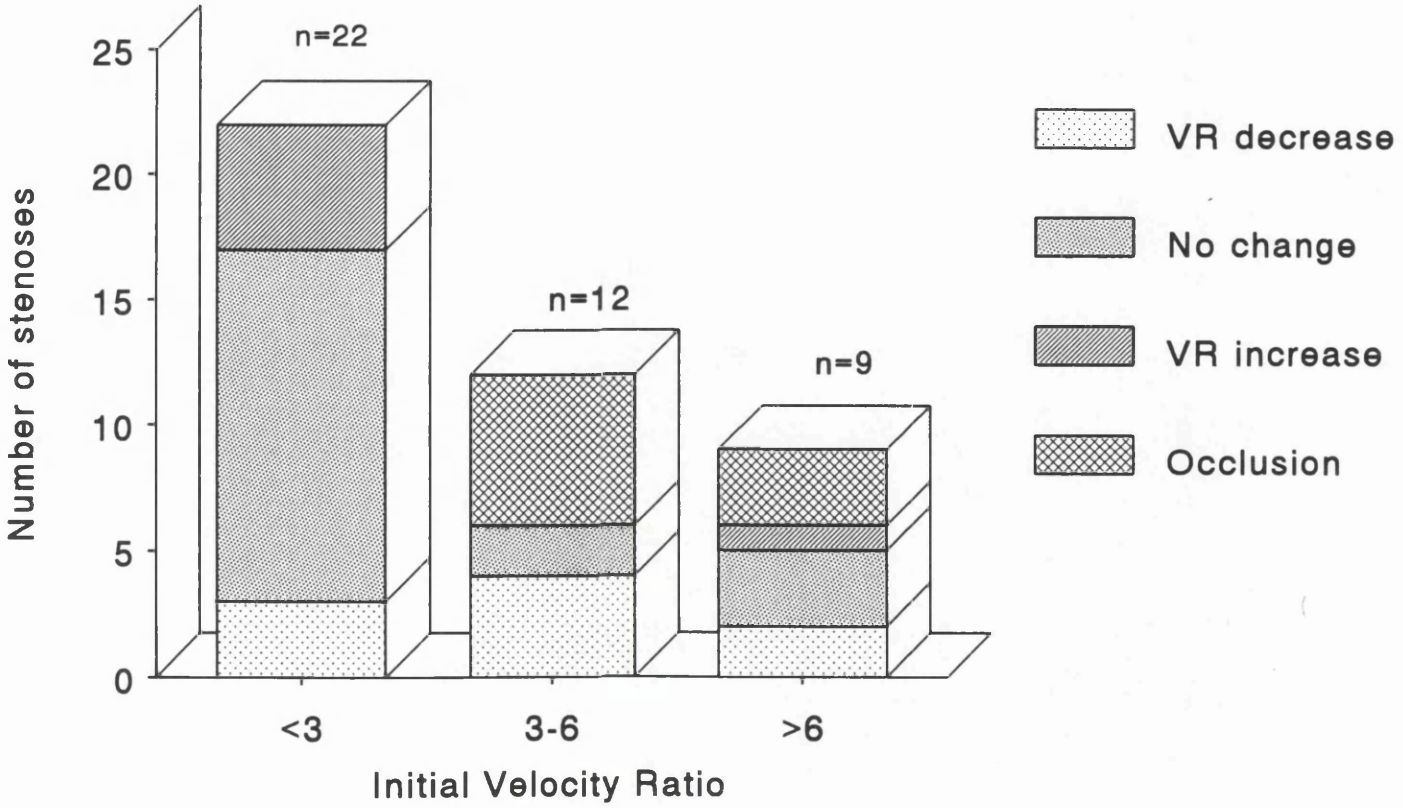


Figure 4.2

Relative change in velocity ratio between first and last duplex examinations for stenoses not progressing to occlusion

Dashed lines are limits representing no significant change in velocity ratio, ie. initial VR ± 20%

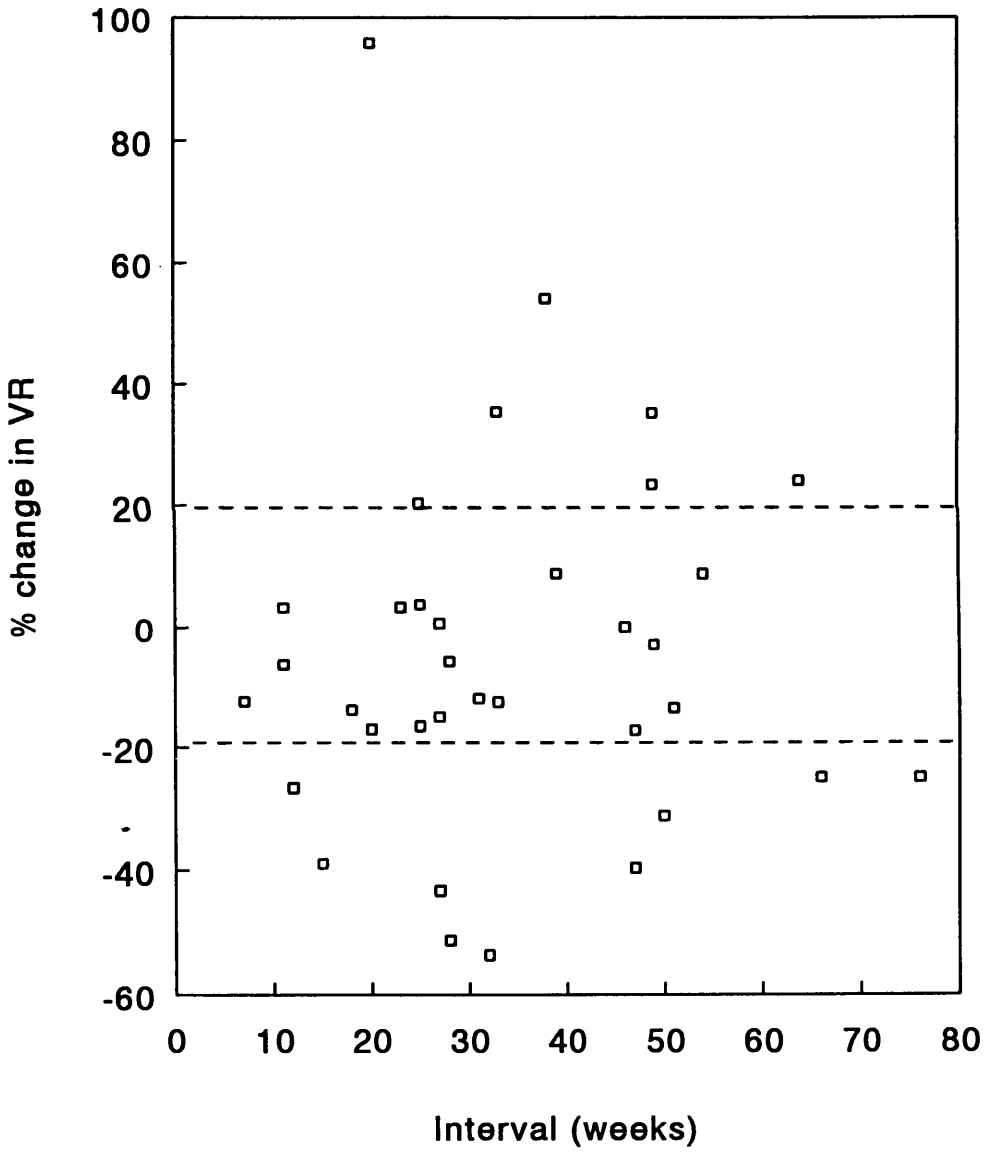
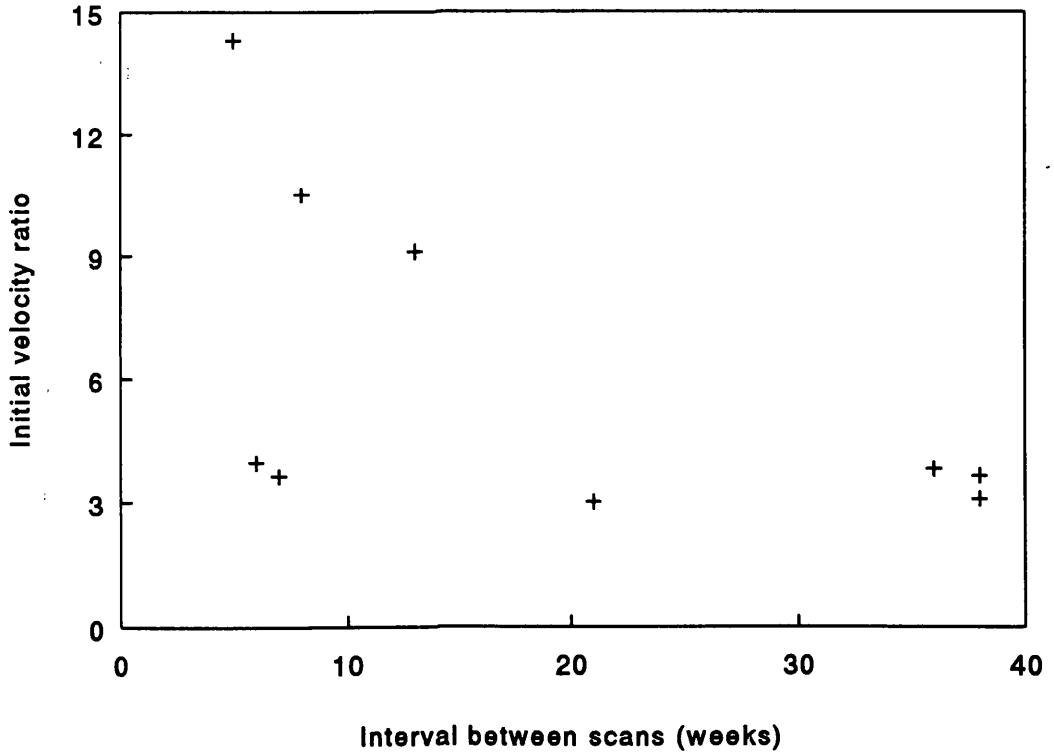


Figure 4.3

Relationship between initial velocity ratio and interval between first and second duplex scans for those stenoses progressing to occlusion



CHAPTER 5

SCREENING PATIENTS WITH CLAUDICATION DUE TO FEMOROPOPLITEAL DISEASE BEFORE ANGIOPLASTY USING COLOUR DUPLEX ULTRASOUND

Contents of chapter

5.1. INTRODUCTION

Since its inception nearly 20 years ago (Barber et al 1974), duplex ultrasound has been used diagnostically in a wide variety of vascular problems (Leng et al 1991, Evens 1991). In lower limb arteries it can distinguish haemodynamically significant from non-significant stenosis, and stenosis from occlusion (Jager et al 1985, Kohler et al 1987, Langsfeld et al 1988, Cossman et al 1989, Legemate et al 1989). It may therefore be a reliable technique for screening patients prior to percutaneous transluminal angioplasty (PTA). However, accuracy in diagnosing atherosclerotic lesions does not necessarily equate to predicting suitability for angioplasty as judged by arteriography. A study was therefore carried out to assess the value of screening patients with claudication by duplex ultrasound.

In the treatment of claudication angioplasty is usually restricted to stenoses or short occlusions. In "limb salvage" situations long occlusions are commonly treated and it is accepted that the chance of long term patency is less (Belli et al 1990). A screening technique in patients with claudication therefore needs to distinguish short lesions from long and significant from non-significant stenoses. The true predictive value of duplex scanning in this context would also allow an estimate of the cost-savings.

5.2. PATIENTS AND METHODS

Patients with intermittent claudication due to femoropopliteal disease were studied. The diagnosis was made if the patient gave a clear history of calf claudication, had an easily palpable femoral pulse and a weak or absent popliteal pulse. If symptoms were significantly disabling the option of angioplasty was discussed, and consent was obtained for arteriography proceeding to PTA if a suitable lesion was found. The superficial femoral artery (SFA) was assessed by uniplanar views only. The definition of a suitable lesion was the arteriographic finding of a stenosis narrowing the luminal diameter by more than 50% or a discrete occlusion 10 cm or less in length (the length of the occlusion being the same as the length needing dilatation) and the remainder of the arterial tree having no haemodynamically significant disease). On the day prior to arteriography all patients underwent duplex ultrasound of the femoropopliteal segment using an Ultramark 9 (Advanced Technology Laboratories, Bothell, WA, USA) colour flow system with a 5 MHz transducer. A significant stenosis was recorded where velocity increased by more than 100% (Jager et al 1985). This value was used because the study was performed before the results of the validation studies described in chapters 2 and 3 were available. The finding of such a stenosis was taken to mean the lesion could be appropriately treated by PTA. A lesion not likely to be treatable by angioplasty (a negative result) was a length of stenosis or occlusion exceeding 10 cm. Length was determined by skin marking the sites of the start and end

of the occlusion and measuring between them. The duplex findings were not available to the radiologist until a decision had been made whether or not to perform angioplasty.

5.2.1. Statistical methods

The kappa statistic (k), which takes into account agreement by chance, was used to measure the agreement between the two methods of diagnosis; k = 1.0 represents perfect agreement, and k = 0 represents agreement no greater than that predicted by chance alone (Fleiss 1973). The accuracy of duplex in predicting lesions suitable for angioplasty was also expressed in terms of sensitivity, specificity, positive and negative predictive values (Fletcher et al 1982).

5.3. RESULTS

Thirty-six limbs in 30 patients (aged 48-85, median 65 years) were studied. The femoropopliteal segment was visualised in all patients. Twenty-four patients had predominantly unilateral symptoms and the worse leg was scanned. In 6 patients claudication was bilateral and equal and both legs were scanned.

5.3.1. Agreement over detection of lesions

The findings detected by duplex and arteriography are shown in Table 5.1. The data show the concordance between the methods. In 26 limbs an occlusion was demonstrated by both methods. In 3 limbs the length of occlusion could not be easily measured by duplex. In another three limbs (two

patients) it was impossible to determine the length of occlusion by duplex because it extended into the tibioperoneal trunk. In one patient arteriography did not allow exact measurement of occlusion length because of severe calcification and very slow flow (velocity proximal to occlusion around 5-10 cm/s on duplex). In the remaining 19 limbs it was possible to measure the length of occlusion by both methods. The correlation between the two measurements is shown in Figure 5.1.

5.3.2. Agreement over prediction of lesions suitable for PTA

A negative result by duplex was defined as an occlusion measuring >10cm. This would preclude treatment by angioplasty. The duplex results compared with the arteriographic assessment are shown in Table 5.2. The predictive accuracy of duplex was calculated on the assumption that arteriography provides a standard for determining lesions suitable for PTA. All patients in this study in whom arteriography suggested PTA was possible underwent a technically successful procedure. Thus for duplex prediction: sensitivity = 94%, specificity = 85%, positive predictive value = 83%, negative predictive value = 94%, overall accuracy = 89%.

True negatives

In 17 limbs duplex demonstrated lesions not amenable to angioplasty (Table 5.2). In one of these patients, who was found to have a clinically unsuspected iliac stenosis, both

tests demonstrated a normal femoropopliteal segment. Ten out of the original 30 patients could have been saved unnecessary angiography had the duplex result been used.

False negative

In one limb duplex measured an occlusion length of 15 cm, while arteriography showed it to be 5 cm (Table 5.2). The reason for the discrepancy is unclear, but would have resulted in the patient being denied angioplasty if duplex had been used.

False positives

In three patients duplex incorrectly predicted that there would be a lesion amenable to angioplasty (Table 5.2). In one arteriography showed the occlusion to be 12 cm long, compared with a duplex measurement at the "angioplasty threshold" of 10 cm. In the other two limbs duplex measured occlusions 6 and 9 cm long, compared to 5 and 8 cm respectively on the arteriogram. These lesions were not suitable for angioplasty because the arterial segment proximal to the occlusion was diffusely narrowed. The actual length of dilatation required to achieve satisfactory results was therefore in excess of 10 cm and duplex had failed to detect this.

True positives

In 15 limbs duplex correctly identified lesions which were suitable for PTA.

5.4. DISCUSSION

This study was restricted to patients with claudication because none required reconstructive surgery and therefore arteriography was unnecessary if a lesion was found to be not amenable to PTA. In two recent studies of duplex screening prior to angioplasty (Collier et al 1990, Edwards et al 1991) patients thought unsuitable for PTA did not proceed to arteriography and the true predictive value of duplex was therefore not determined.

Despite a small effect of magnification, arteriography overestimates occlusion length because of underfilling of the distal vessel (Cossman et al 1989). Close agreement was found between duplex and arteriographic measurement of length in this series. There is a tendency for duplex to overestimate occlusion length when the latter is small, and to underestimate longer occlusions (Figure 5.1). Using the criteria in this study too few patients might proceed to angiography, with some being denied the opportunity for treatment if arteriography were to show a short occlusion. As a result, consideration will be given to raising the "angioplasty threshold" of duplex measured occlusion length to 15 cm.

The primary requirement of this type of screening is to achieve a high specificity. This was achieved, but with more experience the specificity may be improved further. It is important to minimize unnecessary angiography since for many

patients it is an unpleasant and uncomfortable procedure which is not without risk (Hirshberg et al 1988). Other non-invasive diagnostic techniques such as "Quickscan" (deSouza et al 1991) are available in some centres, but their diagnostic accuracy has not been directly compared with duplex ultrasound. However, duplex has the advantage of being useful diagnostically in a variety of other clinical areas. Without prior duplex scanning (or other effective method of screening) the radiologist does not know whether there is a potentially "angioplastiable" lesion until an angiogram has been done. Thus prior duplex scanning might also enable the efficient scheduling of radiology sessions.

Conclusions

1. There is a close agreement between duplex ultrasound and arteriography in detecting the presence of significant lesions in the SFA.

2. Given pre-defined criteria, duplex can accurately predict the likelihood of PTA being possible in patients with intermittent claudication.

3. There is a close correlation (r=0.79) between duplex and arteriography in measuring the length of femoral artery occlusion.

4. Screening patients with claudication before arteriography can lead to clinical benefits and increased efficiency.

Table 5.1

Concordance between lesions detected by duplex and by arteriography

k=0.91

		Arteriography		
		Occlusion	Stenosis	Normal *
Duplex	Occlusion	26	1	0
	Stenosis	0	14	1
	Normal *	0	0	1

* normal = < 50% stenosis

Table 5.2

Concordance between duplex prediction of suitability for PTA and that found after arteriography.

k=0.78

		Arteriography	
		Positive	Negative
Duplex	Positive	15	3
	Negative	1	17

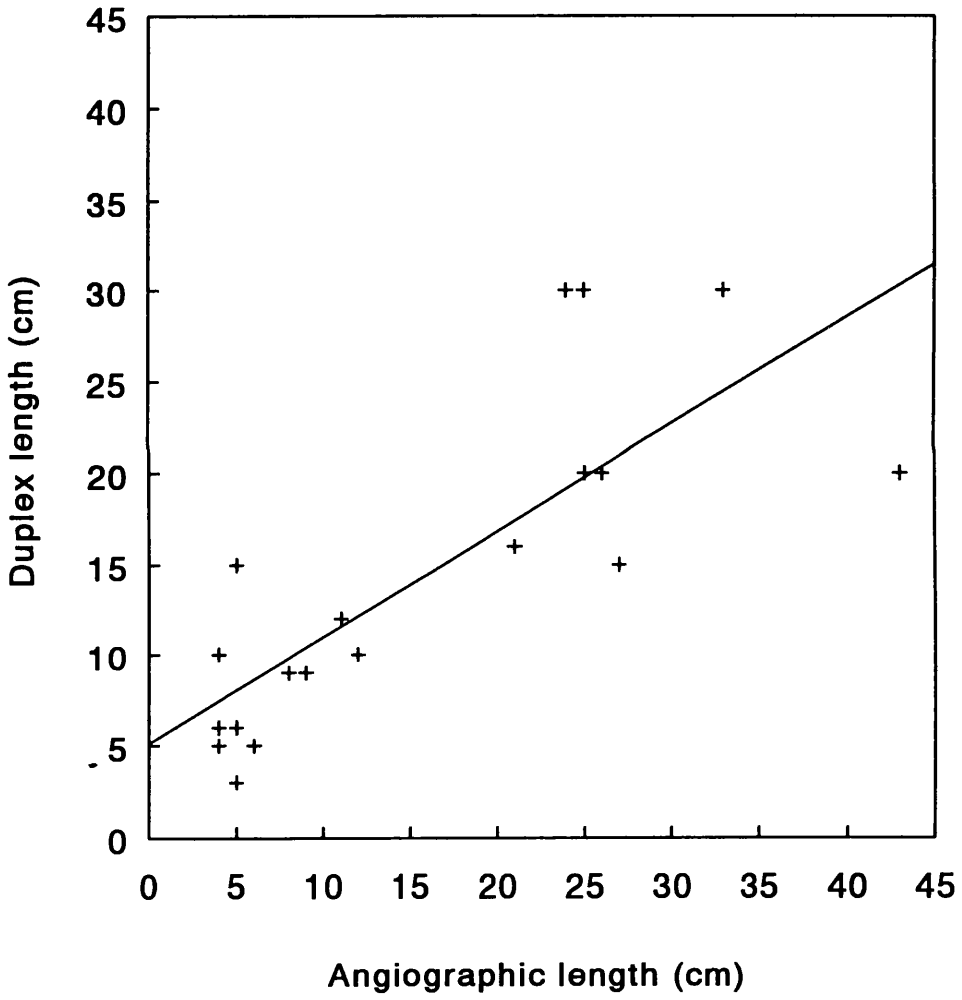
NB. Positive = prediction that PTA is possible

Negative = prediction that PTA is not possible

Figure 5.1

Correlation between length of femoral artery occlusion measured by duplex and arteriography

Least squares fit correlation coefficient, r=0.79 ($p<0.001$)



CHAPTER 6

A RANDOMISED CONTROLLED TRIAL OF ANGIOPLASTY IN THE TREATMENT OF INTERMITTENT CLAUDICATION

Chapter contents

Foreword

This chapter describes a randomised controlled trial of percutaneous transluminal angioplasty (PTA) in the treatment of patients with intermittent claudication.

The validation studies described in the preceding chapters indicate that duplex can be used to monitor the natural history of femoral atheromatous lesions. The severity of a stenosis can be determined, its progression to occlusion monitored, and the length of occlusion measured. The method is non-invasive and it is therefore suitable for the repeated examinations necessary in natural history studies. The use of PTA in treating patients with intermittent claudication was mentioned in chapter 1, and its role is explored further in this chapter. In chapter 5 duplex was shown to be an effective screening method prior to arteriography. In the trial described below it is clear that duplex has an important part to play in the screening and follow up of patients. Firstly, the rationale on which the trial is based is discussed. Secondly, the aims and methods are described. Next, some early patient data at trial entry are presented. The chapter concludes with a discussion of the subject.

6.1. RATIONALE OF THE TRIAL

6.1.1. Introduction

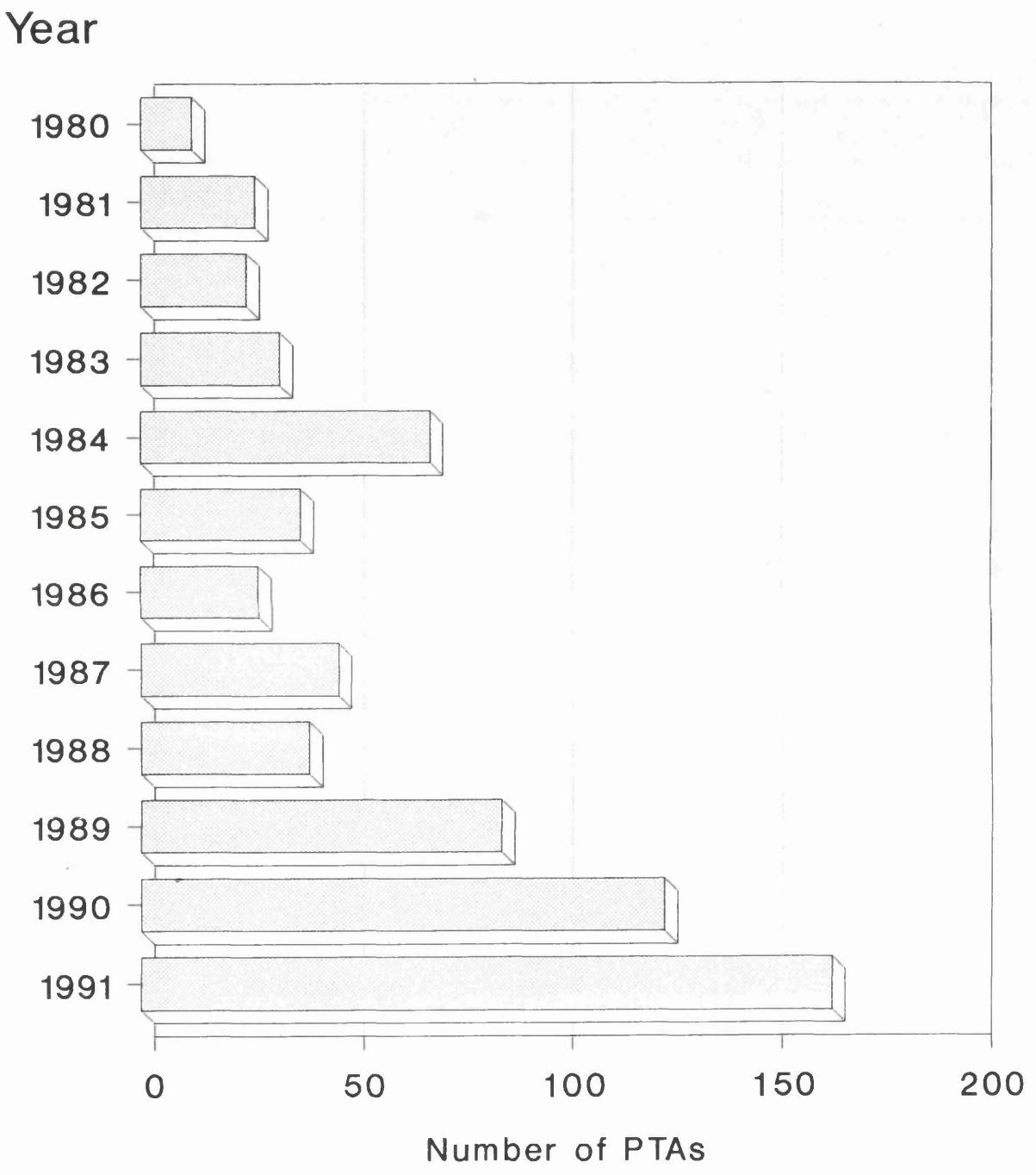
At present, treatment for peripheral arterial disease is restricted mainly to reconstructive surgery or angioplasty for severe claudication or a critically ischaemic limb threatened with amputation. Mild claudication, in which the patient can often walk free of pain for several hundred metres does not generally merit reconstructive surgery because the discomfort and restriction in lifestyle are not considered severe enough to justify the surgical risks. Such patients may be offered drug therapy, but often there is little to be done other than "stop smoking and keep walking" (Housley 1988).

PTA may offer hope to these patients with mild claudication. The technique was conceived over 25 years ago (Dotter and Judkins 1964), but it underwent considerable modification, in particular the development of the polyvinyl balloon catheter (Gruntzig and Hopff 1974) before being widely introduced into clinical practice in the early 1980s. Since then, use has increased dramatically (Figure 6.1). In patients with short iliac and femoropopliteal lesions, results are comparable to reconstructive surgery, but with the advantage of a lower mortality and complication rate (Wilson et al 1989). More than 90% of stenoses can now be successfully dilated in experienced hands (Wayne-Johnston et al 1987). In early claudication the usual lesion is a stenosis or short length occlusion in the superficial femoral artery (SFA).

Figure 6.1

Trends in PTA in the Royal Infirmary Edinburgh 1980-1991

- total number of procedures



Such lesions are technically amenable to angioplasty, and their patency after dilatation is similar (Krepel et al 1985). In more advanced claudication where the entire SFA has occluded, the lesion is often regarded as beyond treatment by angioplasty. Thus in early claudication there may be a "window of opportunity" for non-surgical treatment which could be lost as the disease progresses, leaving surgical reconstruction as the only alternative. Use of PTA in patients with claudication is still largely restricted to patients with severe symptoms who might otherwise have had reconstructive surgery. Increasingly, however, vascular specialists are being pressed to alter this cautious approach and to treat milder claudication by PTA. However, this is a classic example of new technology being adopted and accepted without challenge and before thorough evaluation.

6.1.2. Pros and cons of PTA

PTA, in common with all surgical and radiological interventions, has both advantages and disadvantages (table 6.1).

The procedure is not without risk (table 6.2), and this may account partly for a reluctance to intervene in patients with mild claudication. The most frequent complication, in around 3% of cases, is haematoma at the puncture site. More severe complications requiring surgical intervention are rare - 0.7% if claudication is the only symptom (Belli et al 1990).

Table 6.1

Pros and cons of PTA in the management of claudication

PROS	CONS
May delay/prevent occlusion	May precipitate occlusion
Potential for improved walking	Intensive walking therapy better for symptoms
Possible improved morbidity	Immediate risk
Possible long term saving on reconstructive surgery	Initial expense
? loss of protective effect on distal atherogenesis	Might accelerate stenosis/ atheroma formation
? general health benefits, improved motivation and quality of life	? negative effect on motivation

Limb loss is exceedingly uncommon, involving 0.1-1% of those with severe disease (Belli et al 1990, Adar et al 1989). However, improvements in technique and the design of materials have probably reduced the number of patients needing surgery to rectify complications. In cases of early disease, where the procedure is often technically easier, the risks may well be lower (Belli et al 1990). Nevertheless, there should be surgical back-up even for straightforward cases.

Table 6.2

Frequency of complications after lower extremity PTA

Complication	Incidence (%)	Need for immediate surgery (%)
Haematoma	2.9	1.6
Thrombosis	2.8	0.37
Embolism	2.3	0.34
Perforation	0.4	0.23
False aneurysm	0.4	_

Reproduced with permission (Eikelboom et al 1992)

PTA is not cheap (around £300 per procedure for materials alone). However, the cost of initial treatment might be recoverable if PTA were to offer a better chance of long term patency and relief of severe symptoms than conservative treatment. The initial cost might then be offset by long term savings on expensive reconstructive surgery. This potential saving must be balanced by the cost of repeat dilatations in some patients. Thus the net financial effect is difficult to predict.

PTA *appears* to offer immediate benefits for the patient in terms of walking distance. Although supervised intensive walking therapy may produce better results than PTA alone

over a period of one year (Creasy et al 1990), this supervision may not be available in many U.K. hospitals. There is at least the potential for greater walking distance after PTA compared to walking therapy since limb blood flow and ankle pressures increase after PTA (Lamerton et al 1985, Salles-Cunha et al 1989). It is therefore also necessary to know how patients with claudication who undergo PTA plus a period of intensive walking therapy compare with those receiving walking therapy alone. A randomised trial of surgical reconstruction versus physical training showed surgery to be superior in terms of symptom relief, and surgery plus training to be the best treatment (Lundgren et al 1989b). Furthermore, immobility in the reconstruction group was often due to the general condition of the patient. It is important to bear in mind, therefore, that a patient must have at least the potential to walk further or faster than before surgical or radiological intervention.

It is uncertain whether long term prognosis for the limb is improved after PTA. A recent large study in Maryland revealed that the adoption of PTA was associated with no decline in lower extremity amputations and an increase in the use of peripheral bypass surgery (Tunis et al 1991). However, this is not necessarily the experience of individual specialist units (Vallance 1991), and it is far from certain whether PTA can actually reduce the overall incidence of limb loss due to PAD (Letters by: Pentecost, Veith, Osterman, Hunink, Clugston et al 1992).

A number of theoretical arguments need to be taken into account. Atheroma could be accelerated after restoration of normal or near normal pressure and flow, as disease has been shown to advance more rapidly with sub-critical than critical narrowing (Bomberger et al 1981). On the other hand, clinical deterioration has been found to be worse in patients with occlusion than stenosis (Selvaag et al 1960), and thus preservation of vessel patency by PTA might be advantageous. In a recent descriptive study of the distribution of lower limb atherosclerosis it was suggested that proximal disease did not protect distal vessels (Aston et al 1992). The dilatation causes stretching of muscle fibres in the wall of the artery and splitting of the intimal and medial layers (Castaneda-Zuniga et al 1980, Lyon et al 1987). These changes, not surprisingly, predispose to (re-) stenosis and thrombotic occlusion, events which occur during the natural history of the disease. Whether PTA accelerates or decelerates atherosclerosis is therefore still a matter for debate (Block 1986) and better management strategies will only be found by evaluating in clinical trials whether PTA confers significant advantages over the natural history of femoral atherosclerosis. The morbidity and rates of disease progression in patients with untreated peripheral arterial disease have been summarised in Chapter 1, and the morbidity and vessel patency associated with lower limb PTA has been well documented in the literature (Becker et al 1989, Jeans et al 1990, Belli et al 1990). It is clear that a meaningful comparison of the relative merits of intervention and

conservative treatment is not easy to make.

6.1.3. Potential of PTA beyond symptom relief

Patients with claudication have a high mortality - about two to three times that of an age-sex matched population, and around half the deaths are attributable to ischaemic heart disease (Fowkes 1988). It might be possible to reduce this high mortality if a change in lifestyle of patients with claudication could be brought about. The patient may be able to achieve such a change after PTA by returning quickly to brisk walking, thus engaging in a beneficial form of exercise (Rippe et al 1988), with minimal risk from such levels of exertion. On the contrary, such exercise might be protective against death from coronary artery disease (Slattery et al 1989, Leon et al 1987). The protection is probably a result of many factors including the effects of exercise on fibrinolytic potential (Monte et al 1992) and rheological factors (Ernst and Matrai 1987). It is far from clear, however, whether exercise alone can produce more benefit than PTA alone or in combination with exercise. By using "Quality Adjusted Life Years" it has been calculated that, economically, exercise compares favourable with other preventive measures for coronary heart disease (Hatziandreu et al 1988), but it is speculative to extrapolate this situation to patients with claudication. It is important, nevertheless, that the clinician bears in mind the potential benefits to health in general when treating patients with claudication.

It has been suggested recently that a systemic inflammatory response to intermittent claudication can be abolished by arterial bypass surgery (Hickey et al 1990). If the same were true of PTA, there might be as yet unrecognised benefits from active intervention.

Motivation alone is also an important factor to consider. An all too familiar picture is the vicious circle of exercise restriction, weight increase, depression and smoking, leading in turn to further exercise limitation and further vascular events. Rapid relief of claudication offers a break into this circle. Additional medical benefits might therefore include improved confidence and self-esteem (Larson et al 1987), greater motivation to stop smoking, and better control of body weight.

It is also easy to overlook the extent of disability. For the patient suffering even mild claudication, a return to normal activities of daily living such as walking to the shops free of pain, exercising the dog, or simply walking for pleasure is far from a mundane consideration, and the resumption of these activities may provide a new lease of life with consequent psychological and health benefits (King et al 1989). The vascular specialist will naturally be sympathetic to patients with such needs and might very reasonably opt to treat by PTA to achieve rapid results. However, enthusiasm to alleviate disability in this way must be tempered by careful consideration of the potential long term problems.

6.1.4. Other trials of PTA

At the time of writing there have been only two relevant randomised controlled trials, one comparing PTA with intensive walking therapy (Creasy et al 1990), and the other comparing PTA with surgery (Wilson et al 1989). The former showed exercise therapy to be better overall than PTA in terms of improvement in claudicating and maximum walking distances, despite significant rises in resting ABPI in the PTA group compared to the walking group. With more patients PTA was shown to be superior in patients with iliac lesions, and exercise therapy the treatment of choice in patients with femoropopliteal disease (unpublished work, cited in Creasy and Fletcher 1991). The surgical trial showed the durability of haemodynamic improvement after PTA to be similar to that after surgery.

6.1.5. Ethical considerations

It is surprising that with a strong argument to be made both for and against PTA as a treatment for patients with claudication so few data are available to decide the issue. Creasy and Fletcher (1991) state "it is debatable whether such a trial (a prospective randomised trial of PTA) would now be considered ethical". Ironically, it seems just as convincing to argue that not to conduct such trials is unethical. Even eminent vascular specialists disagree over the role of PTA in treating claudication:

- "Conservative therapy should be the primary treatment. Invasive procedures (PTA...) should be reserved for the treatment of limb-threatening ischaemic events" (Coffman 1991).

- "...these results justify the use of angioplasty in the treatment of intermittent claudication..." (Belli et al 1990).

The trial described in this chapter received ethical approval from the Lothian Health Board Ethics of Medical Research Sub-Committee for Surgery, protocol reference 27/90, on 5th December 1990.

In summary then, percutaneous transluminal angioplasty is being employed on a large and increasing scale. It is a relatively minor procedure which may carry substantial benefits far beyond simple relief of leg symptoms, but has been subjected to little objective evaluation. There is, therefore, an urgent need for randomised controlled trials of PTA, particularly in the more controversial setting of patients with mild claudication, assessing both short and long term benefits, including quality of life.

6.2. AIMS AND METHODS

6.2.1. Aim and objectives

The aim of the trial is to determine if PTA confers additional short or long term benefits over non-interventional therapy in patients with intermittent claudication.

The objectives are to compare the following between angioplasty and control groups at 3 monthly intervals after randomisation, up to a mean follow-up of 2 years:

i) Symptoms

ii) Treadmill walking distances

iii) Ankle brachial pressure index (ABPI)

iv) Body mass index (BMI)

v) Self-assessment of "quality of life" by questionnaire

vi) Arterial patency, by duplex ultrasound

vii) Severity of arterial stenosis, by duplex ultrasound

6.2.2. Plan of investigation (see figure 6.2)

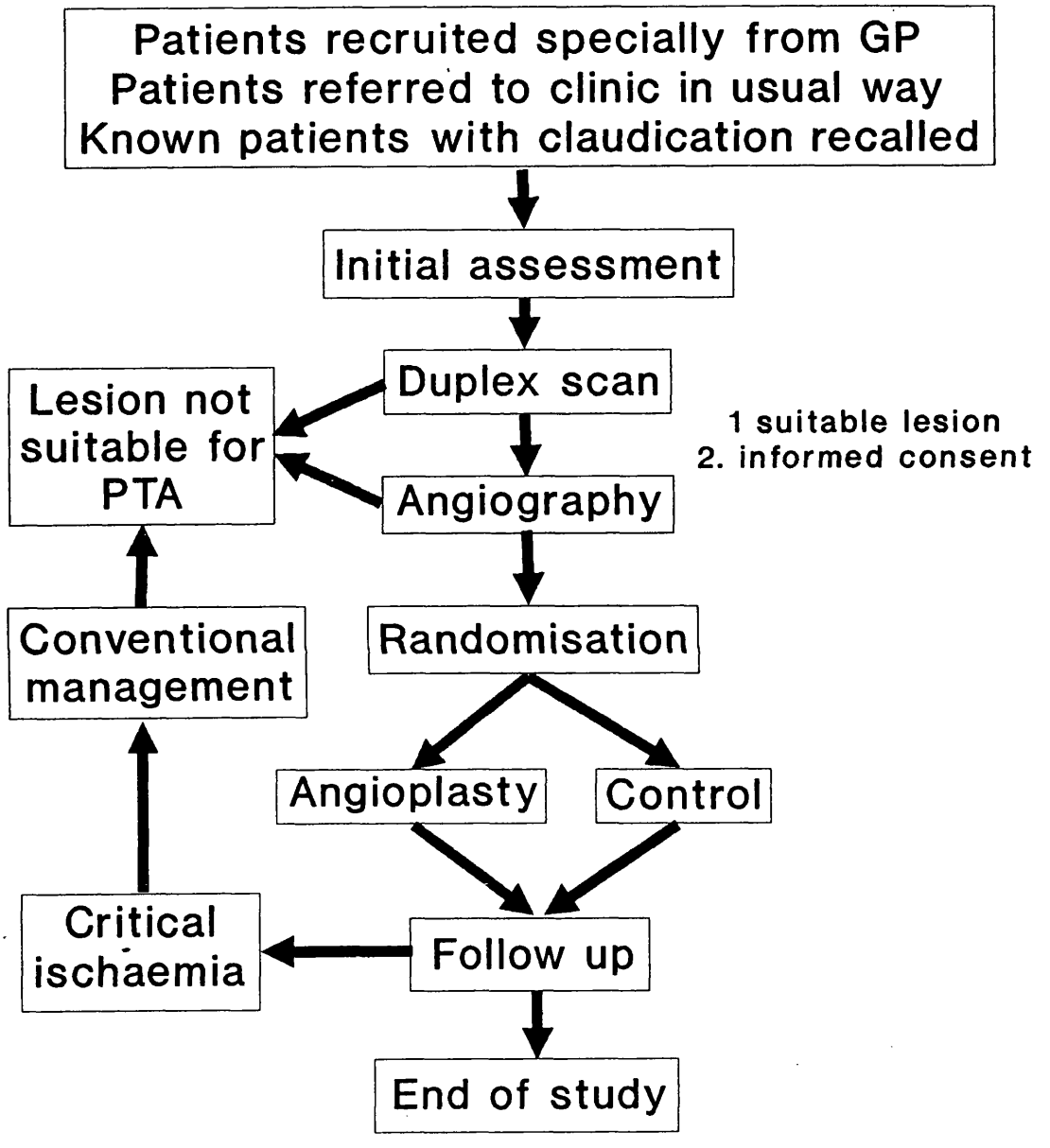
Study design: *A randomised controlled clinical trial*

6.2.2.1. Source of patients

Patients who attend the peripheral vascular clinic (PVC) of the Royal Infirmary of Edinburgh (RIE) with a new diagnosis of intermittent claudication are considered for the trial. Soon after the trial started on April 1st 1991 it became apparent that few patients had claudication caused by a

Figure 6.2

Plan of investigations in the angioplasty trial



single isolated lesion suitable for angioplasty and that recruitment was going to be slow. It therefore became necessary to implement a program in which 600 General Practitioners in and around Edinburgh were sent a letter asking them to refer patients with claudication whom they would not ordinarily have referred. (In Edinburgh, GPs have traditionally adopted a policy of non-referral of patients with mild symptoms, because it is known that these patients are not usually offered surgery or other treatments). At the time of writing, 67 new cases had been referred by this means. The last source of patients is derived from those patients who had been seen in the PVC during the year preceding the start of this trial and discharged with a diagnosis of claudication. A list of 250 such patients was found from the computerised database in the vascular unit of the RIE. Their case notes were examined and 60 apparently suitable patients were asked to attend for initial assessment for inclusion in the trial. Seven were suitable after duplex scanning and have agreed to participate in the trial.

6.2.2.2. Assessment of patients

This is carried out in the PVC jointly by the author and a physiological measurement technician employed to assist with the trial. It involves:-

- full clinical history and examination.
- measurement of body weight and height.
- measurement of ankle brachial pressure index (ABPI). A random zero sphygmomanometer is used to detect the highest of

the three ankle artery systolic blood pressures, and ABPI is found by dividing this by the higher of right and left brachial artery systolic pressures. The variability of the method has been reported elsewhere (Baker and Dix 1981, Fowkes et al 1988).

- venesection for haemoglobin and total serum cholesterol concentration.

- exercise testing on treadmill at 2.5mph on the flat. Onset of claudication and maximum walking distances are measured. The principles have been described elsewhere (Ouriel et al 1982). A zero incline was decided on in order to make a more like-for-like comparison with the patients' estimation of walking distance on the flat under normal walking conditions. The test is ended after 10 minutes or as soon as the patient needs to stop.

- completion of a self-administered questionnaire, the Nottingham Health Profile, which is an assessment of quality of life. The profile has previously shown that the quality of life of out-patients with PAD is much impaired compared to apparently healthy groups (Hunt et al 1982).

- duplex ultrasound scanning of the symptomatic leg to look for a single lesion suitable for PTA. A 5MHz linear array transducer of an Advanced Technology Laboratory - Ultramark 9 colour duplex machine is used. Length of arterial occlusion and velocity ratio of stenosis are recorded.

6.2.2.3. Exclusion criteria

- Age less than 40 or more than 75 years.
- A history of less than 3 months duration.
- Rapidly deteriorating symptoms.
- Previous PTA or reconstructive surgery to the relevant artery.
- Known myocardial infarction within the previous 6 months.
- Serious psychological or other disease rendering follow up difficult.
- History of haemorrhagic/thrombotic diathesis and/or taking oral anti-coagulants.
- Duplex scan (or subsequent angiography) showing diffuse disease, significant disease at more than one level, occluded/stenosed segment of femoropopliteal artery >10cm long, or iliac occlusion of any length.

6.2.2.4. Angiography

Patients still considered suitable after initial assessment are invited to join the trial. An explanation of the rationale of the trial and the risks of angiography and angioplasty is given. It is made clear that there is no obligation to participate in the trial and that treatment would not be biased if the patient declined the invitation. The patient is admitted to the Programmed Investigation Unit of the RIE where an overnight stay after angiography/PTA is usual. Full written consent is obtained (see appendix A). If the angiogram shows disease unsuitable for treatment the

patient is given conventional treatment as judged appropriate for the individual. Lesions considered suitable are:

1. A localised significant iliac artery stenosis
2. A localised significant femoropopliteal artery stenosis
3. A femoropopliteal occlusion not longer than 10 cm in length

If a dilatation of more than 10 cm length of any lesion is necessary, it is not considered to be localised and the patient is therefore not suitable for randomisation.
Transfemoral angiography is performed under local anaesthetic using a Seldinger technique. Digital views are taken of the lesion after PTA, and of the calf vessels if conventional image quality is sub-optimal because of low flow. Biplanar views of the iliac arteries are taken if significant disease is suspected. If the lesion is suitable for PTA the patient is randomised and is regarded as having entered the trial from this point. Angiograms of trial entrants are scored by myself using a semi-quantitative method (Bollinger et al 1981) for later analysis of site and severity of disease. The method is sensitive enough to show significant differences in score before and after PTA of the femoropopliteal artery (Bollinger et al 1982).

6.2.2.5. Randomisation

When a decision has been made to include the patient in the trial, he or she is randomised to one of two treatments:

1. PTA plus low dose (75-150mg daily) aspirin plus conventional advice on smoking and exercise (PTA group).

or

2. Low dose aspirin plus conventional advice on smoking and exercise (control group).

Non-stratified randomisation is by means of computer generated random numbers, and the treatment option is obtained by telephone from the Scottish Cancer Trials Office in Edinburgh.

6.2.2.6. Angioplasty

To date, only conventional balloon angioplasty had been used. Patients able to tolerate aspirin are asked to start taking the low dose from the day prior to angiography and to continue afterwards. Aspirin is thought to reduce the risk of occlusion after lower limb endarterectomy (Lassila et al 1991), although the same has yet to be shown for PTA. Most dilatations have been carried out immediately after randomisation. Two patients have been recalled for PTA, one because the procedure was technically difficult at the first attempt, the other because it was felt necessary to discuss the angiogram at the weekly vascular-radiology meeting before proceeding. Although it is feasible to perform out-patient angioplasty (Rogers and Kraft 1990, Rabbia et al 1990), the usual practice in the RIE is 24 hours of ward observation after the procedure.

6.2.2.7. Follow up

The first follow up clinic appointment is 2-4 weeks after randomisation. This entails a discussion with the patient of the treatment undertaken thus far, and continued advice on cessation of smoking and exercise where appropriate. Further follow up is at 3 monthly intervals thereafter. The tests carried out at each 3 monthly visit are outlined below.

6.2.3. Outcome

The measures of outcome to be used in statistical analysis are as follows:

BINARY VARIABLES

- Arterial occlusion as defined by duplex ultrasound.
- Change in clinical status (becoming symptom free, developing critical ischaemia[1], or undergoing vascular surgery).
- Death.

[1] Persistently recurring rest pain requiring regular analgesia for more than two weeks and/or ulcer or gangrene of the foot or toes, plus ankle systolic pressure < 50mmHg (in non-diabetics) (Dormandy 1989b).

- Maximum walking distance, MWD (patient estimation)
- Onset of claudication and MWD (on treadmill)
- ABPI
- Body mass index
- Nottingham Health Profile score
- Duplex velocity ratio of stenosis. The results of duplex ultrasound performed immediately after PTA can be misleading (Sacks et al 1990). The examination is therefore delayed until 3 months after randomisation.

6.2.4. Sample size

An estimation of sample size depends on the outcome used. It is anticipated that to produce a statistically significant difference between the two groups in the proportion of patients becoming symptom free, and to have a representative sample of patients with claudication in both groups, around 100 patients must be randomised. This is derived from an expectation that 25% of control patients and 60% of angioplasty patients will be symptom free 2 years from the start of the trial, taking both type I and type II errors to be 0.05 (Pocock 1983) (see Appendix B). These figures are, of course, estimates. If they were known as a point of fact, there might be no point in conducting a small trial such as this. There is little chance of being able to demonstrate a difference between the groups in terms of numbers of amputations or reconstructions because the absolute figures

will be so small. It is anticipated, however, that the number of patients will be sufficient to allow an analysis of the differences in other variables. It is planned that recruitment and treatment will take place over 12 months, and that the trial will last 2½ years in the first instance, ie. until October 1st 1993. This would mean an average follow up period of 2 years. The period of follow up might be extended depending on a sufficient number of patients being recruited and sufficient funding.

6.2.5. Data analysis

Statistical advice has been sought from Dr RJ Prescott, Senior lecturer in Medical Statistics, and Mr P Donnan, Research Associate in Medical Statistics, University of Edinburgh. Repeated measures analysis will be used to study the effect of treatment on serial measurements, multiple regression analysis to examine factors associated with favourable outcome, and Chi squared tests to analyse differences in binary outcome between groups. The intention is to analyse the outcome measures primarily on an "intention to treat" basis, although "treatment received" will also be examined.

6.2.6. Financial support

A grant of £51,942 was obtained from the Clinical and Biomedical Division of the Scottish Home and Health Department to support the project.

6.3 PATIENT DATA

The descriptive data which follow are expressed as the median and range because with the small number of patients a normal distribution cannot be assumed. The data given are patient variables at the time of first clinic attendance.

To date, 30 patients, median age 61 (range 45-75) years, have been randomised, 16 to PTA and 14 to the control treatment group. The sex ratio is 4:1 male to female, and there is one patient with diabetes. The rest of the data are tabulated.

Table 6.3

Number of patients and type of lesion

	STENOSIS	OCCLUSION	**TOTAL**
FEMOROPOPLITEAL	17	7	**24**
ILIAC	6	0[1]	**6**
TOTAL	**23**	**7**	**30**

[1] The study does not include patients with iliac occlusion.

Table 6.4

Other measured variables

MEASUREMENT	MEDIAN	RANGE
Duration of symptoms before presenting (months)	6	3-99
ABPI in worse (symptomatic) leg	0.69	0.46-0.94
ABPI in better leg	0.94	0.70-1.10
Maximum walking distance from history (metres)	150	25-999[1]
Maximum walking distance on treadmill (metres)	133	50-667[2]
Onset of claudication on treadmill (metres)	61	26-250
Haemoglobin concentration (g/dl)	14.8	11.9-16.8
Total serum cholesterol level (mmol/l)	6.7	4.9-9.9

[1] 999 metres means a patient can walk this distance or further on the flat (with or without claudication)

[2] 677 metres represents the 10 minute limit imposed on treadmill walking

Table 6.5

Smoking status of patients

CATEGORY OF CIGARETTE SMOKING	NUMBER OF PATIENTS
Current smoker	19
Stopped between 1 month and 1 year ago	3
Stopped between 1 year and 5 years ago	2
Stopped more than 5 years ago	5
Never smoked	1

6.4 DISCUSSION

The trial has been designed to determine differences in several variables between two matched groups. It could be argued that the most important outcome is need for reconstructive surgery or amputation, since a result showing significant advantages for one or the other treatment might substantially alter patient management. If the proportion of claudicants needing above ankle amputation, or surgical or radiological intervention for severe ischaemia in the first year after presentation is taken as 7% (Dormandy 1991), and a desirable treatment effect is to reduce this rate by 1/2, then the minimum number of patients needed to show this result with a 95% degree of confidence is 2100. Only a

multicentre trial would be capable of achieving this, which in turn might attract disadvantages of its own. It was decided instead to study a number of outcomes of arguably less importance, which nonetheless have a place in decision making.

It is inappropriate at this stage in the trial to analyse the equality of randomisation between the two groups in terms of the variables measured. Provided sufficient numbers are acquired there should be little inequality. The original intention was to study only femoropopliteal disease, but it soon became apparent that the total number of patients recruited within the specified time would either be substantially less than expected, or it would take longer to reach the target of 100 patients. Patients with claudication caused by an iliac stenosis were therefore also included (table 6.3). This is reasonable since the same treatment dilemma applies to these patients as it does to those with femoropopliteal disease. However, iliac occlusion has not been included. The technical difficulties and risks are greater than for iliac stenosis, but also the criteria for what constitutes a lesion suitable for PTA are not well defined and the duplex measurement of occlusion length during screening is more difficult.

A number of patients with claudication who would, presumably, be suitable for the trial are still regularly discharged from the vascular clinic, and some undergo angioplasty of isolated

lesions outside the trial. This is a major problem as far as obtaining sufficient numbers is concerned, and is partly a function of consultant and junior staff being pre-occupied with the heavy workload of the vascular clinics and having insufficient time to spend on explaining the details of the trial to patients. There have been a number of reasons for actively excluding patients from trial entry. In the vast majority the length of femoropopliteal occlusion as measured by duplex exceeds the pre-defined upper limit of 10 cm. This is, perhaps, a reflection of how late in the disease process many patients present to a clinician, and we have, to an extent, tried to overcome this by inviting GPs to refer patients as early as possible. It is impossible, however, to estimate how many of the GPs referring patients would have done so regardless of our prompt. Five patients have declined to join the trial. Four of these did not want the slight risk of PTA, and the other did not want to be in the control group! Another four patients who were apparently suitable were not troubled by their symptoms and wished only to be given a diagnosis. One patient was unable to achieve claudication on the treadmill as a result of unsteadiness and shortness of breath. One patient was so obese that, even had iliac angioplasty been considered, it would have been technically difficult to obtain access to the groin. In one patient a duplex scan performed immediately prior to angiography showed that a stenosis had progressed to a full length SFA occlusion. The angiogram was therefore cancelled after giving an appropriate explanation to the patient. The

reasons for patients undergoing angiography, but not being randomised, are outlined below:

1. More extensive disease than expected.
    a. Two patients with multilevel significant disease (had not had duplex scan of both segments)
    b. One patient with severe calf vessel disease
    c. One patient whose occlusion had progressed from 4cm length (duplex) to 25cm (angiography)
    d. Three patients where occlusion length approximated to that found by duplex but more extensive disease made PTA undesirable.

2. Small, heavily calcified arteries with diffuse disease in addition to the stenosis or occlusion found by duplex (3 patients).

3. No significant lesion seen on angiography (2 patients).

4. One patient opted out of the trial having been informed of the angiogram result.

5. Contralateral disease, unsuitable for PTA, was more severe than symptomatic side (1 patient).

6. A large vascular malformation in the pelvis, fed by the internal iliac artery was found (1 patient). The external iliac artery stenosis was dilated.

For the patients randomised in the trial to date the correlation between the most important of the measured variables is shown in table 6.6. In particular there was a poor correlation (r=0.23) between the maximum walking distance as reported by patients (MWDp) and that found by a treadmill walking test (MWDt) despite using no incline in our adapted form of the test, which was a deliberate attempt to simulate normal walking on the flat. Using this test means the results are not strictly comparable to those from other trials. Nevertheless, they will still be meaningful within the context of this trial. Nor is there a good correlation between MWDp and duration of symptoms, onset of claudication (OC) on the treadmill or ABPI. This is a little surprising but emphasises the need for multiple measures of outcome in the trial. When there is a poor correlation between such measures of disease it indicates that none alone is a reliable criterion of severity. It also suggests that the degree of disability as judged by the patient might in itself be an acceptable and appropriate guide to whether active treatment is merited.

The correlation between ABPI and both OC and MWDt is poor (r=0.07 and r=0.09 respectively) and this is at variance with the findings of Puchmayer et al (1991) who found r=0.47 and r=0.46 respectively. The best correlation was between OC and MWDt (r=0.73) which compares favourably with that found by Puchmayer (r=0.96). This implies that in future OC could probably be used as a measure of outcome without the need to test MWD in order to save time and discomfort to the patient.

Table 6.6

Correlation between measured variables

VARIABLE 1	VARIABLE 2	CORRELATION COEFFICIENT
MWDp	MWDt	0.23 (NS)
MWDp	DS	-0.48 ($p<0.01$)
MWDp	OC	0.15 (NS)
MWDp	ABPI	0.09 (NS)
ABPI	OC	0.07 (NS)
ABPI	MWDt	0.09 (NS)
ABPI	DS	-0.14 (NS)
OC	MWDt	0.73 ($p<0.001$)

MWDp = Maximum walking distance judged by patients (metres)

MWDt = Maximum walking distance on treadmill (metres)

DS = Duration of symptoms since onset (months)

ABPI = ankle brachial pressure index in worse leg

OC = distance before onset of claudication on treadmill

NS = not significant

Summary of main points in chapter 6

1. PTA is being used increasingly in the treatment of PAD, particularly in patients with intermittent claudication.

2. There is a lack of controlled data to show that PTA is of benefit to patients.

3. A randomised controlled trial is described, whose aim is to determine the relative benefits of PTA versus conventional medical treatment.

4. Duplex ultrasound has a key role in the trial in monitoring lesions and screening patients before angiography.

PAD is a progressive condition, with a variable rate of progression which can be related to anatomical and pathological features of disease, as well as medical and social factors. The vast majority of patients with PAD are never referred to a specialist centre (Dormandy et al 1989a). However, in patients referred to hospital, who may have a more aggressive condition than those not referred, arteriography indicates that around 75% have a major advance in *disease* within 3-5 years. Most will deteriorate symptomatically in 2 years, but few will require amputation. Once the stage of intermittent claudication is reached, progression of disease as evidenced by arteriography is rapid, although symptomatic deterioration may lag behind if it occurs at all within the life time of the individual. Interpretation of data from published series of the natural history of PAD is not easy. The need for reconstruction or amputation are important end-points in vascular surgery, but in practice they do not constitute reliable criteria of severity of disease or symptoms because surgeons vary in their indications for operation, and indeed their choice of procedure for the same vascular problem. There is therefore a need for standardisation of results. Particularly where relatively new instruments such as duplex ultrasound are being evaluated, it is important to establish objective criteria for various stages of disease, and this was one of the objectives of the studies in chapters 2 and 3.

Many patients with PAD have diffuse disease rather than a discrete lesion. However, diffuse disease is not easy to study whereas single discrete lesions can be measured more readily. There are a number of risk factors for the development of the lesions associated with PAD of which cigarette smoking is perhaps the most important (Leng and Fowkes 1991). In an attempt to determine the prognosis for a particular patient, it might be possible to sum the relevant risk factors and obtain an overall risk for symptomatic deterioration within a certain time. Despite many risk factors having been described in clinical studies, this ideal is not yet achievable in practice. However, if one accepts that a major determinant of prognosis for the limb is the nature of the lesion (ie. site, length, morphology of stenosis etc.), then to determine the prognosis it might be more practical to define the lesion accurately and determine the risk of progression from the characteristics of that lesion, and then to adjust the relative risk in the light of other known risk factors. It has been said that: "If factors in a particular patient permit one to reasonably say that serious worsening is imminent, a decision concerning surgery will be easier to make - and with better justification" (Humphries 1971). This statement could well apply to the patient with claudication caused by a discrete lesion of the SFA.

To date, arteriography has been the chief means of documenting disease progression. Even when meticulously

performed there may be substantial inter-observer variation in interpretation (Bruins-Slot et al 1981, Karkow 1989). Some have tried to minimise this in lower limb studies by standardising methods (Chilvers et al 1974, Barndt et al 1974, 1977, Crawford et al 1979), and adapting the technique (Clifford et al 1985). The improvement in quantification of atherosclerosis by using score systems is also an important step towards standardisation of results (Vogelberg et al 1975, Bollinger et al 1981), but observer variability might still be substantial. New methods of investigation are therefore to be welcomed if they are safer than, and at least as accurate as arteriography. Prior to the studies performed as part of this thesis the observer variability of lower limb arterial duplex scanning had undergone little evaluation. Although there are drawbacks and there is ample room for refinement, it seems a suitable tool for documentation of discrete femoral lesions and their haemodynamic effects. It lends itself to studies of the kind presented in chapter 4 by being non-invasive and more acceptable to patients than conventional arteriography. It might be expected that improvements in technology will enable more reliable measurements of severity of stenosis to be made, notwithstanding the variability in flow parameters due to biological factors. Conversely, detecting occlusion of the femoral artery is generally straightforward, and unlikely to be substantially improved by advances in technology. Many would consider it more important in practice to reliably detect an occlusion than to precisely determine the degree of

severity of a significant stenosis. However, if further research confirms that severity of stenosis is an important risk factor for progression to occlusion, velocity ratio measurements of isolated stenoses might be of fundamental importance in management decisions.

Since different principles are involved in the measurement of a stenosis by duplex ultrasound and conventional arteriography it is, perhaps, fallacious to use one as a reference standard against which to compare the other. The results from the study in chapter 2 indicate that duplex velocity ratio can be used as an index of severity of an isolated stenosis. However, both velocity ratio (VR) and angiographic measurement of stenosis require that the velocity in or the diameter of the presumably normal arterial segment adjacent to the stenosis is known. This is misleading since the segment is unlikely to be entirely free of disease, and a measure of the "relative" extent of narrowing is instead obtained. To give an idea of the total haemodynamic effect of the diseased artery it might be more useful to know the pressure drop across a whole arterial segment. Duplex ultrasound has been used to indirectly estimate pressure gradients across iliac artery stenoses (Langsfeld et al 1988), but the variability of the method and its value in studying the natural history of stenoses is unknown. Velocity ratio suffices when the stenosis can be said to be "isolated", but judgement of this remains subjective. The main value which it has not been possible to obtain from the

studies in chapters 2 and 3 is the percent error which can be ascribed to any VR measurement of a real femoral stenosis, whereas a confidence limit of ±20% could be ascribed to any value of VR for a stenosis in the phantom study. However, performing multiple examinations of a patient within a short period is not feasible and, even if it were possible, the chances of an observer remembering values previously obtained would be high. This is one of the reasons why the data from the two validation studies are presented in different ways. My own impression is that it might be possible to ascribe a single "maximum error" figure to a velocity ratio of a stenosis which is easy to visualise and of simple shape and morphology, but in the case of more complicated and heterogeneous plaques where flow disturbances are often bizarre and measurements are taken from within a minute lumen, this will not be possible.

One of the suggestions from the data in chapter 4 is that occlusion of the femoral artery occurs after a sudden plaque event. This might explain the occasionally abrupt onset of intermittent claudication in some patients and the more urgent situation of acute on chronic ischaemia in others. Whether this situation applies to lesser degrees of stenosis and is responsible for plaque progression occurring in incremental steps has not been determined. In order to improve our understanding of the natural history of femoral atheromatous lesions further studies are necessary. It will be important to take frequent measurements of stenoses at

regular intervals, and over the long term. Increase in length of a short occlusion might also lead to a deterioration in ischaemia or worsening of symptoms. Duplex might, therefore, have a role in monitoring these lesions in order to determine the factors associated with rapid progression of stenosis or occlusion. All risk factors for disease progression including degree of stenosis should be evaluated prospectively in order to gain further insight into the natural history of peripheral arterial disease.

During this research I encountered a number of problems using duplex ultrasound. First, there is a prolonged learning curve. Even studying one area in detail it took around one year to become fully conversant with the technique, its limitations and the variations in pathology. Trying to convey this experience to a technician has highlighted the problem. Second, there are a variety of technical problems which can make the measurement of stenosis particularly difficult. The image quality and flow sensitivity of the UM9 used in these studies is not good at depths of over 4cm. However, it is anticipated that refinements in the technology, such as high definition imaging software, will improve definition of the arterial wall and plaque components, and improve the low flow capabilities of the machine. The iliac arteries are difficult to scan partly because bowel gas often obscures the image but also because movement of the abdominal wall makes precisely placed velocity sampling within a stenosis almost impossible. In a severe stenosis the additional problem of aliasing often

arises. From a practical standpoint this is where the peak systolic velocity is so high that it can no longer be measured, which means that the VR of the stenosis cannot be calculated. No increase in the severity of the stenosis can be monitored, only its progression to occlusion.

Two interesting, related phenomena have been recognised during this period of study.

The first is the presence of a flow signal through an apparently occluded arterial segment. The signal pattern was first noticed in a patient who had a failed angioplasty. The procedure had caused a thrombotic occlusion of the SFA and this was recognised on arteriography. A duplex scan carried out the next day showed that although at first sight the artery appeared occluded, increasing the Doppler gain allowed a weak signal to be obtained along the entire segment as far as the site where normal flow became re-established distally via collaterals. The signal was clearly distinguishable from the arterial "thump" which is found occasionally when insonating within an occluded artery moving as a result of transmitted pulsations. A subsequent patient who experienced a sudden deterioration in his previously mild claudication two weeks before was found to have exactly the same flow pattern in the SFA. Two months later the flow pattern had disappeared and the artery was considered unequivocally occluded by the same ultrasonographer who <u>was</u> aware of the previous findings. The interpretation was that flow was still

present in the fresh thrombus, and that it disappeared only when the thrombus had matured. Similar findings have been recognised since these early examples. The implications are important. If a recent occlusion can be recognised by non-invasive means, there might be scope for attempting thrombolysis in suitable patients.

The second phenomenon, which occurred in a 45 year old male patient in the angioplasty trial, is the apparently spontaneous recanalisation of an occlusion. The patient initially had a duplex scan which showed an occlusion in the adductor canal of the SFA measuring 6cm in length. He took low dose aspirin for two weeks after this, but became unable to tolerate it and stopped. An arteriogram was then performed which confirmed the occlusion in the same location and measuring the same length. The patient was randomised to the control group in the trial and reviewed 3 months later. On this occasion duplex was carried out by two observers blind to each other's results. Both agreed that the vessel was very diseased but patent throughout. The patient claimed that his symptoms had improved, although the ABPI and treadmill walking distances were not significantly different. The assumption is that spontaneous lysis of the thrombus had occurred some time after the arteriogram. The phenomenon would not have been recognised if non-invasive follow up by duplex had not been part of the trial. It is unlikely to be a common occurrence but might explain the improvement in symptoms which occurs in a proportion of patients with

claudication. It also re-emphasises the need for careful non-invasive studies to accurately document the natural history of femoral atheromatous lesions.

In chapter 5 the validity of screening patients before arteriography using duplex ultrasound was studied. One question which arises in relation to screening is the cost-effectiveness. This question was not formally addressed as part of the study. Nevertheless, an estimate of the cost-savings is possible. Arteriography is expensive. Although day-case arteriography would be cheaper, the practice in the RIE is to keep patients overnight. A large number of staff is required for arteriography including a minimum of radiologist, radiographer, nurse and porter. Excess use of X-ray equipment means greater wear and tear and higher maintenance costs. Even if all these components are discounted on the basis that a service is still provided for other patients requiring arteriography, the cost is still appreciable. Consumables including film, contrast, catheter and disposables amount to around £130 per standard (ie. not digital) examination. Thirty patients in the series were seen over a period of 6 months, which suggests around 60 patients per year would be screened. The number of "unnecessary" angiograms in this period would be of the order of 20, ie. a wastage of £2600. The equivalent cost of consumables for a single duplex examination is around £1, ie. around £60 per year. The anticipated annual savings are therefore around £2540 on consumables alone. This also assumes that the duplex

machine and technician time are already paid for.

It has been estimated that a hospital budget might be saved £192,000 and avoid 1,600 invasive investigations if duplex were to be in full time use for one year (Nicolaides and Renton 1990). However, the cost of starting a duplex screening program is prohibitive, with the purchase of a new machine now in the order of £ 70,000, and consideration must also be given to training and employing a technician if a Radiology Unit cannot absorb the extra workload. Nevertheless, duplex is useful not only for screening but also in a variety of other clinical and research fields, and cost-effectiveness alone may not be a primary consideration when choosing a particular screening method. In minimizing unnecessary arteriography, one also has to bear in mind that for many patients it is an unpleasant and uncomfortable procedure which is not without risk.

In chapter 6, a randomised controlled trial of PTA for the treatment of intermittent claudication was described. The role of the randomised controlled trial in surgery is a matter for considerable debate (Stirrat et al 1992). Where there is a major dilemma over the most appropriate management of a particular condition, such a trial often provides objective evidence of the relative benefits of one of the treatments. In the management of mild and moderate severity claudication the question of which is the best form of minimally invasive radiological procedure is often discussed:

balloon dilatation, atherectomy, laser, hot-tipped catheter, thrombolysis, a combination? The question which ought really to be answered first is, should these patients be actively treated at all? The dilemma is largely a function of the introduction of new technology. There has been little in the way of active, moderately safe treatment for patients with claudication until relatively recently, and the surge in the number of angioplasties performed is perhaps a reflection of the zeal with which specialists are now trying to help patients who hitherto would have been offered little treatment until becoming very severely incapacitated.

In addition to the usual measures of outcome, quality of life needs to be taken into consideration in treating patients with claudication. If limbs are not being saved and need for surgery is not reduced by angioplasty then the question of whether quality of life is improved becomes of paramount importance. In today's Health Service quality of life adjusted years and their cost need to be carefully measured before and after angioplasty for all suitable patients with claudication before statements regarding the efficacy of the treatment can be made.

Appendix A

Angioplasty Study - Information and Consent Form.

1. From the information we have so far it is very likely you are now able to have treatment for your narrowed artery. At present it is not known which type of treatment is best for your condition. In this hospital we are now formally testing two well known types, and would like to include you in a study which will give the answers.

2. The next stage is an X-ray of the arteries to finally confirm that you are a suitable candidate for having one of the treatments. This involves feeding a fine tube into the artery under local anaesthetic and then injecting a dye. Complications of this X-ray are rare. The most common is bruising of the leg when the tube is removed. Serious reactions to the dye used are extremely rare. Very rarely the artery blocks up further and this might require surgery to correct.

3. After this X-ray it will be decided which treatment you will receive. One treatment involves taking one aspirin tablet per day and following the advice given by your doctors. The other involves a stretching of the narrowed artery (known as angioplasty) by a special balloon and also taking the aspirin and following the same advice.

4. In approximately 1 in 100 patients, angioplasty may cause damage to or blockage of parts of the artery which may require surgery to correct. Very rarely indeed have complications been known to cause loss of a leg or death. This has not occurred with any of the angioplasties performed in this department since the appointment of the present X-ray staff. However, about 1 in 20 people with your condition who do not have treatment will need surgery at some stage soon in any case, in order to relieve severe symptoms.

5. It would be impractical and probably misleading to describe in detail every single possible complication which might result from this procedure. If you would like more detailed information, we will be glad to discuss this with you.

6. We would like you to decide whether you are willing to go through with this schedule and have your treatment chosen for you, regardless of which type this turns out to be.

7. Signing the consent form below confirms your acceptance, but does not commit you, and you may withdraw later if you wish.

P.T.O.

I have read and understood the above and the doctor has explained the same to me in detail. I consent to undergo any procedures necessary as part of this study and understand the possible risks. I also consent to any further or alternative procedures as deemed necessary at the time. No assurance has been given to me as to which particular practitioner will undertake the procedure(s).

Signed (patient) ..... Date .....

I confirm that I have explained the above in detail to this patient and hereby witness his/her signature.

Signed (doctor) ..... Date .....

Appendix B

1. KAPPA CALCULATION

For a contingency table:

	Result 1 (test A)	Result 2 (test A)	**Total**
Result 1 (test B)	a	b	a+b
Result 2 (test B)	c	d	c+d
Total	a+c	b+d	a+b+c+d

$$kappa = (Po - Pc) / (1 - Pc)$$

where Po = Observed proportion of agreement
and Pc = Expected proportion of agreement
= (sum of cross-products of totals)/(total)^2

Thus Po = [(a+d)/(a+b++c+d)]
and Pc = [(a+b)(a+c)]+[(c+d)(b+d)/(a+b+c+d)^2

2. ACCURACY CALCULATION

For a table of the same format:

Sensitivity = a/(a+c)
Specificity = d/(b+d)
Positive Predictive Value = a/(a+b)
Negative Predictive Value = d/(c+d)
Accuracy = (a+d)/(a+b+c+d)

3. SAMPLE SIZE CALCULATION

The required number of patients (n) on each of two treatments is given by:

$$n = 13 \times \frac{[p_1(100-p_1) + p_2(100-p_2)]}{(p_2-p_1)^2}$$

where 13 is a function of type I and II errors being 0.05, p_1 is the percentage of successes expected on one treatment, p_2 is the percentage of successes on the other treatment which one desires to detect as being different from p_1.

References

Aaslid R, Markwalder T M, Nornes H 1982 Non-invasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 57:769-774

Adams C W M 1987 In: Olsson A G (ed) Atherosclerosis - Biology and Clinical Science. Churchill Livingstone, Edinburgh, London, Melbourne and New York p75-88

Adar R, Critchfield G C, Eddy D M 1989 A confidence profile analysis of the results of femoropopliteal P.T.A. in the treatment of lower extremity ischaemia. J Vasc Surg 10:57-67

Archie J P, Feldtman R W 1981 Intraoperative assessment of the haemodynamic significance of iliac and profunda femoris artery stenosis. Surgery 90:876-880

Armstrong M L, Heistad D D, Megan M B, Lopez J A G, Harrison D G 1990 Reversibility of atherosclerosis. Cardiovasc Clin 20:113-126

Aronson D C, Ruys Th, van Bockel J H, Briet E, Brommer E J P, Gevers Leuven J A, Kempen H J M, Feuth J D M, Giesberts M A H 1989 A prospective survey of risk factors in young adults with arterial occlusive disease. Eur J Vasc Surg 3:227-32

Aschoff L 1924 In: Lectures of pathology. Hoeber Medical Division, Harper and Row Publishers Inc, New York, p131

Aston N O, Lea Thomas M, Burnand K G 1992 The distribution of atherosclerosis in the lower limbs. Eur J Vasc Surg 6:73-77

Auckland A, Hurlow R A 1982 Spectral analysis of Doppler ultrasound: its clinical application in lower limb ischaemia. Br J Surg 6:539-542

Badimon L, Badimon J J 1989 Mechanisms of arterial thrombosis in nonparallel streamlines:platelet thrombi grow on the apex of stenotic severely injured vessel wall. Experimental Study in the pig model. J Clin Invest 84:1134-1144

Baird R N, Bird D R, Clifford P C, Lusby R J, Skidmore R, Woodcock J P 1980 Upstream stenosis. Its diagnosis by Doppler signals from the femoral artery. Arch Surg 115:1316-1322

Baker J D 1978 Poststress Doppler Ankle Pressures. Arch Surg 113:1171-1173

Baker J D, Dix D 1981 Variability of Doppler ankle pressures with arterial occlusive disease: An evaluation of ankle index and brachial-ankle pressure gradient. Surgery 151:134-137

Bandyk D F, Cato R F, Towne J B 1985 A low flow velocity predicts failure of femoropopliteal and femorotibial bypass grafts. Surgery 98:799-807

Barber F E, Baker D W, Nation A W C, Strandness D E, Reid J M 1974 Ultrasonic duplex echo-Doppler scanner. IEEE Trans Biomed Eng 21:109-113

Barndt R Jr, Blankenhorn D H, Crawford D W 1974 Prevalence of asymptomatic femoral artery atheromas in hyperlipoproteinaemic patients. Atherosclerosis 20:253-262

Barndt R Jr, Blankenhorn D H, Crawford D W, Brooks S H 1977 Regression and progression of early femoral atherosclerosis in treated hyperlipoproteinaemic patients. Ann Intern Med 86:139-146

Barnes R W 1980 Haemodynamics for the vascular surgeon. Arch Surg 115:216-223

Barrie W E, Evans D H, Bell P R F 1979 The relationship between ultrasonic pulsatility index and proximal arterial stenosis. Br J Surg 66:366

Beach K W, Isaac C A, Phillips D J, Strandness D E Jr 1989 An ultrasonic measurement of superficial femoral artery wall thickness. Ultrasound Med Biol 15:723-728

Becker G J, Katzen B T, Dake M D 1989 Noncoronary angioplasty Radiology 170:921-940

Begg T B, Richards R L 1962 The prognosis of intermittent claudication. Scott Med J 7:341-352

Bell P R F, Jamieson C W, Ruckley C V 1992 (eds) In:Surgical management of Vascular Disease. WB Saunders Company Ltd. London, Philadelphia, Sydney, Tokyo. University Press, Cambridge

Belli A M, Cumberland D C, Knox A M, Procter A E, Welsh C L 1990 The Complication Rate of Percutaneous Peripheral Balloon Angioplasty. Clin Rad 41:380-383

Bendick P J, Glover J L, Kuebler T W, Dilley R S 1983 Progression of atherosclerosis in diabetics. Surgery 93:834-838

Berguer R, Hwang N H C 1974 Critical arterial stenosis: A theoretical and experimental solution. Ann Surg 180:39-50

Blankenhorn D H, Kramsch D M 1989 Reversal of Atherosis and Sclerosis. The two components of Atherosclerosis. Circulation 79:1-7

Block P C 1986 Transluminal angioplasty and atherosclerosis: Does angioplasty accelerate or decelerate atherosclerosis? Prog Clin Biol Res 219:51-58

Bloor K 1961 Natural History of arteriosclerosis of the lower extremities. Ann R Coll Surg Eng 28:36-52

Bollinger A, Breddin K, Hess H, Heystraten F M J, Kollath J, Konttila A, Pouliadis G, Marshall M, Mey T, Mietaschk A, Roth F.-J, Schoop W 1981 Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. Atherosclerosis 38:339-346

Bollinger A, Schneider E, Pouliadis G, Torres C, Schlumpf M 1982. Erfolgsbeurteilung der peripheren tranluminalen Angioplastie (PTA) mit einem computerfahigen, arteriographischen Score-System. Vasa 11:309-312

Bomberger R A, Zarins C K, Taylor K E, Glagov S 1980 Effects of hypotension on atherogenesis and aortic wall composition. J Surg Res 28:402-409

Bomberger R A, Zarins C K, Glagov S 1981 Resident research award. Subcritical arterial stenosis enhances distal atherosclerosis. J Surg Res 30:205-212

Bone G E, Ammons D 1978 Characterisation of experimental arterial stenosis by numerate analysis of the Doppler velocity waveform. Surg Forum 24:208-209

Brown P M, Johnston K W, Kassam M and Cobbold R S C 1982 A critical-study of ultrasound Doppler spectral analysis for detecting carotid disease. Ultrasound Med Biol 8:515-523

Burns P N, Jaffe C C 1985 Quantitative flow measurements with Doppler Ultrasound: Techniques, accuracy and limitations. Radiol Clin North Am 23:641-657

Byar D, Fiddian R, Quereau M, Hobbs J T, Edwards E A 1965 The fallacy of applying the Poisseuille equation to segmental arterial stenosis. Am Heart J 70:216-224

Campbell W B, Cole S E A, Skidmore R, Baird R N 1984 The clinician and the vascular laboratory in the diagnosis of aortoiliac disease. Br J Surg 71:302-306

Castaneda-Zuniga W R, Formanek A, Toda varthy M, Vlodaver Z, Edwards J E, Zollikofer C, Amplatz K 1980 The mechanism of balloon angioplasty. Radiology 135:565-571

Chilvers A S, Lea Thomas M L, Browse N L 1974 The progression of arteriosclerosis - A radiological study. Circulation 50:402-408

Clarkson T B, Weingand K H, Goodwin B T, Hulsebos L 1987 In: Olsson AG (ed) Atherosclerosis - Biology and Clinical Science. Churchill Livingstone, Edinburgh, London, Melbourne and New York p23-33

Clifford P C, Cole S E A, Rhys Davies E, Baird R N 1985 Detection of arterial stenosis: increased accuracy using biplanar angiography and Doppler signal analysis. J Cardiovasc Surg (Torino) 26:554-7

Coffman J D 1986 Intermittent claudication: Not so benign. Am Heart J 112:1127-1128

Coffman J D 1991 Intermittent claudication - be conservative N Engl J Med 325:577-578

Collier P, Wilcox G, Brooks D, Laffey S, Dalton T 1990 Improved patient Selection for Angioplasty Utilizing Colour Doppler Imaging. Am J Surg 160:171-174

Coran A G, Warren R 1986 Arteriographic changes in femoropopliteal arteriosclerosis obliterans. A five-year follow up study. N Eng J Med 274:643-647

Cossman D V, Ellison J E, Wagner W H, Carroll R M, Freiman R L, Foran R F, Levin P M, Cohen J L 1989 Comparison of contrast arteriography to arterial mapping with colour-flow duplex imaging in the lower extremities. J Vasc Surg 10:522-528

Coughlin B F, Paushter D M 1988 Peripheral pseudoaneurysms: evaluation with duplex ultrasound. Radiology 168:339-342

Crawford D W, Sanmarco M E, Blankenhorn D H 1979 Spatial reconstruction of human femoral atheromas showing regression. Am J Med 66:784

Creasy T S, Mcmillan P J, Fletcher E W L, Collin J, Morris P J 1990 Is percutaneous transluminal angioplasty better than exercise for claudication? - preliminary results from a prospective randomised trial. Eur J Vasc Surg 4:135-140

Creasy T S, Fletcher E W L 1991 Angioplasty for intermittent claudication (Editorial). Clin Radiol 43:81-83

Criqui M H, Fronek A, Barrett-Conner E, Klauber M R, Gabriel S, Goodman D 1985 The prevalence of peripheral arterial disease in a defined population. Circulation 71:510-515

Cronenwett J L , Warner K G, Zelenock G B, Whitehouse W M, Graham L M, Lindenauer M, Stanley J C 1984 Intermittent Claudication. Current results of non-operative management. Arch Surg 119:430-436

Cullen P J, Lehay A L, Ryan S B, McBride K D, Moore D J, Shanik G D 1986 The influence of duplex scanning on early patency rates of in situ bypass to the tibial vessels. Ann Vasc Surg 1:340-346

Da Silva A, Widmer L K, Ziegler H W, Nissen C, Schweizer W 1979 The Basle longitudinal Study: Report on the relation of initial glucose level to baseline E.C.G. abnormalities, peripheral artery disease and subsequent mortality. J Chron Dis 32:797-803

Dawson J M, Raphael M J 1968 Serial aortography in the study of peripheral vascular disease: A clinical radiological study. Br J Radiol 41:333-340

De Backer I G, Kornitzer M, Sobolski J, Denolin H 1979 Intermittent claudication - epidemiology and natural history. Acta Cardiol 34:115-124

Demes M, Soka A, Dubrava M, Kostolny M 1989 Duplex ultrasound examination of arteries of lower extremities. Comparison with angiography. Vnitr Lek 4:358-362

DeMorais D, Johnston K W 1981 Assessment of aortoiliac disease by non-invasive quantitative Doppler waveform analysis. Br J Surg 68:789-792

DePalma R G, Hubay C A, Insull W Jr, Robinson A V, Hartman P H 1970 Progression and regression of experimental atherosclerosis. Surg Gynecol Obstet 131:633-647

DePalma RG 1992 The pathology of atheromas:Theories of aetiology and evolution of atheromatous plaques. In: Bell P R F, Jamieson C W, Ruckley C V (eds) Surgical management of Vascular Disease. WB Saunders Company Ltd. London, Sydney, Philadelphia, Tokyo. University Press, Cambridge p21-34

DeSouza N M, King D H, Pilgrim P, Bates P, Reidy J F, Gosling R G 1991 Quickscan: Doppler ultrasound emulation of angiography -its value prior to arteriography in peripheral vascular disease. Br J Radiol 64:479-484

DHSS 1986, Office of Population Censuses and Surveys. Hospital Inpatient Enquiry. Main Tables London: Her Majesty's Stationary Office

Dixon W J 1988. BMDP statistical software manual. University of California Press, Berkely

Dobson J 1969 John Hunter. E&S Livingstone Ltd, Edinburgh, p373 (Cited in Bell et al 1992, chapter 2, by Barker W F)

Dormandy J, Mahir M, Ascady G, Balsano F, DeLeeuw P, Blombery P, Bousser M G, Clement D, Coffman J, Deutshinoff A, Bletry O, Hampton J, Mahler F, Ohlin P, Rieger H, Stranden E, Turpie A G G, Urai L, Verstraete M 1989a Fate of the patient with chronic leg ischaemia. J Cardiovasc Surg 30:50-57

Dormandy J 1989b European Concensus Document on critical limb ischaemia. Springer, Berlin, Heidelberg, New York

Dormandy J, Murray G D 1991 The fate of the claudicant. A prospective study of 1969 claudicants. Eur J Vasc Surg 5:131-133

Dotter C T, Judkins M P 1964 Transluminal treatment of arteriosclerotic obstruction. Description of a new technique and a preliminary report of its application. Circulation 30:654-670

Doubilet P, Abrams H L 1984 The cost of underutilisation. Percutaneous transluminal angioplasty for peripheral vascular disease. N Engl J Med 310:95-102

Douville Y, Johnston K W, Kassam M, Zuech P, Cobbold R S C, Jares A 1983. An in-vitro model and its application for the study of carotid Doppler spectral broadening. Ultrasound Med Biol 9:347-356

Duffield R G M, Lewis B, Miller N E, Jamieson C W, Brunt J N H, Colchester A C F 1983 Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis. A randomised controlled trial. Lancet 2:639-42

Duguid J B 1946 Thrombosis as a factor in the pathogenesis of coronary atherosclerosis. J Path Bact 58:207-212

Duguid J B 1948 Thrombosis as a factor in the pathogenesis of aortic atherosclerosis. J Path Bact 60:57-61

Duguid J B 1976 Prevention of atherosclerosis. In "The dynamics of atherosclerosis", Aberdeen University Press p67

Edwards J M, Coldwell D M, Goldman M L, Strandness D E 1991 The role of duplex scanning in the selection of patients for transluminal angioplasty. J Vasc Surg 13:69-74

Eikelboom B C, Odink H F, De Valois J C 1992 Percutaneous transluminal angioplasty. In: Bell PRF, Jamieson CW, Ruckley CV (eds) Surgical management of Vascular Disease. WB Saunders Company Ltd. London, Philadelphia, Sydney, Tokyo. University Press, Cambridge, p469-500

Ekroth R, Dahllof A G, Gundevall B, Holm J, Schersten T 1978 Physical training of patients with intermittent claudication: Indications, methods and results. Surgery 84:640-643

Erikson U, Helmius G, Hemmingsson A, Ruhn G, Olsson A G 1983 Measurement of atherosclerosis by arteriography and microdensitometry:Model and clinical investigations. In: Schettler F G, Gotto A M, Middelhoff F, Habenicht A J R, Jurutka K R (eds) Atherosclerosis VI. Procedings of the Sixth International Symposium on Atherosclerosis Berlin, Springer-Verlag p197.

Erikson U, Helmius G, Hemmingsson A, Ruhn G, Olsson A G 1988 Repeat femoral arteriography in hyperlipidaemic patients. A Study of progression and regression of atherosclerosis. Acta Radiol 29:303-309

Ernst E E W, Matrai A 1987 Intermittent claudication, exercise, and blood rheology. Circulation 76(5):1110-1114.

European carotid surgery trialists collaborative group 1991. MRC European Carotid Surgery Trial:interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. Lancet 337:1235-1243

Evans D H, Barrie W W, Asher M J, Bentley A S, Bell P R F 1980 The relationship between ultrasonic pulsatility index and proximal arterial stenosis in a canine model. Circ Res 46:470-475

Evens R G 1991 Doppler Sonographic Imaging of the Vascular System - Report of the Ultrasonography Task Force. JAMA 265:2382-2387

Fischer M, Alexander K 1985 Reproducibility of carotid artery Doppler frequency measurements. Stroke 16:973-976

Fletcher R H, Fletcher S W, Wagner E H 1982 Clinical epidemiology - the essentials. Williams and Wilkins. Baltimore/London p43-58

Fleiss J L 1973 In: Statistical methods for rates and proportions, Wiley, New York, p144-147

Fontaine R 1947 Les Arterites Obliterantes des Membres Inferieurs et leur Traitment. Strasbourg Med 107:303-324

Fowkes F G R 1988 Epidemiology of atherosclerotic arterial disease in the lower limbs. Eur J Vasc Surg 2:283-291

Fowkes F G R, Housley E, MacIntyre C C A, Prescott R J, Ruckley C V 1988 Variability of ankle brachial systolic pressures in the measurement of atherosclerotic peripheral arterial disease. J Epidemiol Community Health 42(2):128-133

Fowkes F G R, Housley E, Cawood E H H, Macintyre C C A, Ruckley C V, Prescott R J 1991 Edinburgh Artery Study. Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. Int J Epidemiol 20(2):384-392

Fox JA, Hugh AE 1966 Localisation of atheroma: a theory based on boundary layer separation. Br Heart J 23:388-399

Friedman M, Van Den Bovenkamp GJ 1966 The pathogenesis of coronary intramural haemorrhages. Br J Exp Pathol 47:347-355

Fry D L 1973 Responses of the arterial wall to certain physical factors. In: Porter R and Knight J (eds) Atherogenesis:Initiating Factors. Ciba Foundation Symposium no 12. Assoc Scientific Publ, Amsterdam, p93-120

Gordon T, Kannel W B 1972 Predisposition to atherosclerosis in the head, heart and legs. JAMA 221:661-666

Gosling R G, King D H 1974 Continuous wave ultrasound as an alternative and complement to X-rays in vascular examination. In: Reneman R S (ed) "Cardiovascular Applications of Ultrasound", North Holland Publ Co, Amsterdam, p266-282

Gresham A 1987 In: Olsson A G (ed) Atherosclerosis - Biology and Clinical Science. Churchill Livingstone, Edinburgh, London, Melbourne and New York, p51-56

Gruntzig A, Hopff H 1974 Perkutane Rekanalisation chronischer arterieller Verschlusse mit einem neuen Dilationskatheter: Modification der Dottertechnik. Dtsch Med Wochenschr 99:2502-2505

Halon D A, Sapoznikov D, Gotsman M S, Lewis B S 1985 Can total coronary occlusions be predicted from a previous coronary arteriogram? Cathet Cardiovasc Diagn 11:455-462

Harris P L, Taylor L A, Cave F D, Charlesworth D 1974 The relationship between Doppler ultrasound assessment and angiography in occlusive arterial disease of the lower limbs. Surg Gynecol Obstet 138:911-914

Hatziandreu E I, Koplan J P, Weinstein M C, Caspersen C J, Warner K E 1988 A cost effectiveness analysis of exercise as a health promotion activity. Am J Public Health 78:1417-1421

Haust M D 1971 The morphogenesis and fate of potential and early atherosclerotic lesions in man. Hum Pathol 2:1-29

Heistad D D, Armstrong D L 1986 Blood flow through vasa vasorum of coronary arteries in atherosclerotic monkeys. Arteriosclerosis 6:326-331

Heliovaara M 1978 Smoking, carbon monoxide and atherosclerotic diseases. BMJ 1:268-270

Hendrickx P, Roth U, Brassel F, Wagner H H 1989 Konnen echokontrastgebende Substanzen die Darstellung der A. femoralis superficialis im Adduktorenkanal mittels Angio-dynographie verbessen? Vasa Suppl 27:363-365

Henschen F 1962 In: The history of diseases. Longmans, Green and Co Ltd, London, p217

Hertzer N R 1991 The natural history of peripheral vascular disease. Implications for its management. Circulation 83 (suppl 1)I12-I19

Hickey N C, Gosling P, Baar S, Shearman C P, Simms M H 1990 Effect of surgery on the systemic inflammatory response to intermittent claudication. Br J Surg 77:1121-1124

Hirshberg A, Thomson S R, Robbs J V 1988 Vascular complications of diagnostic angiography via limb arteries. J R Coll Surg Edinb 33:196-198

Hoskins P R, Anderson T, McDicken W N 1989 A computer controlled flow phantom for generation of physiological waveforms. Phys Med Biol 34:1709-1717

Hoskins P R 1990 Measurement of arterial blood flow by Doppler ultrasound. Clin Phys Physiol Meas 11:1-26

Hoskins P R, Li S F and McDicken W N 1991 Velocity estimation using duplex scanners (letter). Ultrasound Med Biol 17:195-199

Housley E 1988 Treating claudication in five words. B M J 296:1483-1484

Howell M A , Colgan M P, Seeger R W, Ramsey D E, Sumner D S 1989 Relationship of severity of lower limb peripheral vascular disease to mortality and morbidity : a six year follow-up study. J Vasc Surg 9:691-696

Hoye S J, Teitelbaum S, Gore I, Warren R 1959 Atheromatous embolisation - a factor in peripheral gangrene. N Engl J Med 261:128-131

Hughson W G, Mann J I, Tibbs D J, Woods H F, Walton I 1978 Intermittent claudication; factors determining outcome. B M J 1:1377-1379

Humphries A W , DeWolfe V G, Young J R 1963 Evaluation of the natural history and results of treatment in occlusive arterioslerosis involving the lower extremities in 1850 patients. In: Wesolowski S A (ed) Fundamentals of vascular grafting, McGraw Hill, New York, p428-440

Humphries A W 1971 The relation of the natural history of arteriosclerosis to surgical management. In: Dale W A (ed) Management of Arterial Occlusive Disease. Year Book Medical, Chicago, p67-68

Hunt S M, McEwen J, McKenna S P, Backett E M, Pope C 1982 Subjective health of patients with peripheral vascular disease. Practitioner 226:133-136

Ignatovski I A 1908 Influence of animal food on the organism of rabbits. S Peterb Izviest Imp Voyenno-Med Akad 16:154-176 (cited by Ollson 1987)

Imparato A M, Kim G, Davidson T, Crowley J G 1975 Intermittent claudication: its natural course. Surgery 78:795-799

Jacobs S, Reich T 1975 Calf blood flow in intermittent claudication. Arch Surg 110:1465-1468

Jager K A, Phillips D J, Martin R L, Hanson C, Roederer G O, Langois Y E, Ricketts H J, Strandness D E Jr 1985a Non-invasive mapping of lower limb arterial lesions. Ultrasound Med Biol 11:515-521

Jager K A, Ricketts H J, Strandness D E Jr 1985b Duplex scanning for the evaluation of lower limb arterial disease. In: Bernstein E F (ed) Non-invasive diagnostic techniques in vascular disease, C V Mosby Co, St.Louis, p619-631

Jeans W D, Armstrong S, Cole S E A, Horrocks M, Baird R N 1990 Fate of patients undergoing transluminal angioplasty for lower limb ischaemia. Radiology 177:559-564

Jelnes R, Gaardsting O, Hougaard Jensen K, Baekgaard N, Tonnesen K H, Schroeder T 1986 Fate in intermittent claudication: outcome and risk factors. B M J 293:1137-1140

John H T, Warren R 1961 The stimulus to collateral circulation. Surgery 49:14-25

Johnson D E, Hinohara T, Selmon M R, Braden L J, Simpson J B 1990 Primary peripheral arterial stenoses and restenoses excised by transluminal atherectomy: a histopathological study. J Am Coll Cardiol 15:419-425

Johnston K W, Maruzzo B C, Cobbold R S C 1978 Doppler methods for quantitative measurement and localisation of peripheral arterial occlusive disease by analysis of the blood flow velocity waveform. Ultrasound Med Biol 4:209-223

Johnston K W, Rae M, Hogg-Johnston S A, Colapinto R F, Walker P M, Baird R J, Sniderman K W, Kalman P 1987 5 year Results of a Prospective Study of percutaneous transluminal angioplasty. Ann Surg 206:403-413

Jonason T, Ringquist I 1985a Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication. Acta Med Scand 218:27-33

Jonason T, Ringquist I 1985b Mortality and morbidity in patients with intermittent claudication in relation to the location of the occlusive atherosclerosis in the leg. Angiology 36:310-314

Juergens J L, Barker N W, Hines E A 1960 Arterioslerosis obliterans; review of 520 cases with special reference to pathogenic and prognostic factors. Circulation 21:188-195

Kallero K S 1981 Mortality and morbidity in patients with intermittent claudication as defined by venous occlusion plethysmography. A ten year follow-up study. J Chronic Dis 34:455-462

Kannel W B, Thom I J 1984 Declining cardiovascular mortality. Circulation 70:331-336

Kannel W B, McGee D L 1986 Update on some Epidemiological Features of Intermittent Claudication: The Framingham Study. J Am Geriatr Soc 33:13-18

Karkow W S 1989 Variations in interpretation of arterial stenosis. J Cardiovasc Surg (Torino) 30:826-832

Kassam M, Johnston K W, Cobbold R S C 1985 Quantitative estimation of spectral broadening for the diagnosis of carotid arterial disease: method and in vitro results. Ultrasound Med Biol 11:425-433

Keitzer W F, Fry W J, Kraft R O, DeWeese M S 1965 Hemodynamic mechanism for pulse changes seen in occlusive vascular disease. Surgery 57:163-174

King A C, Taylor C B, Haskell W L, DeBusk R F 1989 Influence of regular aerobic exercise on psychological health : a randomized controlled trial of healthy middle aged adults. Health Psychol 8:305-324

Knox R A, Philips D J, Breslau P J, Lawrence R, Primozich J and Strandness D E 1982 Empirical findings relating sample volume size to diagnostic accuracy in pulsed Doppler cerebrovascular studies. J C U 10:227-232

Kohler T, Langlois Y, Roederer G O, Phillips D J, Beach K W, Primozich J, Lawrence R, Nicholls S C, Strandness D E Jr 1985 Sources of variability in carotid duplex examination: a prospective study. Ultrasound Med Biol 11:571-576

Kohler T R, Nicholls S C, Zierler R E, Beach K W, Shubart P J, Strandness D E Jr 1987a Assessment of pressure gradient by Doppler ultrasound: experimental and clinical observations. J Vasc Surg 6:460-469

Kohler T R, Langlois Y, Roederer G O, Phillips D J, Beach K W, Primozich J, Lawrence R, Nicholls S C, Strandness D E Jr 1987b Variability in measurement of specific parameters for carotid duplex examination. Ultrasound Med Biol 13:637-642

Kohler T R, Nance D R, Cramer M M, Vandenburghe N, Strandness D E 1987c Duplex scanning for diagnosis of aortoiliac and femoropopliteal disease: a prospective study. Circulation 76:1074-1080

Kolodgie F D, Virmani R, Rice H E, Mergner W J 1990 Vascular reactivity during the progression of atherosclerotic plaque. A study in WHH rabbits. Circ Res 66:1112-1126

Krepel V M, Van Andel G J, Van Erp W F M, Breslau P J 1985 Percutaneous transluminal angioplasty of the femoropoliteal artery: Initial and long term results. Radiology 156:325-328

Kuthan F, Burkhalter A, Baitsch R, Ludin H, Widmer L K 1971 Development of arterial disease in lower limbs - Angiographic follow-up of 705 medical patients. Arch Surg 103:545-547

Lamerton A J, Nicolaides A N, Sutton D, Eastcott H H G 1985 The haemodynamic effects of percutaneous transluminal angioplasty. Int Angiol 4:93-97

Landwehr P, Lackner K 1990 Farbkodierte Duplexsonographie vor und nach PTA der Arterien der unteren Extremitat. ROFO 152:35-41

Landwehr P, Schindler R, Heinrich U, Dolken W, Krahe T, Lackner K 1991 Quantification of vascular stenosis with colour Doppler flow imaging: in vitro investigations. Radiology 178:701-704

Langsfeld M, Nepute J, Hershey F B, Thorpe L, Auer A I, Binnington H B, Hurley J J, Peterson G J, Schwartz R, Woods J J Jr 1988 The use of deep duplex scanning to predict haemodynamically significant aortoiliac stenoses. J Vasc Surg 7:395-399

Larsen O A, Lassen N A 1966 Effect of daily muscular exercise in patients with intermittent claudication. Lancet ii:1093-1096

Larson E B, Bruce R A 1987 Health Benefits of Exercise in an Ageing Society. Arch Intern Med 1987 147:353-356

Lassila R, Lepantalo M, Lindfors O 1986 Peripheral arterial disease - Natural Outcome. Acta Med Scand 220:295-301

Lassila R, Lepantalo M, Lindfors O 1991 The effect of acetylsalicylic acid on the outcome after lower limb arterial surgery with special reference to cigarette smoking. World J Surg 15:378-382

Last R J 1984 Anatomy - regional and applied. Churchill Livinstone, New York.

LeFevre F A, Corbacioglu C, Humphries A W, DeWolfe V G 1959 Management of arteriosclerosis obliterans of the extremities. JAMA 170:656-661

Legemate D A, Teeuwen C, Hoeneveld H, Ackerstaff R G A, Eikelboom B C 1989 The potential of Duplex scanning to replace aorto-iliac and femoropopliteal angiography. Eur J Vasc Surg 3:49-54

Leng G C, Fowkes F G R, Allan P L, Ruckley C V 1991 Doppler Colour Flow Imaging in peripheral vascular disease. Br J Hosp Med 45:200-207

Leon A S, Connet J, Jacobs D R Jr, Rauramaa R 1987 Leisure time physical activity levels and risk of coronary heart disease. The Multiple Risk Factor Intervention Trial. JAMA 258:2388-2395

Lewis B D, Meredith J, Welch T J 1989 Current applications of duplex and colour Doppler ultrasound imaging: Carotid and peripheral vascular system. Mayo Clin Proc 64:1147-1157

Lindbom A 1950 Arteriosclerosis and arterial thrombosis in lower limb. Roentgenological study. Acta Radiol suppl 80:1-80

Lundgren F, Dahllof A G, Schersten T, Bylund-Fellenius A C 1989a Muscle enzyme adaptation in patients with peripheral arterial insufficiency:spontaneous adaptation, effect of different treatments and consequences on walking performance. Clin Sci 77:485-493

Lundgren F, Dahllof A, Lundholm K, Schersten T, Volkmann R 1989b Intermittent claudication - surgical reconstruction or physical training? A prospective randomised trial of treatment efficiency. Ann Surg 209:346-355

Lyon R T, Zarins C K, Lu C T, Yang C F, Glagov S 1987 Vessel, plaque and lumen morphology after transluminal balloon angioplasty: Quantitative study in distended human arteries. Arteriosclerosis 7:306-314

Malinow M R 1984 Atherosclerosis: Progression, regression and resolution. Am Heart J 108:1523-1537

Marchand F 1904 Uber Arteriosklerose. Verhandlung der Deutscher Kongress fur innere Medizin 21:23-59 (cited by Woolf 1982)

Martin T R P, Barber D C, Sherriff S B, Prichard D R 1980 Objective feature extraction applied to the diagnosis of carotid artery disease using a Doppler ultrasound technique Clin Phys Physiol Meas 1:71-81

Mathieson F R, Larsen E E, Wulff M 1970 Some factors influencing the spontaneous course of arterial vascular insufficiency. Acta Chir Scand 136:303-308

Mavor G E 1956 Pattern of occlusion in Atheroma of Lower Limb Arteries. Br J Surg 43:352-364

McAllister F F 1976 The fate of patients with intermittent claudication managed non-operatively. Am J Surg 132:593-595

McDaniel·M D, Cronenwett J L 1989 Basic data related to the natural history of intermittent claudication. Ann Vasc Surg 3:273-277

McDicken W N 1986 A versatile test object for the calibration of ultrasonic Doppler flow instruments. Ultrasound Med Biol 12:245-249

McDonald D A 1974 Blood flow in arteries, 2nd edn. The Williams and Wilkins Co, Baltimore

McPherson D S, Evans D H, Bell P R F 1984 Common femoral artery Doppler waveforms: a comparison of three methods of objective analysis with direct pressure measurements. Br J Surg 71:46-49

Meritt C R 1987 Doppler Colour Flow imaging. J C U 15:591-7

Milnor W R 1980 Principles of haemodynamics. In: Mountcastle V B (ed) Medical Physiology, 14th edn, Volume 2, part ix, CV Mosby Company, St Louis, Toronto, London, p1017-1032

Mitchell J R A, Schwartz C J 1965 Arterial disease. Blackwell, Oxford

Moneta G L, Strandness D E 1987 Peripheral arterial duplex scanning. J C U 15:645-651

Monte G, Melissari E, Kakkar V V 1992 The effect of training exercise on fibrinolytic potential. Proceedings of the International Congress "Fibrinogen-a cardiovascular risk factor", 27-28 January, Vienna

Morin J F, Johnston K W, Law Y F 1987 In vitro study of continuous wave Doppler spectral changes resulting from stenoses and bulbs. Ultrasound Med Biol 13:5-13

Muller-Mohnssen H, Kratzer M, Baldauf W 1978 Microthrombus formation in models of coronary arteries caused by stagnation point flow arising at the predilection site of atherosclerosis and thrombosis. In: Nerem R M and Cornhill J F (eds) The role of Fluid Mechanics in Atherogenesis. Ohio University, p 12-1 - 12-8 (cited by Woolf 1982)

Mulligan S A, Matsuda T, Lanzer P Gross G M, Routh W D, Keller F S, Koslin D B, Berland L L, Fields M D, Doyle M, Cranney G B, Lee J Y, Pohost G M 1991 Peripheral arterial occlusive disease: prospective comparison of MR angiography and colour duplex ultrasound with conventional angiography. Radiology 178:695-700

Murphy E A, Rowsell H E, Downie H G, Robinson E A, Mustard J F 1962 Encrustation and atherosclerosis: The analogy between early in vivo lesions and the deposits which occur in extracorporeal circulations. Can Med Assoc J 87:259-274

Murphy P, Jeans W D, Horrocks M, Baird R 1990 A retrospective study of the fate of asymptomatic superficial femoral artery stenoses. Proceedings of BIR meeting Harrogate June

Nelson T R, Pretorius D H 1988 The Doppler Signal: Where does it come from and what does it mean? AJR 151:439-447

Nicholls S C, kohler T R, Martin R l, Neff R, Phillips D J, Strandness D E 1986 Diastolic flow as a predictor of arterial stenosis. J Vasc Surg 3:498-501

Nicolaides A N, Gordon-Smith I C, Dayandas J, Eastcott H H G 1976 The value of Doppler blood velocity tracings in the detection of aortoiliac disease. Surgery 80:774-778

Nicolaides A N, Renton S C 1990 Duplex Scanning: The second sight of the vascular surgeon. Eur J Vasc Surg 4:445-447

Olsson A G 1987 Atherosclerosis - Biology and Clinical Science. Churchill Livingstone, Edinburgh, London, Melbourne and New York.

Ost C R, Stenson S 1967 Regression of peripheral atherosclerosis during therapy with high doses of nicotinic acid. Scand J Clin Lab Invest suppl 99:241-245

Ouriel K, McDonnell A E, Metz C E, Zarins C k 1982 A critical evaluation of stress testing in the diagnosis of peripheral vascular disease. Surgery 91(6):686-693

Paterson J C 1938. Capillary rupture with intimal haemorrhage as a causative factor in coronary thrombosis. Arch Pathol 25:474-487

Pentecost M J; Veith F J, Perler B A, Bakal C W; Osterman F A; Hunink M G M, Meyrovitz M F; Clugston R A, Eisenhauer A C, Matthews R V 1992 N Engl J Med 326:413-415. Letters in reply to: Tunis SR, Bass EB, Steinberg EP 1991 The use of angioplasty, bypass surgery and amputation in the management of peripheral vascular disease. N Engl J Med 325:557-562

Persson A V, Robichaux W T, Silverman M 1983 The natural history of carotid plaque development. Arch Surg 118:1048-1052

Pocock S J 1983 Clinical trials - A practical approach. Wiley, The Bath Press, Avon, p124-125

Poisseuille J L M 1846 Recherches experimentales sur le mouvement des liquides dans les tubes de tres-petits diametres. Memoirs Presentes par divers savants, a l'Acad.Sci. de l'Intitute de France 9:433

Polak J F, Dobkin G R, O'Leary D H, Wang A M, Cutler S S 1989 Internal carotid artery stenosis: accuracy and reproducibility of colour-Doppler-assisted duplex imaging. Radiology 173:793-798

Polak J F, Karmel M I, Mannick J A, O'Leary D H, Donaldson M C, Whittemore A D 1990 Determination of the extent of lower extremity peripheral arterial disease with colour-assisted duplex sonography: comparison with angiography. A J R 155:1085-1089

Poli A, Paoletti R 1987 Regression of the atherosclerotic lesion in man: The impact of non-invasive techniques. Int Angiol 6:327-329

Pourcelot L 1974 Applications cliniques de l'examen Doppler transcutane. Velocimetrie Ultrasonore Doppler (Paris:Seminaire INSERM) p213-240

Puchmayer V, Albrecht V, Herdova J, Muchova I, Skachova A, Hromadkova J, Novotna S, Matejkova A 1991 Some interrelations between blood pressure parameters and claudication distances. Int angiol 10:19-24

Rabbia C, DeLucchi R, Cavalot G, Cirillo R 1990 Transluminal angioplasty in ambulatory care. Radiol Med (Torino) 79:79-82

Reunanen A, Takkunen H, Aromaa A 1982 Prevalence of intermittent claudication and its effect on mortality. Acta Med Scand 211:249-256

Reynolds O 1883 An experimental investigation of the circumstances which determine whether the motion of water shall be direct or sinuous, and of the law of resistance in parallel channels. Philos Trans 174:935(cited in Milnor W R 1980 (ed) Principles of haemodynamics)

Richards R L 1957 Prognosis of intermittent claudication. Br Med J·2:1091-1093

Rippe J M, Ward A, Porcari J P, Freedson P S 1988 Walking for health and fitness. JAMA 259:2720-2724

Roberts W C 1984 Extreme hypercholesterolaemia = malignant atherosclerosis. Am J Cardiol 54:242-243

Robertson J H 1960 Influence of mechanical factors on structure of peripheral arteries and the localisation of atherosclerosis. J Clin Pathol 13:199-204

Rogers W F, Kraft M A 1990 Outpatient angioplasty. Radiology 174(3pt1):753-755

Rosario J A, Hachinski V C, Lee D H, Fox A J 1987 Adverse reactions to duplex scanning. Lancet Oct:1023

Ross R, Wight T N, Strandness E, Thiele B 1984 Human atherosclerosis I. Cell constitution and characteristics of advanced lesions of the superficial femoral artery. Am J Pathol 114:79-93

Rutherford R B, Darrell N J, Lowenstein D, Fleming P 1982 The effects of changes in lumen and flow on the arterial velocity waveform. J Surg Res 32:110-120

Sacks D, Robinson M L, Marinelli D L, Perlmutter G S 1990 Evaluation of the peripheral arteries with duplex ultrasound after angioplasty. Radiology 176:39-44

Salles-Cunha S X, Andros G, Dulawa L B, Harris R W, Oblath R W 1989 Changes in peripheral hemodynamics after percutaneous transluminal angioplasty. J Vasc Surg 10:338-342

Salonen R, Salonen J T 1990 Progression of carotid atherosclerosis and its determinants: a population based ultrasonography study. Atherosclerosis 81:33-40

Sawchuk A P, Flanigan D P, Tober J C, Eton D, Schwarcz T H, Eldrup-Jorgensen J, Meyer J P, Durham J R, Schuler J J 1990 A rapid, accurate, non-invasive technique for diagnosing critical and subcritical stenoses in aortoiliac arteries. J Vasc Surg 12:158-167

Schadt D C, Hines E A, Juergens J L, Baker N W 1961 Chronic atherosclerotic occlusion of the femoral artery. J A M A 175:937-940

Schroll M, Munck O 1981 Estimation of peripheral arteriosclerotic disease by ankle blood pressure measurements in a population study of 60 year old men and women. J Chron Dis 34:261-269

Selvaag O, Myren J, Thorsen R K, Bjornstad P 1960 Progressive tendency of arteriosclerosis obliterans of the lower extremities. Acta Chir Scand suppl 253:187-195

Shattock S G 1909 A report upon the pathological condition of the aorta of King Menephtah, traditionally regarded as the Pharaoh of the Exodus. Proceedings of the Royal Society of Medicine, Pathological Section 2:122-127

Shortland A P, Cochrane T 1989 Doppler spectral waveform generation in vitro: An aid to diagnosis of vascular disease. Ultrasound Med Biol 15:737-748

Silbert S, Zazeela H 1958 Prognosis in arterioslerotic peripheral vascular disease. J A M A 166:1816-1821

Singer A, Rob C 1960 The fate of the claudicator. B M J 2:633-636

Skidmore R, Woodcock J P 1980 Physiological interpretation of Doppler-shift waveforms. Ultrasound Med Biol 6:7-10 and 219-225

Slattery M L, Jacobs D R Jr, Nichaman M Z 1989 Leisure time physical activity and coronary heart disease death. The U.S. Railroad Study. Circulation 79:304-311

Slot H B, Strijbosch L, Greep J M 1981 Interobserver variability in single plane aortography. Surgery 9:497-503

Spaulding W B 1956 The prognosis of patients with intermittent claudication. Can Med Assoc J 75:105-111

Stehbens W E 1974 Haemodynamic production of lipid deposition, intimal tears, mural dissection and thrombosis in the blood vessel wall. Proc R Soc Lond [Biol] 185:357-373 (cited by Olsson 1987)

Stehbens W E 1979 Haemodynamics and the blood vessel wall. C.C.Thomas, Springfield p294 (cited by Olsson 1987)

Stirrat G M, Farrow S C, Farndon J, Dwyer N 1992. The challenge of evaluating surgical procedures. Ann R Coll Surg Engl 74:80-84

Strandness D E, Stahler C 1966 Arteriosclerosis obliterans, manner and rate of progression. J A M A 196:1-4

Taylor P R, Tyrell M R, Crofton B, Bassan M J, Grigg A N, Nicolaides A N, Wolfe J H N 1990 Prediction of femorodistal grafts at risk of occlusion using colour flow imaging: improved criteria. Procedings of ESVS meeting Rome, Italy

Taylor G W, Calo A R 1962 Atherosclerosis of arteries of lower limbs. B M J 1:507-510

Tessler F N, Kimme-Smith C, Sutherland M L, Schiller V L, Perrella R R, Grant E G 1990 Inter- and intra-observer variability of Doppler peak velocity measurements: An in vitro study. Ultrasound Med Biol 16:653-657

Tillgren C, Stenson S, Lund F 1963 Obliterative arterial disease of the lower limbs (I) studied by means of repeated femoral arteriography. Acta Radiol 1:1161-1178

Tunis S R, Bass E B, Steinberg E P 1991 The use of angioplasty, bypass surgery and amputation in the management of peripheral vascular disease. N Engl J Med 325:557-562

Ulrich J, Engell H C, Siggaard-Andersen J 1973 A plethysmographic study of the spontaneous course of obliterative arterial disease in the lower leg. Scand J Clin Lab Invest 31 (suppl 128):75-81

Ulrich J, Siggaard-Andersen J 1975 The natural history of arteriosclerosis in the lower extremities II. A plethysmographic study of non-occlusive arteriosclerotic disease in the lower limbs. Dan Med Bull 22:136-140

Vallance R 1991 How does lower limb balloon angioplasty affect vascular surgical practice? Journal of Interventional Radiology 6:5-9

Virchow R 1856 Phlogose und Thrombose in Gefass-System. Gesammelte Abhandlungen zur wissenschaftlichen Medizin, Meidinger, Frankfurt, p458 (cited by Woolf 1982)

Vogelberg K H, Berchtold P, Berger H, Gries F A, Klinger H, Kubler W, Stolze Th 1975 Primary hyperlipoproteinaemias as risk factors in peripheral arterial disease documented by arteriography. Atherosclerosis 22:271-285

Von Rokitansky C 1844 Handbuch der Pathologischen Anatomie, 2nd vol, Braunmuuler u Seidel, Vienna (cited by Woolf 1982)

Von Rokitansky C 1852 A manual of pathological anatomy. 4th volume, translated by Dan GE, The Sydenham Society, London. (Cited by DePalma RG. In: Bell et al 1992, chapter 2)

Walden R, Adar R, Rubinstein Z J, Bass A 1985 Distribution and symmetry of arteriosclerotic lesions of the lower extremities: An arteriographic study of 200 limbs. Cardiovasc Intervent Radiol 8:180-182

Walton L, Martin T R P, Collins M 1983 An objective feature extraction technique applied to the Doppler waveforms from the groin: a prospective study. In "Procedings of the Third Meeting of the World Federation for Ultrasound in Medicine and Biology", Pergamon Press, Oxford

Ward A S, Martin T P 1980 Some aspects of ultrasound in the diagnosis and assessment of aortoiliac disease. Am J Surg 140:260-265

Warren R, John H T, Shepherd R C, Villavicencio J L 1961 Studies on patients with arteriosclerotic obliterative disease of the femoral artery. Surgery 49:1-13

Warren R, Gomez R L, Marston J A P, Cox J S T 1964 Femoropopliteal arteriosclerosis obliterans - arteriographic patterns and rates of progression. Surgery 55:135-143

Wesolowski S A, Fries C C, Sabini A M, Sawyer P N 1965 The significance of turbulence in hemic systems and in the distribution of the atherosclerotic lesion. Surgery 57:155-162

Widmer L K, Greensher A, Kannel W B 1964 Occlusion of peripheral arteries. A Study of 6400 working subjects. Circulation 30:836-841

Widmer L K 1985 Incidence and course of occlusive peripheral artery disease in geriatric patients. Possibilities and limits of prevention. Int Angiol 4:289-294

Wilson S E, Schwartz I, Williams R A, Owens M L 1980 Occlusion of the superficial femoral artery. What happens without operation. Am J Surg 140:112-118

Wilson S E, Wolf G L, Cross A P 1989 Percutaneous Transluminal Angioplasty versus operation for arteriosclerosis. Report of a prospective randomised trial in a selected group of patients. J Vasc Surg 9:1-9

Wissler R W, Vesselinovitch D 1976 Studies of regression of advanced atherosclerosis in experimental animals and man. Ann N Y Acad Sci 275:363-378

Woodcock J P, Gosling R G, FitzGerald D E 1972 A new non-invasive technique for assessment of superficial femoral artery obstruction. Br J Surg 59:226-231

Woolf N 1982 Pathology of atherosclerosis. Butterworth and Co. Ltd, London

Zarins C K, Bomberger R A, Glagov S 1981 Local effects of stenoses: increased flow velocity inhibits atherogenesis. Circulation 64:221-227

Zarins C K, Giddens D P, Bharadvaj B K, Sottiurai V S, Mabon R F, Glagov S 1983 Carotid bifurcation atherosclerosis: quantitative correlation of plaque localisation with velocity profile and wall shear stress. Circ Res 53:502-514

Zbornikova V, Lassvik C 1986 Duplex scanning in presumably normal persons of different ages. Ultrasound Med Biol 12:371-378

Zierler R E 1990a Hemodynamic considerations in evaluation of arterial disease by Doppler ultrasound. In:Duplex Doppler ultrasound, Churchill-Livingston, N York, p13-24

Zierler R E 1990b Duplex and colour-flow imaging of the lower extremity arterial circulation. Semin Ultrasound CT MR 11:168-179