Duplex Ultrasound in the Assessment of Peripheral Arterial Disease

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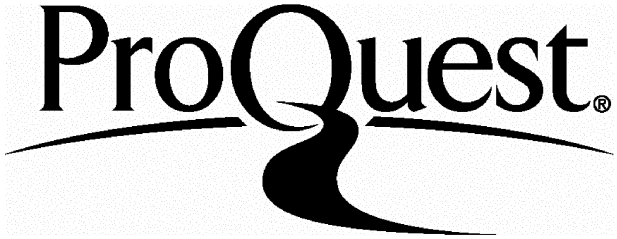

Abstract

Duplex Ultrasound in the Assessment of Peripheral Arterial Disease

Arteriography plays a central role in the assessment of peripheral arterial disease. Arteriography is associated with the risk of damage to the artery, peripheral embolisation, hazards of intra-arterial injection and exposure to ionising radiation. Arteriography provides an anatomical assessment of arterial stenosis but does not measure the functional results of the stenosis.

Modern high resolution ultrasound imaging technology enables non-invasive assessment of vascular diseases and allows functional assessment of blood flow. This investigation is of proven value in studying carotid disease.

The aim of the study was to determine the accuracy of duplex ultrasonography (DUS) in assessment of lower limb arterial disease in comparison with arteriography (IA DSA).

A technical comparison has been made between the description of arterial lesion as indicated by DUS and IA DSA. In addition, the sensitivity of DUS in assessing multisegmental arterial disease has been determined.

The clinical decision has been investigated in a further study in which five surgeons were asked to determine patient management based on IA DSA and DUS data in the same patient group. Concordance between management strategies was assessed.

DUS was used as the primary method of investigation in further series of patients. Criteria were established to determine which patients would require angiography.

The computer-assisted image analysis was used to study the ultrasound images of arterial stenosis and a method of analysing such images objectively was established. Two studies have been included in this section. These assess the technical accuracy of

ultrasound image analysis compared with histological examination of plaque. The reproducibility of the image analysis has also been tested.

I have developed a classification for peripheral arterial disease to be used to facilitate the communication between vascular laboratory staff who perform the duplex ultrasonography and surgeons who use this information.

Finally I demonstrated the effect of the plaque morphology on the out come following balloon angioplasty in iliac and femoro-popliteal lesions. The results of this study may be used to assess which patients may be best treated by balloon angioplasty and which would be best managed by bypass surgery.

This series of investigations has shown that DUS provides an assessment of arterial disease in the limb which probably exceeds the sensitivity and accuracy of conventional angiography. Information about the nature of the stenotic plaque can be obtained and the outcome of the balloon angioplasty predicted. Vascular surgeons will rely more on this investigation in the future.

Table of Contents

List of figures:..... .Page

Lists of tables ..... **Page**

List of abbreviations

IA DSA	Intra-arterial digital subtraction angiography
DUS	Duplex ultrasound scanning
IMC	Intermittent claudication
PSV	Peak systolic velocity
PSVR	Peak systolic velocity ratio
ABPI	Ankle-brachial pressure index
PTA	Percutaneous transluminal angioplasty
MPV	Mean pixel value
AI	Aortoiliac
FA	Femoral artery
FP	Femoro-popliteal
ROF	Run-off vessels

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Part I- Literature Review:

Chapter 1: Introduction

1.1- Background:

Atherosclerosis is a disease of large and medium sized arteries[1]. It is a common disease in westernised countries[2] and the most frequent cause of death. Atherosclerosis is the most common cause of lower limb ischaemia[3].

Atherosclerosis has existed as a named entity for less than a century. However it is a pathological process of great antiquity. Atherosclerotic changes have been found in mummies of the Eighteenth Dynasty of the pharaohs of Egypt, including that of Merneptah (reigning 1224-1214 BC), who has been traditionally regarded as the pharaoh of the Exodus[4,5].

Despite the length of its history; which has been reviewed by Morgan[6], and Long[7] , our understanding of many of the fundamental aspects of the formation and progression of atherosclerosis is still far from complete.

Crawford[8] defined the atherosclerosis at Royal Society of Medicine in 1960 as "the widely prevalent arterial lesion characterised by patchy thickening of intima, and consists of accumulations of fat and layers of collagen-like fibres, both being present in widely varying proportions".

Atherosclerotic plaques have a focal distribution and the intima rather than the deeper layers of the arterial wall is predominantly, but not exclusively, involved. The atherosclerotic lesion is a complex consisting of lipid, most of which is derived from plasma, necrotic connective tissue at the plaque base and a layer of fibromuscular

tissue, forming a covering (cap) which separates the other plaque constituents from the blood flowing in the arterial lumen[9].

1.2- Pathogenesis of Atherosclerosis:

There have been great advances in our understanding of the pathogenesis of atherosclerosis during the last two decades. These have been derived mainly from modern epidemiological studies, and intensive clinical and pathological investigations, improved animal model research, pioneering cellular biology and molecular biochemical studies.

I will discuss briefly some hypotheses explaining atherogenesis:

1. Trauma Theory:

The current concept emphasises that the impairment of endothelial function and structure plays a key role in the pathogenesis of atherosclerosis. The Injury theory formulated by Ross[10,11] in 1976 and modified[12] in 1986 states that the atherosclerotic changes are initiated as a response to some form of trauma to the endothelium. This lead to desquamation of endothelial cells which increases the permeability of the intima to plasma constituents, including lipids, and permits platelets and monocytes to adhere to sub-endothelial connective tissue. The initial interaction of platelets with the damaged surface is important in stimulating the smooth muscle cell changes that can occur with the loss of the endothelium and exposure of the sub-endothelium. Platelet derived growth factor (PDGF) released from the activated platelets stimulates smooth muscle cell proliferation and migration from media to the intima. It has been suggested that smooth muscle cells in their synthetic state (in contrast to the

contractile state) can be stimulated to proliferate. Platelets can also influence smooth muscle cell proliferation[10].

2-Other hypotheses have been proposed to explain the origin of the atherosclerotic plaques.

a-Insudation Hypothesis:

This hypotheses states that the lipid in atherosclerotic plaques is derived from plasma lipoproteins. Kritchevski[13] in 1986 stated that lipid insudation of the vessel wall is probably a normal physiological event. Experimental evidence suggests that low density lipoproteins (LDL) enter the arterial wall through LDL. endothelial receptors or engulfed macrophages,[14,15] which then migrate to a sub-endothelial layer. Monocytes attract and accumulate lipids as a result of trans-endothelial transport and alter their appearance to that of foam cells. These changes continue to attract more monocytes by chemo-attraction. At a later stage smooth muscle cells migrate from the media to accumulate in the intima where they attract more lipids and become foam cells. Both monocytes and smooth muscle cells are capable of secreting a number of growth factors which are believed to contribute to the atherogenesis[15].

b-Encrustation (Thrombogenic) Hypothesis:

It was suggested by Rokitansky[16] in 1852 that small mural thrombi represent the initial event in atherosclerosis. Organisation of these thrombi leads to the formation of plaques and expansion of these lesions reflects repeated episodes of thrombosis and organisation. Duguid[17] in 1946 reported in his study of the coronary blood vessels that adhesion of micro thrombi to the vessel intima appear to be a common event, and the majority of these thrombi undergo dissolution. This is also supported by Lusby et al[18].

However Born[19] in 1992 observed that although the presence and adherence of thrombi to atherosclerotic plaques is a common event, it does not mean that they are part of the atherosclerotic plaque.

1.3- Pathology of atherosclerotic lesions of the lower limbs; Morphology of the atherosclerotic lesion:

Atherosclerosis of the peripheral arteries of the lower limbs has the same macroscopic and microscopic appearance as in other part of the arterial system. The earliest lesion of the atherosclerosis (premature plaque) is still debatable.

1-Fatty streaks:

These can be seen in large elastic and muscular arteries, such as the aorta and the coronary vessels, from childhood onwards. They have been observed in blood vessels during post-mortem examination and have been seen in a wide variety of races and many geographical locations[20].

The extent of intimal surface involvement and distribution pattern of fatty streaks can be determined by macroscopic examination.

Histological appearance:

This is a localised thickening of the intima associated with fat droplets, easily seen in frozen sections stained with fat soluble dyes. Although the cell population of the streak is much larger than in the uninvolved intima, the nature of the cells is not easily identifiable on light microscopy[20].

At least two type of cells can be identified :

- An intimal smooth muscle cell identifiable by its elongated profile and the presence of dense bodies (Z band).
- The second cell lacks these bands, and has other features suggestive of macrophages.

Controversy still clouds the issue of whether or not the fatty steaks progress to mature fibrolipid atherosclerotic lesions, but certainly not all fatty streaks do so.

2-Gelatinous lesions :

Virchow[21] was the first to suggest that small blister-like elevations in the arterial intima may be the precursors of mature atherosclerotic plaques[22]. These translucent droplet-like lesions are more difficult to detect than fatty streaks. Most available descriptions of gelatinous elevations suggests their presence in all parts of the aorta[23]. They are small, oval, or sometimes streak-like, and are most often colourless or a very pale pink. Occasionally a yellowish tinge may be noted. Smith and her associates[24,25] stated that virtually all plasma proteins, particularly haemostatic components, are capable of entering the intima.

Histological appearance:

These lesions consist of elements of connective tissue separated by interstitial space, and are associated with a predominance of intimal smooth muscle, but in general the gelatinous plaque is relatively acellular. The importance of these lesions is that they signal the conversion of an initially innocuous process of lipid accumulation in the

arterial intima, to a progressive and clinically serious process that may eventually result in arterial occlusion.

There is no available data to explain whether the gelatinous elevations are precursors of mature atherosclerotic lesions or not.

3- Raised lesions (fibrolipid plaques):

The raised lesion or fibrolipid plaque is the archetypal lesion of atherosclerosis, and complications of this lesion (fissure and ulceration) are the basis of the vast majority of cases of occlusive arterial diseases[26].

All fibrolipid plaques share two basic morphological components:

Fibrous cap: a thick layer of fibrous connective tissue, which is much thicker and less cellular than the normal intima and contains fat-filled macrophages and smooth muscle cells.

Atheroma: A necrotic mass of lipid that forms the middle part of the lesion. Loss of continuity of the endothelium is the main step in the progression of a plaque and:

- increases the permeability of the intima to lipoproteins.
- permits platelet-vessel wall interaction and release of growth factors.
- allows formation of thrombus on the vessel wall.

1.4- Complications of atherosclerotic plaques :

Unstable atheroma can cause clinical complications which differ according to the target organ they supply. In the case of the lower limbs they vary from intermittent claudication, ulceration, rest pain, to acute ischaemia and gangrene which threatens both the limb, and the life of the patient[26].

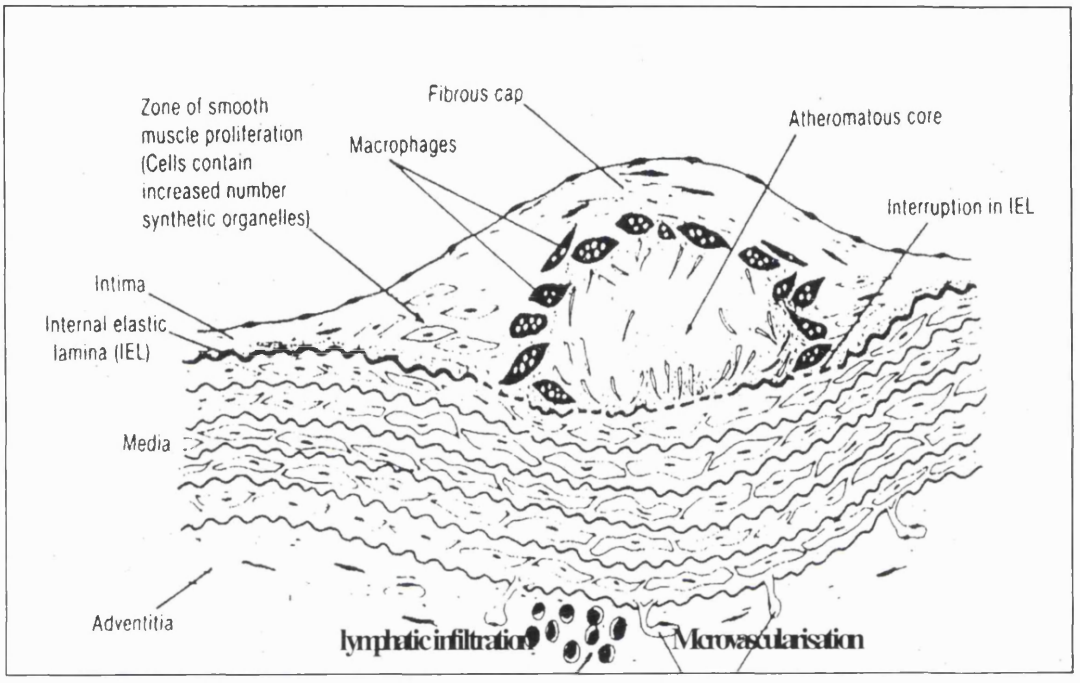


Fig. -1-

Atherosclerotic plaque

Chapter 2: Natural History Of Peripheral Arterial Disease of the Lower Limb

2.1- Introduction:

Since the advent of medical therapy, it has become more difficult to document the natural history of such a disease. Natural history[27] in this context refers to the fate of patients who receive the standard medical treatment available at the time. Knowledge of natural history and its implications for the management of asymptomatic and symptomatic patients is essential to both the patients and the physicians concerned. Although peripheral arterial disease is part of a generalised disease, the local disease can be classified into: asymptomatic disease, intermittent claudication, critical ischaemia, and amputation.

2.2-Asymptomatic Disease:

Non-invasive vascular investigations are the only tests that can be used in these subjects since arteriography is unjustifiable. The more sensitive the test, the more frequently the disease can be detected.

The prevalence of asymptomatic peripheral arterial disease is reported and documented only in the Basle study[28] as 5.7% three times as frequent as symptomatic disease. However, although the number of the subjects in this study was large (6400) but all recruited from pharmaceutical companies in Basle, were males and were of a similar age group. Such bias was avoided in the Edinburgh artery study[29] where 1500 subjects were recruited from the family doctor registry. Patients were examined clinically and ankle pressure studies were performed. The incidence of asymptomatic arterial disease of the lower limb in men was 25% (age group of 55-74).

Little is documented about the clinical course of the disease. Whilst the Basle study showed that over a 10 year period 20% of asymptomatic subjects developed intermittent claudication and 8% developed critical leg ischaemia, Walsh et al[30] reported that a third of asymptomatic subjects will become symptomatic within a 2-3 year period. They also showed that site, length, and disease morphology have a bearing on the clinical course of the disease.

2.3- Intermittent claudication:

2.3.1- Incidence:

Intermittent claudication is the most common manifestation of peripheral arterial disease. Assessment of its prevalence and incidence are subject to a number of errors:

- Many claudicants do not seek medical advice since they consider their illness a matter of ageing.
- Self referral to the family doctor varies between 10-50% between cities and rural areas. Records show that many are never seen by a hospital specialist[32,33].

Although the prevalence of intermittent claudication is consistently reported between 1.7-2.2% in several studies[38,40,41,43,47], one suggested that the prevalence may be as high as 14%[31]. In the Framingham study[42], it was reported that the incidence of intermittent claudication was 0.07% in age range 35-44 years and 1.4% in age range 65-74 years. Such discrepancy may be due to the method of assessment that has been used in these patients. One would expect a study incorporating questionnaires to show a higher prevalence than that using more sophisticated tests.

Juergens et al[51] reported in 1960 that the male to female ratio was 11 : 1. In contrast, more recent studies[36,37,40,49] have shown that the gender ratio is less than 2 : 1. This

also was supported by Jelnes[46] in his recent study where the gender ratio was reported to be 1.6 : 1.

Predominance of male subjects in the early studies has been avoided in more recent work. However the continuous increase in smoking among women and increase in the rate of referral of women to both family doctor clinics and hospital specialists are the main reasons for this discrepancy. Table 2.1 summarises the reported prevalence of intermittent claudication in epidemiological studies.

2.3.2 Risk factors:

Smoking, hypercholesterolaemia, hypertension, diabetes mellitus, and increasing age are the major risk factors for the intermittent claudication.

Smoking is the most important factor which influences the clinical course of the disease. Juergens et al[51] reported an amputation rate of 11% among the smokers compared to no amputation in the non-smokers. Cronenwett et al[47] found that surgical intervention was required three-times more frequently among smokers (more than 40 packs /year) than those who had smoked less. Houghson et al[44] reported that the risk of having intermittent claudication was about nine times greater among those who smoke more than 15 cigarette daily than in the non-smokers, and the risk among those who smoke less than 15 cigarette daily was 6 : 1 while among those smoke the pipe and cigar was 7 : 1.

Study	year	age	No/ M	No/F	Population	Prevalence
Basle[28]	1964	>39	6400	NO-F	companies	average 2.9*
Schroll[34]	1981	60	360	306	Denmark	5.8%
Agner[35]	1981	70	230	210	Glostrup	9%
Agner[35]	1981	80	120	181	Glostrup	7%
Reunanen[36]	1982	30-59	5738	5224	Finland	2.1%
Criqui[37]	1985	38-82	275	338	lipid clinic	2.2%
Hale[31]	1988	>65	621	1083	Geriatrics	14.4%
Davey-Smith[38]	1990	40-64	18388	NO-F	civil servants	0.8%
Dagenais[39]	1991	35-64	4570	NO-F	Quebec	0.4%
Fowkes[29]	1991	55-74	1592 M&F		Ed. A.S.	all 4.6%
Newman[40]	1993	>65	2214	870	cardiovascular	2%
Vogt[41]	1993	>65	No-M	1492	O.F.S.	----------

Table 2.1

A summary of epidemiological studies of the prevalence of intermittent claudication.

* In the Basle study the prevalence was 5% in the age of 60-69 years, 3% in 50-59years and was less than 1% in age of 40-49 years.

OFS= Osteoporotic fracture study. **F**= Female, **M**=Male. **Ed A S**= Edinburgh artery study.

Diabetes mellitus also affects the clinical course of the disease. The risks of critical ischaemia and amputation rate are increased in diabetic patients[43,52,58,59]. 35% of diabetic claudicants developed critical leg ischaemia and 21% had an amputation[52]. Similar findings were reported by Mc Allister[43].

Myers[58] et al showed that there was a significant difference between diabetics and non-diabetics noted from 4 years onwards. At 2 years the survival rate was 60% in diabetics and 70% in non-diabetics while at 5 years the survival rates were 35% and 60% respectively.

Dormandy et al[53] in his large study (1969 claudicants) looked at these risk factors and reported that the most significant predictor was the ankle-brachial pressure ratio. He stated that an ankle-brachial pressure ratio of less than 0.5 is an important predicator for development of ischaemia of the lower limb. This is also supported by Jelnes[42] who reported that no patient with ankle pressure above 70mmHg required amputation. Hughson[44] reported that intermittent claudication in patients with a systolic blood pressure of more than 160 mmHg was 3.4 times more likely than in those with less than 160mmHg, was more likely in those who had a diastolic blood pressure of more than 90mmHg. Jelnes[46] reported that the mean arterial blood pressure was also a significant predictor, and the risk increased by 1.33 for each 10 mmHg rise in the pressure.

2.3.3-Course of the disease:

Intermittent claudication has a benign clinical course although local disease can be progressive. Non-surgical series[55,56,59] suggested that over a period of 5-years, 75% of claudicants will stabilise their symptoms. This figure is supported by recent studies[43,46]. In the remaining 25% of claudicants 7-9% will deteriorate within one year, and then another 2-3% annually will deteriorate[54].

Jelnes et al[46] reported that 44% (113 patients out of 257 patients were recruited to his study with intermittent claudication) died whilst the rate of clinical progression to lower limb critical ischaemia was 7.5% (the mean follow-up period was 78 months).

O'Riordain[50] reported that where 33% of his patients died, 21% deteriorated (decreased their claudication distance) and 13% developed critical ischaemia in a series of 112 patients followed with a median of 82 months.

Surgical intervention will be required in 15-20% in patients with intermittent claudication who present to a doctor[49,50].

Imparato et al[49] reported that 79% of 104 patients with intermittent claudication became stable, while surgical intervention was required in 15%. In the same series he reported that 21% deteriorated (6% gangrene and 6% rest pain treated with surgery). O'Riordain[50] reported 13% required surgical intervention.

Basle[28] and Framingham[42] reported that the rate of amputation in a non-selected population was less than 2%. Bloor[56] in his study (1476 patients with intermittent claudication) reported that the rate of amputation in the claudicants was 7% at a 5 year period and 12% at a 10-year period.

Study	Year	No	Age/year	Follow up	worse	Amputation	Bypass	Predictors
Imperato[49]	1975	600	not given	30m	15%	6%	-------	distal disease
Hughson[44]	1978	60	47-79	57m	--------	---------	23%	smoking
Hughson[45]	1978	160	35-90	60m	---------	30%	33%	DM,Age
Cronenwett[47]	1984	91M	38-86	30m	60%	---------	20%	smoking,ABPI
Jonason[48]	1985	224	63	72m	12% rest pain	-------	-------	multifocal
Jelnes[46]	1986	257	36-85	78m	44%died 16%CLI	6.8%	9.5%	BP, ABPI
O'Riordain[50]	1991	112	40-80	82m	37% died, 21% worse, 13% CLI	29. P	30. P	ABPI

Table 2.2

The clinical course of intermittent claudication and predictors associated with the progression of the disease from a number of series.

The data available in the Basle study[28] suggested that 40% of asymptomatic patients have bilateral disease compared with 33% in patients with intermittent claudication. In the case of patients with critical ischaemia the rate of bilateral disease was 15%.

In summary, intermittent claudication is a disabling disorder with an incidence of 1.7-2.2%. Smoking is the most important risk factor. The clinical course of the disease is always described as benign. 75% of the claudicants will stabilise in a 5-years period. While surgical intervention is required in about 20%. Only 7% will deteriorate to critical ischaemia. The amputation rate is 7% at 5 years and 12% at 10 years follow-up.

2.4- Critical Ischaemia of lower extremities.

The pathophysiology and the management of critical leg ischaemia has always been a problem[57]. In 1988 a series of small workshops were held by the European Working Group on Critical Limb Ischaemia to discuss the definition, pathophysiology, investigation and management of this condition[66].

2.4.1- Definition:

Critical limb ischaemia is ischaemia which endangers the limb or part of the limb[66]. It was recommended that critical limb ischaemia (CLI) is defined by the following criteria:

- Persistently recurring rest pain requiring regular analgesia for more than two weeks.
- And/ or ulceration or gangrene of the foot or toes in addition to an ankle pressure of less than 50mmHg. In the case of calcified diabetic vessels the blood pressure measurement is unreliable.

2.4.2- A more precise definition can be achieved; if:

- Toe systolic pressure < 30mmHg.
- Trans-cutaneous oxygen pressure of the ischaemic area (tcPO2) < 10mmHg which does not increase with inhalation of oxygen.
- Absence of arterial pulsation in the big toe measured after vasodilatation by strain gauge or photoplethysmography.
- Marked structural and functional changes of the skin capillaries in the affected area.

2.4.3- Incidence and prevalence:

There is little information available on the incidence and prevalence of critical leg ischaemia. The only statistical data of help are the number of amputations performed. On the assumption that all amputations were performed for ischaemia and only 25% of patients with critical ischaemia have amputation, multiplying by four gives approximately the number of the patients with critical leg ischaemia.

The incidence of CLI is 500-1000/million/year. On the other hand if one assumes that an overall prevalence of claudication is 3% and that 5% of this group will have CLI over a 5 years period, the incidence is close to 300/million/year[58].

2.4.4- Course of the local disease:

The fact that many patients have some form of interventional therapy has made it impossible to describe of the natural history of CLI. The only source of information in this context are a series of the studies in the pre-angioplasty era. However at that time the definition of CLI was not clear, and many of these studies involved patients that would now be considered claudicants.

Bloor[56] et al in reported that 75% of those limbs with pre-gangrenous criteria occurred in the first year of the onset of claudication. Taylor[54] et al noted that 29% of 84 limbs with CLI recovered.

The European Working Group on Critical Leg Ischaemia[66] reported that in the diabetic group of CLI patients 55% required an urgent intervention, 20% underwent balloon angioplasty, 15% had surgical reconstruction, and 20% had amputation. Whilst in a mixed group, 60% required surgical reconstruction, 20% primary amputation, and 20% some other form of temporary treatment. This report also stated that after one year 20% of this group were dead, 25% had major amputations, and 55% will still had both legs

Jelnes et al[46] reported that during the follow-up (a mean of 78 months) 42 patients out of 257 developed CLI, while 24 (57%) of them had vascular reconstruction. This report also supported by Myer[58] Wolfe[60] and Griffith[61] in which the rate of surgical reconstruction was 50-60%. Veith et al[62] reported that vascular reconstruction was planned in 90% of patients with CLI and this was also supported with Hickey et al[63]. In this series (315 patients) Hickey reported that 329 limbs with CLI had by-pass surgery, among them 25 limbs had inflow procedures (8%), femoro-popliteal by-pass in 65 limbs (20%) and femorocrural by-pass was required in 239 limbs (73%). Nevertheless the amputation rate was 20%.

Also it was reported that presence of gangrene and ulceration carry a poorer prognosis than rest pain, and distal vessel disease is another predictor of progression and deterioration of the limb[64]. Allen et al[65] reported that 30-70% of acutely ischaemic limbs required amputation.

2.4.5- Summary:

The incidence of CLI is between of 300-1000 /1000,000/year. 60% will require urgent surgical reconstruction, 20% amputation, and 20% some other forms of temporary

treatment. Within a year 20% will die, 25% will have a major amputation, and 55% will still have both legs. Gangrene and ulceration carry a poorer prognosis than rest pain.

2.5- Amputation and amputee:

This subject is beyond the scope of this thesis but I will explain some points of interest.

The incidence of amputation performed for ischaemic limb is 300/1,000,000/annum in the U.K[64]. Kelly[67] supported by Scott[68] and Dowd[69] reported that 70% of all below knee amputations will heal primarily, whilst 15% (of the rest) will require above-knee amputation. They also reported that two year after successful below-knee amputation 15% will need an above-knee amputation (AKA), 15% will need a contra-lateral amputation and 30% will die. Following AKA, it can take up to 9 months for full mobilisation, but in two-years 30% of amputees do not use their prosthesis[70].

2.6- Mortality rate of patients with peripheral arterial disease:

It has been reported in many studies that the mortality rate is 30% at 5 years, 50% at 10years, and 70% at 15 years[28,35,36,47,55,56,62,71,72,73,74,75,76]. Coronary artery disease (CAD) is the leading cause of both early and late mortality following surgical reconstruction in peripheral arterial disease. The prevalence of CAD in patients with peripheral artery disease is summarised in table 3. The major cause of the death is cardiac disease (40-60%), whilst cerebrovascular problems contribute between 10-20%[81,82]. Other vascular accidents, commonly ruptured aortic aneurysm is about 10%, and between 20-30% die with non-cardiac causes[28,35,47,55,56,72,73,76,78]. Missouris[83] supported by Choudhri[84] showed that the prevalence of renal artery disease in patient

with intermittent claudication is 31-59%. Age, CAD, cerebrovascular disease, ABPI <0.5, hypertension, DM, and smoking are the most important predictors of both morbidity and mortality[71,72,73,74,76,79,80].

Study	No Of Subject	Investigation	CAD prevalence
Taylor[54] 1962	412	history	17%
Begg[55] 1962	198	history/ECG	19%
DeWeese[71] 1962	103	history/ECG	34%
Malone[72] 1977	180	history/ECG	58%
Hughson[44] 1978	160	history/ECG	36%
Szilagyi[74] 1979	531	history/ECG	38.5%
Crawford[75] 1981	949	history/ECG	38%
Hertzer[76] 1981	256	history/ECG	47%
Vecht[77] 1982	100	stress ECG	62%
Hertzer[78] 1984	381	angiography	90%
Brewster[79] 1985	54	Thallium scan	63%
Dormandy[53] 1991	1969	history/ECG	47%

Table 2. 3

The prevalence of CAD in patient with peripheral arterial disease.

Chapter 3: Duplex Ultrasound Scanning

3.1- Duplex concept:

3.1.1- Introduction:

Duplex ultrasound scanning is a relatively new diagnostic modality in the field of vascular surgery. Due to its non-invasive nature its applications have been extended in this speciality aiming to avoid both the morbidity and the mortality of arteriography (morbidity of 1% and mortality of 0.1%)[85].

Historically the Doppler effect was first described by Christian Andreas Doppler (1803-1853) an Austrian physicist[86,87]. Both ultrasound cardiovascular imaging and Doppler analysis systems were originally developed independently and reported for the first time in the nineteen fifties[88].

Keidel[89] in 1950, demonstrated ventricular contractions by continuous transmission of ultrasound and the first scientific paper on the development of non-invasive ultrasound Doppler flow-meter was presented by Satomura[90] a physicist at Osaka University. He noticed a high frequency Doppler noise during the examination of heart motions, pulsation of the eye ball, and blood vessel walls which he interpreted as resulting from blood flow and not the movements of the blood vessel wall.

In close clinical collaboration with Kaneko[91], a neuropsychiatrist at Osaka University Medical School, the so called ultrasound blood rheograph was further developed. Such a name was used because it was thought that ultrasound Doppler device could not measure the blood flow quantitatively; but it could examine quantitatively the characteristic rheographical changes of the blood flow in relation to various clinical

conditions. Olinger[92] in 1967 by using ultrasonic vascular imaging to evaluate 60 carotid plaques compared to arteriography reported that the role of the ultrasound imaging technique was unclear.

Over the last thirty years tremendous progress has been made in development of more sophisticated ultrasound imaging and Doppler systems and in the early seventies the two ultrasonic modalities were built into one system[93]. It was also found that analysis of the blood flow characteristics could best be obtained by Doppler ultrasound[94].

3.1.2-Basic Principle:

Ultrasound is high frequency sound wave beyond the range of normal human hearing and includes frequencies in the range $2x10^3$ - $50x10^6$ cycle/ second (Hz). These sound waves travel poorly in air, compared to their transmission in the soft tissues of the body and the water[94]. These waves can be produced when short pulse radio frequency (RF) is applied to a Piezoelectric crystal, which adsorb the electrical energy, and then emit this energy as a sound wave.

This pulses travel through soft tissue until a change in tissue density or tissue interface is encountered. A small component of the signal is reflected back toward the receiver, and a small component is absorbed as the interface producing thermal energy. The largest component continues into the deeper tissues until new interfaces are encountered and the process is repeated. Eventually the strength of the signal in the deeper tissues is so weak, that no reflected echoes occur.

The reflected signal from strong interfaces travels back toward the receiver where it is received by the same crystal used for generation of the signal during a period when no

transmission is occurring. If the interface is at right angles to the ultrasound beam, the major component of the returning signal will be detected by the receiving crystal, but if the beam strikes the interface at an angle, some of the signal will be reflected away from the receiver. A time-gain compensation (TGC) is normally applied to the returning pulse to equalise the intensity of the signals as displayed on the monitor. While the scattering interaction of most of the soft tissues structure have roughly the same wave length of the ultrasound beam, the red blood cells due to their very small size, do not send strong echoes (Rayleigh scattering) [94,95,96].

3.1.3: Duplex US equipment:

I will discuss briefly the Ultrasound equipment :

a-Transducer

b-Ultrasound image

c-Types of US scanning

a- Transducer:

A transducer as its name suggests can convert the one form of energy to another form. In the case of ultrasound, a transducer converts the electrical voltage to ultrasound, and vice versa. A transducer can operate in either a continuous fashion, if the voltage is applied continuously, or a pulsed fashion, if the voltage is applied intermittently.

The ultrasound probe (transducer) is composed of several components, including the piezoelectric element or crystal, a backing material, a matching layer, and a case to cover the components. (Fig 3.1.1)

Structure of the transducer:

1-Piezoelectric crystal: Most modern transducer crystals are made of Lead Ziroconate Titanate, and are made piezoelectric by placing them in a strong electric field under high temperature. These single transducer elements are then formed into discs of varying diameter and thickness. When a voltage is applied to the transducer element via thin metallic film electrodes which are applied to both the front, and the back surfaces of the crystal, it causes the crystal to deform (thickness propitiate with the voltage) and create a pressure wave.

$$\text{Operating Frequency} = \frac{\text{Propagation speed of transducer material}}{2 \text{ X Thickness of transducer}}$$

From the above formula, it is apparent that the operating frequency will increase with increasing propagation speed of the transducer element, and decrease with increasing thickness of transducer element.

2- Damping Material: This material is a mixture of plastic and metallic powder, bonded with epoxy to the back side of the crystal, to reduce the pulse duration, and then the number of cycles in the pulse.

3- Matching layer: This is always composed of a material having an acoustic impedance lies between that of the transducer element and the tissues. It is applied to the face of the crystal to reduce the reflection that occurs at the transducer-skin impedance. The ideal thickness of this layer is one quarter of the wave length of the transducer element[94 ,95, 96,97,98].

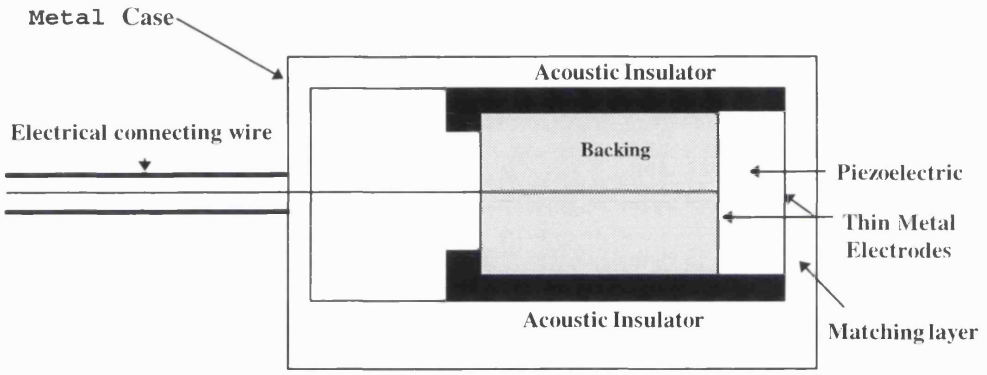


Fig -3.1.1- Demonstrates the structure of the transducer.

b-Ultrasound Image:

1-A-Mode (Amplitude Mode):

The earliest and simplest mode of presenting the reflected echoes on a display screen is A- mode. In this mode, a transducer is positioned in the desired direction, and the ultrasound pulse is directed to the subject. The returning echoes are then received by the transducer, amplified by the ultrasound unit, and displayed on a cathode ray tube (CRT). [Fig 3.1. 2]

2- T-M Mode image (Time motion): Also known as M-Mode. While A -Mode, and B - Mode are dealing with stationary structure, the M-Mode is dealing with movable structure, as in the case of the heart.

3-B-Mode (Brightness Mode) : Whilst A- Mode represents the amplitude in a spike pattern, the B - Mode the image is represented as a dot pattern, the echogenicity of each of which varies according to the returning echoes.(Fig 3.1.2) Development of the B-Mode expanded the role of the diagnostic ultrasound scan.

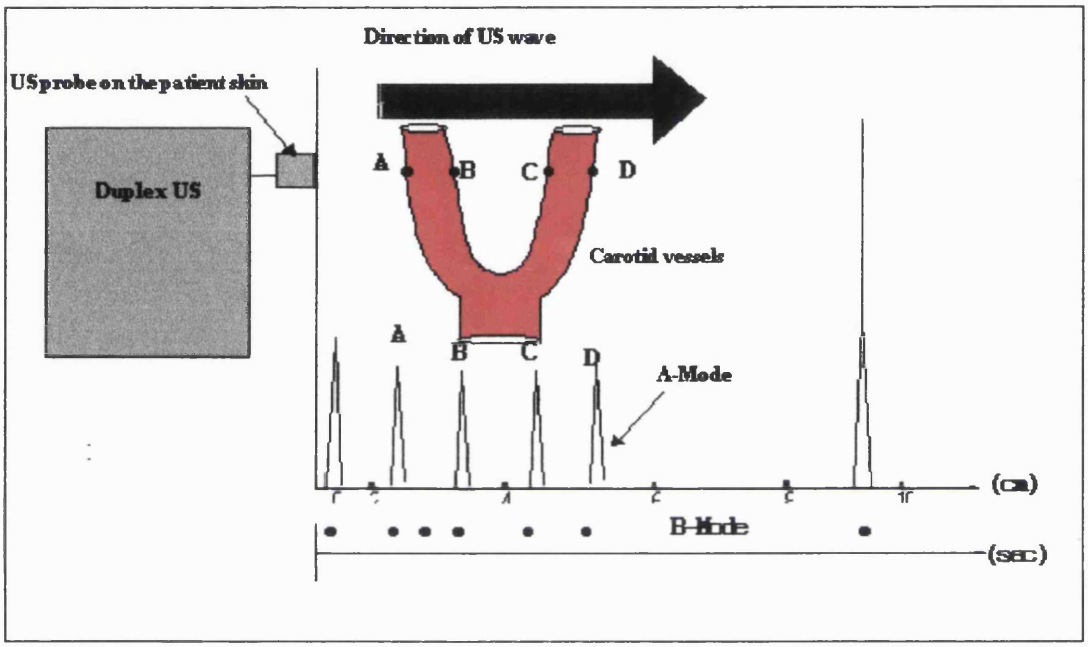


Fig -3.1.2-

The principles of the different Modes of ultrasound

(A,B,C,D represent the vessel wall where the ultrasound wave reflect)

c- Types of the scanning: Two types of B- scan formats are in use today, static B-scan, and Real time imaging.

1-Static B-Scan: This can display a very large field of view, but no information regarding the reflectors motion can be obtained. In addition an experienced operator is required to obtain an accepted image [95,96,97,98].

2-Real-time imaging: In this method all the limitations of the static B-scan are avoided. Real time scanning systems produce several images per second(10-60) in order to reproduce movement on the display monitor. Each individual scan produced by the transducer is called a frame, and each frame is composed of scan lines. The greater the number of the scan lines, the higher the resolution of the image. The ultrasound image memory can be achieved either by processing the returning echoes analogue (electrical) scan converter, or digital (computer memory) scan converter. Real-time scanning display formats (rectangular, or sector) can be performed mechanically, or electronically[97,98,99,100].

Mechanical Scanning : There are several variations on mechanical real- time scanning instruments, the following are the most common three

-Oscillating single transducer,

-Rotating group of transducers,

-Stationary transducer with oscillating mirror.(Fig 3.1.3)

Electronically array scanning: Electronically array consists of an assembly with multiple transducer elements which can arranged in three different ways:

Linear switched array, Linear phased array, or Annular array [95,96]. (Fig.3. 1.4)

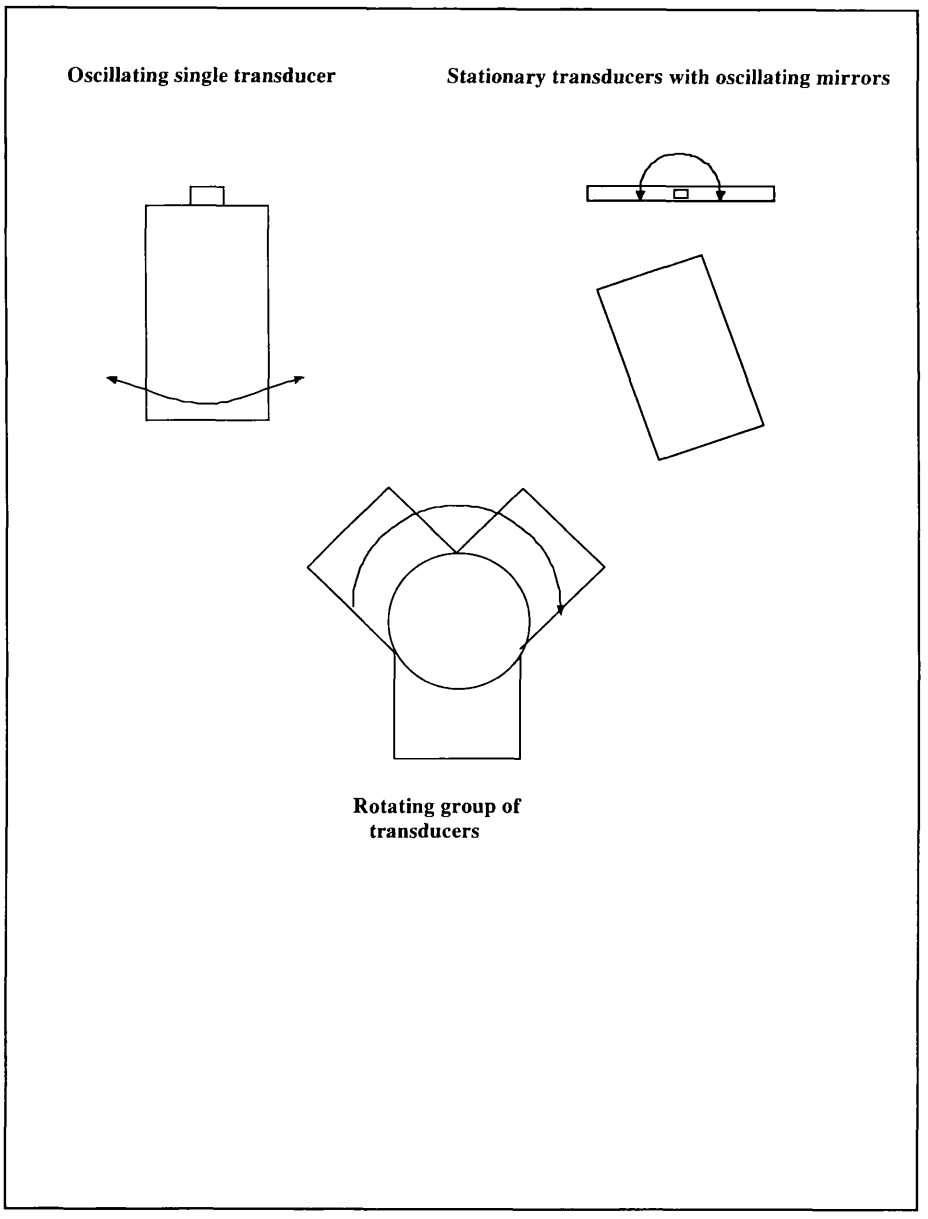


Fig -3.1.3-

Mechanical scanners

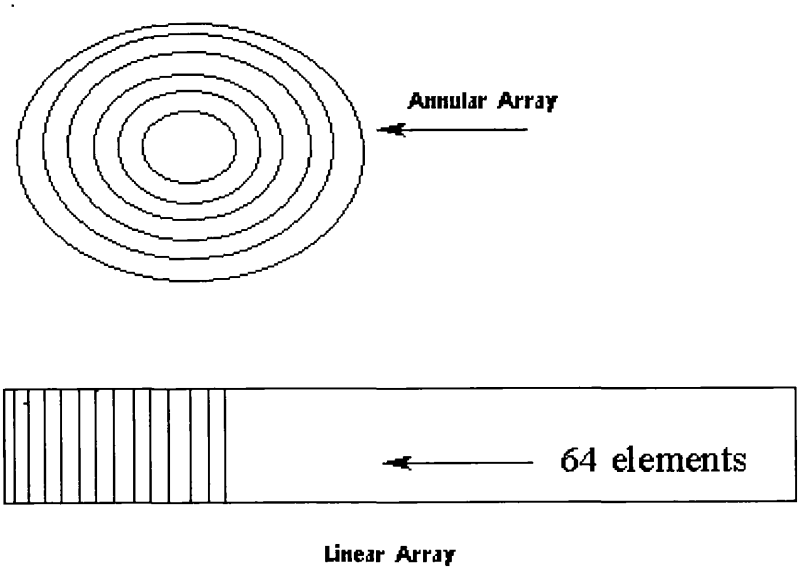


Fig -3.1.4- Electronic scanners

3.1.5- Doppler effect :

The Doppler effect is a change in the perceived frequency of echo signals emitted by a moving reflector. The resulting shift in the Doppler frequency is related to the velocity of the reflectors[94,95]. Mathematically, the Doppler shift which occurs when the ultrasound is scattered by a moving object is given by

$$F_D = 2 F_o (v \cos \theta) / c$$

where F_D is the Doppler shift, F_o is the ultrasound frequency, **v** is the speed of the movement of the scatterer, θ is the angle between the direction of movement of the moving object and the ultrasound beam, and **c** is the speed of sound propagation in the scattering media (1570 m/s for blood). It obvious that the Doppler shift will fall to zero if the object is moving at right angles to the beam, since cos 90^o = zero. When the ultrasound is scattered by blood, the actual scattering elements are the red cells[100,101]. Being considerably smaller than the wave length of the ultrasound, these produce weak scattering in all directions and despite the very large number of red cells per unit volume, the resulting signal is also weak, as suggested by the echo-free nature of blood in B-mode ultrasound images. Typical values for the Doppler shifts which may be encountered can be calculated from the Doppler shift equation. For example, a 5 MHz Doppler system interrogating arterial blood with a maximum velocity of 1m/s, at an angle of 60^o, the maximum Doppler shift will be 6.4kHz. As is virtually always the case, the Doppler shift falls within the audible range of the human ear. This has allowed aural monitoring of Doppler signal to be used as the primary means of assessing quality of the signals during the examination.

$$F_D = 2 F_o (v \cos \theta) / c$$

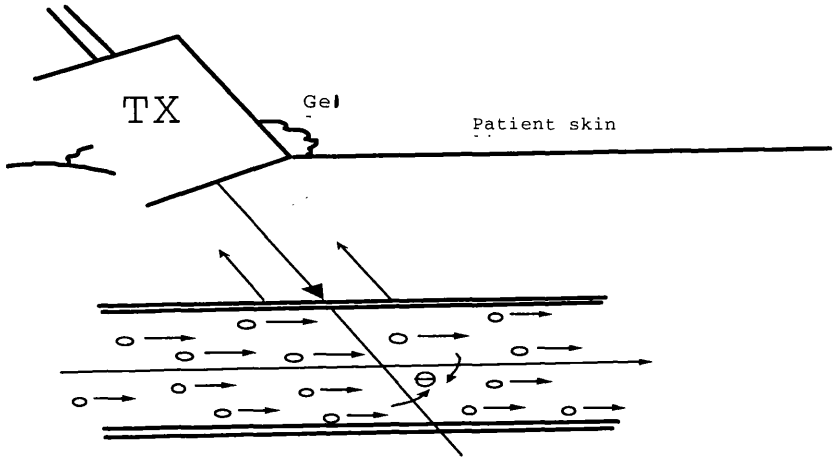


Fig -3.1.5-

the Doppler shift

The Doppler angle(Θ) is defined as: The angle between the direction of the flow and the direction of the sound propagation. In real life a small Doppler shift is evident even at an angle of 90 degree because the ultrasound beam has a certain width and the lateral edges of the beam do in fact intersect the flow vector at an angle other than 90 degree.

3.1.6- Doppler instruments:

1-Continuous-wave Doppler.

2-Pulsed Doppler.

3-Colour Flow.

1- Continuous-wave Doppler:

The simplest type of Doppler equipment is the continuous-wave (CW) device first used by Satomura[90]. These instruments utilise a transducer that contain two crystals, one acting as a transmitter, and the other as a receiver. The transmitting and receiving transducers may be adjacent, so that the sample volume of the instrument is simply the region of overlap of the transmitted beam and the received one. It is sensitive to moving objects real-time Doppler shift information can be obtained from the region of sensitivity (sample volume). The size of the region of the sensitivity varies with the frequency of the transducer. Low frequency CW transducers have a larger zone than the high frequency. Any flow within the sensitivity zone will result in a Doppler shift being detected by the instrument. For instance, if two vessels were side by side in the area of the sensitivity, flow from both will be detected simultaneously, and the resulting Doppler shift would be inseparable. CW Doppler therefore have relatively poor spatial selectivity, particularly in depth[102].

2- Pulsed-Wave Doppler:

Pulsed Doppler was developed to overcome the limited spatial resolution associated with CW Doppler. The transmitted signal consists of a short bust of ultrasound containing 3-20 cycle per second at a fixed frequency. The instruments utilise a transducer that contains one crystal which acts as transmitter and receiver. Real-time Doppler shift information can be obtained from the volume sample[96,97,102]. After the

weak echo signals have been amplified, a range gate circuit selects only those echoes arriving at a particular time delay after each of the transmit busts. This ensures that the signals originate from a fixed depth.

3- Colour-Flow:

In most systems, pulses of the sound are sent through all regions in the 2-D image, and the returning echoes are displayed with colours that correspond to the direction of flow that their positive or negative Doppler shift represent. Red colour indicates positive flow (toward the transducer), while blue colour represents negative flow (away from the transducer) [97,98,100].

3.1.7- Doppler Signal Processing: The complexity of the Doppler signal is due to its four part composition:

1-Doppler shift frequency,

2-The amplitude of that frequency,

3-The spatial distribution of flow with the sample volume,

4-The temporal variation due to the pulsatile flow.

Many methods have been developed to extract information from the Doppler signal, ranging from simple inexpensive CW Doppler device to a very expensive duplex scanning machine. These can be audible Doppler signal analysis and analogue Doppler Wave Generation.

Zero-Crossing Detector (ZCD): This is the most commonly used method of recording the Doppler signal and uses a number of zero crossings in the Doppler signal to produce a voltage output which drives a strip-chart recorder. Studies have shown that the analogue wave forms generated by Zero Crossing Detector can be used

to analyse the carotid arteries for stenosis with high degree of accuracy. (Fig. 1.8) The failure of the ZCD to detect minor degrees of stenosis, is a major limitation of using the technique, and it has been replaced by the digital Fast-Fourier transform spectrum analysis (FFT). FFT has become the most popular method of digital frequency analysis used to display the Doppler frequency spectrum for pulsatile flow[103].

3.1.8- Doppler Signal Waveform Analysis:

The flow pattern in the main arteries of the upper or lower limbs normally has three components or phases during each cardiac cycle[97,98] .

The first phase has the highest Doppler frequency and is the large forward velocity peak produced by cardiac systole. This is followed by a second, brief phase of flow reversal in early diastole. The third, low-frequency phase of forward flow is in late diastole. There many factors modify this wave pattern and the most important factor is the peripheral resistance.

When a wave form is obtained from an arterial site distal to a stenosis or occlusion, a single, forward velocity component is observed with flow remaining above the zero line throughout the cardiac cycle. The peak systolic frequency is lower than normal, and the waveform becomes flat and rounded. These changes result from decreased velocity of flow and from the compensatory fall in the peripheral resistance that occurs in limbs with arterial occlusive disease. If the Doppler probe is placed directly over a stenotic lesion, the signal has an abnormally high peak systolic frequency. The character of the Doppler obtained proximal to an arterial obstruction depends on the capability of the collateral circulation.

If there are well developed collaterals[98,99,100] between the Doppler probe and the point of the obstruction, the wave form may be normal. In the absence of collateral flow the signal has a harsh quality. Failure to achieve any signal over the vessel indicates occlusion.

An important difference between spectral waveform analysis and colour-duplex imaging is that wave forms reveal the entire frequency and amplitude content of the pulsed Doppler signal at a specific site, whereas the colour duplex image provides a single estimate of the Doppler shift frequency or flow velocity for each site within the image. Thus spectral waveform analysis actually provides considerably more flow information from each individual site than colour-duplex imaging.

Once the normal features of the spectral wave forms have been recognised, a set of criteria for classifying arterial disease in the lower extremities can be developed. (Table 4.1 represents these criteria)

Both the absolute velocity values and velocity ratios (stenotic jet velocities to proximal velocities) can be obtained. Recently the peak systolic velocity ratio (PSVR) has been used as the most important parameter in estimating the degree of stenosis in the blood vessel[97,98,99,100].

3.2- Haemodynamic changes with critical stenosis:

3.2.1: Introduction:

In this part of the review, I will briefly discuss; the main haemodynamic changes which associate critical disease (i.e. stenosis more than 50% and occlusion) in the peripheral vessels of lower extremities. The understanding of these changes is essential for interpretation of non-invasive diagnostic tests in the modern vascular laboratory.

Encroachment on the lumen of an artery by an atherosclerotic plaque can reduce both pressure and flow distal to the lesion, but it has to be relatively extensive before haemodynamic changes are manifested, since the arteries offer relatively little resistance to the flow compared to the resistance vessels.

Studies in human subjects and animals have indicated that about 90% of the cross sectional area of the aorta has to be encroached upon before there is a change in the distal pressure and flow, whereas in smaller vessels, such as the iliac, carotid, renal, and femoral arteries, the critical stenosis level varies from 70-90% [97,98].

It is important to differentiate between percentage of reduction in the cross-sectional area of a vessel and such reduction in its diameter. For example, a decrease in diameter by 50% corresponds to a 75% decrease in cross-sectional area.

Factors influencing the haemodynamic changes in a vessel are the length and diameter of the narrowed arterial segment, roughness of the endothelial surface and degree of irregularity of the lesion and its shape[97,98] (whether the narrowing is abrupt or gradual). The ratio of the cross-sectional area of the narrowed segment to the nearest normal vessel is another factor. The rate of flow, arteriovenous pressure gradient, and

peripheral resistance beyond the stenosis are among the important factors which influence these changes.

It is important to recognise that two or more stenotic lesions that occur in series have a more pronounced effect on distal pressure and flow than does a single lesion of equal total length.

3.2.2- Pressure Changes:

The diastolic pressure does not fall until the stenosis is very severe and the decrease in systolic pressure is a sensitive index of reduction in the diameter of a vessel[97]. Reduction is seen in both the mean pressure and the amplitude of the pressure wave distal to a relatively minor stenosis. Damping of the waveform, increased time to peak, and greater width of the wave at half-amplitude are duplex finding that can be detected distal to an arterial stenosis or occlusion[97].

3.2.3- Flow Changes:

At rest the total blood flow to an extremity may be normal in the presence of a severe stenosis or even a complete obstruction of the main artery because of the development of a collateral circulation, which is aided by a compensatory decrease in the peripheral resistance. In such circumstances, measurement of systolic pressure is a better method of assessing the presence and severity of the occlusive or stenotic process than measurement of blood flow.

Resting blood flow is reduced in acute occlusion when the collateral circulation has not had a chance to develop. It will also be reduced in the case of a chronic arterial obstruction when the occlusive process is very extensive and consists of two or more lesion in series.

Although single lesions might not be associated with symptoms or significant changes in blood flow at rest, such lesions can significantly affect blood supply during exercise. In such cases, the sum of the resistance of the obstruction (stenosis, collateral resistance, or both) and peripheral resistance may prevent a normal increase in flow, and symptoms of intermittent claudication may develop[97,98].

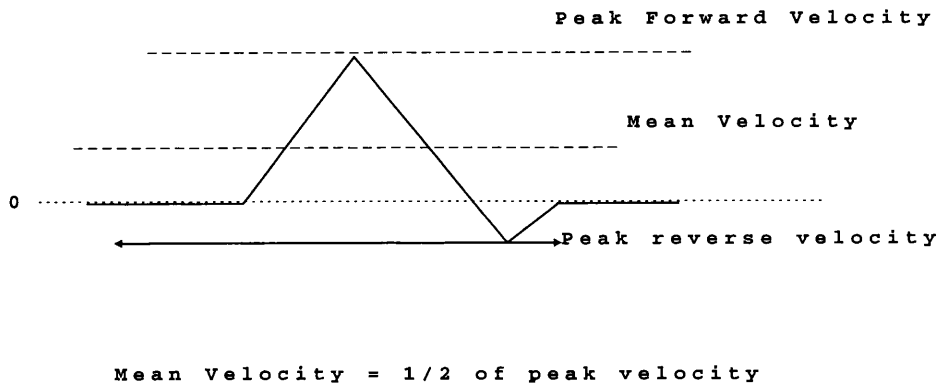
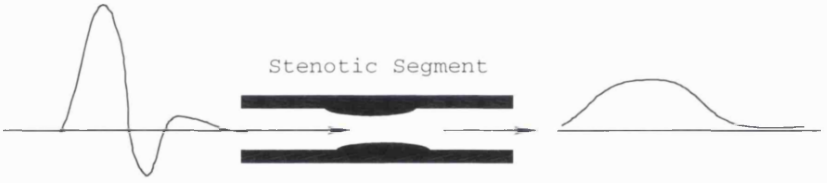


Fig -3.2.1- Velocity wave profile



PSVR = PSV at the stenotic segment divided by PSV at pre or post-stenotic segment

Fig -3.2.2-

Changes in the wave due to critical arterial disease

3.2.4- Velocity Changes:

In normal arteries the flow velocity increases rapidly to a peak diastole when flow reversal can occur. The shape of the resulting pulse velocity wave resembles the pressure gradient.

The character of this velocity profile can be quantified from analogue velocity recording by calculating various indices of pulsatility and damping. The characteristics of wave form can also be appreciated by listening to arterial flow sounds emitted by Doppler flow detectors.

Double or triple sounds are heard over normal peripheral arteries. The first sound represents the forward systolic flow, whilst the second sound represents the reversal diastolic flow. The third sound is the second forward component.

Distal to an arterial stenosis the pulse velocity wave is more damped than normal and is similar in pattern to the pressure wave. Flow reversal disappears distal to an arterial stenosis. The calculated wave indices are altered and the audible Doppler signals have a single component rather than the double or triple components usually heard. The disappearance of reversed flow distal to a stenosis probably results from a combination of several factors. Recordings of flow velocities at and distal to arterial obstruction are useful in the assessment of occlusive processes. The recent introduction of on-line frequency spectrum analysis allows better detection and quantification of flow abnormalities resulting from stenotic lesions

Chapter 4: Duplex ultrasound scanning in the assessment of peripheral arterial disease.

Atherosclerosis is the most common cause of chronic occlusive vascular disease of the lower extremities. Arteriography continues to play a central role in diagnosis and management of arterial disease. Seldinger[104] described the percutaneous placement of an intra-arterial angiographic catheter in 1953. Yet despite advances in the catheter design, contrast materials, and techniques however, arteriography remains invasive and carries the risk of damage to the vessels under investigation, peripheral embolisation and even risk of mortality. Arteriography gives an anatomical representation of vascular lesions but not the functional consequences of them. Atherosclerotic lesions are often eccentric, occasionally the angiographic appearance may be misleading especially if only views in a single plane are obtained[105].

Tremendous improvements have occurred during the last thirty years in both ultrasound equipment and technique. Duplex ultrasound imaging in modern vascular laboratories has reduced the indications for arteriography in routine assessment of carotid artery disease and graft patency.

Peak systolic velocity ratio (PSVR) has been shown to be a valuable parameter in identifying the degree of the stenosis of arterial disease in lower limb arteries. PSVR can be obtained by comparing the PSV at the stenotic segment to either pre or post stenotic normal segment. In many reports a peak systolic velocity (PSVR) of 2.0 was used to differentiate between a lesion with less than 50% diameter reduction and more than 50%. This arbitrary value has been used in most of the studies apart from those of Legemate[112,116] who used PSVR 2.5 and Baxter[123] who used PSVR 1.8.

Diameter reduction	Features
normal	triphasic wave, no spectral broadening
1-19% diameter reduction	min. spectral broadening (S.B.), peak systolic velocity. ratio < 1.5
19-50% diameter reduction	moderate. S.B, peak systolic velocity ratio <2
50-99% diameter reduction	severe S.B, monophasic wave, peak systolic velocity. ratio > 2
occluded	no flow detected in the ex. segment, distal wave is monophasic.

Table 4.1

Summary of the criteria for classifying arterial lesion based on Duplex scanning with spectral wave analysis.

A series of studies has been published in which the accuracy of duplex ultrasound has been tested in comparison with accepted measures of arterial testing. Arteriography has been regarded as the gold standard in all studies[101-120] apart from that of Legemate[112-116] who used intra-arterial pressure gradient measurements as a reference standard. In most of the studies patients with intermittent claudication were included, while a few involved patients with critically ischaemic limbs. (Table 4.2)

Legemate et al[112-115,116] used a PSVR of 2.5 to define lesions with more than 50% reduction in diameter, and reported that duplex has a sensitivity of 84% and specificity of 96% in differentiating between normal and diseased arterial segments and for the occlusion, the sensitivity and specificity were 92%, and 99% retrospectively. Baxter et al[123] used a PSVR of 1.8 to differentiate between normal and diseased segments and reported an accuracy with a sensitivity of 80% and specificity of 98%. Table 4.1 shows the criteria used by several authors to quantify the degree of the stenosis.

Cossman[107] was the first to scan a group of patients undergoing excimer laser angioplasty and reported a sensitivity 87% and specificity 99% in detecting stenoses and a sensitivity 81% and specificity 99% for occlusion. This is also supported by Whyman[125], Davis[124], Landwehr[126], Baumgarner[127], and Heijden[128] who also scanned patients were referred for Balloon angioplasty.

Study	year	population	Scanning	PSVR	No limbs	Stenosis		Occlusion		Both	
Moneta[108]	1992	IMC /CLI	colour coded	> 2	286	--	--	--	--	89%	99%
Jager[109]	1985	IMC /CLI	B/W	> 2	54	--	--	--	--	82%	100%
Langsfeld[111]	1988	IMC /CLI	B/W	> 2	46	80%	95%	100%	100%	86%	94%
Legemate[112,113]	1989	IMC /CLI	B/W	> 2.5	90	81%	96%	88%	100%	--	--
Legemate[114,115]	1991	IMC /CLI	B/W	> 2.5	122	--	--	--	--	89%	98%
Vashisht[117]	1992	claudication	colour coded	> 2	18	--	--	--	--	88%	100%
Allard[118]	1994	IMC /CLI	B/W	> 2	99	80%	95%	94%	99%	86%	97%

Table 4. 2

Duplex Scanning in Aortoiliac disease in the published studies

Jager et al[109,110] established the relationship between the arterial diameter and age of the subject using pulsed Doppler ultrasound, and demonstrated that the peak aortic velocity decrease with the age. In his report, Jager stated that although arteries tend to be smaller in women than men, the arterial flow velocities are not significantly different between men and women.

Kohler[105] scanned 393 arterial segments in 32 patients with duplex ultrasound between 1984 and 1987. It was shown that duplex scanning had a sensitivity 82% and specificity 92% but there was difficulty in detecting lesions distal to critical stenosis or occlusion (multisegmental disease).

The effect of multisegmental arterial disease in reducing the duplex accuracy has been shown by Bergamini[129] and Polak[121] but denied by Legemate[112-115,116] and Jager[109,110].

Much of the existing published data refer to assessments of the accuracy of duplex ultrasound in the aorto-iliac and femoro-popliteal segments. Few studies have evaluated the duplex scanning in the infrageniculate arteries where the status of arteries may determine the likelihood of success when undertaking a vascular reconstruction. (Table 4.2,4.3,4.4)

Although Legemate[112-115] reported good sensitivity of duplex scanning in most regions, he also reported that in some segments of the femoro-popliteal segment (distal femoral and proximal popliteal) a sensitivity of only 60-70% was achieved. This probably represents difficulty in visualising deeply placed arteries using early generations of ultrasound imaging equipment.

Study	year	population	Scanning	PSVR	No limbs	Stenosis		Occlusion		Both	
Koennecke[119]	1989	IMC	colour coded	> 2	82	71%	96%	87%	96%	95%	100%
Polak[121]	1990	IMC/CLI	colour coded	> 2	34	76%	96%	100%	96%	88%	96%
Whelan[120]	1992	IMC	colour coded	> 2	100	88%	96%	95%	99%	---	---
Moneta[108]	1992	IMC/CLI	colour coded	> 2	286	--	--	--	--	79%	98%
Hatsukami[122]	1992	IMC	colour coded	wave form	58	---	---	90%	97%	70%	96%
Baxter[123]	1993	IMC/CLI	colour coded	>1.8	40	82%	96%	--	--	--	--
Jager[109]	1985	IMC/CLI	B/W	> 2	54	--	--	--	--	75%	96%
Legemate[112,113]	1989	IMC/CLI	B/W	> 2.5	122	--	--	--	--	76%	97%
Whyman[125]	1992	IMC	colour coded	> 2	36	93%	96%	100%	94%	98%	100%
Davis[124]	1992	IMC	colour coded	> 2	65	97%	97%	94%	98%	96%	100%
Vashisht[117]	1992	IMC	colour coded	> 2	20	--	--	--	--	100%	92%
Allard[118]	1994	IMC/CLI	B/W	> 2	99	--	--	--	--	87%	93%

Table 4.3

Summary of the published studies illustrating the accuracy of duplex of femoro-popliteal vessels

In the aorto-iliac region some authors[112-116] scanned subjects fasted for 6 hours prior to scanning whilst Whiteley[130] reported a more aggressive policy of bowel preparation (klean prep) to improve the visualisation of this area. Most of the studies used colour duplex ultrasonography to detect the lesions and pulse-wave Doppler to quantify the degree of the stenosis; some studies were satisfied with the wave form assessment at the common femoral artery to exclude lesions in the aorto-iliac regions. Table 4.2- summarise the results of these reports in the aorto-iliac region.

Although most of the studies reported high sensitivity and specificity for the femoro-popliteal segment, some authors[112-116] found less sensitivity and specificity in distal femoral and proximal popliteal segment. The deep vessels in this area may explain the difficulty of the scanning. Table 4.3 summarise the results of the published studies in this area.

The reported overall accuracy of duplex ultrasound scanning in aorto-iliac and femoro-popliteal area is a sensitivity of 86%, and specificity of 97%, 80% 98% respectively. In the infragenicular region a sensitivity of 74% and specificity of 93% have been reported[109]. Table 4.4 summarises the results of these studies.

The homogeneity of the sensitivity and the specificity among studies indicates that duplex scanning is reproducible in different study centres in patients with intermittent claudication and critical ischaemia. However the heterogeneity of the sensitivity and the specificity in differentiating between more than 50% stenosis and occlusion in the femoro-popliteal region could not be explained by differences in diagnostic criteria or duplex technique.

At the University of Amsterdam, Koelemay et al[106] recently reported that, the integrated use of duplex scanning has significantly reduced the need for diagnostic arteriography. Whyman[125] and Davis[124] used duplex scanning for localisation and characterisation of atherosclerotic lesions and also selected suitable lesions for balloon angioplasty.

Although diagnostic arteriography can be combined with percutaneous balloon angioplasty in the same session, it is not uncommon that the diagnostic arteriography is followed by a therapeutic procedure at a later date. This increases the risk of complications. Elsman et al[116] have shown by using the duplex ultrasound scanning as main method of investigation that out of 100 patients conservative treatment was considered in 22 patients (18 of them did not need diagnostic arteriography), 36 patients underwent balloon angioplasty without diagnostic arteriography (2 of them; the lesions could not confirmed by diagnostic arteriography). Also in his report Elsman stated that in 62 patients the treatment strategy could be determined without the need for diagnostic arteriography.

In conclusion, duplex colour ultrasound scanning is accurate and able to discriminate between normal and diseased arterial segments. It is able to quantify the degree of arterial stenosis. However, the effects of multisegmental disease on accuracy of detecting stenoses as well as the application of duplex data in the clinical decision making processes have yet to be elucidated.

Study	year	population	Scanning	PSVR	No limbs	Stenosis		Occlusion		Both	
Koennecke[119]	1989	IMC	colour coded	> 2	49	--	--	73%	95%	94%	91%
Moneta[108]	1992	IMC/CLI	colour coded	no flow	286	--	--	73%	91%	---	---
Hatsukami[122]	1992	IMC	colour coded	wave form	58	---	--	78%	100%	78%	79%

Table 4.4

Duplex Scanning in infragenicular disease in previous studies

Chapter 5: Computer-assisted of duplex ultrasound image analysis:

Constant advances in technology make the computer assisted analysis of the grey scale ultrasound image possible.

A few terms have to be defined before any further discussion[131],

1- Bits: are the smallest units of measurements of computer data.

2-Byte: eight bits together form one byte.

3-Kilobyte: contain one-thousand and twenty four (2^{10}) bytes

4-Megabyte (MB): contain one-thousand and twenty four kilobytes.

5-Pixel: is the smallest unit of an image manipulated by a computer.

Digital image processing enables image manipulation to obtain the maximum information from such images. Every image consists of a range of shades of colour. In digital images, numbers are used to express the degree of the brightness[132]. Because the main interest of this thesis is the grey scale image, I will concentrate my discussion on this type of image.

A digital image in which each pixel is represented by one byte may have up to 256 shades of grey. The brightness value of each pixels ranges between 0-255, with 0 representing the blackest spot and 255 representing the whitest[133].

For the purposes of image analysis, two tools in the computer programme can be used.

1-Image statistics

2-Histogram.

In this work I have used Adobe Photoshop computer programme for the purposes of ultrasound image analysis. (Adobe system Incorporation, Mountain View, CA 94039) The image analysis used have been confined to simple descriptive statistics since these are rapidly computed and have been employed successfully by previous authors.

a-Image statistics:

This function provides the statistics of the digital image, this includes the highest and lowest pixel value, pixel count, the mean, median, and standard deviation of all the pixels.

b-Histogram:

The histogram consists of 256 vertical lines[134,135], the height representing the number of pixels with that value, while the horizontal axis represents the pixel value (0-255). (see fig. 5.1) So for example, if a single line at point 200 (pixel value) represents the number of pixels with a brightness value of 200.

The value of such technology (computer-assisted grey scale image analysis) has been demonstrated in both diagnostic and prognostic assessment in fields such as hepatic tumours, breast tumours, and thyroid neoplasms[136-140].

Einenkel et al[136] in 1992 demonstrated the value of the grey scale statistics and reported that in 30 children with juvenile goitre treated by levothyroxine, iodide or a combination of both, the mean grey scale value of thyroid image changed significantly in the second and the third group but not the group treated by levothyroxine alone. This was interpreted as reflecting a decease in the follicle size and colloid content. Becker et al[137] in 1989 reported similar findings when he used the same technique in 248 patients. He reported that in the case of Hashimoto's thyroditis and Grave's disease, there was an obvious drop in the echogenicity (mean grey scale) which was not the case in the euthyroid patients.

In 1994 Huber et al[138] used this technique to differentiate between malignant and benign breast tumours, and concluded that computed-assisted ultrasound image analysis may be superior to conventional ultrasound in helping to identify the nature of breast tumours.

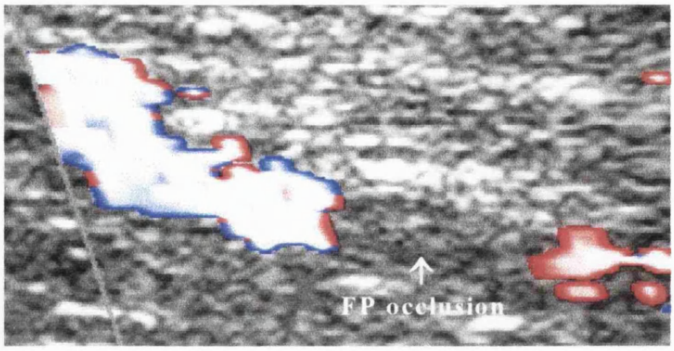


Fig 5.1

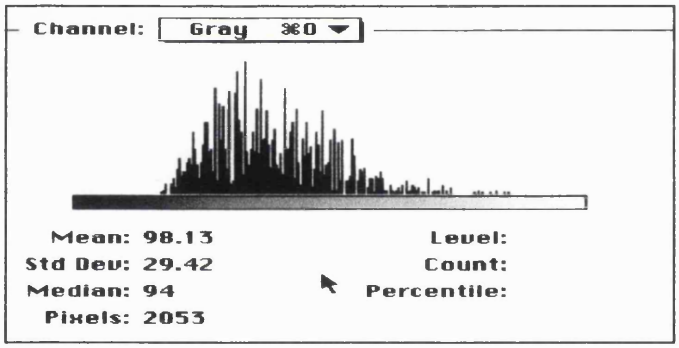


Fig 5.2

The ultrasound image of femoro-popliteal occlusion, and computer-assisted image processing techniques in the image analysis using both image statistics, and histogram.

Zendel et al[139] reported the value of the grey scale statistics in identifying fatty change in hepatic tissues; where he found that the value of the grey scale of normal hepatic ultrasound image tend to decrease in hepatic fatty change. This was also supported by Hess et al[140]. Duplex ultrasound scanning has a leading role in both carotid artery disease assessment. The advances in ultrasound image resolution made the characterisation of atherosclerotic plaque possible[141]. The implications of atherosclerotic plaque morphology in cerebrovascular circulation have been demonstrated by Lusby[141,142] in 1987. Fisher[143-145] in 1951 were the first to demonstrate the association between extra-cranial carotid disease and development of the ipsilateral amaurosis fugax, and contralateral stroke.

In 1986 Leahy[146] demonstrated that various elements of the plaque are available as potential emboli. This includes the fibrous cap overlying complex plaques, the contents which include cholesterol crystals, the breakdown products of intra-plaque haemorrhage, fibrous or cartilaginous material as well as calcified bony materials. He also considered that the ulcer is the doorway through which these elements pass to the blood stream. Moore[147-149] in 1968 who stressed the importance of plaque ulceration as likely source of emboli which might results in cerebral vascular events. Hollenhorst[150] in 1961 that the showed the presence of cholesterol emboli in the retinal artery of patients suffering from amaurosis fugax when bright plaques were seen in the extracranial carotid vessels. Bock et al in 1992 has shown and reported[151] that soft plaques (lipid laden and haemorrhagic plaque) behave in an unstable way and tend to ulcerate, whilst fibrous, or calcified plaques behave differently. Grey-Weale[152] classified carotid plaques on the basis of their ultrasound images into four types, based on the echogenicity as follows :

Type 1=predominent echolucent with echogenic cap,

Type 2= substantially echolucent with area of echogenicity,

Type 3= dominantly echogenic with area of echolucency,

Type 4= uniformly echogenic.

Geroulakos[153] in his modification to this classification added type 5, in which the plaque is calcified. This is identified on ultrasound imaging by the presence of 'shadows' cast by plaques attributable to strong absorption of ultrasound energy by this plaque. He also stated that intra-plaque haemorrhage and ulceration were frequently found in plaque type 1, and 2 while these of type 3, and 4 were more calcified and largely fibrous.

This classification was used by Langsfeld[154,155] in 1989 who examined a group of 250 volunteers in a shopping centre (asymptomatic), in addition to an asymptomatic and a symptomatic group of hospital patients. He reported that in the 'shoppers group' 81% had either no plaque or plaques of type 1. In the asymptomatic hospital patients over two thirds had either type 3 or 4, whilst in the symptomatic group 69% had plaques of type 1, or type 2.

Despite advances in ultrasound imaging, plaque characterisation remain a subjective process and is observer dependent. Workers in this field reported that the use of computer-assisted image analysis is possible. El-Barghouty[156] demonstrated the ability of this technique in detecting soft unstable carotid plaques which tend to ulcerate and develop undesirable consequences. The use of image processing to evaluate ultrasound images in an objective way has been studied in a number of pathologies. Response to treatment has been measured objectively using this technique. It has been reported that plaque morphology in symptomatic patients with carotid artery disease is a strong determinant of the subsequent clinical course. At present plaque characterisation relies on subjective judgement and could be improved by application of modern image processing.

Chapter 6: Balloon angioplasty of lower limb arterial disease

6.1- Introduction:

Early in 1963, a catheter was passed retrogradely through an occluded iliac artery to provide an abdominal aortogram. Such an event was behind the following statement made by Dotter[157]:

" ***Perhaps it is wishful, but in any event I am convinced that the relief of atheromatous obstruction in small arteries can best be accomplished by catheter techniques. A flexible guide introduced percutaneously into an artery proximal to an area of atheromatous narrowing can be manipulated so as to transverse the obstruction. A mechanical attack upon the lesion would then become feasible, perhaps by gradual direct dilation".***

Dotter was the first to report the results of his combined work with Judkins late in 1964, using a percutaneous coaxial catheter system in 11 patients. A variable degree of success was described following this type of treatment[158]. The technique worked well when moving the catheter distally from larger to smaller diameter arteries but not in the opposite direction, for which ever larger puncture wounds were required. Charles Dotter was the first to carry out a successful attempt using balloon angioplasty for an iliac lesion 1965.

In 1973 Porstmann[159] developed a device which consisted of a Teflon catheter with longitudinal slits containing a Latex balloon. This Teflon cage lent strength to the weak elastic balloon, but it was traumatic when used in practice.

The real advance in the balloon angioplasty was credited to Andreas Gruntzig[160] who used a polyvinyl chloride (PVC) balloon in 1974, but due to its limited strength, the practical applications of this device were restricted. Subsequently a strong non-elastomeric polyethylene (PE) balloon was made. Gruntzig revolutionised the field of the balloon angioplasty in areas such as visceral, renal and coronary vessels.

6.2- Mechanism of balloon angioplasty:

Our understanding of the mechanism by which balloon angioplasty results in increase of vessel diameter is still incomplete. In their original description, Dotter and Judkins attributed the results of balloon angioplasty to compression and redistribution of the intimal plaque[161].

Increasing evidence from the both experimental and clinical studies has suggested such a mechanism is unlikely. Block et al[162] reported that tears, fractures, cracks, and breaks of the native atherosclerotic lesion were evident. Morphological and histological observations in human vessels after coronary artery angioplasty are limited. However a number of histological studies indicate that dramatic alterations in the vessel architecture are observed in the early post-angioplasty period. This was supported by La Delia[163], and Castaneda-Zuniga[164]. Angiographic descriptions of such changes are well documented. The outcome of balloon angioplasty has two basic aspects, morphological and physiological.

Morphological assessment can be achieved by using post-dilation arteriography to evaluate the degree of the residual stenosis and degree of smoothness or irregularity of the dilated segment. If the residual stenosis is less than 30% it is considered that the procedure was successful. The assessment of the irregularity of the surface of the dilated segment is subjective. Linear dissection confined to the dilatation site, and relatively smooth contours are general held to be more favourable than dissections which are non-linear, dissections extending beyond the dilatation site, or a post-dilatation channel with markedly irregular contours[165].

Zarins et al[166] reported that dissection may occur in the area where the artery has been maximally stretched. The plaque may become entirely separated from the arterial wall, although, it remains attached proximally, and distally.

More stress can be obtained by using an oversized balloon to produce irreversible stretching of the arterial wall, the mechanism which is usually used[167].

6.3- The balloon angioplasty procedure:

Angioplasty like all endovascular procedures is performed in X-ray suites rather than the operating theatres. Under local anaesthetic, and fluoroscopic control, the balloon angioplasty catheter can be placed accurately by the percutaneous route.

The arterial lesion is localised by the injection of contrast medium, and can be transversed by the deflated balloon along a guide wire. On inflating the balloon across the arterial lesion, waisting of the balloon is seen, as a sign of correct positioning of the balloon. This disappears as the balloon is inflated further. Contrast filing within the atheroma, and increase the luminal diameter are the signs of successful balloon angioplasty[166].

6.4- Complications of the balloon angioplasty:

Full consideration of this topic is beyond the scope of this chapter. The commonest complications of this procedure[166] are:

- Complications at the site of puncture (2-4%)
- False aneurysm (2%)
- Intimal dissection (4%)
- Arterial wall rupture (3%)
- Distal embolisation (2-5%)
- Restenosis (the major late complication)

6.5- Balloon angioplasty in previous studies:

Balloon angioplasty continues to have a growing role in management of peripheral arterial disease. There are number of points in common between the published studies in this area which should be highlighted:

1-The variability in study design, patient selection, lesion description, criteria of success of balloon angioplasty, patency rate, and the methods of the follow up of patients are the main source of heterogeneity in the reported results.

2-Another source of confusion is whether patients are claudicants, present with critical leg ischaemia, or are a mixed population.

3-Although the initial failure rate ranges from less than 10% to 30% it is rare to find an explanation for the failures or even for them to be included in the final long term patency rate.

4-The patency rate represents the long term improvement in selected groups of patients. It can be described as :

Primary patency rate: Which represents the natural history of an intervention.

Assisted primary patency rate: which induced second interventions for recurrent stenosis.

Secondary patency rate: Which refers to the effectiveness of an intervention after close surveillance and persistent re-intervention as required[168].

5-The reported long term patency varies accordingly to the method of follow-up assessment used. So if clinical history and examination are used one can expect a higher patency rate than in the case when using a more sophisticated non-invasive method.

Table (6.1) demonstrates some of the studies which used balloon angioplasty in mixed population (with intermittent claudication and critical ischaemia) with an initial success rates of more than 70% . ABPI and clinical examination are the main methods of follow-up. The patency rate at one year was 60-90%, at two years 42-84%, while at 5 years was 48-60%.

author	population	No patients, vessels	Site & initial success	Follow-up	Follow-up	Patency Rate
Privatdozent[171]	not clear	71 - 161	M/70%	not clear	not clear	90%
Lechwierny[172]	not clear	74 - 100	M/76%	12m	C/M	37-40%
Colapinto[173]	IMC	80/59P - 109	M/88%	15m	C,ABPI	64%
Freiman[174]	IMC/CLI	81/192P - 208	M/91%	30m	C,ABPI	86-83%
Greenfield[175]	IMC/CLI	80/70P	IA/81%	24m	C,ABPI	89-84%
Martin[176]	not clear	81/46P	FA/76%	24m	C,ABPI	60-42%
Kaufman[177]	not clear	82/86P - 94V	M/90%	20m	C,ABPI	not clear
Ckien-tia [178]	CLI	82/30P	M/83%	2-17m	C,ABPI	73%
Russel[179]	90% CLI	83/175P - 206V	M/90%	36m	C,ABPI	M 64% per 4Y
Krepel[180]	90% IMC	85/129P - 164V	FP/84%	72m	C,ABPI	70-60%
Johnson [181]	Mixed	87/902P - 984V	M/88%	96m	C,ABPI	48% per 5Y
Brewester[182]	Mixed	89/75P - 79V	M/87%	144m	C,ABPI	not clear

Table 6.1

Summary of the overall outcome of the available angioplasty studies in the period between 1971-1989.

IMC= intermittent claudication, CLI= critical leg ischaemia, p=patient, v= vessels, M=mixed lesions iliac, and femoro-popliteal, IA= iliac artery, FA= femoral artery, FP=femoro-popliteal vessels, m=month, C=clinical, ABPI= ankle-brachial pressure index, Y=year.

Uniform standards for evaluating and reporting the results of therapeutic intervention for peripheral arterial disease are obviously needed[169,170]. (see table 6.2)

1- Patients undergoing treatment of PVD should not be excluded from subsequent consideration for failure to successfully complete the treatment.

2-Acutely ischaemic limbs should be classified according to the pre-treatment status into: viable, threatened and irreversible.

3- Chronically ischaemic legs should also classified into7 groups: Asymptomatic, mild, moderate, severe, rest pain, minor and major tissue loss based on clinical examination and ABPI

4-Change the limb status following the treatment should be graded into: -3 to + 3 in which grade +3 represents good response, grade 0: no change, and grade +3 represent worse outcome.

5-Initial failure should reported and analysed into: 1.Cancelled due to complications. 2.Carried out but was not technically successful, 3. Clinically successful but not clinically or haemodynamically.

6-If the results separated into initial success and late patency the overall success rate should be reported.

7-To determine the patency success:
a-An established imaging method should be used (IADSA, duplex, MRA).
b- Maintenance of the achievement should be assess by proper method (Segmental pressure studies),
c- pulse volume recording (PVR) distal to the reconstruction at 5mm above preoperative tracing (only for diabetic patients with incompressible arteries),
d- palpable pulse or wave form (triphasic} or at two points directly over the graft.
e-direct observation at surgery and post-mortem examination.

8-Primary patency refers to uninterrupted patency with no procedures on or at the margin of the treated segment (anastmosis).

9-If any procedure is performed before thrombosis that might prevent eventual failure (as well as any procedure that restores patency after thrombosis), primary patency is lost. Secondary patency requires that flow be restored through most of the original graft or treated segment of native vessel and in the case of grafts, at least one of the original anastmosis i.e., not all "secondary reconstruction confer secondary patency"

10- Assisted primary patency term can be used as a procedure be carried out in still by-pass or disoblitrated segment to prevent eventual failure and thrombosis.

11-Life table methods are recommend for analysing the patency rate.

12-Operative mortality should be reported using the 30- day limit unless it occurs during the same but longer hospitalisation period

13-Complications should be reported.

14-Risk factors that may modify the outcome should be recorded and graded.

Table 6.2

The recommendations of the SVS/ISCVS committees

Table 6.1 summarises the overall outcomes of the available studies in this field in the period between 1971-1989. In this table the following points can be observed:

1-The follow-up period in these studies was 2-144 months and the methods of follow-up were based mainly on clinical history and pressure measurements (ABPI) as the outcome measures of balloon angioplasty[171-182].

2-While the initial failure rate was between 10-30%, the patency rate at one year was 60-90%. This was supported by Privatdozent et al[171], Calapino[173] Greenfield[175], Martin[176], and Ckien-tia[171].

The patency rate at 2- years was 42-84% [167,168,169,171] and the patency rate[179,180,181] at 5 years was 48-60%.

The anatomical site of the lesion is important in that it influences the outcome of balloon angioplasty. It is suggested that the outcome of PTA with iliac lesions was better than for the distal lesions[181]. In the same report the author stated that the outcome of PTA in the common iliac artery is superior than in the external iliac artery. Although most studies reported their outcomes in relation to the arterial site, some failed to do this[175,176,180].

Also some studies were designed to assess the outcome of balloon angioplasty in patients with intermittent claudication[173], whilst some assessed patients with CLI[178]. Most of the studies assessed the outcome of the PTA in mixed population[174,175,179,180,181].

In 1991 Capek et al[183] reported a series of 217 balloon angioplasties performed for femoro-popliteal lesions on 152 patients. Patients were followed-up for a mean of 7 years (2-11 years). The initial technical failure was 10%, with one year patency rate of 81%. At 3 years patency was 61%, and at 5 years was 58%. The methods of follow-up were segmental pressure measurement, and pulse volume recording at 48 hours, 3, 6,

12 months. These investigations were repeated annually, and if the ankle-brachial pressure index fell more than 0.2 an angiogram was repeated.

It is important to recognise that lesions treated by balloon angioplasty can also be treated by surgical intervention, but not *vice versa*.

It is surprising that there are few studies to address the cost difference between both therapies. In the UK, Jeans et al[184] assessed the cost of the procedure and the duration of the inpatient stay. For surgical treatment this was with a mean stay of 13 days at a cost of £1577 while for PTA, the mean stay was 1.7 days and the cost was £301.

6.6- In summary :

Balloon angioplasty is an endovascular procedure, used commonly as a day procedure, with a reasonable outcome. The major limitation of this procedure is restenosis. Variability in study design, patient selection, lesion description, criteria of both success, and failure of the procedure, and also the methods of follow-up are the main source of confusion.

Chapter 7: Atherosclerotic Plaque Morphology, and Balloon Angioplasty.

The morphology of the atherosclerotic plaque in this context refers to the shape of the lesion (concentric or eccentric), its distribution (focal or multifocal), length of the lesion (short or long), and stenotic or occlusive as they are described on an X-ray film.

Plaque characterisation can not be obtained using arteriography. Angiographic studies can provide a description of diameter reduction, but plaque structure can only be obtained by ultrasound scanning[185]. Recently intra-vascular ultrasound has been used in atherosclerotic plaque characterisation. Most of this work has been performed in the coronary vessels[186], although some have reported the value of this technique in peripheral arterial disease treated by PTA[187].

Such variables have been considered in very few studies assessing the outcome of balloon angioplasty, and their influence on both the short and long term follow-up is poorly documented.

Krepel et al[180] in 1985 reported the results of 164 PTAs in 129 patients, and demonstrated the influence of some morphological criteria on both the initial and long term outcome of balloon angioplasty in the femoro-popliteal artery. In his initial assessment, he reported that lesions with a length of > 3 cm were associated with a 26% success rate compared with 89% for those < 3 cm. In the long term follow up of 5 years, he demonstrated and reported that the patency rate of concentric lesions was 69% compared with 77% for eccentric, while the restenosis was 43%, and 27% respectively.

Krepel classified the surface of the lesion as either regular or irregular, and he found that the patency rate for lesions with a regular surface was 83%, and 62% for irregular surface- lesions with. Whilst the restenosis rate was 23%, and 46% respectively. The patency of lesions < 3 cm was 77% whilst those > 3 cm lesions were occluded by the

end of the study. Similar findings were reported by Greenfield[175] , Martin et al[176], and Russel et al[179].

It was also reported[181] that the outcome of the balloon angioplasty was better in stenotic than in the occluded segments. Krepel found no significant influence of this factor on patency rate during long term follow up.

In 1987 Johnston et al[181] reported a series of 984 PTAs in 902 patients. He found that the indication for intervention, site of the disease, severity of the disease, and the run-off vessel status are among the most important and influential factors determining outcome. The outcome of PTA in patients with intermittent claudication was better than in critical leg ischaemia, and PTA of the common iliac artery better than the external iliac and infrainguinal arteries. The best outcome can be achieved in patients with intermittent claudication, with stenotic disease in the common iliac artery and good run-off vessels (94% initial, 63% 5 years patency rate). An occlusive lesion in the femoro-popliteal segment in a patient with CLI and poor run-off; will have an initial patency rate was 73% and 5 year patency rate of 10%. The influence of vessel calcification on the outcome of PTA is unclear from the literature with many series reporting contradictory results[182-187].

In summary

There is agreement among most of the available reports that the morphological description of a lesion may play a significant role as a predictor for balloon angioplasty outcome.

Chapter 8: Hypothesis:

Aim of the thesis:

Since its advent, arteriography has been regarded as the main investigation and reference standard for the assessment of peripheral arterial disease. Advances in ultrasound equipment have reduced the indications for arteriography in both routine assessment of carotid artery disease and in graft surveillance. Duplex ultrasound can obtain both anatomical and functional data concerning arterial lesions.

In this thesis, the clinical studies can classified into two parts

Part A: Duplex scanning in lower limb arterial disease: aims in this part of the thesis were:

1-To assess the accuracy of duplex scanning in evaluation of peripheral arterial disease of the lower limbs compared to the arteriography.

2-To determine the effect of multisegmental arterial disease on accuracy of duplex ultrasonography .

3-To assess the concordance of the clinical decision based on duplex scanning compared to that based on arteriography.

4-To determine the accuracy of duplex ultrasound scanning when used as the main line of investigation.

Part B: Computer-assisted grey scale image analysis for atherosclerotic plaque characterisation. The aims were:

1-To obtain a digital ultrasound image, and also to assess the reproducibility of this technique.

2-To determine the value of this technique in plaque characterisation.

3-To determine the effect of the plaque morphology on the outcome of balloon angioplasty.

4-To develop an objective classification for the arterial lesion in the lower limb based on atherosclerotic plaque characterisation.

Part II: Clinical Studies:

Chapter 9

9.1- Duplex scanning in evaluation of peripheral arterial disease:

9.1.1- Introduction: Peripheral arterial disease of lower extremities are common disabling condition. Arteriography is still regarded as the only accepted pre-operative investigation for the purposes of localisation of the disease.

The aim of the study was to assess the accuracy of duplex ultrasound scanning to determine the degree of the diameter reduction (stenosis and occlusion) in lower limb arteries.

9.1.2- Location of the study: This study was carried out at the Vascular laboratory The Middlesex Hospital, Mortimer Street, London. Ethics committee approval for this study was obtained from UCL Medical School Ethics Committee and patients gave their written consent for inclusion in the study.

9.1.3- Patients

Lower limb arterial duplex scanning and intra-arterial digital subtraction arteriography (IA DSA) were performed in 90 patients (177 lower limbs, 59 M, 31 F, Median age 68). This group of patients was referred to the vascular outpatient clinic at University College London Hospitals NHS Trust, London with peripheral arterial disease (81 with intermittent claudication, 1 with ischaemic ulceration, and 8 with rest pain).

9.1.4. Method

9.1.4.1- Duplex ultrasound scanning:

Duplex ultrasound scanning was performed by two trained vascular technologists. An Acuson ultrasound machine 128XP/10v (Acuson 1220 Charleston Road, Mountain view, CA94039 USA) was used. A 2.5 MHz, and 7.0 MHz linear array probes were used to examine the pelvic and the infra-inguinal vessels respectively. All patients were fasted for 6 hours prior to scanning to minimise the presence of bowel gas. In all patients the aorta distal to the renal vessels was scanned routinely with the patient lying in a supine position and the scanning proceeded to the ankle vessels. In this study, the distal part of the superficial femoral artery and the proximal part of the popliteal artery were scanned from the medial side of the thigh and also from the posterior aspect to minimise the chance of missing short lesions. Run-off vessels were examined with the patient in supine and sitting positions to obtain the optimal view of these vessels.

The colour flow mode was used to outline the arterial wall and setnotic or occlusive arterial lesions. For each arterial segment the peak systolic velocity was recorded. The angle of insonation for the Doppler sampling was always as close as possible to 60 degree to the vessel axis. The peak systolic velocity ratio (PSVR) of any stenosis was obtained for each arterial segment by comparing the peak systolic velocity (PSV) at the stenotic area to the peak systolic velocity of the pre-or post-stenotic area. A peak systolic velocity ratio of 2.0 was used prospectively to differentiate between significant stenoses with more than 50% reduction in the diameter and insignificant stenoses with less than 50% reduction in the diameter.(table 9.1.1.1) For the purpose of assessment the peripheral arterial vessels were divided into 17 segments in which the iliac vessels were divided into common iliac, external and internal iliac, whilst the femoral vessels

into common femoral, superficial femoral (SFA) and profunda femoris. The SFA was divided into proximal, mid, and distal segment, whilst the popliteal was divided into proximal and distal, and the run-off vessels into the posterior tibial, peroneal and anterior tibial arteries. (see fig 9.1.1.1)

The length of the arterial lesions detected in this way was determined. The length of iliac stenosis was determined by using the duplex measuring calliper. For the femoro-popliteal lesions, a non-permanent skin marker was used to mark the proximal and the distal end of the arterial lesion detected by duplex scanning and the distance between the marks was then determined with a ruler.

The mid-inguinal point and knee-crease were used as reference points in the duplex report to provide the surgeon with the exact site and length of the lesion.

The length was described by both radiologist and vascular technologists as:

- Less than 5 cm.
- Between 5 and 10 cm.
- More than 10 cm.

This information (degree of the stenosis, site, and length of the lesion) were reported to the surgeon on a special form (figure 9.1.1.1). Figures 9.1.1.2-4 illustrate colour flow in normal vessels, whilst figures 9.1.1.5-10 represent samples of iliac, femoral, and popliteal vessels with arterial disease detected by DUS.

9.1.4.2. Intra-arterial Digital subtraction arteriography:

All patients had intra-arterial digital subtraction arteriography (IA DSA) within a week of duplex scanning. IA DSA was performed by a consultant radiologist using the Seldinger technique. Local anaesthetic (lignocaine 2.0%) was routinely infiltrated subcutaneously. A sheath with an internal diameter of 7 French was introduced

through the common femoral artery. A catheter with an external diameter of 5 French was then introduced trans-femorally through the sheath into the aorta. Contrast medium was injected and a printed copy of the X-ray film was obtained for each case. Intra-arterial pressure measurements were not done routinely and only uni-planar views of the IA DSA was obtained.

The percentage of stenosis on the IA DSA was obtained by dividing the actual diameter at of the artery at the stenosis by the diameter of the nearest normal segment. Five grades were used by the radiologist (1= normal diameter, 2= less than 20% reduction, 3= 20-less than 50% reduction, 4= 50-99% reduction, and 5= occlusion).(table 9.1.1.2) All the IA DSA films were reviewed and classified by two consultant radiologists.

The length of the iliac and femoro-popliteal stenosis and occlusion were measured from IA DSA film by the radiologist and expressed as less than 5cm, 5-10 cm, or more than 10 cm.

PSVR	Diameter reduction
1	Normal
< 1.5	< 20%
1.5 to < 2.0	20% to <50%
2.0 or more	>50% to 99%
No signal	100%

Table-9.1.1.1-

The system based on PSVR used prospectively to assess the diameter reduction of the blood vessel as has been described in several previous studies. PSVR of 2.0 was used to identify significant stenoses prospectively.

Grade	The diameter reduction on X-ray
1	No diameter reduction
2	< 20% diameter reduction
3	20-<50% diameter reduction
4	50% -99% diameter reduction
5	100% i.e. occluded

Table -9.1.1.2-

The grading system used by the radiologist to describe the degree of stenosis, based on comparing the diameter of the vessels at the diseased segment to the nearest normal segment.

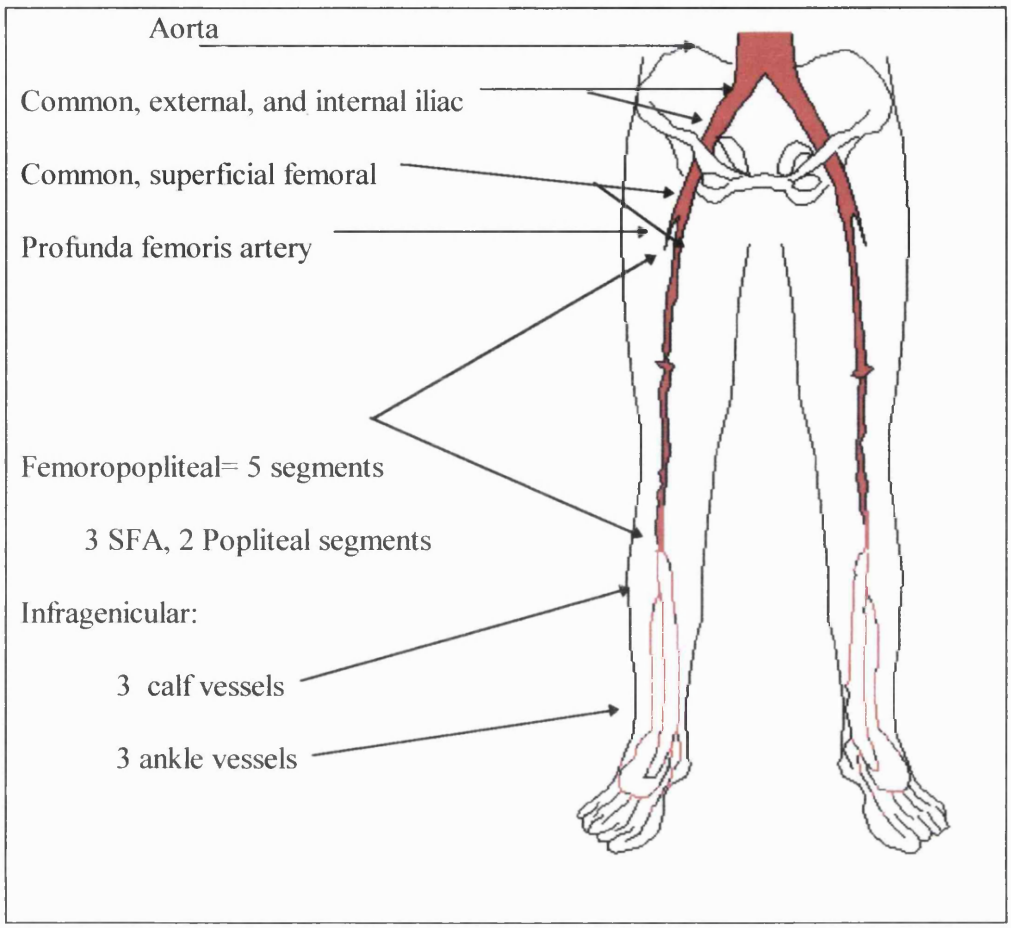


Figure -9.1.1.1-

Peripheral arterial tree of the lower extremities (both limbs) was divided into 35 arterial segments for the purpose of assessment.

9.1.5. Statistical analysis:

1-All the data obtained are shown in a two-way table. The sensitivity, specificity, positive and negative predictive value of duplex scanning compared to arteriography (as a gold standard) in detecting non significant(< 50%) and haemodynamically significant lesions (>50%) or occlusion were calculated.

2-Kappa statistics:

The kappa statistic (k) was used to measure the level of the agreement between the radiologists and technologists. For agreement by chance alone k value is 0, and for perfect agreement, k is 1.

The results of (k) can be interpreted as following:

- Poor agreement : kappa less than 0.20
- Fair agreement : kappa between 0.21- 0.40
- Moderate agreement: kappa between 0.41- 0.60
- Good agreement: kappa between 0.61- 0.80
- Very good agreement: kappa between 0.81- 1.0

Mathematics of kappa:

Kappa is calculated from both observed and expected frequencies[189-192].

To obtain kappa (k) as following:

	Rater 2		
Rater 1	**+Ve**	**-Ve**	
+Ve	***a***	***b***	***a+b***
-Ve	***c***	***d***	***c+d***
	a+c	**b+d**	**n**

Observed measure of agreement ($\mathbf{I_o}$) = $\frac{\mathbf{a+d}}{\mathbf{n}}$ (1)

Expected measure of agreement ($\mathbf{I_e}$) = $\frac{\mathbf{(a+c)(a+b)+(b+d)(c+d)}}{\mathbf{n^2}}$ (2)

Kappa (k) = $\frac{\mathbf{I_o - I_e}}{\mathbf{1 - I_e}}$ (3)

To obtain the 95% Confidence interval of Kappa statistics; the standard error (Se k) of the kappa should be obtained by the following equation:

$$\mathbf{Se\ k} = \sqrt{\frac{\mathbf{Po\ -(\ 1-\ Po)}}{\mathbf{n\ \ (\ 1-\ Pe)^2}}} \quad \text{(a)}$$

95% confidence interval of kappa statistics = k $\pm$ 1.96 x **Se (k)** (b)

9.1.6. Results:

3108 arterial segments of 177 lower limbs (630 aorto-iliac segments, 531 femoral, 885 femoro-popliteal, and 1062 run-off vessels in both calf, and ankle) were examined in 90 patients.

466 Arterial lesions were identified and graded on arteriography, compared to 451 lesions identified and graded on duplex scanning (table 9.1.1.3, 9.1.1.4).

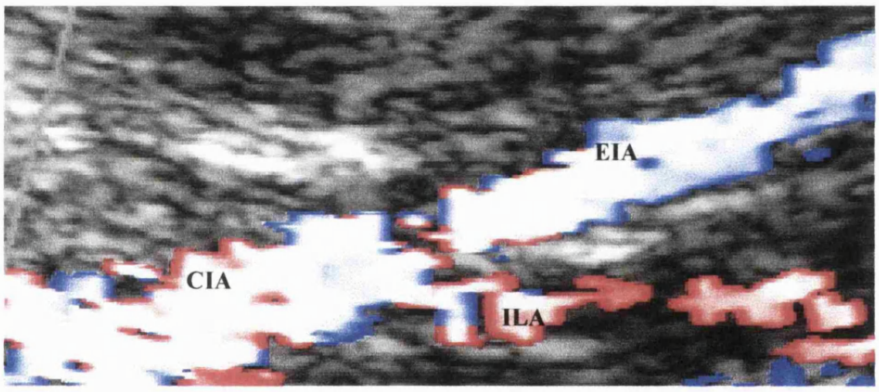


Fig.9.1.1. 2

Sample of duplex US demonstrated normal common iliac (CIA), external iliac(EIA), and internal iliac arteries(ILA)

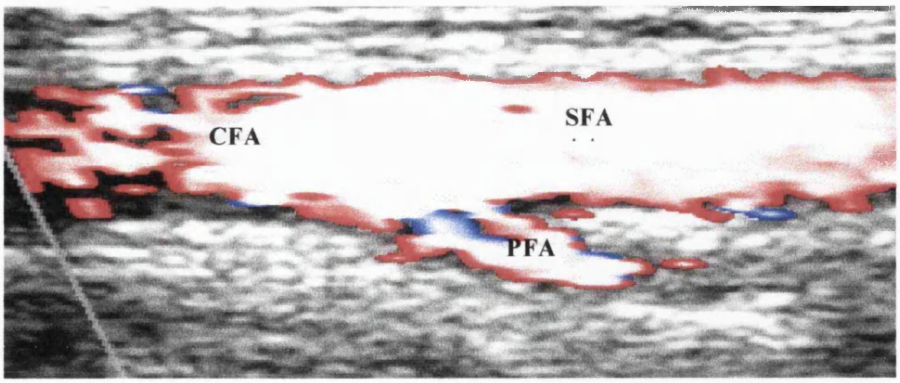


Fig. -9.1.1.3-

Sample of duplex US demonstrates normal common femoral(CFA), superficial femoral(SFA), profunda femoris arteries(PFA)

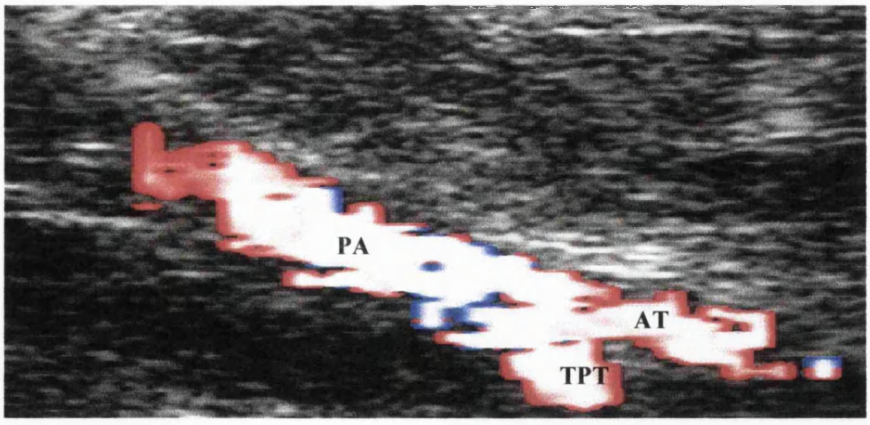


Fig -9.1.1.4-

This figure demonstrates a duplex US image of normal popliteal artery(PA), tibio-peroneal trunk(TPT), anterior tibial(AT).

% of stenosis	AI	FA	FP	ROF	Total
< 20%	**6**	3	6	0	15
20-49%	6	**2**	**5**	0	13
50-99%	23	13	**55**	45	136
occlusion	22	27	170	**83**	302
total	57	45	236	128	**466**

Table -9.1.1.3 -

This table demonstrates the distribution of arterial disease based on **IA-DSA** of 466 lesions. AI= aorto-iliac, FA= femoral artery, FP= femoropopliteal , ROF= run-off vessels.

On Duplex (PSVR)	AI	FA	FP	ROF	Total
< 1.5	**2**	1	8	0	11
> 1.5	2	**1**	6	0	9
>2.0	27	14	60	45	146
NO PULSE	19	28	159	**79**	285
Total	50	44	233	124	**451**

Table -9.1.1.4-

The distribution of arterial disease found by Duplex ultrasonography in 451 lesions PSVR= peak systolic velocity ratio. AI= aorto-iliac, FA= femoral artery, FP= femoro-popliteal region ROF= run-off vessels.

In the aorto-iliac region 570 of 630 segments were normal on both duplex and arteriography. Of the 90 patients, two iliac scans were described as 'difficult' by the vascular technologist involved (this was due to the bowel gas in one and obesity in the second patient. However, the common iliac artery and its bifurcation were clearly seen in both patients).

In the femoral artery 485 of 531 arterial segments were normal on both duplex and arteriography. Duplex was able to identify significant stenoses in the femoral segment with a sensitivity and a specificity of 100% and 99%, while for the occlusions the sensitivity and specificity were 93% and 99% respectively.

	Grading on IA DSA					
PSVR	**Normal**	**<20%**	**20- <50%**	**50-99%**	**occlusion**	**Total**
1	**570**	6	2	1	1	580
<1.5	1	**0**	1	0	0	2
1.5-<2.0	0	0	**2**	0	0	2
>=2.0	2	0	1	**21**	3	27
no-pulse	0	0	0	1	**18**	19
Total	573	6	6	23	22	**630**

Table -9.1.1.5-

Two-way table shows the distribution of the aorto-iliac lesions shown by duplex scanning as detected by PSVRs of various ranges and IA DSA as indicated by diameter reduction.

	Grading on IA DSA based on diameter reduction					
PSVR	**Normal**	**<20%**	**20- <50%**	**50-99%**	**occlusion**	**Total**
1	**485**	2	0	0	0	487
<1.5	0	**1**	0	0	0	1
1.5-<2	0	0	**1**	0	0	1
2	0	0	1	**13**	0	14
no-pulse	1	0	0	0	**27**	28
Total	486	3	2	13	27	**531**

Table -9.1.1. 6-

Two-way table demonstrates the distribution of the femoral artery lesions detected by duplex scanning and IA DSA.

In the femoro-popliteal region 648 Segments were normal by both modalities. 213 Arterial lesions were identified on both IA DSA and duplex ultrasound scanning. (table 9.1.1.7)

At the level of run-off vessels 905 of 1044 segments were normal, 37 significant stenoses and 68 occlusions were recognised by both modalities of investigation.

The summary of over all accuracy of duplex scanning at all segments is shown in table 9.1.1.8.

	Grading of IA DSA based on diameter reduction					
PSVR	**Normal**	**<20%**	**20- <50%**	**50-99%**	**occlusion**	**Total**
1	**648**	0	0	1	3	652
<1.5	0	**4**	3	1	0	8
1.5-<2	0	1	**1**	4	0	6
2	1	1	1	**49**	8	60
no-pulse	0	0	0	0	**159**	159
Total	649	6	5	55	170	**885**

Table -9.1.1.7-

Two-way table demonstrates the distribution of arterial lesions in femoro-popliteal region found by both modalities of investigation (duplex scanning & IA DSA)

Grading of IA DSA based on diameter reduction						
PSVR	**Normal**	**<20%**	**20- <50%**	**50-99%**	**occlusion**	**Total**
1	**2618**	8	2	10	19	2657
<1.5	1	**5**	4	1	0	11
1.5-<2	0	1	**4**	4	0	9
2	11	1	3	**120**	6	141
no-pulse	12	0	0	6	**272**	285
Total	2642	15	13	141	297	**3081**

Two -Way Table -9.1.1.8-

The over-all relation between the intra-arterial arteriography and the duplex findings. The first row represents the grading of IA DSA (1-5) and first column represents the PSVR.

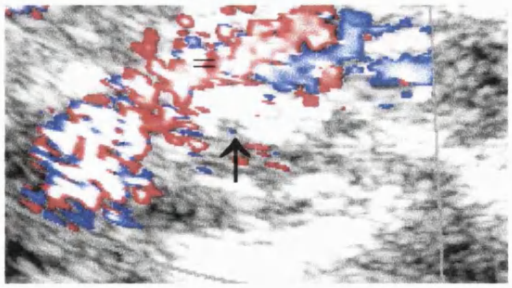


Figure 9.1.1.5

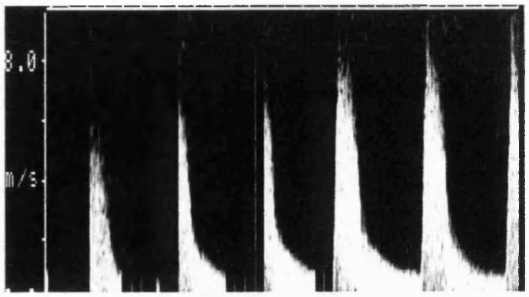


Figure 9.1.1.6

A fibrocalcified iliac stenosis has been assessed by the pulsed Doppler and PSVR was obtained (>2.0)

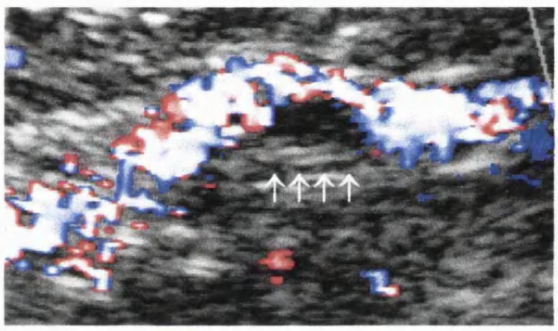


Figure 9.1.1.7

Common iliac artery stenosis

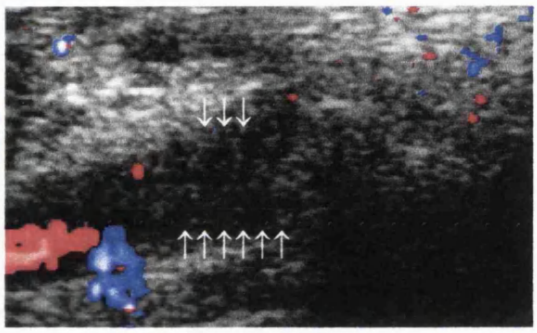


Figure9.1.1.8

Popliteal artery occlusion

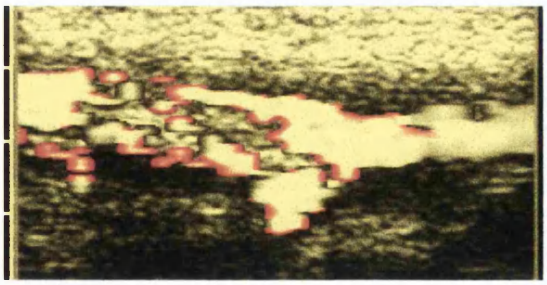


Figure9.1.1.9

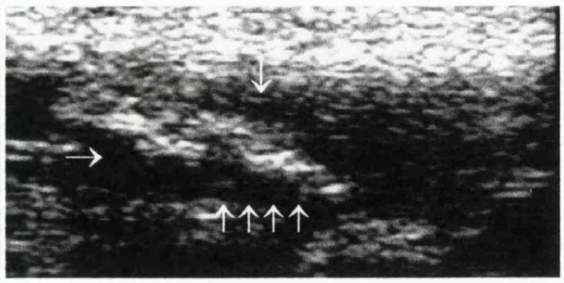


Figure 9.1.1.10

These two figure demonstrate an eccentric atherosclerotic plaque in the common femoral artery in both colour display and grey scale.

Statistical analysis of duplex accuracy compared to the IA was summarised in table 9.1.1.9.

Artery	Sensitivity	Specificity	PPV	NPV	K.(95% CI)
AI	89%	99%	92%	99%	0.81 (0.7-0.92)
FA	100%	99%	95%	100%	0.94 (0.89-0.99)
FP	95%	99%	94%	99%	0.92 (0.9-0.94)
ROF	82%	99%	82%	100%	0.81 (0.75-0.87)
Overall	92%	99%	91%	100%	0.87 (0.81-0.93)

Table -9.1.1.9 -

Summary of statistical assessment of the duplex examination compared to IA DSA, for all arterial segments. AI= aorto-iliac, FA= femoral artery, FP=femoro-popliteal region and ROF= run-off vessels, PPV= positive predictive value, NPV=negative predictive value. k= kappa statistics 95% C.I. limits.

As explained, a PSVR of 2.0 was used prospectively to identify significant arterial stenoses in accordance with the methodology of most of the recent studies. I have also used Receiver Operating Characteristic curves (ROC)[193] to identify the most appropriate value of PSVR to discriminate significant stenoses.

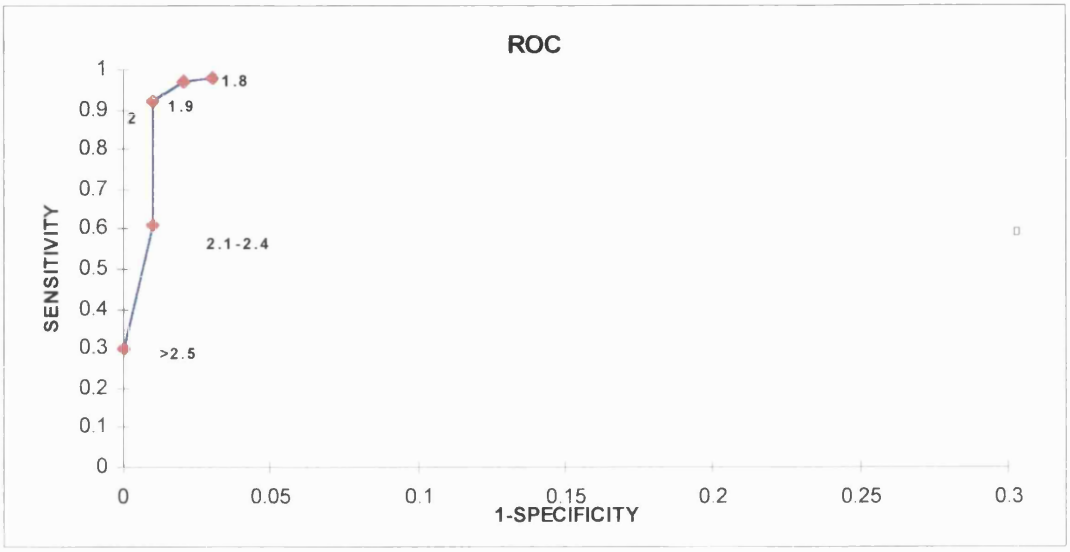


Fig. 9.1.1.11

Receiver Operating Curve

In this curve the PSVR of 1.8 is the most sensitive point to discriminate between significant stenosis and insignificant stenosis.

PSVR	1.8	1.9	2	2.1-2.5	> 2.5
Sensitivity	98%	97%	92%	61%	30%
Specificity	97%	98%	99%	99%	100%

Table 9.1.1.10

This table demonstrates the accuracy of various values of PSVR in identifying significant stenoses.

9.1.2: Accuracy of duplex scanning in detection the arterial lesion length in the lower extremities.

9.1.2.1 Introduction:

The length of arterial occlusions and stensoses has implications for the clinical decision making process. Whilst short lesions can be treated by balloon angioplasty, longer lesions require by-pass surgery.

9.1.2.2. Location of the study:

Vascular Laboratory at the Middlesex Hospital, Mortimer street, London, UK.

9.1.2.3. Patients: Same group of patients scanned in 9.1.1.

9.1.2.4. Methods: See the general methodology in 9.1.1.

9.1.2.5. Results:

807 Arterial segments in 177 limbs of 90 patients were examined (630 aorto-iliac, and 177 femoro-popliteal) 624 were found to be free of disease (559 aorto-iliac and 65 femoro-popliteal). 152 Arterial lesions were detected by both modalities of investigation (44 aorto-iliac and 108 femoro-popliteal). Eighty-nine lesions were found to be less than 5 cm (44 aorto-iliac, and 45 femoro-popliteal), 31 lesions 5-10 cm, and 32 lesions more than 10 cm. (Fig.9.1.2.1)

Duplex ultrasonography showed a sensitivity of 89%, specificity of 98% PPV of 92% and NPV of 97% in indicating the length of stenoses and occlusions compared to IA DSA (reference standard) and Kappa with k = 0.88 (95% confidence interval = 0.86-0.92).

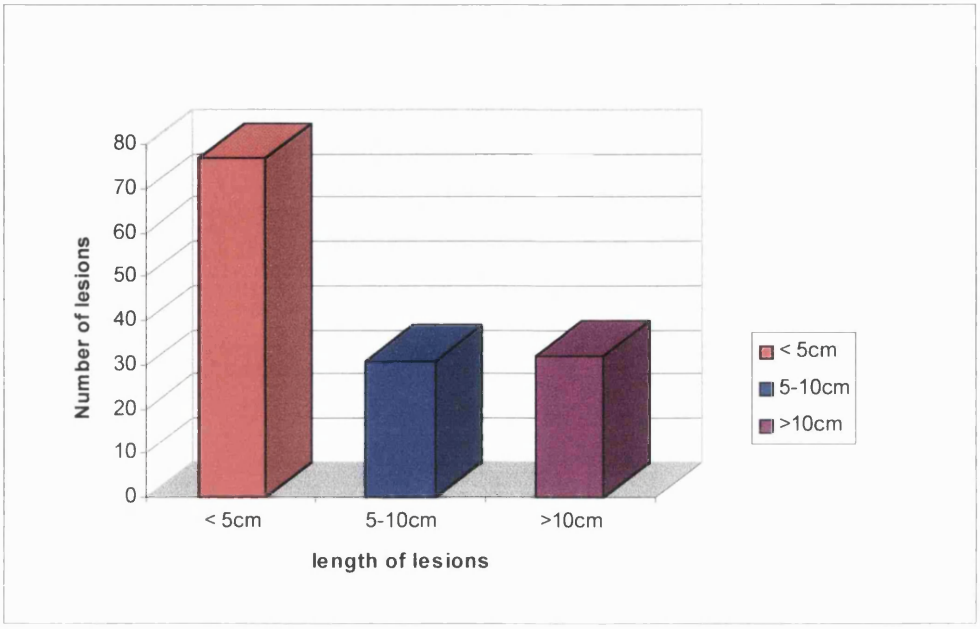


Fig.-9.1.2.1-

The distribution of aorto-iliac and femoro-popliteal lesions according to the length as measured by duplex ultrasonography.

9.1.3 - Effect of multisegmental disease on duplex accuracy:

9.1.3.1. Introduction:

A possible source of error in assessing patients in whom there are several arterial stenoses in one limb is reading of the peak systolic velocity at the more distal sites. Therefore patients with multisegmental arterial disease of the lower limb may be more difficult to evaluate using duplex ultrasonography.

The aim of this study was to determine the effect of multisegmental arterial stenoses and occlusion on the accuracy of duplex ultrasonography in evaluating arterial disease of the lower limb.

9.1.3.2. Location of the study:

Vascular laboratory at the Middlesex Hospital, Mortimer street, London, UK.

9.1.3.3. Patients:

Same group of patients scanned in 9.1.1.

9.1.3.4. Methods: See the general methodology in 9.1.1.

For the purpose of assessment, the lower limbs were classified according to nature of the arterial disease as assessed by IA DSA. The following categories were used:

1- Limb with a single haemodynamically significant stenosis (> 50% diameter reduction).

2- Limb with a single occlusion.

3-Limb with multisegmental haemodynamically significant stenoses.

4-Limb with multisegmental occlusions.

5- Limb with multisegmental mixed (stenoses & occlusions) arterial disease.

9.1.3.5 Statistics: The same statistics in chapter (9.1.1) were employed.

9.1.3.6. Results:

In 177 limbs, 66 limbs had single lesions, and there were 68 limbs had multisegmental lesions. In the case of single lesions (using IA DSA as reference gold standard) duplex showed a sensitivity of 90%, specificity of 99%, PPV of 96%, and NPV of 99% in detecting arterial stenoses and occlusions. For limbs with multisegmental lesions the corresponding figures were 95%, 97%, 91%, and 99% respectively.

The accuracy of duplex ultrasonography for all types of arterial stenosis and occlusion is summarised in table 9.1.3.1.

accuracy	Single		Multisegmental		Mixed
	Significant	Occlusive	Significant	Occlusive	Mixed
No of limbs	28	38	21	20	27
Sensitivity	87%	92%	95%	97%	94%
Specificity	99%	100%	96%	99%	97%
PPV	92%	100%	83%	99%	91%
NPV	99%	99%	99%	99%	98%
Kappa (95% CI)	0.81(0.73- 0.89)	0.96(0.94-0.98)	0.81(0.73- 0.89)	0.98(0.95-1.1)	0.89(0.84-0.94)

Table -9.1.3.1-

The accuracy of duplex in both single and multi-segmental lesions. The limbs with arterial disease were classified into five groups according to the methods shown in section 9.1.3.4.

9.1.3.7. Discussion:

In most vascular units, arteriography remains the main investigation in assessment of lower limb arterial disease. In this study I used IA DSA (uni-planar view film) as the reference standard to assess the accuracy of duplex scanning. Intra-arterial pressure gradient measurements were not obtained routinely.

Visualisation of iliac vessels was obtained in 98% of patients by a regime of fasting patients for 6 hours prior to scanning (only oral fluids were allowed). In only two patients was the iliac artery not visualised.

A PSVR of 2.0 was used prospectively to identify haemodynamically significant stenoses and showed a sensitivity of 92% and specificity of 98% identifying stenosis of 50-99% diameter reduction. (see table 9.1.1.6 and 9.1.1.8) This is very similar to the data reported in most previous studies, apart from that of Legemate[112-115,116] who used PSVR of 2.5 to identify significant stenoses. Retrospective assessment, using ROC statistics showed that a PSVR of 1.8 has a sensitivity of 98% and specificity of 97% in identifying significant stenoses. (See Fig. 9.1.1.5, and table 9.1.1.10) This would appear to be a more satisfactory value to use in future studies, since more arterial stenoses are detected without loss of specificity.

In the aorto-iliac region a very tight stenosis in the common iliac artery on duplex scanning was found to be occluded on IA DSA. Another lesion in the common iliac artery was thought to be occluded on duplex scanning but was reported to be a stenotic lesion on IA DSA. The reason for this error is that in very tight stenoses the velocity of flow falls to very low values and may be overlooked. This has been documented as

limitation of duplex US in differentiating between very tight stenoses and occlusive lesions in carotid artery scanning.

Occasionally duplex scanning in the aorto-iliac region identified a lesion which was considered by IA DSA to be either insignificant stenosis or normal vessel.

In the femoral artery duplex scanning showed high accuracy (sensitivity 100% and specificity 100%) in differentiating between the normal and the diseased segment. Assessment of the profunda femoris artery is sometimes difficult. In this study one profunda occlusion on duplex was reported as an insignificant stenosis on IA DSA and another profunda occlusion was missed on duplex scanning). This may be due to the angle of the profunda origin leading to difficulty in assessing the PSV to assess degree of stenosis.

In the femoro-popliteal region duplex was able to identify significant stenotic lesions with a sensitivity of 89% and a specificity of 99% and to identify occlusions with a sensitivity of 100% and a specificity of 98% respectively. Three lesions in the distal femoral and proximal popliteal arteries were reported on duplex scanning as having significant stenosis but were found to be occluded on IA DSA. This may be explained as follows: in changing the position of the ultrasound probe from the medial side of the thigh to the back of the knee, short stenoses or occlusions of the superficial femoral artery may be missed. Subsequently the scanning technique was revised to scan the distal part of superficial femoral artery and proximal popliteal artery again from the posterior aspect of the lower limb.

In the run-off vessels duplex scanning was able to identify significant stenosis and occlusions with a sensitivity of 82%. Fifteen occlusions, mainly in the peroneal artery

were missed by duplex scanning, whilst 11 other normal arterial segments were reported to be occluded by duplex scanning. Again, many of these lesions were in the peroneal artery. Reduced duplex accuracy can not be explained by either poor ultrasound scanning technique or lack of skill by the investigator. Changing the scanning technique by examining the peroneal artery from the back of the leg while the patient was sitting did not help to improve the outcome.

Duplex ultrasound scanning showed poor correlation with IA DSA in quantifying clinically insignificant lesions. Stenoses of less than 20% reduction in diameter and those from 20% to less than 50% reduction in diameter detected by IA DSA correlated poorly with the ultrasound findings based on the measurements of PSVR. (tables 9.1.1.3, 9.1.1.4, 9.1.1.5, 9.1.1.6). Loss of reliability for these trivial lesions is neither surprising nor clinically important since failure to detect them would not alter patient management.

Duplex scanning was able to establish the length of the stenoses and occlusions with good reliability since the proximal and distal ends were marked and measured. In an example from this study one patient who had multiple stenoses in the femoro-popliteal region, was treated surgically and had undergone femoro-popliteal by-pass grafting. Duplex ultrasound scanning of the graft post-operatively showed that the distal anastomosis was proximal to a short high grade stenosis, for which balloon angioplasty was performed to save the by-pass graft. Although some studies reported that the accuracy of duplex scanning in lower limb arteries is reduced when investigating multi-segmental disease, my study did not support this view. (see table 9.1.3.1)

In conclusion, duplex ultrasound scanning is as accurate as arteriography in the evaluation of lower limb arteries. Duplex provides functional data concerning the severity and length of arterial lesions. This is obtained without intra-arterial pressure gradient measurements during arteriography. Multisegmental disease had no significant effect on the accuracy of diagnoses reached by duplex ultrasonography.

9.2.1- Concordance of the clinical decision based on duplex scanning compared to that based on IA DSA.

9.2.1.1- Introduction:

Duplex scanning is a relatively new modality of investigation for peripheral arterial disease. Although this technique has shown to be accurate in detecting arterial disease in lower limb, most surgeons feel that arteriography is mandatory before arterial reconstruction.

The aim of this study was to determine the concordance of the clinical decision based on duplex scanning compared to that based on arteriography.

9.2.1.2. Location of the study:

Vascular laboratory at the Middlesex Hospital, Mortimer street, London, UK.

9.2.1.3. Methods:

1-Patients: 82 patients with peripheral arterial disease from the group of patients used in section 9.1.1

2-Duplex ultrasound scanning and IA DSA: See the methodology as described in 9.1.1

3-One-hundred and sixty-four anonymised reports (82 duplex and 82 IA DSA) were prepared and supported with the patient's age, sex, occupation, smoking status, diabetes mellitus, cerebrovascular and cardiovascular status. The patient's presenting complaint, its duration and claudication distance also were included. Five vascular surgeons (Consultant grade) were asked to suggest a clinical management plan, with brief reasons, for each of the reports. Each of these reports was coded to ensure that the surgeon was unable to identify either the patient or the modality of investigation.

(duplex scanning or arteriography) To allow statistical assessment of the data, the clinical management decision was recorded as a code. (table 9.2.1.1) The actual treatment that the patient received was used as the reference standard to assess the accuracy of the management suggested by the surgeons based on duplex and IA DSA reports. In addition, the decision based on IA DSA of the same surgeon was used as a reference standard to assess his decision based on duplex scanning as a consistency check, since as we have seen in the sections above from the two modalities was very similar.

9.2.1.5. Statistics:

Kappa statistics was used to assess the accuracy of the clinical decision based on the two modalities of investigations compared to the actual treatment the patient received. Full details see section 9.1.1 in this thesis.

Therapy	Code
Conservative	1
Balloon angioplasty	2
By-pass surgery	3
Combined (balloon angioplasty + by-pass surgery)	4
Thrombolysis	5
Sympathectomy	6

Table -9.2.1.1-

Treatment codes used by the five vascular surgeons to indicate treatment strategies.

9.2.1.6. Results: 177 lower limbs, 59 M, 31 F, Median age 68. This group of patients was referred to the vascular outpatient clinic at University College London Hospitals NHS Trust, London with peripheral arterial disease. 81 with intermittent claudication, 1 with ischaemic ulceration, and 8 with rest pain. Of 82 patients 44 (54%) had balloon angioplasty as definitive treatment, 17 patients (21%) had surgery and one patient had sympathectomy, and in another intra-arterial thrombolysis was given, 4 had combined therapy, while the remainder (15 patients) had conservative treatment.

A-When the actual treatment the patient received was used as a reference standard, the mean accuracy of the clinical decision based on duplex data for all vascular surgeons was 84%, and the accuracy of that based on intra-arterial digital subtraction arteriography data (IADSA) was 85%. When the decision based on IA DSA was used as a reference standard, the mean duplex accuracy was 91%. (Table 9.2.1.2)

Reference standard	Test	S1	S2	S3	S4	S5	mean
Final treatment patient received	**duplex**	93%	78%	79%	83%	87%	84%
Final treatment patient received	**IA DSA**	90%	83%	77%	80%	95%	85%
Decision based on IA DSA	**duplex**	98%	89%	88%	85%	95%	91%

Table -9.2.1.2-

The accuracy of the decision based on duplex scanning and **IA DSA** using the actual treatment the patient received as a reference standard. The third row shows the results when **IA DSA** was used as a reference standard.

S1-S5= Surgeon 1, 2, 3, 4, 5.

B-kappa statistics with 95% confidence interval have been obtained to assess the agreement between the clinical decision based on both modalities (duplex and IA DSA) of investigation compared to the reference standard.

The results are summarised in table 9.2.1.3.

Reference standard	Test	S-1(95%CI)	S-2(95%CI)	S-3(95%CI)	S-4(95%CI)	S-5(95%CI)	Mean K(95%CI)
Actual treatment	duplex	0.79(0.68-0.9)	0.46(0.25-0.76)	0.56(0.38-0.74)	0.63(0.45-0.81)	0.65(0.45-0.85)	0.62(0.48- 0.76)
Actual treatment	IA DSA	0.80(0.63-0.97)	0.60(0.42- 0.78)	0.56(0.37-0.73)	0.55(0.36-0.74)	0.63(0.43- 0.83)	0.63(0.49-0.77)
IA DSA	duplex	0.88 (0.76-1)	0.72(0.57- 0.87)	0.75(0.61-0.89)	0.65(0.48-0.82)	0.85(0.71-0.99)	0.77(0.63-0.91)

Table 9.2.1.3

This table demonstrates the agreement using kappa statistics with 95% C.I. limit to assess the accuracy of the clinical decision based on both modality compared to the reference standard. Both decisions based on duplex scanning and on IA DSA showed an agreement with k of good agreement, while when compared that decision based on duplex scanning to that based on IA DSA k with good agreement was also obtained.

S1-S5= Surgeon 1, 2, 3, 4, 5, CI= 95% confidence interval.

C- In this study, 72 of 82 cases (88%) had similar reports on both duplex ultrasonography and IA DSA. In 10 cases (12%) there were some differences however.

I- In 5 cases the difference in the data was not significant to justify any change in the treatment plan (insignificant arterial stenoses were found on IADSA and missed by the duplex ultrasonography, in four of these cases the treatment plan did not change among the surgeons by such difference whilst in the fifth case, both conservative, and balloon angioplasty were suggested as treatment)

II-In one case IA DSA showed significant SFA disease (1 cm, grade 5 stenosis) followed by 5 cm insignificant disease. On duplex this was described as a 1 cm occlusion, the insignificant part was not identified by DUS. This difference should not justify a change in the management plan (the patient was treated by balloon angioplasty). Based on duplex data, the choice of the suggested treatment by the surgeons was either balloon angioplasty and conservative treatment (3 surgeons suggesting PTA, and 2 surgeons conservative treatment). Using the IA DSA report 1 surgeon suggested PTA, 2 suggested surgery and two surgeons suggested by-pass surgery.

III-In another patient a 1 cm significant SFA lesion was not identified by DUS in a patient complaining of symptoms in the other limb. This did not change the suggested treatment strategy between the surgeons.

IV-In one patient, duplex scanning identified a significant iliac lesion which was missed on IA DSA while an insignificant lesion (grade 3) was missed on duplex scanning. Both of these lesions were treated with PTA.

V-In 2 patients duplex identified significant iliac lesions which were either missed or underestimated by uniplanar arteriography. These lesions were detected on a repeated

oblique views of IA DSA and the patient had balloon angioplasty for these iliac artery stenoses.

D- Looking at the accuracy of the duplex data compared to IA DSA date provided in these reports: 72 cases have no difference in the data obtained by both modalities of investigations (table 9.2.1.4).

Reference standard	**Test**	**S1**	**S2**	**S3**	**S4**	**S5**	**mean**
Final treatment patient received	**duplex**	95%	82%	83%	85%	95%	88%
Final treatment patient received	**X-ray**	95%	85%	84%	84%	95%	89%
Decision based on IA DSA	**duplex**	96%	96%	93%	95%	99%	96%

Table 9.2.1.4

The accuracy of the clinical decision based on duplex and IA DSA in 72 cases

E- Example of the data presented to the surgeons in this study:

Duplex scanning ***IA-DSA***

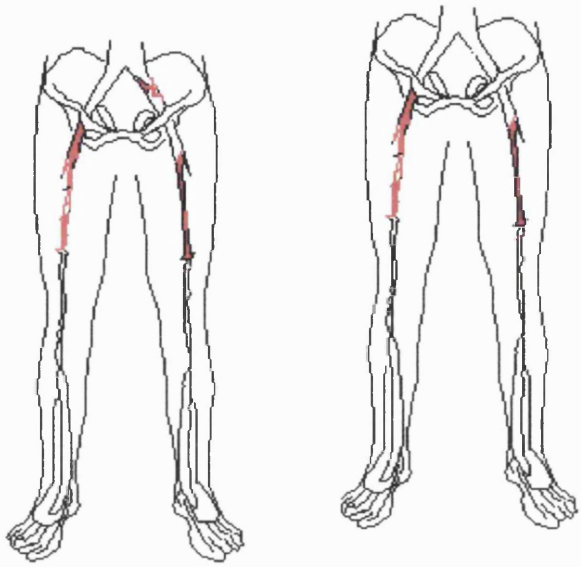


Fig. 9.2.1.1

Duplex and IA DSA data as represented in figures

Duplex scanning reported a 50% left iliac stenosis, 22 cm left SFA occlusion and a 50% stenosis of length 2.4 cm in the right SFA in a patient with bilateral claudication after walking 100 yards. On the IA DSA, the iliac lesion was not identified. All five surgeons decided on balloon angioplasty based on the duplex data, while they decided on either conservative or femoro-popliteal by-pass surgery on IA DSA. The iliac lesion treated by balloon angioplasty while the femoro-popliteal lesion by a by-pass surgery.

***F*-**In table 9.2.1.5. the all-over agreement among the consulting surgeons on both modalities of investigations compared to the actual treatment the patient received.

No of cases	%	No of surgeons agreed on both duplex, IA DSA with actual treatment
43 cases	52%	all the five surgeons agreed with the actual treatment by both modalities
22 cases	27%	Four surgeons agreed with the actual treatment by both modalities
4 cases	5%	Three surgeons agreed with the actual treatment by both modalities
13 cases	15%	Less than 3 surgeons agreed with the actual treatment by both modalities

Table 9.2.1.5

Demonstrates the over-all agreement of the clinical decision based on both modalities of investigation. In 13 cases there was agreement with the reference standard by less than 3 surgeons.

There was an agreement between less than three surgeons on 13 cases (table 9. 2.1.5):

In 7 Cases the Duplex and IA DSA reports were similar.

In 6 Cases there were differences between duplex scanning and IA DSA.

In three cases the femoro-popliteal region was involved. In three patients, difference lay in the aorto-iliac region.

G- Below are listed some examples of patients with similar duplex and IA DSA reports in which the clinical decision making process varied amongst the surgeons and with the reference standard used to compare the suggested treatment.

Case 1:

A 70 year male patient, non-diabetic, with no history of either cardiovascular or cerebrovascular problems. His main complaint was intermittent claudication in the left calf of gradual onset, with a claudication distance of 100 yards. On both tests (Duplex and IA DSA) a significant, short SFA stenosis was reported. He was booked for balloon angioplasty, but due to waiting list restraints he was admitted 4 months later. On admission, he was pain-free and the procedure was cancelled. On the basis of the duplex and IA DSA reports three surgeons decided that balloon angioplasty was appropriate whilst the other two surgeons preferred a conservative policy.

Case 2:

A 60 year old asthmatic patient with no history of diabetes, cerebrovascular or cardiovascular problems. His main complaint was intermittent claudication in the left leg with a claudication distance of 25-50 yards. On both Duplex and IA DSA an 8 cm occlusion was identified in the left iliac system (common, external iliac artery). The patient underwent balloon angioplasty. On the basis of both IA DSA and duplex reports two surgeons agreed with this treatment, whilst three surgeons felt that lesion was too long and the patient might need surgery.

Case 3:

A 79 year female, non-diabetic patient, with a history of unstable angina, but no cerebrovascular problem. Her claudication distance was 50 yards. Both duplex and IA DSA demonstrated multi-segmental disease in both lower limbs, with two localised significant stenosis in the left and right SFA (2cm lesions). Two surgeons decided that balloon angioplasty would help while the other three surgeons preferred a conservative policy. The patient underwent balloon angioplasty.

9.2.1.7. Discussion:

The management of chronic ischaemic limb is a subject of great debate. Classification of chronic leg ischaemia into intermittent claudication and critical ischaemia is important for the purpose of the clinical decision-making process. In this study 74 patients had intermittent claudication, 8 had critical limb ischaemia. There appears to be a discrepancy between the accuracy of the decision based on the duplex report using the final treatment as a reference standard (84%) compared to the accuracy when the decision based on IA DSA as a reference was used (91%). This could be due to a number of factors:

The indications for interventional therapy vary among surgeons. In 13 cases, conflict in the surgeons' decision was between balloon angioplasty and conservative therapy, whilst in another 7 cases it was between surgical intervention and conservative policy. The ideal lesion for balloon angioplasty is a short iliac artery lesion rather than a long femoro-popliteal occlusion. However, the precise limits of technical feasibility and

success of balloon angioplasty in the hands of interventional radiologists in different anatomical situations and stenotic lesions are still a matter for debate.

In the presence of combined arterial pathology in the same limb (e.g. iliac artery disease associated with femoro-popliteal disease) some surgeons address the inflow problem with balloon angioplasty and leave more distal lesion untreated. Others prefer to use combined therapy (balloon angioplasty and by-pass surgery) on the same occasion.

Hence it is not surprising that surgeons disagreed to some extent when presented with the same data, especially in the isolation of a clinical study when the patients were not available for clinical examination. Clearly many features of each particular case influence the course of clinical management, not simply the results of vascular imaging investigations.

In recent study of 112 patients, Elsman et al demonstrated that duplex scanning of peripheral arterial disease of lower limbs was sufficient as the main line of preoperative assessment for 100 patients. He was reported that 36 patients underwent angioplasty without any diagnostic arteriography whilst in 62 patients the treatment strategy could be determined without diagnostic arteriography. Our data support this viewpoint, in which the accuracy of the clinical decision based on duplex compared to that based on IA DSA was 91%. This suggests that pre-operative arteriography provides no additional diagnostic benefit over duplex. A possible advantage of using duplex ultrasonography as the first line of assessment of peripheral arterial disease may be to reduce the number of diagnostic angiograms, allowing the radiologist to concentrate on interventional and endovascular procedures.

Conclusion:

In conclusion the author believes duplex to be an accurate, non invasive method for the routine assessment of all patients presenting with symptomatic peripheral arterial disease. This study has shown that management decisions can safely be made from the information provided by duplex scanning alone in patients with lower limb peripheral arterial disease.

9.2.2: Criteria for arteriography following duplex evaluation of peripheral arterial disease.

9.2.2.1. Introduction:

Recent advances in ultrasound imaging technology allow accurate assessment of arterial pathology in lower limb arteries. Most of the recent studies in this context reported that duplex ultrasound scanning has high sensitivity and specificity. Limited steps to use the duplex ultrasound scanning as the main investigation in peripheral arterial disease have been reported. However, using duplex findings as the sole basis for vascular intervention and reconstruction is still debatable.

The aim of this study was to establish the criteria for proceeding to arteriography following duplex evaluation of lower limb peripheral arterial disease.

9.2.2.2. Location of the study:

Vascular laboratory at the Middlesex Hospital, Mortimer street, London, UK. Ethical committee approval for this study was obtained from UCL Medical School Ethical Committee and patients gave their written consent for inclusion in the study.

9.2.2.3. Patients:

156 patients with peripheral arterial disease were referred to the vascular outpatients clinic at University College London Hospitals NHS Trust, London. They were divided into two groups.

Group A: 90 patients (59 Male, 31 Female and median age 68 years) in whom 177 lower limbs were examined with both duplex ultrasound scanning, and intra-arterial digital subtraction arteriography (IA DSA). 81 with intermittent claudication, 1 with ischaemic ulceration, and 8 with rest pain. In this group we used IA DSA as the

reference standard to determine the accuracy of duplex scanning in specifying the degree of the arterial stenosis. This group of patients is the same sample used in section 9.1.1.

Group B: 66 patients (43 Male, 23 Female and mean age was 67 years, 60 with intermittent claudication, 5 rest pain, and 1 with ischaemic ulceration) in whom I used duplex ultrasound scanning as the main investigation and the surgeon ordered IA DSA selectively. For cases referred to the radiology suite for IA DSA, duplex data was compared to that of IA DSA and the accuracy of duplex scanning was obtained.

9.2.2.4- Duplex Ultrasound Scanning:

The same methodology and criteria of duplex ultrasound scanning were used as described in section 9.1.1.

9.2.2.5. Intra-arterial Digital Subtraction arteriography (IA DSA):

The same methodology and criteria for analysing IA DSA were used as described in section 9.1.1.

9.2.2.6. Statistical analysis:

For the purposes of assessment in Group A, I used the following terms to assess the accuracy of duplex scanning compared to IA DSA:

1- Missed lesion: Term used to describe a significant lesion on IA DSA which was not identified by duplex US

2-Underestimated lesion: Term used to identify underestimation of the disease, for example, an occlusion on IA DSA diagnosed as significant stenosis, or significant stenosis diagnosed as insignificant stenosis.

3- Overestimated lesion: The reverse of the above.

The same statistical methods described in 9.1.1 were used for analysis of the resulting data.

9.2.2.7. Results:

1-In group A

In the aorto-iliac region:

630 arterial segments were examined by duplex ultrasonography and IA DSA, of which 570 arterial segments were disease free by both modalities. On duplex 27 significant stenoses, and 19 occlusions were detected compared to 23 and 22 on IA DSA respectively. (table 9.1.1.3, 9.1.1.4)

10 Lesions were misdiagnosed on the duplex ultrasonography in the aorto-iliac region, 8 insignificant stenoses (<50%) and one significant stenosis (>50%), while the remaining one was occluded. 4 lesions were underestimated by duplex and a further 4 lesions were overestimated by duplex scanning. (table 9.1 1.5, 9.2.2.1)

In the femoral artery area:

530 arterial segments were examined by both modalities. 485 were disease free. 2 lesions were not identified by duplex, but were clinically insignificant. There were two further lesions which were overestimated by duplex scanning. (see table 9.1.1.6, 9.2.2.1)

In the femoro-popliteal area :

648 arterial segments were disease free. On duplex 60 significant stenoses, and 159 occlusions were detected compared to 55 and 170 lesion on IA DSA respectively. 4 lesions were not identified by duplex ultrasonography (1 significant stenosis, and 3

occlusions) whilst 15 lesions (3 insignificant, 4 significant, and 8 were occlusions) were underestimated, and four lesions were overestimated. (table 9.1.1.7, 9.2.2.1)

In the Infragenicular area:

915 arterial segments were disease free on both modalities. On duplex scanning 45 significant lesion, and 79 occlusions were detected compared to 45 and 83 on IA DSA. 23 Lesions were not identified on duplex (8 significant stenosis, 15 occlusions). 17 Lesions were overestimated, although none were underestimated.(table 9.2.2.1) This table includes two significant lesions were not identified in the aortoiliac region. One was a high grade stenosis, and the other was an occlusion. In the femoral artery two insignificant lesions of less than 20% were missed on duplex scanning, while in the femoro-popliteal area. 12 significant lesions were not identified (4 stenosis and 8 occlusions). In the run-off vessels 23 significant stenoses and occlusions were missed, mainly in the peroneal artery. Details of these lesions are summarised in table 9.2.2.1, and table 9.2.2.2.

No of segment	Aorto-iliac	Femoral artery	Femoro-popliteal	Run-off vessels	Total
Disease-free	570	485	648	915	2618
Significant/X	23	13	55	45	136
Significant/D	27	14	60	45	146
Occlusion/X	22	27	170	83	302
Occlusion/D	19	28	159	79	285
Missed lesions	10(8 ins, 2 si)	2 ins (<20%)	4(1 si, 3 oc.)	23(8 si, 15 oc.)	39
underestimated	4(1 ins,3 si)	0	15(3 in,4si,8oc.)	0	19
overestimated	4	2	4	17	27
Total No Lesion	18	4	23	40	85

Table 9.2.2.1

The overall distribution of the arterial lesions in group A as described by duplex ultrasonography and compared with IADSA.

(Significant/X= on X-ray, significant/D=on duplex, Ins=insignificant, si=significant, oc.=occlusion)

Artery	No of lesions	PSVR	IADSA	Explanation suggested by the author
CI	1	3.5	grade 1	No reasonable explanation
CI	1	1	grade 4	Poor visualisation due to bowel gases or obesity
CI	1	1	grade 5	Poor visualisation due to bowel gases or obesity
CI	3	3-4	grade 5	No reasonable explanation
CI	1	no pulse	grade 4	Tight stenosis can be misdiagnosed as occlusion on duplex scanning
CI	1	2.5	grade 3	Uniplanar x-ray view can be misleading
PF	1	no pulse	grade 1	The angle of the origin of profunda femoris
PF	1	no pulse	grade 3	The angle of the origin of profunda femoris
SFA/POP	2	2.5	grade 2,3	Distal femoral and proximal popliteal arteries: short lesion can be missed
SFA/POP	1	1	grade 4	Distal femoral and proximal popliteal; short lesion can be missed
SFA/POP	3	1	grade 5	Distal femoral and proximal popliteal arteries: short lesion can be missed
SFA/POP	8	3	grade 5	No reasonable explanation
Run-off	6	no pulse	grade 1	Calcification of the arteries with low blood flow
Run-off	15	1	grade 5	Mainly peroneal vessels, but no reasonable explanation
Run-off	8	1	grade 4	Mainly peroneal vessels, but no reasonable explanation
Run-off	8	2	grade1	No reasonable explanation
Run-off	5	no pulse	grade 4	Tight stenosis can be misdiagnosed as occlusion on duplex scanning

Table-9.2.2.2-

Misdiagnosis of arterial lesions by duplex compared to IA DSA, with the author's suggested explanation.

CIA=common iliac, PF= profunda femoris SFA= superficial femoral, PA= popliteal artery.

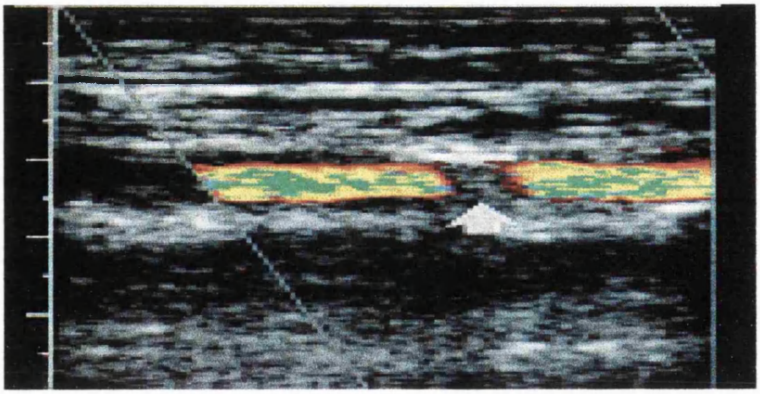


Fig 9.2.2.1

Calcification of the anterior vessel wall will prevent assessment of atheromatous plaque as well as interfering with Doppler ultrasound assessments of blood flow

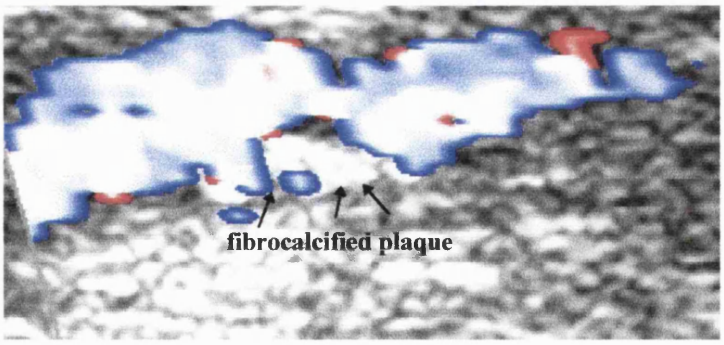


Fig.9. 2.2.2

A calcified posterior wall plaque will not alter the duplex image significantly.

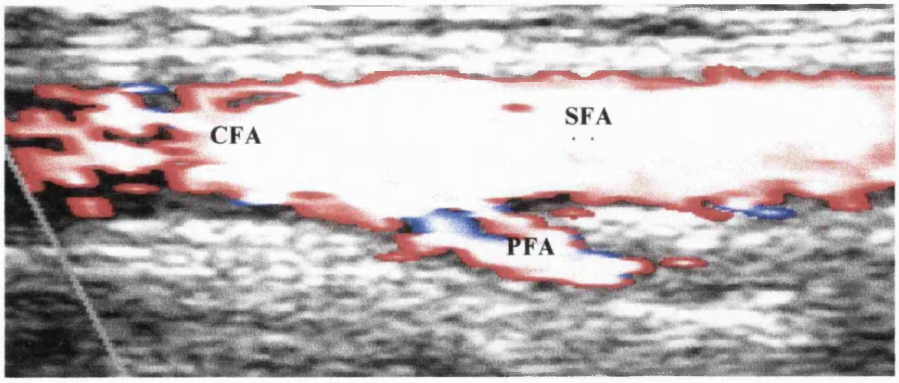


Fig.9.2.2.3

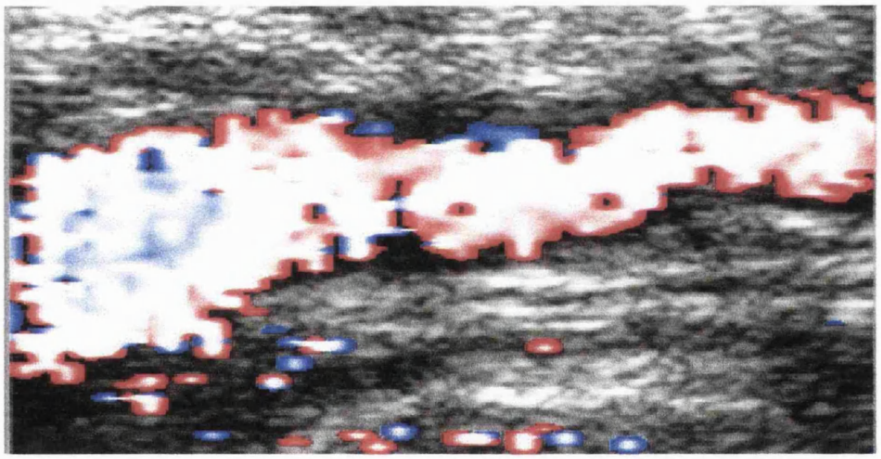


Fig. 9.2.2.4

Fig. 9.2.2.3, and 9.2.2.4 demonstrate anatomical variation of the angle of the profunda femoris artery (two examples of patients from group A).

2-Results of group B:

1- In 66 patients referred to the vascular outpatient with intermittent claudication (23 Female, 43 Male, mean age 67 years with range of 47-88 years) duplex scanning was used as the first line of assessment for lower limb pathology. (table 9.2.2.3)

2- Eight patients (12%) were referred in whom the main complaint was intermittent claudication and underwent duplex scanning. 7 patients (7/8; 88%) were found to have no vascular pathology in the lower limb arteries, and one patient (1/8;12%) had a clinically insignificant popliteal artery stenosis. The clinical management decision for this group was taken on the duplex data alone, and all patients were discharged from the outpatient clinic without further vascular investigation.

3- In twenty-five patients (25/66; 38%) a diagnosis of peripheral arterial disease was made and conservative treatment was recommended (table 9.2.2.4):

- Two patients (2/25; 8%) with grade 2, 3 insignificant disease (<50%).
- Three patients (3/25; 12%) refused any form of intervention (balloon angioplasty or by-pass surgery in one patient with mid-popliteal artery stenosis, another with superficial femoral artery stenosis, and a third with femoral artery stenosis).
- One patient (1/25; 4%) agreed to participate in a drug trial and has bilateral SFA and run-off vessel disease.
- Six-patients (6/25; 24%) with poor run-off vessels, in whom operative intervention was not indicated.
- Eleven patients (11/25; 44%) with variable grades of peripheral arterial disease. In ten patients intervention was not indicated unless deterioration of the lower limb circulation occurred. A further patient had internal iliac artery disease where

intervention would only be indicated if he developed impotence as a consequence of this.

- Two patients(2/25; 8%) who had previously been treated by lower limb by-pass procedures more than one year previously. Both were still complaining of intermittent claudication although the grafts were patent without stenosis on duplex scanning. Both patients were reassured and continued under clinic review.

4- Twenty- one patients (21/66; 32%) In this group 23 lesions underwent balloon angioplasty (6 iliac artery and 17 femoral and superficial femoral arteries).

5- In only three patients (5%) surgical intervention was decided upon on the basis of duplex scanning. One-patient (1/3; 33%) with an infected FP by-pass graft, one-patient with an abdominal aortic aneurysm in addition to the peripheral arterial disease, and in the last femoro-popliteal by-pass surgery was arranged following arteriography .

6-Eight-patients (9/66; 14%) underwent arteriography:-

The indications (table 9.2.2.5) were:

- Four patients (4/8; 50%) because they were booked for FP by-pass surgery and the surgeon required exact anatomical data.
- One-patient (1/8; 12.5%) had a FP by-pass graft stenosis. The surgeon planned re-exploration and wanted an angiogram for this purpose.
- One-patient (1/8; 12.5%) had an aorto-bi-iliac by-pass graft, and duplex was not able to assess the left limb of the graft, largely due to obesity of the patient.
- One-patient (1/8; 12.5%) with combined bilateral popliteal disease and run-off vessels disease where the surgeon planned distal reconstructive surgery.

- In one-patient (1/8; 12.5%), the popliteal artery could not be visualised by duplex scanning and the sonographer recommend IA DSA for further assessment after discussion with the surgeon,.
- Only one patient of this group (1/66; 2%) with SFA, FP disease and a venous ulcer, had arteriography because the clinician was not satisfied with the duplex scanning report. He also wished to exclude any proximal (inflow) disease. The arteriography findings were similar to the duplex findings and the patient was scheduled for conservative treatment and regular ulcer dressings.

Management decision	No of patients	%	No of patients had IA DSA
Discharge	8	12%	NO
Conservative	25	38%	NO
Balloon angioplasty	21	32%	NO
Surgery	3	5%	2
Arteriography	9	14%	9

Table -9.2.2.3-

This table shows the treatment in group B based on the duplex scanning. In this table 82% of the patients (54 patients 8 discharged, 25 conservative, 21 balloon angioplasty) did not need diagnostic arteriography while 33 patients (50%) did not have arteriography at all.

Indication for Conservative treatment	No of the patients	%
Insignificant disease	2	8
Patient refused intervention	3	12
Referred to clinical trial	1	4
With distal disease	6	24
Stable with a view of reassessment	11	44
Had intervention > year and reassurance	2	8

Table -9.2.2.4-

This table demonstrates the different reasons for conservative treatment in 25 patients. In 6 patients there was distal disease, 10 were stable claudicants and intervention was deferred until significant deterioration occurred, while one patient has bilateral internal iliac disease, and intervention was planned only if he developed symptoms of impotence.

Indications of IA DSA	No of patients	Duplex accuracy
Femoro-popliteal by-pass surgery	4	no difference between duplex and IA DSA
Re-intervention	1	no difference between duplex and IA DSA
Duplex failure	2	vessels inaccessible (1 iliac, 1 popliteal) by duplex scanning
Distal reconstruction	1	no difference between duplex and IA DSA
To confirm duplex findings	1	no difference between duplex and IA DSA

Table -9.2.2.5-

The indications for intra-arterial digital subtraction arteriography in group B.

9.2.2.8. Discussion:

Intermittent claudication is a common disabling disorder. Although a high degree of accuracy of duplex ultrasound scanning has been reported in previous studies arteriography is still the commonest diagnostic investigation of choice in patients with lower limb arterial pathology.

The aim of this study was to determine indications for arteriography following duplex scanning.

In part A of this study 39 lesions were missed, 10 of them were insignificant stenosis. The suggested explanation by the author was listed in table 9.2.2.2.

Conditions found to alter the duplex accuracy in this study:

1-Obesity and bowel gas can reduce visualisation of the iliac arteries. Once the iliac system was visualised the accuracy of the duplex is high (the iliac vessels in two scanning in my study were difficult to visualise).

In circumstances where duplex fails to visualise the iliac arteries, the sonographer is unable to assess the degree of the stenosis, and arteriography should be recommended. In an example of part A of this study two lesions (one significant stenosis greater than 50% diameter reduction, and an occlusion) in the common iliac artery were missed.

2-Occasionally duplex ultrasound scanning is unable to differentiate between a very tight stenosis (99% diameter reduction) and a total occlusion. In this study, one such lesion in the common iliac artery and another five in the infrageniculate vessels were found.(Table 9.1.1.6) The reason for this is that in a very tight stenoses the velocity of flow falls to a low level and may be overlooked unless the Doppler detecting system is adjusted correctly by the investigator.

It is also well documented that duplex scanning ultrasound has a limitation in differentiation between a tight carotid artery stenosis and occlusion[195]. This obviously has a profound influence on the management of the patient.

3-Anatomical variability of the origin angle of profunda femoris[196] can be a source of confusion for the investigator. (Fig.9.2.2.3, 9.2.2.4) This also a well known problem in uniplanar arteriography. In this study, two such lesions were misdiagnosed by duplex. (table 9.2.2.2) Careful assessment of this region is essential as the profunda femoris artery may play a key role in vascular intervention.

4-Occasionally short lesions in the distal segment of the femoral artery and proximal popliteal artery can be missed by transferring the position of the ultrasound probe from the medial side of the thigh to the posterior aspect of the knee, on moving distally. In this study, 4 such lesions were missed and two were misdiagnosed. Changing the scanning technique in this study to assess the distal segment of the femoral artery and the proximal popliteal segment from the posterior aspect of the limb improved the outcome.

5-Calcification of the lesion can alter the duplex image especially when it involves the anterior segment of the arterial wall. (Fig. 9.2.2.1) Calcification of the posterior wall does not cause such difficulties for the duplex image. (Fig. 9.2.2.2)

6- A combination of calcification and low blood flow especially in the small diameter vessels such as the peroneal artery is the main reason for low duplex accuracy in assessing the degree of the disease in run-off vessels. In this study, the disease in 17 arterial segments in the calf was overestimated.

In this study, the run-off vessels were examined with the patient in supine, and sitting positions to obtain the optimal view of these vessels.

In part B of this study, duplex ultrasound scanning was used as the main investigation. This part of the study shows that the vascular surgeon was able to discharge patients from the vascular outpatient clinic, and follow-up patients treated conservatively on the basis of duplex scanning alone in 50% of the cases. Although diagnostic arteriography can be combined with PTA, yet it can be done on a separate session. In this study it was possible to plan balloon angioplasty based on duplex findings in 32% of cases. Diagnostic arteriography is still required prior to vascular reconstruction.

In this study 14% (9 patients) of the patients had diagnostic arteriography. Only 2 patients had arteriography because duplex failed to visualise the vessels (one iliac, and one popliteal). In 5 of these 9 patients arteriography was performed because patients underwent vascular reconstruction. In 6 patients out of these nine, arteriography did not add further information than that available from the duplex report. In one patient of this group, the arteriography findings did not affected the management plan.

This study has shown that lower limb duplex scanning is accurate, and clinical decisions can safely based on duplex data in most of cases. A number of factors can alter the accuracy of the duplex scanning. In such cases, arteriography can be justified to provide complete information .

In conclusion based on the data from this study, I believe that the criteria for proceeding to arteriography following duplex scanning are as follows:

1- Failure of duplex scanning to visualise or accurately assess any arterial segment of surgical interest e.g. iliac arteries in an obese patient.

2-Failure of the sonographer to accurately determine the condition of the profunda femoris artery, if it is considered important in clinical management.

3-In patients requiring femoro-popliteal bypass surgery, failure of accurate visualisation of the popliteal segment to permit a decision to be made as whether an above knee or below knee graft should be used.

4-In the case of femoro-distal by-pass grafting, arteriography may be required, especially if the peroneal artery is the only run-off vessel remaining.

B) Computer-assisted technique for duplex US grey scale image analysis.

10.1.1- QV 200 : A Computer-assisted technique for ultrasound image analysis.

10.1.1.1- Introduction :

The importance of the plaque morphology in the pathophysiology of cerebral ischaemic events is now well accepted and plaque structure has been implicated as an important factor in development of embolic events[197] .

The aim of this study was to record ultrasound images electronically to avoid loss of resolution of the transferred image. A computer system with ability to record the image in digital form, direct from the duplex scanner and store it for analysis was used.

10.1.1.2- Location of the study:

This study was performed at the Vascular laboratory at the Middlesex Hospital, Mortimer street, London, UK. Both UCLH Ethics Committee approval was obtained and patients included in this study gave informed consent.

10.1.1.3- QV 200 computer system:

a-Specifications of the system

The system is an Apple Macintosh computer with a 200 MB hard disk, 20 MB RAM (Random Access Memory), and removable 128 MB magneto-optical disk{ Acuson Corporation, 1220 Charleston Road, P.O.Box 7393, Mountain View, California 94039-7393}.

This system contains a real-time frame grabber to allow acquisition of images from a video source, which in this case was the video output from the ultrasound scanning machine. The Adobe Photoshop 3.0.4 program was installed (Adobe system Incorporation, Mountain View, CA 94039) for the purposes of the image analysis, and

provides a number standard image processing functions used in this study. The system unit case (44x44x14 cm) is connected to a 14 inch Apple Macintosh colour monitor. Fig 10.1.1.1.

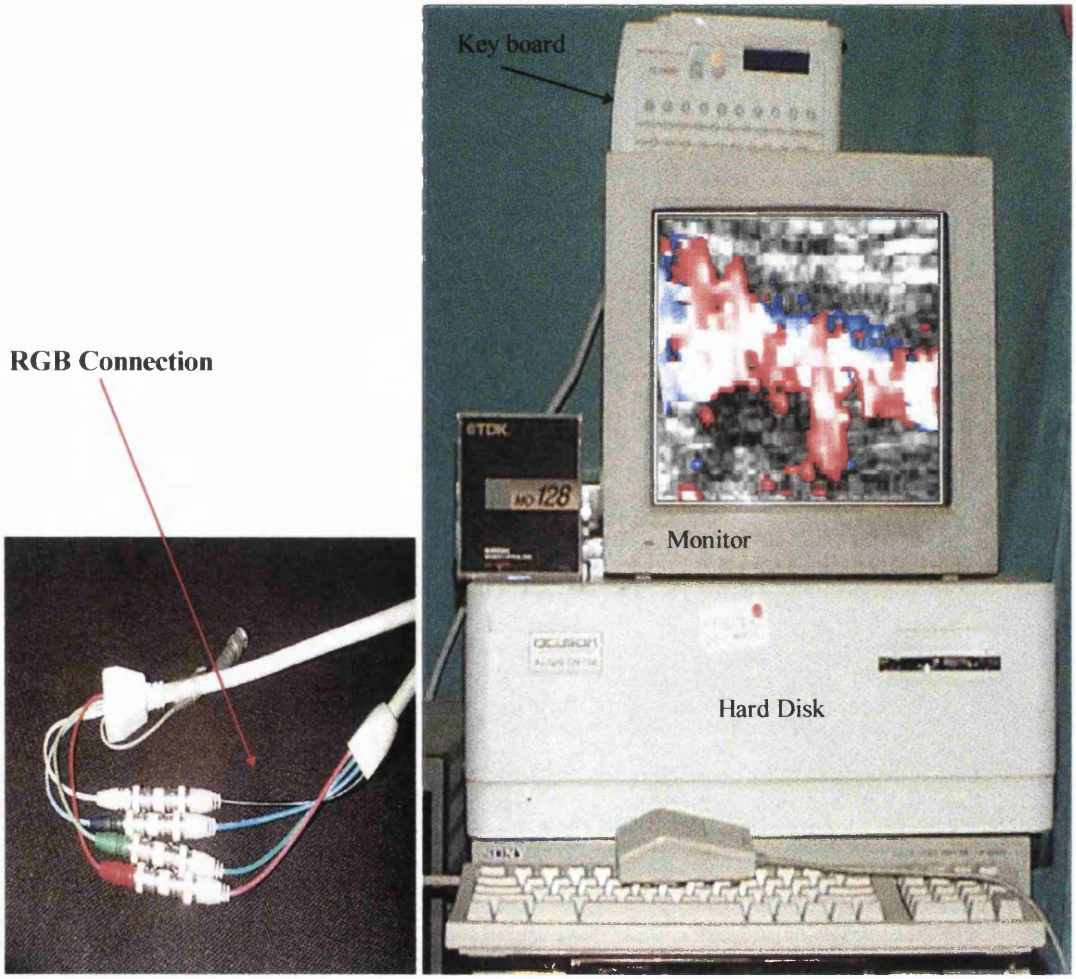


Fig. 10.1.1.1

QV 200 a computer image analysis system connected to Acuson duplex machine through RGB cables

The system is also supplied with two types of key-board:

1-Controls the purposes of recording.

2-Standard key-board for the manipulation of the image.

b-Connection to the duplex scanner:

The QV200 was connected to the Acuson ultrasound machine by RGB cables (R = Red, G = Green, B = Blue). This type of connection allows the QV200 to record the image in a digital form and Adobe Photoshop allowing image analysis. This type of interface allows the best quality of image transfer since the video image is acquired before any degradation associated with assembly into a composite video signal.

10.1.1.4- Methodology:

1-QV200 was connected to the Acuson machine as described above.

2-30 Patients with peripheral arterial disease referred to Middlesex vascular laboratory for arterial scanning (27 patients with intermittent claudication, 2 with ischaemic ulceration of the leg and one patient with rest pain) were included in this study. Their lower limbs arteries were scanned with a 7 MHz linear array probe as described in section 9.1.1.1.

3- All vascular lesions in this group of patients were assessed by colour flow to outline the arterial stenoses, and spectral analysis was used to assess the reduction in the arterial diameter.(9.1.1.1.) The grey-scale image of each lesion was recorded digitally and stored on 128 MB Magneto-optical disk. For the purposes of standardisation, all Acuson duplex machine parameters were pre-sett the machine start-up settings (power output at 0, Log Compression at 40 dB, gain at -5dB, pre-processing at 0, persistence

of image at 2, and post-processing at 0). All images were recorded using the same scanning set-up.

4- For the purposes of image analysis, the standard keyboard was used to control the Adobe Photoshop program, and the grey scale image displayed on the QV200 monitor.

5- Each plaque was outlined using the selecting tool of the Adobe Photoshop program. In the case of stenosis the plaque was divided into an anterior compartment, and a posterior compartment and each has been read separately and then the over-all mean grey scale value was obtained. (fig 10.1.1.2)

6- The overall grey scale content was displayed as a histogram supported by the statistical data in the manner described above. (see figure 10.1.1.2, 10.1.1.6, 10.1.1.4) This data include the mean grey scale value, median, standard deviation, and total pixel count.(see fig. 10.1.1.3, 5, and 7)

7- To assess the validity of this technique, two observers (the author, and another research registrar) were included to analyse these images of the ultrasound arterial lesions. All these lesions were classified into iliac and femoro-popliteal lesions and each group was analysed separately. Each of the observers was unaware with the results of the other.

10.1.1.5- Statistical analysis:

The kappa statistic was computed to measure the level of the agreement between the observers. For agreement by chance alone the k value is 0, for the perfect agreement, k value is 1.(9.1.1)

10.1.1.6- Results:

In this group of patients (30 patients) 65 atherosclerotic plaques {52 stenosis (104 anterior and posterior compartment), and 13 occlusions}were found, recorded and analysed by two observers. 11 plaques were in the iliac arteries and 54 atherosclerotic plaque femoro-popliteal arterial lesions.

I used the mean grey scale value of the plaque derived from the image analysis as the main indicator of overall echogenicity of the plaque in these 65 atherosclerotic plaques.

The mean pixel value (MPV, image brightness) of 15 plaques was above 150, in 13 plaques it was below 50, and in the remaining plaques was between 50-150.

The validity of this technique was obtained. The method showed high reproducibility with k of agreement of 0.92 (95% confidence interval 0.062).

The average time taken to analyse the ultrasound image was 4 minutes (range 2-6 minutes).

Figure 10.1.1.2 and 3 demonstrate a plaque in the common iliac artery with an MPV of 90, and figure 10.1.1.4, and 5 demonstrate a fibro-calcified plaque in distal superficial femoral artery with an MPV of above 150, while an echolucent femoral occlusion demonstrated in fig. 10.1.1.6, and 7.

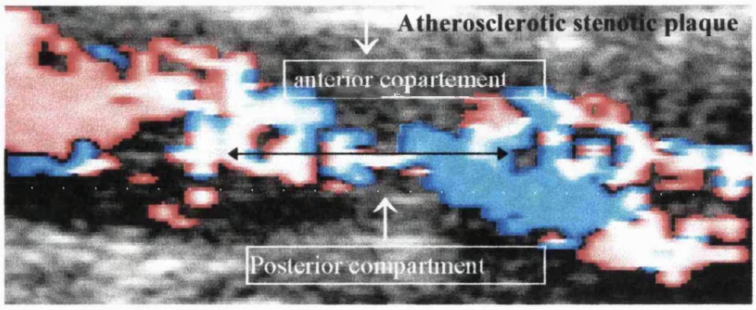


Fig. 10.1.1. 2

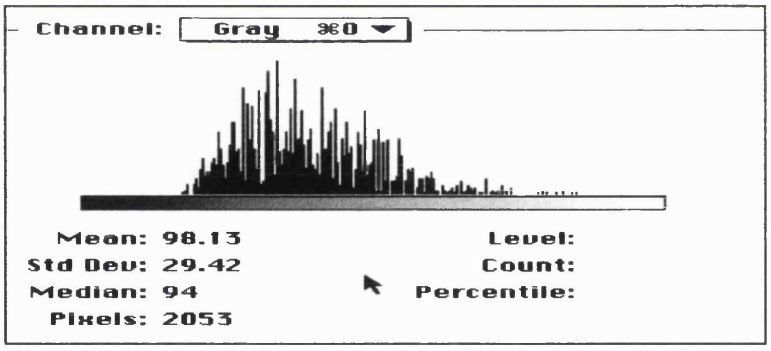


Fig. 10.1.1.3

In these two figures an atherosclerotic plaque in the common iliac artery with MPV of 90.

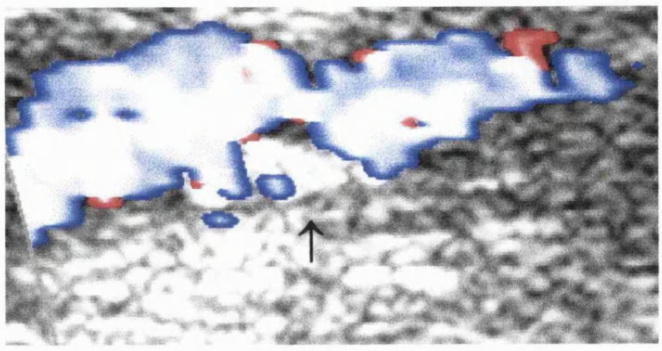


Fig. 10.1.1.4

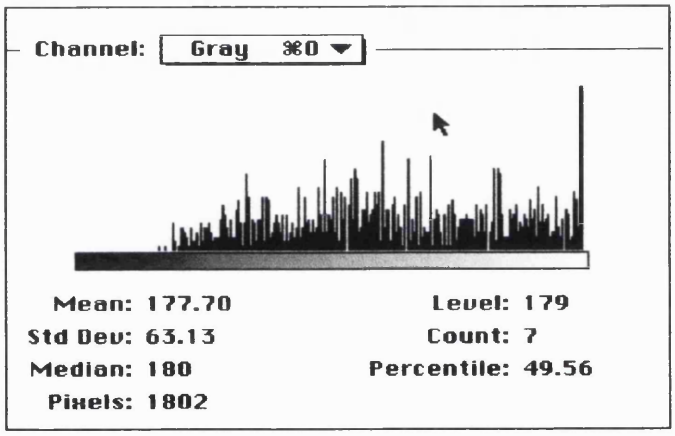


Fig. 10.1.1.5

These two figures demonstrate the image and the histogram of an atherosclerotic plaque of fibrocalcified type in the femoro-popliteal region with MPV of 177.

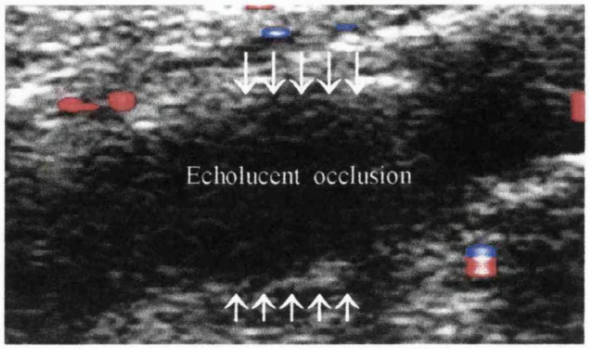


Fig. 10.1.1.6

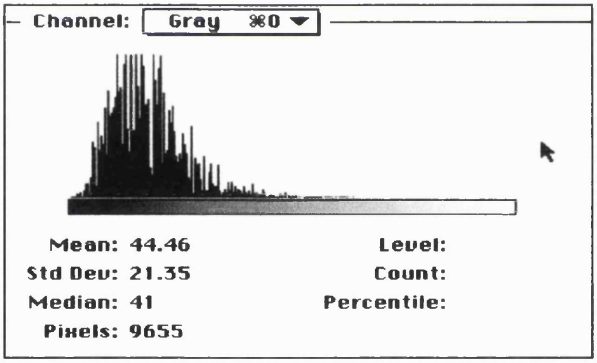


Fig. 10.1.1.7

These two figures demonstrate the image and the histogram of an echolucent occlusion in the common femoral artery with mean of MPV 44.4.

10.1.1.7. Discussion & Conclusion :

A number of clinical studies have shown that plaque characterisation may assist in predicting the outcome of arterial stenoses. This has been described most frequently in the carotid artery[149] but the currently used methods are subjective and depend greatly on the observer.

In this study, I used computer-assisted grey scale ultrasound image analysis to assess plaque echogenicity in the aorto-iliac and femoro-popliteal area. This may eventually be used to predict the outcome of balloon angioplasty or other interventions to treat arterial stenoses in these vessels. The image was recorded in a digital format; allowing analysis without further loss of image quality. This study has shown that the QV200 can record the ultrasound image in digital form, allowing computer assisted image analysis. Good agreement was obtained between independent observers in this preliminary study.

10.2.2 Which duplex ultrasound image should be analysed using computer-assisted technique?

10.2.2.1. Introduction:

Computer-assisted ultrasound image analysis has been used successfully in the assessment of atherosclerotic plaques and in the section above was found to achieve reproducible results. The accuracy of the technique and reproducibility have also been studied (see the previous section) and also the results were supported by previous studies[156]. However, in order to standardise the results and ensure that all data is as consistent as in the pilot study described above. Many factors in the duplex ultrasound machine can affect the ultrasound image, in addition to the patient variables. These particularly concern the settings of a number of controls provided to enhance the image. These factors are:

- the overall gain,
- pre-processing,
- persistence of the image,
- post-processing of the image,
- logarithm of the compression (Log compression),
- transmit power,
- image depth,
- transmit zone,
- depth gain compensation.

The aim of this study was to assess the effects of these settings on the reliability of computerised image analysis based on stored images and to identify the machine

settings which gave greatest differentiation between tissues of different grey scale intensity.

1-Gain: Adjusting the overall receiver gain changes the intensity of the image by increasing or decreasing the amplification of the received echoes. The range can be adjusted using this function between +20 to -20 dB (+20 represents the highest gain, and –20 lowest gain).

2-The Pre-processing function provided by the Acuson 128 XP/10 provides for edge enhancement in the ultrasound image. The function has a range between 0, and 2. A setting of 0 represents no edge enhancement and 2 represents an image with a crisp edge.

3-The Persistence setting allows reduction of the image noise, perceived as 'speckliness' of the ultrasound image. Consecutive images are averaged to achieve the currently displayed image, improving the image 'quality' at the expense of reduced response to moving features within the image. The Acuson 128 XP/10 duplex scanner has 6 settings for this function in the range 0-5. 0 represents no frame averaging and 5 represents greatest frame averaging.

4-Post-processing function: The Acuson system displays a 2-D image by mapping echo amplitudes to shades of grey, different colours, or different hue of a colour. The relation between the echo amplitude and the displayed grey or colour map is defined as the post-processing function. A series of 10 re-defined functions may be selected to provide various features to improve the appearance of the image. The range of this function is 0-9, with 0 representing a linear relationship between the echo amplitude and pixel intensity, 1-4 represent low contrast, and 5-9 represent high contrast transfer functions.

5-Transmit power refers to the power emitted by the ultrasound and has a range between 0dB and -9dB, with 0dB represents the maximum output, and -9dB represents the minimum output.

6-Log compression: The ultrasound machine maps the intensity of returning ultrasound signal intensity to different shades of black and white in the displayed image. The number of shades of grey which may be discerned is 256, whereas there is a much larger range of intensities of returning ultrasound signal. The ultrasound machine uses a logarithmic transformation to map ultrasound signal levels to grey scale levels in the image. The range of signal levels represented the image may be adjusted from a 30dB (20:1) range to a 70 dB range (2000:1) range. A setting of 55 - 60 dB is usually used for general purpose vascular imaging.

7-Depth Gain compensation (DGC) allows enhancement of specific areas of interest by increasing or decreasing the amplification of echoes at different depths. It compensates for the losses in signal strength as the ultrasound passes through anatomical structures. The field of the examination is normally divided into 8 DGC zones, with individual controls for each

8-Image depth: Changing the image depth increases or decreases the field of view, and usually set to the in the range 40 - 60 mm for 7MHz peripheral vascular imaging transducers.

9-Transmit Zone: This sets the focus region for the ultrasound transducer. This can be set for on depth or a range of depths.

The aim of this study was to assess the effect of changing these parameters on computer-assisted ultrasound image analysis. In addition the aim was to establish the settings which best enabled the image analysis computer to differentiate between

such as blood, fat, muscle, fibrous, and calcified tissues in the resulting grey scale image.

Fig. 10.2.2.1. Acuson duplex US machine

10.2.2.2. Location of the study:

Vascular laboratory at the Middlesex Hospital, Mortimer street, London, UK. Ethical committee approval for this study was obtained from UCL Medical School Ethical Committee and controls gave their written consent for inclusion in the study.

10.2.2.3. Controls:

Nine controls were investigated for this study. These were 7 men and 2 women, mean age 33 years, with no history of connective tissue disease, and receiving no treatment for any condition. Seven were doctors from the vascular team, and two were vascular technologists.

10.2.2.4. Methodology:

1-Nine healthy subjects were scanned with Acuson 128 XP/10 duplex scanner using a 7MHz linear array transducer. All subjects lay supine while the duplex scanning was carried out.

2- The following areas were examined:

- Carotid artery (for assessment of blood).
- Subcutaneous fat (axillary and abdominal).
- Muscle (quadriceps, and abdominal)
- Iliotibial fibrous tract for assessment of fibrous tissue.
- Tibia and skull for assessment of calcified structures.

These structures were scanned while adjusting the ultrasound machine parameters and acquiring images for analysis.

The machine settings were adjusted in the following ranges: One parameter was changed at a time.

- Transmit power of Acuson machine was kept at 0 dB to produce the maximum power output.
- Log compression 40, 50 dB. (middle range of intensity)
- Pre-processing was kept at zero to obtain a smooth edged image.
- Persistence of the image: 2 or 3 to obtain moderate frame averaging..
- Post processing of the image: 0, 2 or 6 to assess the effect of the contrast and image brightness on the grey scale mean value.
- Gain of the received echoes at -5, 0, +5dB.
- At single transmit zone and multiple transmit zones.

Each of the anatomical regions was scanned and the image was recorded at 72 different settings of the ultrasound machine, obtained by adjusting one of the above parameters at once.

6- All images were recorded electronically by using the QV200 computer and saved on magneto optic disks (128 Mb). Using the Adobe Photoshop computer program to examine the stored image, the area of interest was selected using the program's selecting tool. The mean pixel value of the selected anatomical region are was calculated using the analysis tool.

10.2.2.5. Statistics: The aim of this preliminary study was to determine the ideal duplex ultrasound machine settings to discriminate between the tissues under investigation. A statistical model was designed with the assistance of Professor Senn, Department of the Statistics at University College London.

In the model:

1-The mean pixel value of blood, fat, muscle, fibrous, and calcified tissues in the recorded images was obtained by using the QV200 computer system for image analysis. (See further details in section 10.1.1). For each tissue, 72 grey scale images had been recorded and from which 72 mean pixel values for that tissue were obtained.

2-From these data, 72 tables containing the mean pixel value of the selected tissue in these images were prepared. Each table contains readings of the mean pixel value (MPV) of the five materials in 9 controls. (See example Table 10.2.2.3)

3-For each of these 72 tables the means of the MPV for each of the controls have been calculated, as well as the variance for each set of data. {Stat View Statistics computer programme (version 4.5 for Apple Macintosh, Abacus Concepts, Inc.Berkeley, 1996) }

4-In the second step the variances of these means were calculated (A), and the means of the variances were also obtained (B).

The Heuristic Index of Discrimination (HID) was calculated by using the following equation:

$$\mathbf{HID} = \frac{\mathbf{A}}{\mathbf{B}}$$

This was done for each of the duplex ultrasound machine settings to determine the most suitable scanning parameters to discriminate between soft and fibro-calcified structures.

10.2.2.6. Results:

1-A total of 3240 grey scale duplex ultrasound images were recorded using the QV200, in the following anatomical regions: of the carotid artery, axilla, quadriceps, ilio-tibial sheath, and skull.

2-The data calculated as described above have been plotted in figure 10.2.2.2. For each of the ultrasound machine settings on the horizontal axis the HID function (reliability of discrimination) has been plotted on the vertical axis. A fairly small range of settings resulted in favourable levels of discrimination, and these have been annotated on the graph.

I found that setting the log. compression to 40 dB, pre-processing at 0, persistence at 2 and post-processing at 0, with gain of -5dB offered an HID if 82%. Changing the persistence setting to a value of 3 made no difference to the HID. (Fig10.2.2.2).

3-Increasing the machine gain to 0 dB from -5 dB but leaving other parameters unchanged resulted in an HID of 64% whether the persistence setting was 2 or 3. The remaining settings resulted in an HID with a range between 6% and 42%.

4-Computer-assisted image analysis for the duplex image recorded at Log 40dB, 0/2/0, with gain of -5dB has shown that the mean pixel value of the soft tissues (blood, fat, muscle) was < 50 (Blood MPV range 1-4, Fat 2-16, Muscle 1-43), while that of the fibro-calcified tissues was > 150 (MPV: 135 - 200 MPV).

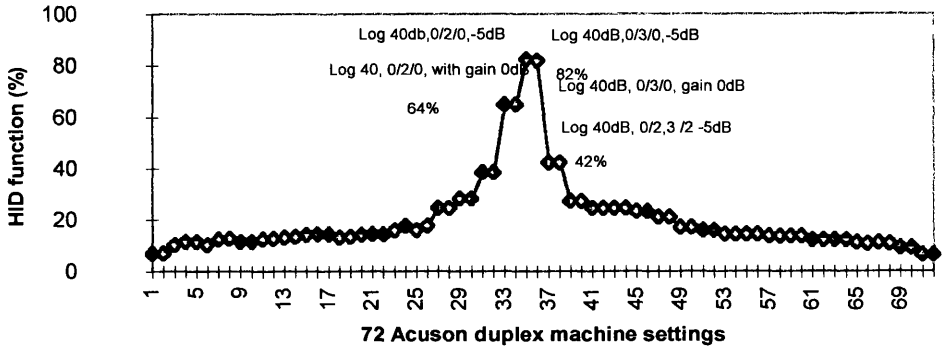


Fig. 10.2.2.2.

This figure demonstrates the HID accuracy % of each duplex machine setting and its ability in discriminating between blood, fat, muscle, fibrous, and calcified tissue. Duplex machine setting at Log 40 dB, 0/2/0, and 0/3/0, with gain of -5dB showed HID with accuracy of 82%

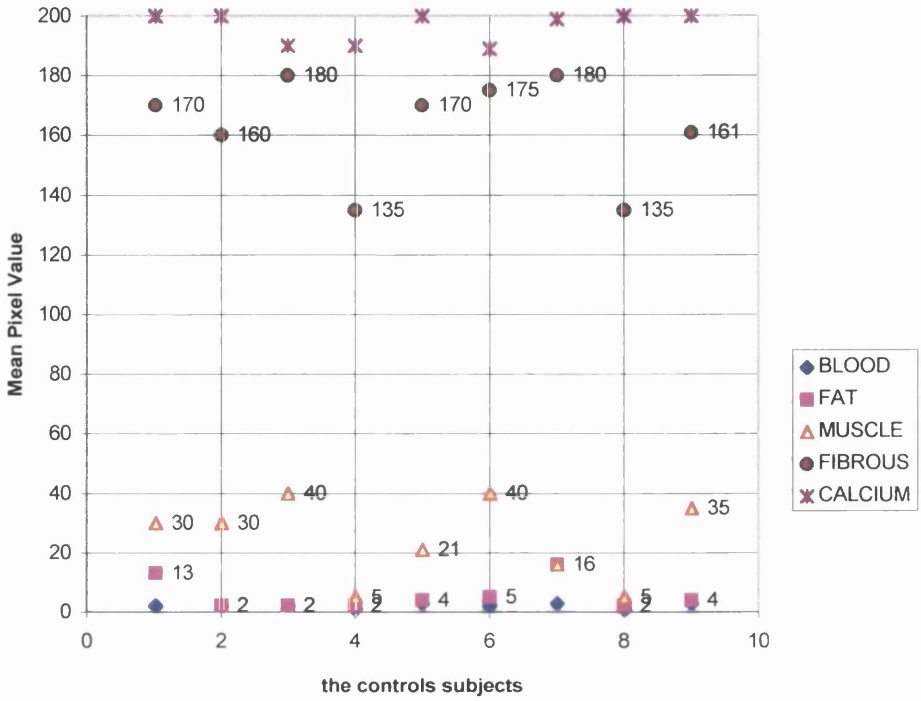


Fig. 10.2.2.3

This figure demonstrates the ability of the mean grey scale analysis of duplex machine setting at Log 40, 0/2/0 and with gain of -5 dB in discriminating between the soft components (blood, fat, and muscle) 0-50 mean pixel value, and fibro-calcified structures > 150 mean pixel value with HID of 82%.

CONTROL	BLOOD	FAT	MUSCLE	FIBROUS	CALCIUM
1	2	13	30	170	200
2	2	2	30	160	200
3	2	2	40	180	190
4	1	2	5	135	190
5	3	4	21	170	200
6	2	5	40	175	189
7	3	16	16	180	199
8	1	2	5	135	200
9	3	4	35	161	200

Table 10.1.2.1. (These numbers are the mean grey scale in mean pixel value)

(with mean of Blood=2, fat= 6, muscle =25, fibrous=163, and calcium =196 MPV)

Demonstrates the mean pixel value reading for the various tissues in the control subjects (7M, 2 F).

The MPV of soft components < 50, while that of the fibrocalcified tissues above 150.

10.2.2.7. Discussion and Conclusion:

Many factors can have influence on the mean grey scale of the duplex 2D image. This study has shown that the mean of the grey scale value of duplex image recorded at Log 40dB, 0/2/0 with -5 dB gain was able discriminate between soft tissues such as fat, blood, and fibrocalcified tissue with high reliability.

10.1.3: Value of computer-assisted grey scale image analysis in assessment the nature of atherosclerotic plaque.(Histology study)

10.1.3.1. Introduction:

The Grey-Weal classification of atheromatous plaques has been used successfully to predict the clinical course in patients with carotid artery disease. However, it relies on subjective interpretation of the ultrasound image and this may vary between observers[152,153] Computer image analysis might be used to reduce the variability between observers and recently El-Barghouty has reported the value of the computer-assisted grey scale image analysis in characterising the atherosclerotic plaque. He showed by using the median value of the grey scale that the symptomatic carotid artery disease associated with more lipid, and haemorrhage, also less fibrous tissue than in the asymptomatic carotid artery disease[156].

The aim of this study was to compare the results of ultrasound imaging in interpreting and classifying atheromatous plaque against the findings established by histological examination of the same plaque. In the previous section I identified the settings for the duplex ultrasound machine which I best resolved tissues of different types. These settings (log compression 40dB, pre-processing: 0, persistence: 2, post-processing: 0 with a gain of -5 dB) were used in this study as the best for differentiating tissues of different ultrasound echogenicity.

10.1.3.2. Location of the study:

The histological part of this study was carried out in the department of Histopathology UCL.

The duplex imaging parts in this study was performed by the author in the Vascular laboratory at the Middlesex Hospital, Mortimer Street, London.

10.1.3.3. Instrumentation:

1- Acuson duplex scanner, with a 7 MHz linear array probe was used.

2-QV200 image processing computer for image recording, and analysis.

3-Specimen tank for ultrasound imaging of excised atheromatous plaques.

4-Histology image analysis system.

1- QV 200 Tank (Fig.10.1.3.1): This tank is made of acrylic sheet and has 5 walls, measuring 20x16x12 cm, designed by the author and manufactured by the department of Medical Physics, UCL,- London. The floor of this tank was cover with two layers, a dark red leather and on top of this a sponge sheet was used to allow better visualisation, and scanning. Two stainless steel needles were fixed at the middle of the side wall of the tank, on which the carotid plaque could be mounted. A ruler was fixed transversely at the middle of the tank to control the movement of the US probe. Before scanning the tank was filled with tap-water and to avoid the air bubbles, the tank was filled slowly while the water run on the side-wall. The 7 MHz linear array transducer could be used in this tank by immersing the imaging face of the transducer in the water and clamping it in position.

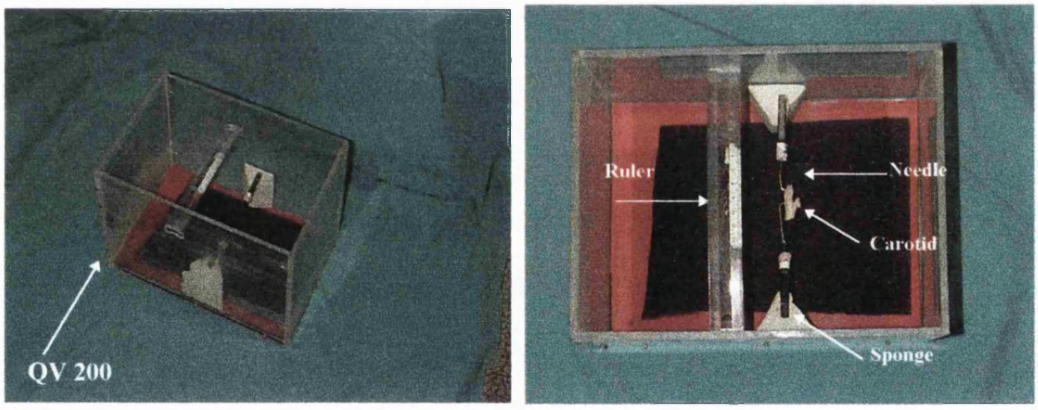


Fig. 10.1.3. 1 QV200 Tank as designed by the author to examine the carotid artery specimens by duplex US

2-Histology image analysis (Fig 10.1.3.2) :

This is a PC computer, with 1.3 Megabyte hard disk, and 32 MB Ram, supported with a Lucia image analysis computer programme [Version 3.52a copy right 1991-97. Laboratory imaging for Nikon UK]. This computer system was connected to a CCD camera (Microscope-Nikon Labophot-2 Camera- JVC TK-1281) installed on a microscope (Olympus), with times 1, 2, 4, 10, 40 objective lenses. The image was displayed on the computer monitor and by using the Lucia computer programme, measurement of linear dimensions, area, image intensity could be then made

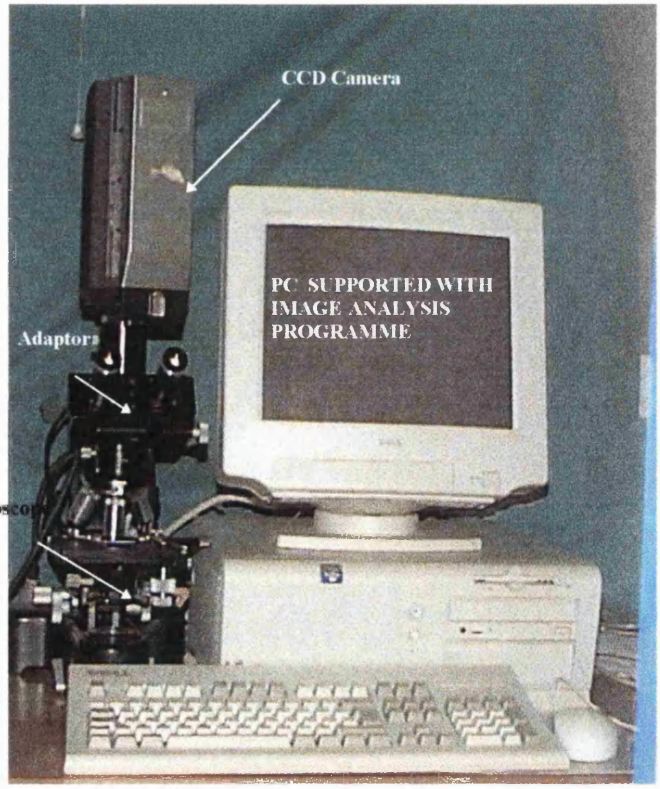


Fig.10.1.3. 2.

Histology image analysis system which consists of a microscope, connected to a CCD camera. The camera is connected to a computer system (PC) and with an image analysis computer programme.

10.1.3.4. Methodology:

17 carotid atherosclerotic plaques of were obtained from patients (15 M, 2 F, mean age 65 years) undergoing carotid endarterectomy for internal carotid artery stenosis. (Transient ischaemic attacks (TIAs) were reported by 15 patents, while 2 with asymptomatic with 99% carotid artery stenosis). All patients were being treated by the Vascular Unit, UCLH, London. Ethics committee approval was obtained and all patients gave informed consent for subsequent use of the excised specimens.

These plaques were underwent the following examination:

1-Macroscopic examination: As soon after the carotid endartectomy as possible, each of the excised specimens was examined macroscopically. The length of the plaque was determined (measured with a ruler). The interior surface of each plaque was examined by the author and described either ulcerated or smooth and also any calcified area was reported according to its macroscopic appearance.

2-Duplex ultrasound examination: All these specimens were scanned within 4 hours post-operatively. The carotid plaques were fixed in the specimen tank and covered with water. All plaques were scanned in both longitudinal, and transverse section. The machine set-up was kept at Log. compression of 40 dB, pre-processing, persistence and post-processing at 0, 2, /0 respectively, while the gain at - 5dB, in accordance with the finding from the previous chapter. The examination started from the cranial end of the plaque towards its caudal end. The ultrasound probe was moved along the ruler at 0.5 cm intervals and transverse images of the plaques were acquired by the QV200 computer system and recorded on magneto optical disk.

The QV 200 computer system was used to examine the stored images in order to obtain the mean pixel value of the plaque. The Adobe Photoshop programme was used to perform the calculations which were done in a manner identical to that used in the previous chapter. Briefly, the area of interest was highlighted and the mean pixel value

recorded for each of the transverse scans. Each 0.5 cm of the atheromatous plaque was treated as a block of tissue, and for which the MGS of the ultrasound was correlated to its histological structure.

3-Microscopic examination: Following the duplex ultrasound examinations, each specimen was fixed in formalin-saline 10% for 24 hours. All specimens were anatomically oriented and embedded in paraffin, with the common carotid end at the base, and the internal carotid end at the top. Specimens were cut transversely at 0.5mm intervals along whole specimen length. Elastin Van Giesen stain was used to assess the overall histological structures of the slides. Slides were examined by the histology image analysis system to assess the percentage area of soft materials (fat and blood), and fibrocalcified plaque. The area of histological section occupied by each tissue type was calculated with the aid of the Lucia computer programme which was used in area measuring mode to assess these histological sections.

For the purpose of statistical assessment, a group of consecutive sections in each plaque (8-10 slides) were treated as a block of atherosclerotic plaque. For each of these blocks, the percentage of the area for the soft materials (fat and blood), and fibro-calcified tissue were calculated, using a function of the Lucia computer system.

The mean pixel value (MGS) for each block (68 blocks) which had been determined using ultrasound imaging with the aid of the QV 200 computer was compared to the quantitative histological composition obtained by examination using the Lucia computer system. Correlation between the results obtained by these techniques were calculated.

4-Statistics: Spearman and Wilcoxon correlation were used.

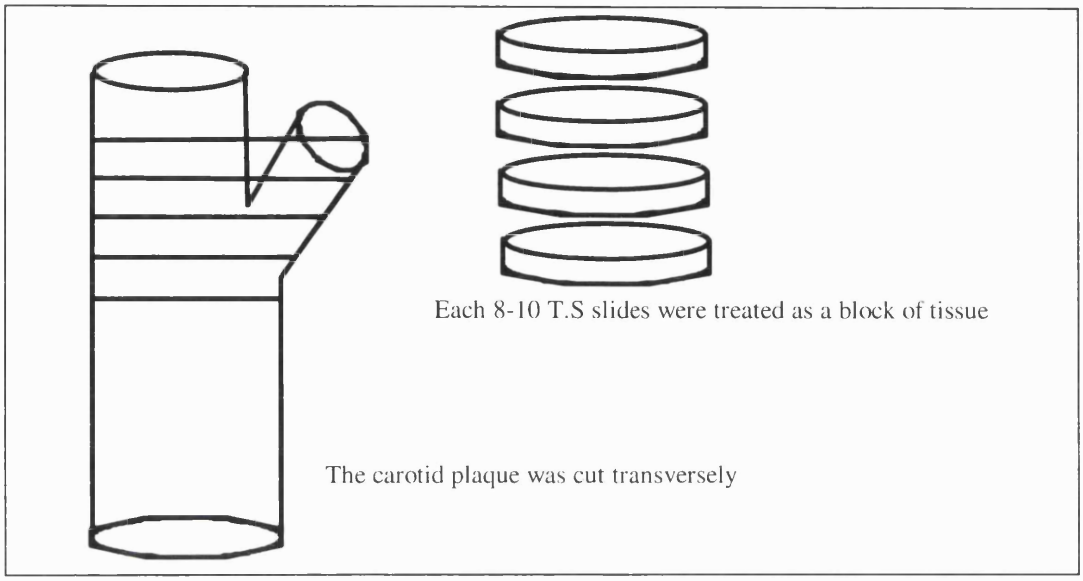


Figure 10.1.3.3.

The above diagram shows, the endarterectomy specimen which was prepared for duplex scanning in the QV200 tank. The duplex ultrasound transverse section was recorded and analysed by the QV200 computer system, and the mean pixel value (MPV) obtained. For microscopic examination, the plaque was oriented anatomically, and fixed in wax, cut transversely at 0.5 mm intervals, and stained (EVG). Each 0.5 cm scanned by duplex represented 8-10 histological slides which were treated as a single block. 68 blocks were examined by both modalities. The % of fat, blood, fibrocalcified material were obtained, and correlated to the mean grey scale of each block of tissue.

10.1.3.5. Results: 68 Atherosclerotic blocks (each equal one centimetre) of 17 carotid plaques of 17 patients were analysed by both techniques.

Spearman Rank Correlation for MPV of ultrasound image and soft materials

Sum of Squared Differences	7787.000
Rho	.851
Z-Value	6.969
P-Value	<.0001
Rho corrected for ties	.850
Tied Z-Value	6.961
Tied P-Value	<.0001
# Ties, MGS	13
# Ties, Hard stractures	12

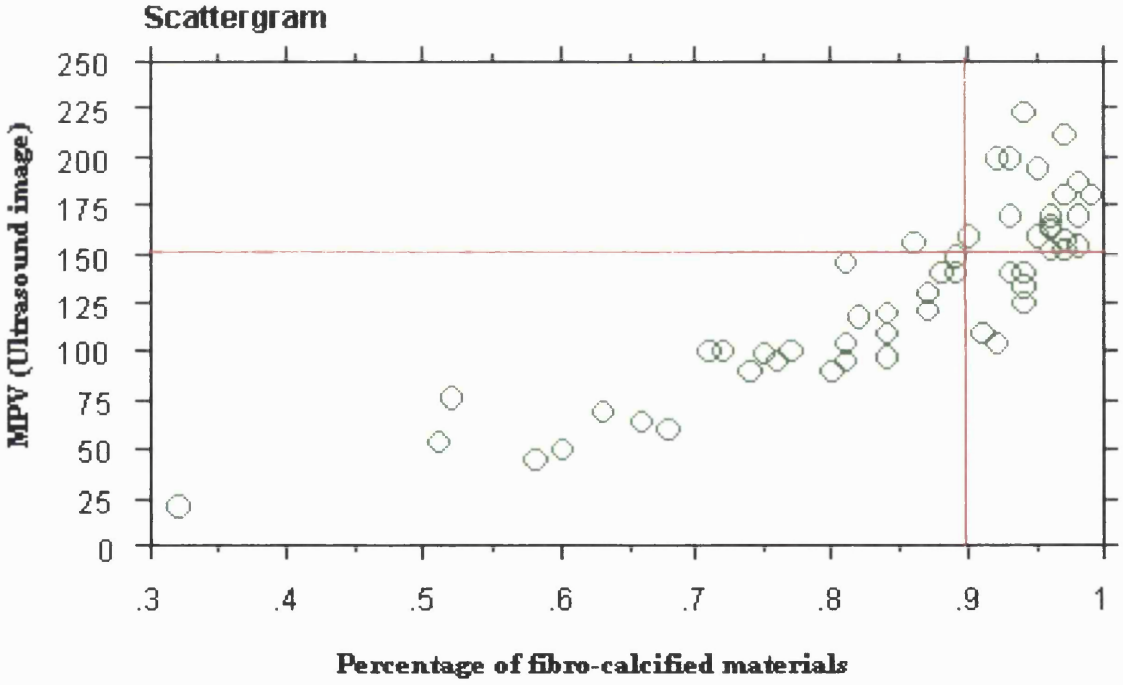


Table -10.1.3.1, Fig.10.1.3.4-The correlation between the mean pixel value (MPV), and the percentage of fibro-calcified material in the histological examination of atherosclerotic plaque analysis. Where the percentage of fibro-calcified material is 90% or greater, the mean pixel value in the ultrasound image is above 150MPV.

Spearman correlation for the soft contents of the atherosclerotic plaque:

Spearman correlation for MPV of ultrasound image and soft material contents

Sum of Squared Differences	96571.500
Rho	-.843
Z-Value	-6.902
P-Value	<.0001
Rho corrected for ties	-.855
Tied Z-Value	-6.998
Tied P-Value	<.0001
# Ties, MGS	13
# Ties, soft stracture	13

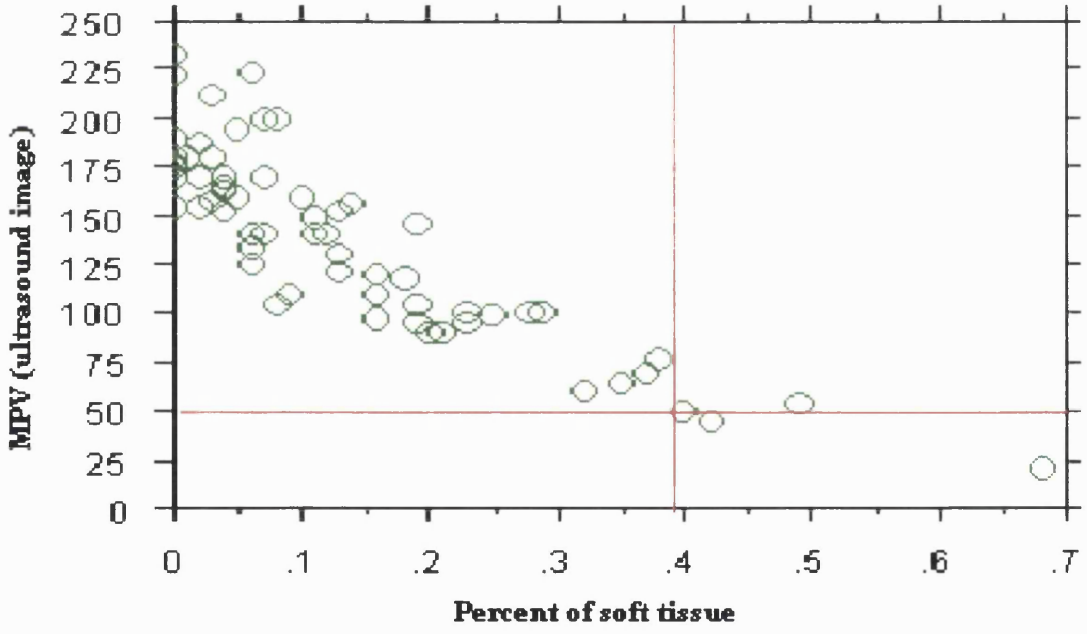


Table -10.1.3.2, Fig.10.2.3.5-Correlation between the histological findings (percentage of soft tissues - lipid and blood) with the MPV shown on ultrasound imaging. As the soft tissues (fat, haemorrhage) reach 40% of the total content, the mean pixel value drops to 50.

3-Wilcoxon Rank correlation of the fibrocalcified material of the atherosclerotic plaque, and mean pixel value.

Wilcoxon Signed Rank Test for MPV and fibrocalcified materials

# 0 Differences	0
# Ties	4
Z-Value	-7.167
P-Value	<.0001
Tied Z-Value	-7.168
Tied P-Value	<.0001

Wilcoxon Rank Info for MPV and fibrocalcified materials

	Count	Sum Ranks	Mean Rank
# Ranks < 0	0	0.000	.
# Ranks > 0	68	2346.000	34.500

Table -10.1.3.3-Demonstrates the statistical analysis using Wilcoxon Rank and the correlation between the MPV, and the histological findings and it reached the statistical significance.

4-Wilcoxon Rank correlation for the soft material in the atherosclerotic plaques and mean pixel value:

Wilcoxon Signed Rank Test for MPV of ultrasound image and its histology

# 0 Differences	0
# Ties	4
Z-Value	-7.167
P-Value	<.0001
Tied Z-Value	-7.168
Tied P-Value	<.0001

Wilcoxon Rank Info for MPV of ultrasound image and its histology

	Count	Sum Ranks	Mean Rank
# Ranks < 0	0	0.000	.
# Ranks > 0	68	2346.000	34.500

Table -10.1.3.4-

In this table by using Wilcoxon Rank the correlation between the both MPV and histological findings has shown statistical significance.

Also to validate the computer-assisted histology image analysis both intra-observer and inter-observer variations have been measured.

10% of the carotid histology specimens were re-examined by the author with 6 months intervals, and also by another researcher. I used the difference between the reading and its standard deviation to assess the intra-observer, and inter-observer variations. (table)

variation	D / SD	whole area	fat	SMC	Fibrous	calcified
intra-	D	0	.012	.00001	.00003	0
	SD	0	.03	.00001	.00008	0
inter-	D	.013	.12	.006	0	0
	SD	.034	.62	.075	0	0

Table 10.1.3.5.

Demonstrates both intra-observer and inter-observer variations

D= difference between the readings, SD= standard deviation, SMC= smooth muscle cell

All measurements were in millimetres square.

10.1.3.6. Discussion:

Atherosclerotic plaque characterisation has a role in predicting the clinical course of the disease in the cerebrovascular circulation. Ultrasound assessment of the atherosclerotic plaque is able to characterise this disease. Until recently ultrasound atherosclerotic plaque characterisation was based on the subjective impressions of the observer.

In this study a system was devised to obtain ultrasound images of excised carotid plaques and store them using an image processing computer. Using the results from the previous study the best machine settings for the ultrasound machine were determined in advance and used for all recordings of ultrasound data. Subsequently the carotid plaques were examined histologically and the percentage content of soft tissues (blood, fat) and fibro-calcified tissue calculated using a histology image processing system. The soft tissue (blood, fat) regions of the plaque were find to have a mean of pixel value 50 or less in the ultrasound image, and fibro-calcified tissue had a MPV more than 150, while the mixed tissues ranged between 51-150MPV.

Conclusion:

This technique has been shown to be accurate, reliable, and can be used objectively to assess atherosclerotic plaques.

10.2.1. Objective classification for peripheral arterial disease (Developed by the Author)

Introduction:

Atherosclerosis is the main cause for arterial pathology of the lower limb. Since duplex ultrasound scanning has a growing role in assessment, and follow up of this disease, a classification based on duplex ultrasound analysis of peripheral arterial disease may have a diagnostic and prognostic value.

Variables assessed in the clinical studies of this thesis were considered for inclusion in this classification.

1- The degree of diameter reduction of the blood vessel: To determine the degree of the reduction in the blood vessel diameter, PSVR was used to identify significant stenosis and occlusion (as in most of previous studies). ROC statistics was used to determine the most accurate value of PSVR which able to identify significant stenoses. A PSVR of 1.8 was found able to identify stenoses of greater than 50% in the vessel diameter with a sensitivity of 98% and specificity of 97%. (see 9.1.1)

2- Length of the disease: The length of stenotic or occlusive lesions has implications for patient management. It is generally agreed that balloon angioplasty may be appropriate for lesions of less than 5 cm, and by-pass surgery for lesions of more than 10 cm lesion. The management of arterial lesions of with length between 5 and 10cm remains a point for debate. (9.1.2)

3-Degree of the plaque echogenicity on ultrasound imaging: In this thesis I proved that computer-assisted image analysis technique reliably differentiates between plaques comprising soft structures (fat or thrombus) and those containing

fibrocalcified structures. Image processing was also able to identify plaques of mixed composition.

I found that the mean pixel value of soft structures fell between 0-50 , while for fibrocalcifed plaques, the mean pixel value was found to be > 150 MPV. In mixed lesions, the mean pixel value was between 50-150 MPV. (10.1.1,10.1.2, 10.1.3)

4-The surface integrity of the lesion: The surface of the plaque can also be examined by duplex scanning and ulcerated plaques can be identified. (see figure 10.2.1.2)

The Middlesex classification (**MIDL**) was devised using these duplex variables as the basis. The classification is described in table 10.2.1.1.

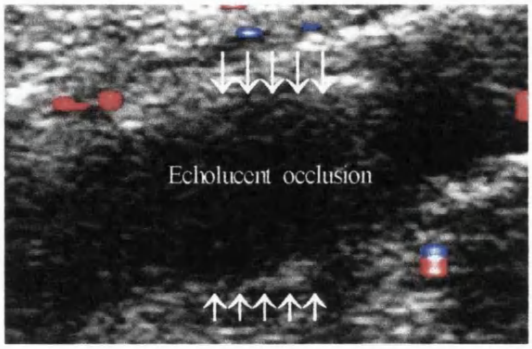


Figure 10.2.1.1

Echolucent common femoral artery occlusion

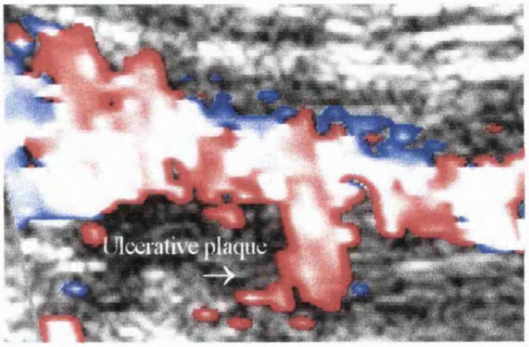


Figure 10.2.1.2

An ulcerated atherosclerotic plaque in SFA

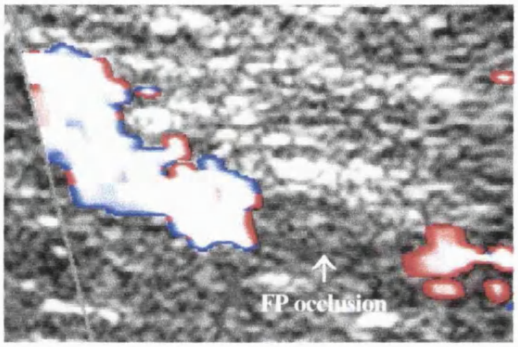


Figure 10.2.1.3

A short occlusion in SFA with MPV 90

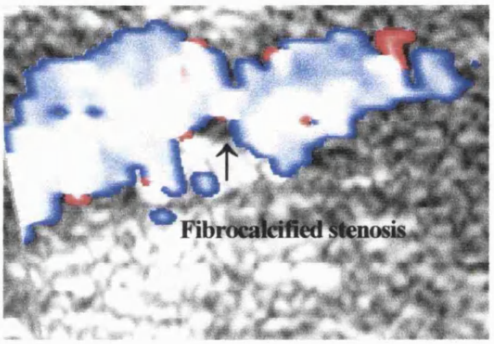


Figure 10.2.1.4

A fibrocalcified SFA stenotic plaque MPV > 150

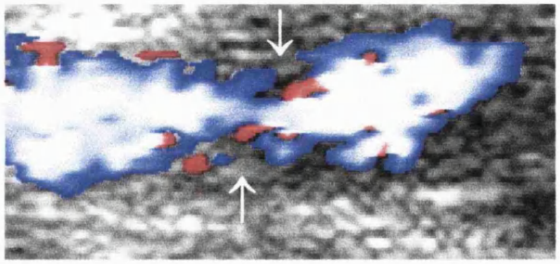


Figure 10.2.1.5

Atherosclerotic SFA mixed (MPV 80) stenotic plaque with smooth surface

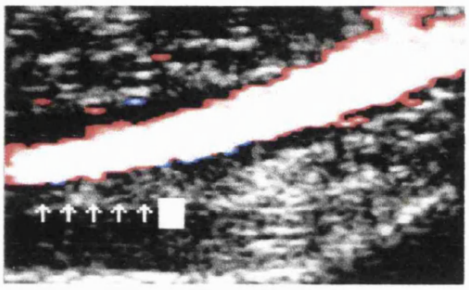


Figure10.2.1.6

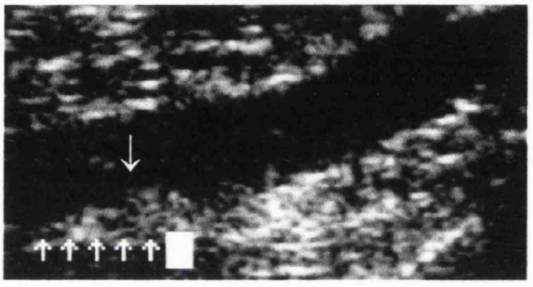


Figure 10.2.1.7

A mixedatherosclerotic plaque in the superficial femoral artery

The **MIDL** (Middlesex) classification has been suggested by the author based on the series of the studies included in this thesis. Four items are the main parameters in this classification:

A-**M**orphology (Echogenicity) of the disease:

This based on the mean grey scale findings (Chapter 10.1.1,2,3):

1-If the mean grey scale is less than 50 MPV = Echolucent lesion.

2-Mean grey scale 51-150 MPV = Mixed lesion

3-Mean grey scale > 150 MPV = Echogenic lesion

B-**I**ntegrity of the endothelial surface, and this can determine easily with observer:

1-Smooth surface 2-Ulcerated.

C-**D**iameter Reduction, based on PSVR of 2.0 (chapter 9.1.1):

1-PSVR < 1.8 = Insignificant disease,

2-PSVR is =>1.8 = Significant disease

3-No pulse = Occlusive disease.

D-**L**ength of the lesion, the length can be measured as has been described in chapter 9.1.2.:

1-Length is less than 5 cm

2- Length is 5-10 cm

3- Length is more than 10 cm.

Table 10.2.1.1

Middlesex Classification as developed by the author

Discussion and conclusion:

Lower limb arterial disease is mainly due to atherosclerotic disease. Buerger's disease, cystic degeneration of popliteal artery, and entrapment of popliteal artery are examples of non-atherosclerotic disease affect lower limb arteries.

The evaluation of patients with peripheral arterial disease of lower limbs consisted of a careful history taken, physical examination, indirect non-invasive haemodynamic testing and arteriography. This approach relied mainly on arteriography for the purposes of localisation of the lesion. A single-plane angiographic study especially in area like aortoiliac can be a source of misdiagnosis since most of atherosclerotic lesions are eccentric.

Value of the duplex ultrasonography in peripheral arterial disease is demonstrated in my clinical studies and also supported by pervious studies[106,107-122].

A classification based on its findings could of value in both diagnostic and communication purposes.

In the following study, I used this classification (MIDL) to determine the value of the computer-assisted image analysis of the ultrasound grey scale duplex image of atherosclerotic plaque on the outcome of balloon angioplasty.

10.2.2. Influence of the plaque morphology on the outcome of balloon angioplasty:

10.2.2.1. Introduction:

Balloon angioplasty plays an important role in the current treatment for peripheral arterial disease of the lower limbs. Relief of symptoms and improved the ankle-brachial pressure index are the main indicators to assess the outcome of the balloon angioplasty in following up these patients.

The initial failure rate of the balloon angioplasty is vary between 10-30%, while the long term outcome is 70%, 50%, 30% at 1, 3, 5 years[171-178].

The aim of the study was to assess the influence of plaque characterisation in lower limb arteries using the computer-assisted image analysis technique developed in earlier chapters on the outcome of balloon angioplasty.

10.2.2.2. Location of the study:

The Vascular Unit, and the Vascular laboratory at the Middlesex Hospital, Mortimer street, London, W1N 8AA. Both Ethical Committee agreement and patients consent were obtained.

10.2.2.3. Instruments:

1- Acuson duplex machine supplied with 2 ultrasound probes (2.5, 7 linear array MHz).

2- QV 200; the computer system for image analysis, with facilities for recording images on 128 Mb Magneto-optic disks. (see the specification in chapter 10.1.1)

10.2.2.4. Patients & Methods:

30 patients with peripheral arterial disease (all with intermittent claudication, none with critical ischaemia) had suitable lesions for balloon angioplasty. These were scanned using duplex ultrasonography in the Middlesex Hospital Vascular Laboratory one day prior to undergoing balloon angioplasty.

The duplex machine was adjusted to Log compression of 40dB, pre-processing set to: 0 persistence at 2, post-processing at 0, with -5dB overall receiver gain.
The Acuson duplex scanner was connected to the QV 200 for digital recording of images of atherosclerotic plaques.

The methods of scanning were described in 9.1.1.

I used **MIDL** classification to record the status of the arterial lesion in the initial visit, and at subsequent follow-up visits. (see sample of the clinical record form in the appendix)

All patients were scanned one day prior to the procedure, and then followed up at 24 hours, 3 weeks, 3 months, 6 months, 12 months. Identical scanning procedures were used on each occasion.

All recorded images of atherosclerotic plaque either in the iliac or femoro-popliteal vessels have been analysed by the QV200 and the mean pixel value of atheromatous plaques was determined at the time of the scanning.

All patients were studied for the complete follow-up period to assess progress of the angioplastied lesions. Figures 10.2.2.1 till 10.2.2.11 are DUS examples of these lesions. Actuarial life table analysis was used to determine the influence of plaque

morphology on outcome following balloon angioplasty. Stat View computer program (version 4.5 for Apple Macintosh, Abacus Concepts, Inc. Berkeley, 1996) was used for statistical calculations.

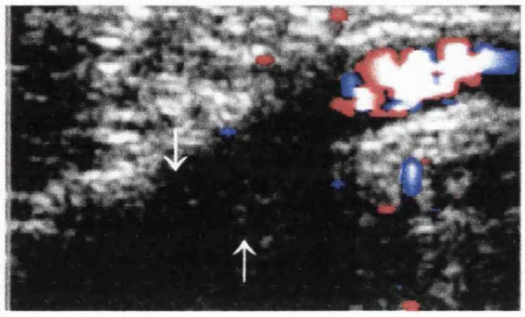


Figure 10.2.2.1

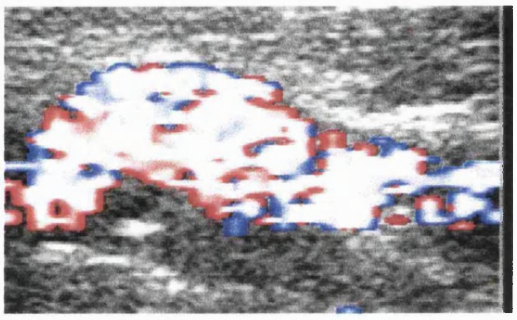


Figure 10.2.2.2

Demonstrate an echolucent occlusion in the common, and external iliac arteries treated successfully by balloon angioplasty.

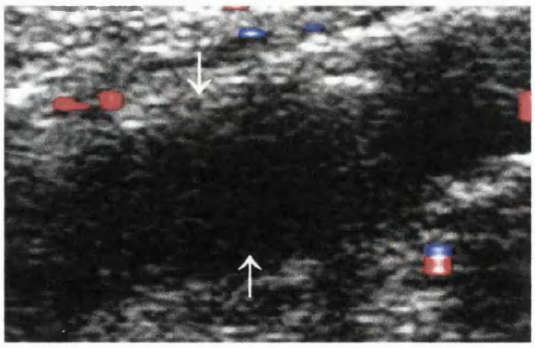


Figure 10.2.2.3

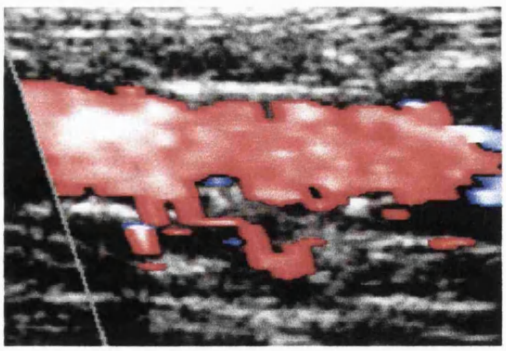


Figure 10.2.2.4

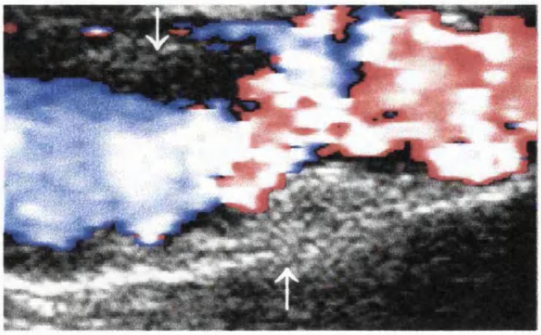


Figure 10.2.2.5
An echolucent CFA occlusion treated successfully by balloon angioplasty, which restenosed at 3 weeks of the follow-up.

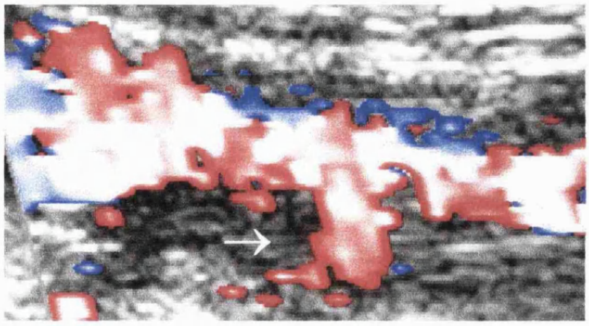


Figure 10.2.2.6

Ulcerated plaque in the SFA was treated by balloon angioplasty, in patient who presented with long history of intermittent claudication, and a sudden history of blue toe syndrome. The did well without recurrence of the stenosis, but the patient died 6 months after balloon angioplasty due to myocardial infarction.

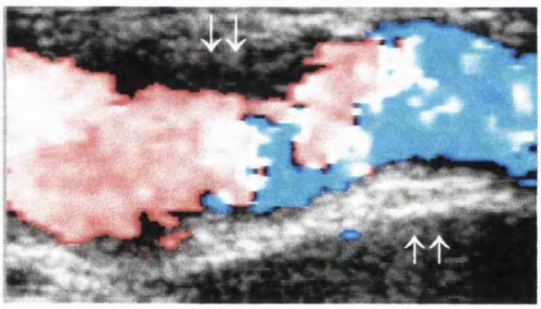


Figure 10.2.2.7

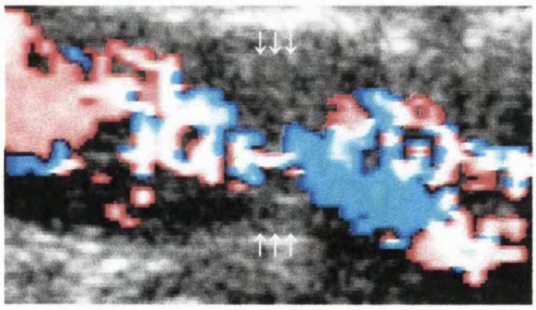


Figure10.2.2.8

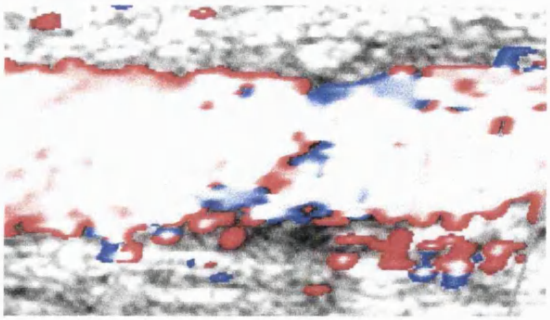


Figure 10.2.2.9

Concentric stenosis in the EIA of mixed echogenic type treated successfully by balloon angioplasty

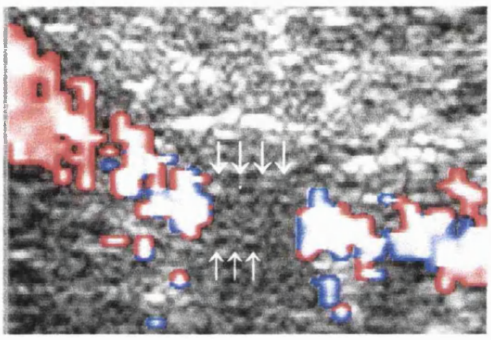


Figure 10.2.2.10

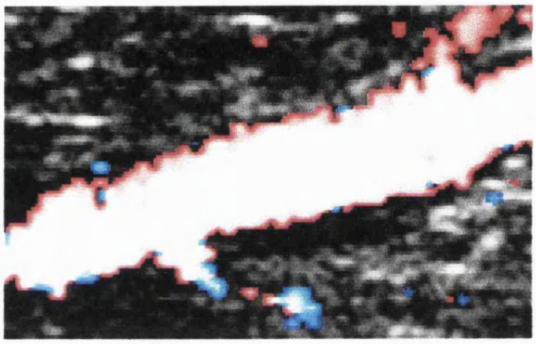


Figure 10.2.2.11

An occlusion in the femoro-popliteal segment was treated by balloon angioplasty and found patent at 64 weeks follow up

10.2.2.5. Results:

In 30 patients (20 M, 10 F, mean age 63 range from 53-85 years), where 15 of them were non-smokers, 11 were smokers, and 4 gave up shortly prior to the study. Four of them were diabetics (3 on insulin, and one on diet). 3 Patients had coronary by-pass surgery, 8 with stable angina, and 2 were hypertensive. The duration of the patients complaint was between 6-168 months before angioplasty was undertaken (In 4 patients the duration of symptoms was 6 months, in 5 it was one year, in 19 it was 2 years, in one it was 6 years, and one patient had had symptoms for 14 years). The mean of their intermittent claudication distance was 100 yards. All patients in this group had successful balloon angioplasty and also had symptomatic relief. The range of follow up was 1 to 15 months (65 weeks). In this group of patients 42 arterial lesions were found and all successfully dilated by balloon angioplasty. The distribution of these lesions were as follows: 18 Iliac lesions: 15 significant stenoses, and 3 occlusions

24 Femoro-popliteal lesion: 17 significant stenoses and 7 occlusions.

41 lesions were < 5 cm length and one was 7 cm (SFA).

Figures 10.2.2.12 demonstrate the actuarial analysis of these 42 lesions based on the site of lesion. There was no significant difference in the recurrence rate between iliac and femoro-popliteal lesions with P value of > 0.89. (See tables 10.2.2.1, 2, 3, 4)

Actuarial analysis of these 42 lesions based on the degree of echogenicity is demonstrated in figures 10.2.2.13, 14. The recurrence rate in the early stage of follow-up of the echolucent lesions is higher than in the other two groups (P value < .0001). Further details included in tables 10.2.2.5, 6, 7, 8, 9.

The data in this study was not enough to assess the cumulative recurrence rate based on the lesion type (stenosis or occlusion).

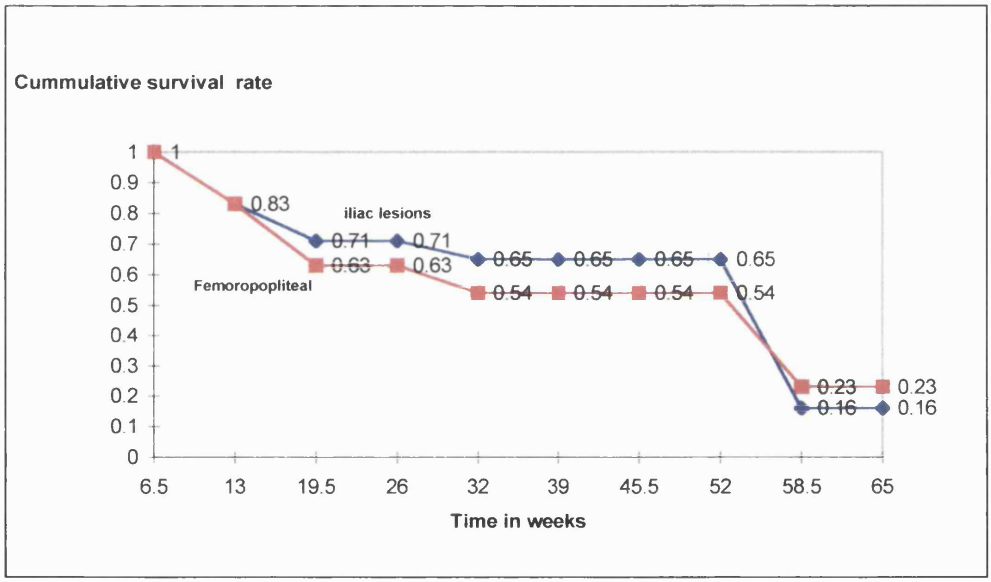


Fig. 10.2.2.12

Recurrence rate of the disease in the two groups (18 iliac and 24 femoro-popliteal lesions). There was no significant difference in the recurrence rate in these two groups. In this figure iliac lesions behaved slightly better than femoro-popliteal lesions but this is insignificant.

Survival Summary Table for event time
Censor Variable: censor variable
Grouping Variable: group variable

	# Obs.	# Events	# Censored	% Censored	# Missing	# Invalid
iliac	18	12	6	33.333	0	0
fem-pop	24	18	6	25.000	0	0
Total	42	30	12	28.571	0	0

Actuarial Survival Table for event time
Censor Variable: censor variable
Group: group variable: iliac

From (•)	To (<)	Num. Enter	Num. Censor	Num. Events	Eff. At Risk	Cond. Prob. Event	Cond. Prob. Surv	Cum. Surv.	Cum. Fail	Surv. Std. Err.
0.000	6.500	18	1	3	17.500	.171	.829	1.000	0.000	0.000
6.500	13.000	14	0	2	14.000	.143	.857	.829	.171	.090
13.000	19.500	12	0	0	12.000	0.000	1.000	.710	.290	.109
19.500	26.000	12	0	1	12.000	.083	.917	.710	.290	.109
26.000	32.500	11	1	0	10.500	0.000	1.000	.651	.349	.115
32.500	39.000	10	2	0	9.000	0.000	1.000	.651	.349	.115
39.000	45.500	8	0	0	8.000	0.000	1.000	.651	.349	.115
45.500	52.000	8	0	6	8.000	.750	.250	.651	.349	.115
52.000	58.500	2	1	0	1.500	0.000	1.000	.163	.837	.104
58.500	65.000	1	1	0	.500	0.000	1.000	.163	.837	.104
65.000	•	0	0	0	0.000	•	•	.163	.837	.104

Table 10.2.2.1,2 demonstrate the actuarial analysis of iliac lesions in general (regardless the degree of echogenicity).

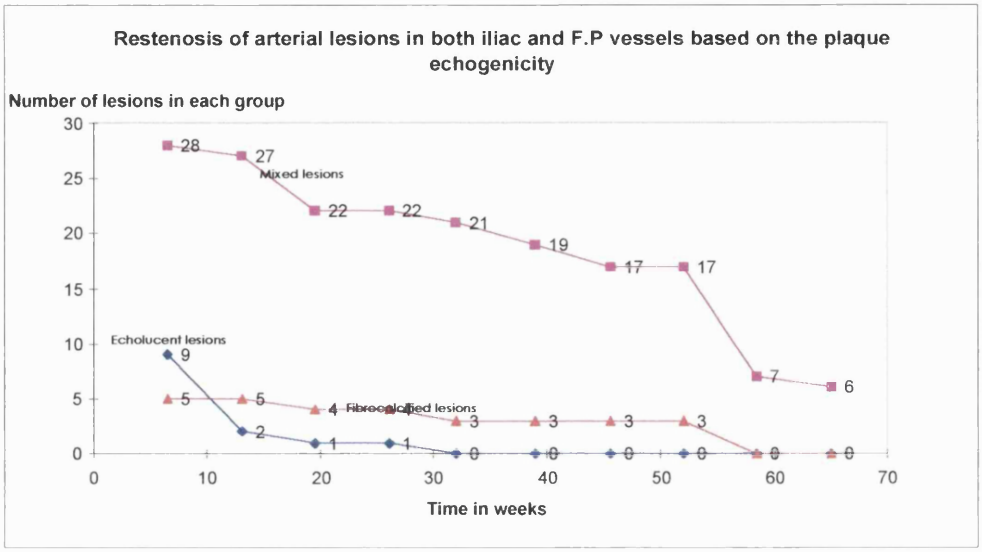
Rank Tests for event time
Censor Variable: censor variable
Grouping Variable: group variable

	Chi-Square	DF	P-Value
Logrank (Mantel-Cox)	2.777E-4	1	.9867
Breslow-Gehan-Wilcoxon	.050	1	.8239
Tarone-Ware	.018	1	.8924
Peto-Peto-Wilcoxon	.049	1	.8240
Harrington-Fleming (rho = .5)	.009	1	.9251

Actuarial Survival Table for event time
Censor Variable: censor variable
Group: group variable: fem-pop

From (•)	To (<)	Num. Ente	Num. Censo	Num. Event	Eff. At Risk	Cond. Prob. Eve	Cond. Prob. Sur	Cum. Surv	Cum. Fail	Surv. Std. Err.
0.000	6.500	24	0	4	24.000	.167	.833	1.000	0.000	0.000
6.500	13.000	20	0	5	20.000	.250	.750	.833	.167	.076
13.000	19.500	15	0	0	15.000	0.000	1.000	.625	.375	.099
19.500	26.000	15	0	2	15.000	.133	.867	.625	.375	.099
26.000	32.500	13	1	0	12.500	0.000	1.000	.542	.458	.102
32.500	39.000	12	0	0	12.000	0.000	1.000	.542	.458	.102
39.000	45.500	12	0	0	12.000	0.000	1.000	.542	.458	.102
45.500	52.000	12	0	7	12.000	.583	.417	.542	.458	.102
52.000	58.500	5	0	0	5.000	0.000	1.000	.226	.774	.088
58.500	65.000	5	5	0	2.500	0.000	1.000	.226	.774	.088
65.000	•	0	0	0	0.000	•	•	.226	.774	.088

Table 10.2.2.3,4: Actuarial analysis of femoro-popliteal lesions (regardless their degree of echogenicity)



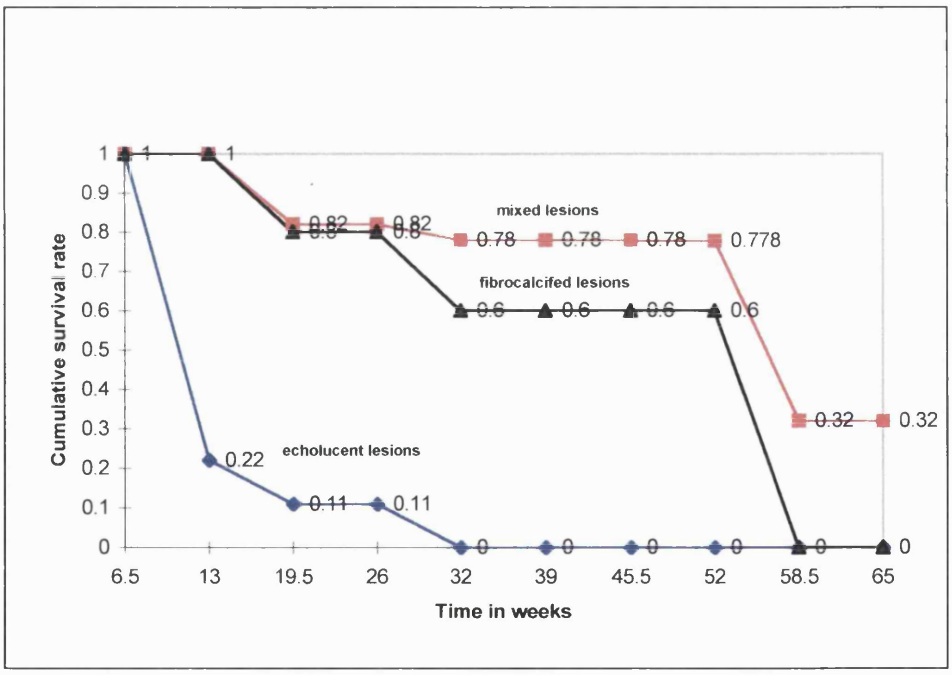


Fig. 10.2.2.13,14: The restenosis rate in echolucent, mixed, and fibro-calcified plaques.

Survival Summary Table for event time
Censor Variable: censor variable
Grouping Variable: group variable

	# Obs.	# Events	# Censored	% Censored	# Missing	# Invalid
1	9	9	0	0.000	0	0
2	28	16	12	42.857	0	0
3	5	5	0	0.000	0	0
Total	42	30	12	28.571	0	0

Actuarial Survival Table for event time
Censor Variable: censor variable
Group: group variable: 1

From (•)	To (<)	Num. Enter	Num. Censo	Num. Events	Eff. At Risk	Cond. Prob. Even	Cond. Prob. Surv	Cum. Surv.	Cum. Fail.	Surv. Std. Err.
0.000	6.500	9	0	7	9.000	.778	.222	1.000	0.000	0.000
6.500	13.000	2	0	1	2.000	.500	.500	.222	.778	.139
13.000	19.500	1	0	0	1.000	0.000	1.000	.111	.889	.105
19.500	26.000	1	0	1	1.000	1.000	0.000	.111	.889	.105
26.000	32.500	0	0	0	0.000	•	•	0.000	1.000	•
32.500	39.000	0	0	0	0.000	•	•	•	•	•
39.000	45.500	0	0	0	0.000	•	•	•	•	•
45.500	52.000	0	0	0	0.000	•	•	•	•	•
52.000	58.500	0	0	0	0.000	•	•	•	•	•
58.500	65.000	0	0	0	0.000	•	•	•	•	•
65.000	•	0	0	0	0.000	•	•	•	•	•

Table 10.2.2.5,6: Summarise the statistics of the restenosis of the **echolucent arterial lesions** in both iliac, and femoro-popliteal regions in plaques with an MPV of 0-50.

Rank Tests for event time
Censor Variable: censor variable
Grouping Variable: group variable

	Chi-Square	DF	P-Value
Logrank (Mantel-Cox)	35.454	2	<.0001
Breslow-Gehan-Wilcoxon	34.795	2	<.0001
Tarone-Ware	35.174	2	<.0001
Peto-Peto-Wilcoxon	35.059	2	<.0001
Harrington-Fleming (rho = .5)	35.177	2	<.0001

Actuarial Survival Table for event time
Censor Variable: censor variable
Group: group variable: 2

From (•)	To (<)	Num. Enter	Num. Censo	Num. Events	Eff. At Risk	Cond. Prob. Even	Cond. Prob. Surv	Cum. Surv.	Cum. Fail.	Surv. Std. Err.
0.000	6.500	28	1	0	27.500	0.000	1.000	1.000	0.000	0.000
6.500	13.000	27	0	5	27.000	.185	.815	1.000	0.000	0.000
13.000	19.500	22	0	0	22.000	0.000	1.000	.815	.185	.075
19.500	26.000	22	0	1	22.000	.045	.955	.815	.185	.075
26.000	32.500	21	2	0	20.000	0.000	1.000	.778	.222	.080
32.500	39.000	19	2	0	18.000	0.000	1.000	.778	.222	.080
39.000	45.500	17	0	0	17.000	0.000	1.000	.778	.222	.080
45.500	52.000	17	0	10	17.000	.588	.412	.778	.222	.080
52.000	58.500	7	1	0	6.500	0.000	1.000	.320	.680	.099
58.500	65.000	6	6	0	3.000	0.000	1.000	.320	.680	.099
65.000	•	0	0	0	0.000	•	•	.320	.680	.099

Actuarial Survival Table for event time
Censor Variable: censor variable
Group: group variable: 3

From (•)	To (<)	Num. Enter	Num. Censo	Num. Events	Eff. At Risk	Cond. Prob. Even	Cond. Prob. Surv	Cum. Surv.	Cum. Fail.	Surv. Std. Err.
0.000	6.500	5	0	0	5.000	0.000	1.000	1.000	0.000	0.000
6.500	13.000	5	0	1	5.000	.200	.800	1.000	0.000	0.000
13.000	19.500	4	0	0	4.000	0.000	1.000	.800	.200	.179
19.500	26.000	4	0	1	4.000	.250	.750	.800	.200	.179
26.000	32.500	3	0	0	3.000	0.000	1.000	.600	.400	.219
32.500	39.000	3	0	0	3.000	0.000	1.000	.600	.400	.219
39.000	45.500	3	0	0	3.000	0.000	1.000	.600	.400	.219
45.500	52.000	3	0	3	3.000	1.000	0.000	.600	.400	.219
52.000	58.500	0	0	0	0.000	•	•	0.000	1.000	•
58.500	65.000	0	0	0	0.000	•	•	•	•	•
65.000	•	0	0	0	0.000	•	•	•	•	•

Table 10.2.2.7,8,9

Summarise the statistics of the group 2, and 3 with MPV of > 50.

Discussion:

Percutaneous transluminal angioplasty (PTA) has become widely used in recent years. However, in view of the pace of its development, confusion has arisen over the indications for various procedures and the relative roles of PTA and conventional surgery.

The initial failure[171-182] of the technique (PTA) varies between 10-30%. (see chapter 6) Most of the published angioplasty studies showed a higher restenosis rate of femoro-popliteal lesions compared to iliac lesions[171-182]. This preliminary study has shown that there was not significant difference in restenosis rate between the iliac and femoro-popliteal lesions (P value > 0.89). (see figures 10.2.2.12) Looking at the follow-up methods used in the angioplasty studies, most of them used the clinical improvement, and ABPI as the main methods of follow-up. In this study I followed all patients up with duplex ultrasound scanning using the described criteria in the previous chapter.

The influence of the plaque morphology on the outcome of balloon angioplasty has been reported in both studies of the coronary blood vessels and peripheral arteries where IVUS (Intra-vascular ultrasound) was used for atherosclerotic plaque characterisation[178,179,180].

Using the **MIDL** classification in atherosclerotic plaques in iliac and femoro-popliteal vessels, I found that plaques of grade 1 (echolucent lesion with a mean grey scale of 0-50 MPV,) showed much greater rate of re-stenosis in the early stages of follow-up (up to 3 months) compared to grade 2 (mixed echogenicity with MPV of 50-150), and 3 (fibrocalcified with MPV > 150).

Looking at the results at three months, most of the echolucent lesions were found restenosed compared to the fibrocalcified group (MPV > 150) and the mixed group (51-150 MPV).

Looking at the patency rate at 52 weeks, the fibrocalcified group (MPV > 150) 60% of the treated lesions were patent compared to 78% of the mixed group (51-150 MPV).

Conclusion:

1-The echolucent atherosclerotic plaque has high rate of re-stenosis after successfully treated by balloon angioplasty.

2-The MIDL classification is an objective classification based on the duplex finding and can be used for both diagnostic and follow up purposes.

Part III: General Discussion and Conclusion:

11.1. Introduction:

This thesis consists of three sections:

1-Duplex US and evaluation of peripheral arterial disease.

2-Computer-assisted grey scale image analysis.

3-Influence of the plaque morphology on the outcome of balloon angioplasty in both iliac and femoro-popliteal disease.

11.2. Duplex US and evaluation of peripheral arterial disease

Arteriography has been regarded as the main investigation for peripheral arterial disease and it is the traditional gold standard for peripheral arterial diagnosis. Its major drawback is that the information it provides is morphological, from which the haemodynamic impact of individual occlusive lesions has to be inferred. Knowing that most atherosclerotic plaques are eccentric, it is recognised that using uniplanar views for arteriography could result in missed or occasionally underestimated arterial stenoses[93,105]. Although advances in the technique of arteriography and contrast materials, this procedure is still with associated complications. Egglin et al[199] recently reported that the arteriography is associated with 2% complications. These may be due to contrast reaction, contrast induced renal failure, vascular injury (haematoma, dissection, false aneurysm, and distal embolisation), and wound complications.

Duplex ultrasound scanning provides both an anatomical and functional description of arterial stenoses. Advances in duplex ultrasound machine technology have permitted

the development of the modern generation of colour flow duplex scanner. These machines give improved B-mode image quality, allowing diseased segments of arteries to be identified more easily. The use of duplex ultrasonography in the management of carotid artery disease and graft surveillance has been increasing rapidly in recent years.

The criteria for the diagnosis of vascular stenoses on duplex ultrasound scanning used in the previous studies[105-130] have been based mainly on the colour flow display and Doppler velocity spectrum analysis. The colour flow display allows identification but not quantification of vascular lesions. Doppler spectrum analysis has become widely used in the quantification of stenoses.

A number of Doppler velocity parameters are used in the assessment of the severity of stenoses, including the absolute value of peak systolic velocity and the peak systolic velocity ratio (PSVR).

Peak systolic velocity ratio (PSVR) is a parameter of a proven value in detecting the degree of diameter reduction in blood vessels[105-130]. The main advantage of using PSVR is that it is independent of individual variations in blood pressure, vascular compliance, and cardiac function.

Traditionally a 50% reduction in arterial diameter is considered to be associated with a significant fall in the arterial blood flow, and distal pressure. This is a concept with which most of the interventional radiologists agree.

The value of PSVR which has been taken to denote significant arterial stenosis varies in the previously published studies. While most studies used a PSVR of 2.0 to identify the clinically significant stenoses, a range from a PSVR of 1.8[118] to more than 2.5 has been reported [112-115,116].

In this thesis I used the PSVR of 2.0 prospectively to identify significant arterial stenosis, a value which has been used in many of the more recent papers and is more easily calculated.

By using ROC statistics to examine my data, objective determination of the most appropriate value of PSVR was obtained. A PSVR of 1.8 was found to have a sensitivity of 98% and specificity of 97% compared to 92% and 98% respectively for PSVR of 2.0.

In the aorto-iliac region, the depth and angles at which iliac vessels run make this segment difficult to insonate. The main problems of ultrasound imaging in this region are caused by the presence of obesity and bowel gas. Some authors improved visualisation by fasting the patient for several hours prior to investigation[112-116], or by using bowel preparation agents[130]. In my study, all patients fasted 6 hours prior to scanning.

The preciously reported accuracy of duplex in this region was a sensitivity 87% and specificity 98%. (see for further details chapter 4, table 4.2) In my study the duplex ultrasound scanning showed accuracy with a sensitivity of 89%, and specificity 99%. (table 9.1.1.9)

Occasionally duplex scanning identified lesion in the iliac vessels, which were missed or misdiagnosed by arteriography. This was found in my study and also supported by previous studies. That could be due to nature of the lesion (eccentric iliac lesion) and can be better identified by bi-planar arteriography (as it happened in this study).

Most previous studies regarded the femoral artery as part of femoropopliteal region, while in this thesis I look at it as a single region. This included the common femoral, profunda femoris and the origin of superficial femoral artery. The accuracy of duplex

scanning in this area in my study was found to be a sensitivity of 100%, and specificity of 99%. (table 9.1.1.9)

The femoro-popliteal arterial region is more superficial than the aortoiliac and hence a higher frequency ultrasound probe (5-7MHz linear array) could be used, which offers higher B mode resolution. The overall accuracy of duplex scanning in this region in previously published series was a sensitivity 86% and a specificity 97%. In my study duplex showed accuracy with a sensitivity of 95% and specificity of 99%.

Popliteal artery scanning was reported in some studies[101,107-111] to have less accuracy than the rest of femoro-popliteal region. The reason behind the better accuracy reported in my study may be because I adopted a 'double check' scanning technique for the distal part of SFA and proximal popliteal artery. I ensured that this section of artery was scanned from both the medial aspect of the thigh as well as from the posterior aspect of the limb.(see the methodology of scanning)

There have been relatively few studies[108,119,122] have investigated the efficacy of duplex scanning at imaging infragenicular disease. The reported accuracy of the duplex ultrasound scanning in these few studies with an overall sensitivity of 75%, and specificity of 95%. (further details chapter 4, and table 4.4) In my study I found that the accuracy of duplex scanning was reduced here compared to more proximal segments. Its sensitivity was 82%, and specificity 99%. This reduction in duplex accuracy may be due to the fact that these vessels are small in diameter making them difficult to identify and assess and calcification causes further problems, reducing the Doppler signal from within these vessels.

The length of arterial disease has its own implications for therapeutic measures. While short lesions can be treated successfully by balloon angioplasty, long lesions might need by-pass surgery. It was essential to investigate the reliability of duplex ultrasonography in assessing this feature of arterial stenoses and occlusions. In the work described above I found that that duplex scanning was able to establish the length arterial lesions with considerable accuracy. Other authors have found similar accuracy in this aspect of the data obtained from duplex ultrasonography[200].

Atherosclerosis is a generalised disease and may occur simultaneously in several arteries in the same limb[201]. Some authors have reported that where arterial stenoses or occlusions are present at several levels (multisegmental disease) the peak systolic velocity will drop in the more distal vessels and this reduce the accuracy of duplex in more distal vessels [105,121,129]. Since the use of PSVR corrects for segment to segment variation in flow velocity, the presence of upstream disease should not affect the sensitivity of the flow-dependent PSVR. In the work I have described above this question was examined in a group 90 patients. The distribution of the disease was classified into 5 grades according to presence of multi-segmental stenoses (see for further details chapter 9.1.3). The accuracy of duplex scanning in limbs with multiple stenoses was compared to that of limbs with only a single affected artery (IA DSA was used as the reference standard). The accuracy of duplex ultrasonography in detecting lesions in limbs with multisegmental arterial disease was the same as that in limbs with single vessel disease. This has also been suggested by some recently published studies[112-115].

The real test of duplex ultrasonography is using its findings in determining the clinical management of patients. Looking at the previous studies in this area, some authors

used the duplex data for selecting patients for balloon angioplasty[117,202,203,204,205], and a few authors used the data in planning vascular reconstruction[194,198] However has also been reported that most surgeons feel the arteriography is mandatory for planning vascular reconstruction, especially femoro-distal by pass surgery[106]. In this thesis, two clinical studies were designed to determine the capability of duplex ultrasonography in clinical decision planning.

In the first study reported here, the clinical decision based on duplex was compared to that based on arteriography. In this study there was no difference between the decision based on the duplex findings , and that based on arteriography findings. Both differed to some extent from the actual treatment received by the patients, but this mainly reflected the variations in indications for interventional therapy among surgeons. In addition, surgeons disagreed to some extent when they were presented with the same data, especially in absence of the patient.

In the second study I used the duplex ultrasonography used prospectively as the main investigation to assess arterial disease of lower extremities in a group of patients (66 patients). Arteriography was arranged at the request of the surgeon treating the patient. This study has shown that; surgeons were able discharge patients from vascular outpatient clinic, and select patients for conservative treatment on basis of duplex data.

Although diagnostic arteriography can be combined with PTA in the same session, duplication of arteriography is not uncommon[106]. This subsequently increases both complication rates and patients' inconvenience. In this study; 21 patients (32%) had balloon angioplasty based only on duplex scanning without diagnostic arteriography. This reduction in diagnostic arteriography has been reported in other studies[117,203,204,205,206.] and More recently Elsman et al[116] reported that in his study of 100 patients with

peripheral arterial disease of lower limbs, the treatment strategy could be planned on basis of duplex scanning. However, Elsman reported that 62 patients (62%) had diagnostic arteriography.

Bodily et al[194] reported recently that out of 54 patients with lower limb arterial disease 13 had both duplex and arteriography, 30 had only arteriography, and 11 had only duplex ultrasound scanning. 10 patients in group 1, 15 patients in group 2, and 9 patients in-group 3 had an occluded aorta or iliac artery and all required aortoiliac reconstruction. Two patients (3 anastmosis) required placement of the distal anastmosis on common femoral artery rather than the external iliac artery and non of the group 3 patients required diagnostic arteriography. As well he concluded that aortoiliac reconstruction can be performed without needs to pre-operative diagnostic arteriography.

In my study; although the surgeon was also able to select patients for vascular reconstruction on the basis of duplex ultrasonography, he felt that arteriography was mandatory before vascular reconstruction was undertaken. In all 9 patients (14%) had diagnostic arteriography, and the main indication for this was in preparation for vascular reconstruction. In just two patients duplex scanning failed fully to assess the vessel where clinical important disease was present (iliac, popliteal). In contrast to this outcome, Pemberton et al[198] showed that infra-inguinal vascular reconstruction can be planned safely on duplex US findings.

The reliability of duplex ultrasonography in assessing lower limb arterial disease has not yet changed the practice of the modern vascular surgeon. Technical limitations of duplex US have to be highlighted and appreciated by both the sonographers and vascular clinicians. In this way arteriography may be reserved to assess those cases

where it is impossible to achieve reliable diagnostic data from duplex ultrasound. In my studies some of these limitations have been identified and described in detail.

Misdiagnosis of very tight stenoses is recognised as a limitation of duplex technique due to the very low flow velocities that may result. Sonographers are aware of this limitation and use appropriate machine settings to search for low velocity blood flow in apparently occluded arteries.

In the case of heavily calcified lesions, especially those in the anterior wall of the blood vessel poor quality B-mode images will be obtained of the vessel contents. This will prevent assessment of atheromatous plaque as well as interfering with Doppler ultrasound assessments of blood flow. On the other hand the calcification of the posterior wall has a less significant role in altering the visualisation of arteries, since this does not generally impede the view of structures or blood flow in the anterior wall or lumen of the vessel.

Small diameter run-off vessels are also difficult to assess on ultrasound, so if femoro-distal by-pass surgery is planned, pre-operative diagnostic arteriography may be justified.

I have identified a set of criteria which may be used as indications for arteriography following duplex ultrasound scanning based on two clinical studies (9.2.1, 9.2.2).

11.2.2. Summary:

1-Duplex scanning is an accurate and reliable for the assessment of peripheral arterial disease.

2-A PSVR of 1.8 showed a sensitivity of 98% and specificity of 97% in detecting significant stenosis and I consider that this is an optimum value to use for clinical purposes, based on ROC analysis.

3-Clinical management decisions can be planned safely on the basis of duplex ultrasonography.

4-There are recognised limitations of duplex ultrasound scanning on which surgeons can base their use of arteriography.

11.2.3. Remaining issues requiring further research:

1-Although most studies including the work described above have reported that duplex scanning has a high degree of accuracy, very little has been to assess the clinical use of duplex findings as the main basis for vascular reconstruction.

2-Subdivision of lesions with less than 50% diameter reduction: There was poor correlation between PSVR and arteriography findings, although duplex showed a good accuracy in differentiating between the normal and the diseased segments. Fortunately the subdivision of stenoses of less than 50% diameter reduction is of a limited value in clinical practice. Legemate et al, Jager, and Kohler have reported similar findings.

3- I did not look at subdividing significant lesions of greater than 50% stenosis. Legemate tried to subdivide the significant stenosis into 50-75%, and 76-99%, and reported that end diastolic velocity of $\geq$ 60 cm/s is highly predictive for stenosis with > 75% diameter reduction. No analysis of this type was attempted in this study.

II.2.4: Future Directions for Research

The results of this study show that duplex scanning is reliable in evaluating lower limb arterial disease. The limitations of duplex ultrasound scanning have been identified and this, may justify a prospective multi-centre study in which the duplex findings can be used as the main basis for vascular reconstruction.

11.3. Computer-assisted grey scale image analysis and atherosclerotic plaque characterisation:

11.3.1. Introduction:

The implications of atherosclerotic plaque morphology as shown by ultrasound imaging on the cerebrovascular circulation is accepted as fact. Arteriography has no role in atherosclerotic plaque characterisation, since this investigation provides no information about the arterial wall. The relation between the atherosclerotic plaque morphology and patient symptoms are documented in duplex carotid studies[141-151]. Grey Weal[152] classified the ultrasound appearance into four types, and reported that type 1, and 2 are associated with intra-plaque haemorrhage and ulceration, while type 3 and 4 associated with more fibrous, and calcified. In which type 1,and 2 more risky than type 3, and 4.

Geroulakos[153] added a fifth type (the calcified plaque) to this classification which difficult to be assessed by duplex ultrasound scanning.

The value of these classifications[152,153] has been questioned due to the fact that they are observer-dependent and are subject to errors which may arise from different settings of the ultrasound scanning machine[156].

El Barghouty et al[156] reported the possibility of using computer-assisted grey scale image analysis to obtain an objective assessment of atherosclerotic plaque. In his histological study, El Bargouty[156] scanned the patient prior to surgery, and selected the centre part of the atherosclerotic plaque (post-carotid endartectiomy). In his report El Barghouty correlated the median of grey scale image intensity (determined by computer-assisted image analysis technique) to their histological structures. He stated that the median of the grey scale (MGS) of US image of the carotid plaque dropped as the mean percentage of the fat and haemorrhage increased while it increased as the fibrocalcified material increased. Also he reported that in the symptomatic group MGS decreased, and its fat and haemorrhage content increased, while in asymptomatic group both MGS and fibrocalcified content increased.

The pitfall in this work is the methodology. In his report, El Barghouty, did not include the effect of the surgical manipulation (carotid endarterectomy) on plaque architecture. This may led to discrepancy between the centre of the plaque in the ultrasound image and that of the carotid specimen.

El Barghouty[156] demonstrated that image analysis may be of value in objective assessment of plaque morphology, but he did not record the duplex ultrasound image electronically. This led to loss of resolution of these image.

In this thesis I recorded the ultrasound images electronically to avoid loss of resolution by using QV 200 image processing computer. Validity of this technique has been

demonstrated by the author. Further studies to assess the accuracy of this technique were designed :

A study in which a tissue of known type in a human volunteer was examined (blood, fat, muscle, fibrous and calcified tissues) using a range of different duplex ultrasound machine settings. These allowed me to identify those settings at which images were obtained in which the computer was best able to differentiate between the tissues. All image were analysed and the image statistics were obtained objectively. I used the mean intensity of the pixels in the tissue of interest (the mean pixel value MPV) of the grey scale of the image as the parameter to identify the echogenicity of the structure.

The histological study in this thesis was designed to test whether the findings in the previous study could be extended to assessment of the morphology athermonatous plaques. The findings of computer-assisted grey scale image analysis of these specimens have been verified by the histological findings, and a good correlation has been shown.(see further details in 10.2.3.) I found that as the soft materials (fat, blood) content of the plaque increased the mean pixel value decreased, also as the fibro-calcified tissue content of the plaque increased the mean pixel value increased. This relation between the MPV and the plaque histology has been found significant (p value < 0.0001). To avoid any potential error both intra-observer, and inter-observer variation were obtained.

The role of duplex scanning in assessment of peripheral arterial disease is growing, and communication between the modern vascular laboratory and the vascular surgeon is progressing. The findings of these two studies were added to the previous studies of the duplex scanning in this thesis and a classification (**MIDL**) of atheromatous lesion lower limb arteries was developed to provide an objective classification for peripheral

arterial disease based on investigation of patients by duplex ultrasonography. (for further details see chapter 10.2.1) This can be used as method of communication between the vascular laboratory and the vascular physician. The data used to describe an atheromatous lesion include functional description of the stenosis (severity of stenosis), length, endothelial covering, and also the morphology of the disease.

The duplex findings in arterial lesions of the lower limbs help the surgeon in planning his clinical management, and provide the interventional radiologist information about the lesion before embarking on balloon angioplasty.

To demonstrate the value of this classification, another study was designed to assess the influence of plaque echogenicity on the outcome of balloon angioplasty of iliac and femoro-popliteal arterial disease.

11.3.2. Future direction:

A classification for peripheral arterial disease is justified, since the role of duplex US is growing in both diagnosis of the vascular disease and follow up. In this classification I used the main findings that are obtained on duplex ultrasonography to provide the basis for an objective description of such disease. Another study could be required:

1-To assess this classification as a method of communication between the sonographer and surgeon.

2- To determine the value of this classification in both diagnostic and prognostic aspects of the peripheral arterial disease.

11.4. Atherosclerotic plaque morphology and balloon angioplasty:

11.4.1 Introduction:

Balloon angioplasty is less invasive than surgery and it is also a cost effective treatment. Restenosis is the major limitation of balloon angioplasty. The influence of the plaque morphology on the outcome of balloon angioplasty is unclear in the literature and most of the published work in this area is based on data obtained by using intravascular ultrasound imaging. A number of studies have correlated plaque morphology and the outcome of balloon angioplasty in coronary vessels[185,186] , while only a few studies have been reported concerning lower limb arteries[187].

The cost and invasive nature of intravascular ultrasound are the main reasons for its limited use in the clinical practice. No published work correlates computer-assisted grey scale image analysis and the outcome of balloon angioplasty of lower limb arteries.

In this part of the thesis I used the Middlesex classification (**MIDL**) to assess the arterial lesions in both iliac and femoro-popliteal arteries.

In this preliminary study of 30 patients (42 arterial lesions), the Middlesex classification criteria was used. These lesions were quantified prior to balloon angioplasty and followed up to 65 weeks. All these patients had successful balloon angioplasty. I found that the echolucent lesions with a mean pixel value of the grey scale less than 50MPV showed a high rate of restenosis in the period of 3 months following treatment (p value < 0.0001), compared to plaques with a mean pixel value of the grey scale greater than 150 MPV and those with a mean pixel value of the grey scale between 51-150MPV (p value < 0.0001).

This could be explained as follows: echolucent lesion has a higher content of lipid and haemorrhage, which makes it softer than the other plaques and more responsive for the balloon angioplasty trauma and subsequent increase in neointimal formation.

The relation between the injury response and neointimal formation was demonstrated in the experimental work done by Andersen et al[206] in which he used an over-sized angioplasty balloon in coronary vessels of 20 pigs and reported that injury correlated strongly with neointimal formation (p value < 0.0001). Also he stated that neaintimal formation did not explain late luminal narrowing (p value 0.07). Carter et al[207] in his study placed 28 oversized stents in the coronary arteries of 23 juvenile domestic pigs. Both histological degree of injury and smooth muscle cell proliferation measured by immunolocalisation with a monoclonal antibody to proliferating cell nuclear antigen (PCNA) were assessed at 24 hours, and 7, 14, and 28 days after stent placement. He reported as the degree of injury increase the neointimal formation increased.

Future directions:

It is important to recognise plaques with a high tendency for restenosis rate before the treatment by balloon angioplasty. A prospective study with larger number of patients in each group may be of value to obtain more information about the behaviour of the echolucent atherosclerotic plaques.

A control study may be justified to examine effect of combination of warfarin therapy with balloon angioplasty in echolucent plaque to determine any change in the outcome of balloon angioplasty.

General conclusion:

1. Duplex ultrasound scanning of lower limb arterial disease is accurate, reliable non-invasive investigation.
2. Peak systolic velocity ratio is an important parameter and can be used safely to quantify the arterial disease of lower extremities.
3. By using receiver operating curve analysis a PSVR of 1.8 was found to be the optimum value in identifying significant stenoses.
4. Duplex can reliably determine the length of arterial stenoses and occlusions.
5. Identification of lower limb arterial stenoses based on the use of PSVR correctly identified vascular lesions, even when several stenoses are present if arteries at different levels in the same limb.
6. Duplex scanning of lower limb arteries has recognised limitations which have to be fully accepted by both surgeon and sonographer.
7. Computer-assisted image analysis in atherosclerotic plaque characterisation is reliable, accurate, and observer-independent.
8. The set-up of duplex machine considerable influence on the grey scale duplex image. The optimum settings to be used on an Acuson 128 XP/10 machine were identified
9. The mean grey scale of soft materials (blood, fat, muscle) in atherosclerotic plaque have a mean pixel value of less than 50 on the digitised ultrasound image. Fibrocalified plaque has an MPV of more than 150.
10. The MIDL classification of lower limb arterial disease includes all duplex data, and may be of value for communication between the physician and sonographer.

11. Arterial lesions of low echogenicity (c MPV of less than 50) have a high restenosis rate after balloon angioplasty and which exceed that of the most echogenic lesions (MPV of >150).

Part IV References:

1-Fattah A., Abdulla A.: The pathology of atherosclerosis in Occult atherosclerotic disease, Edited by Salmasi A, Nicolaides A., published by Kluwer academic publishers P.O box 17, 3300 AA Dordrecht, The Netherlands,1991 pp: 19-31.

2- DePalma R: The pathology of atheroma: Theories of aetiology and evolution of atheromatous plaques. Textbook of Surgical management of vascular disease. Ed by Bell P., Jamieson C., C. Ruckley, W.B. Saunders Company Ltd. 1992, pp: 21-34.

3-Jamieson C.: Management of chronic ischaemia of the lower limbs. Textbook of Surgical management of vascular disease. Ed by Bell P., Jamieson C., C. Ruckley, W.B. Saunders Company Ltd 1992, pp 433-461.

4- Woolf N.: Pathology of atherosclerosis, British Medical Bulletin 1990, Vol 46:960-985.

5-Ruffer M.: An Arterial lesion found in the Egyptian mummies. J. Pathol. Bacteriol. 1911, 15, 453-62.

6-Morgan AD.: The pathogenesis of coronary occlusion, Oxford, Blakwell, 1956.

7-Long ER.: Development of our knowledge of atherosclerosis in Blumenthal, HI, Ed. Cowdrys atherosclerosis, Springfield, Charles C. Thomas 1967, 15-20.

8-Crawford T: Some aspects of the pathology of atherosclerosis. Proc. Roy. Soc. Med. 1960, 53: 62-9.

9-Woolf N.: Atherosclerosis and its genesis. Atheroma, Atherosclerosis in ischaemic heart disease, Cardiovascular- Bayer, 1990, V. 1, Page 1.2

10-Ross R. : The pathogenesis of atherosclerosis A text book of cardiovascular medicine. E. Barrnard ed. Heart disease, 3rd Ed 1988; page 1135.

11-Ross R, Horker L.: Hyperlipidaemia and atherosclerosis, Chronic hyperlipidaemia in initiate and maintain lesions by endothelial cell desquamation and lipid accumulation, Science 1976; 193: 1094.

12-Ross R.: The pathogenesis of atherosclerosis, An up date, N.Engl.J.Med. 1986; 2, 4888.

13-Kritchevsky D.: Atherosclerosis and nutrition. Nutrition Int. 1986; 2:290.

14-Anitschkow N.: Experimental atherosclerosis in animal In: Atherosclerosis, Cowdry EV Ed; New York, Macmillan 1933; 271-322.

15-Stender S, Silversmit DB: Transfer of plasma lipoprotein components and of plasma proteins into aortas of cholesterol-fed rabbits. Atherosclerosis 1981; 1:38.

16-Rokitansky C. Von.: A manual of pathological anatomy. 4th Vol. Translated by Dan G. London, The Sydenham Society. 1852.

17-Duguid J.: Thrombosis is a factor in the pathogenesis of coronary atherosclerosis J.Pathol. 1946; 58: 207.

18-Lusby RJ: Vessel wall and blood flow dynamics in arterial disease. Phil. Trans. R. Soc. Lond. B, 1981; 294, 231-9

19-Born G.: Arterial thrombosis and its prevention. In : Hayase S. and Murao S. eds. Proceedings of the 8th World Congress of Cardiology. Amsterdam. Excerpta Medica. 1978: 81-91.

20- Davies MJ.: Atheroma, Atherosclerosis in ischaemic heart disease, Cardiovascular Bayer, 1990, V. 1, Page 1.4-1.15.

21-VirchowR.: Gesammelt abhandungen zur wissen-schaftlichen medicin. Frankfurt: Meidinger Sohn & Co., 1856; 496.

22-Haust M.: The morphogenesis and fate of potential and early atherosclerotic lesions in man. Human pathol. 1971; 2:1.

23-Smith B.: Identification of the gelatinous lesions. In Schettler G., Gotto A. Ed Atherosclerosis VI New York:Springer-Verlag, 1983:170.

24-Smith B., Staples E.: Intimal and medial plasma protein concentrations and endothelial function. Atherosclerosis 1982; 41:295.

25-Smith B., Staples E.: Haemostatic factors in human aortic intima. Lancet 1981; i:1171.

26-Rubin E, Farber L: Essential pathology, first Ed, JB Lippincott Company, Philadelphia 1990, Chapter 10, p 255-256.

27-Dormandy.JA.: The natural history of peripheral arterial disease; A textbook of vascular medicine; ed. Oxford University Press, Inc., 1996, part 3, 162.

28-Widmer LK, Greensher A, Kannel WB.: Occlusion of peripheral arteries. A study of 6400 working subjects. Circulation 1964; 30, 836-42.

29-Fowkes FGR, Housley E. Cawood E. et al. : Edinbrough artery study; prevalence of asymptomatic and symptomatic peripheral arterial disease in general population. Int J Epidemiol. 1991; 20: 384-92.

30-Walsh DB, Gilbertson JJ, Zwolak RM et al. :The natural history of superficial artery stenosis. J. Vasc. Surg 1991; 14; 299-304.

31-Hale WE., Marksrg, May FE, et al: Epidiemiology of intermittent claudication: Evaluation of risk factors Age ageing 17: 57-60, 1988.

32-Dormandy J., Mahir M.: Natural history and fate of patients with ischaemia of the legs. In Surgical management of vascular disease. Ed by Bell P., Jamieson C., C. Ruckley, 1992 W.B. Saunders Company Ltd pp 35-45.

33-Dormandy.JA.: The natural history of peripheral arterial disease; A textbook of vascular medicine; Ed. Oxford University Press, Inc., 1996, part 3, 162-65.

34- Schroll M., Munck O.: Estimation of peripheral arterial disease by ankle blood pressure measurements in a population study of 60-year-old men and women. J. Chronic Disorder; 34: 261-269.

35-Agner E.: Natural history of angina pectoris, possible previous myocardial infarction, and intermittent claudication during the eighth decade. Acta Med Scand. 1981; 210: 271-276.

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

37-Criqui MH, Fronek A., Barret Cannon E. et al: The prevalence of peripheral arterial disease in a defined population, Circulation 1985, 71: 510-515.

38-Davey-Smith G., Shipley MJ, Rose G.: Intermittent claudication, heart disease risk factors, and mortality. Circulation 1990, 82: 1925-31.

39-Dagenais GR., Maurice S, Robitalli NM, et al: Intermittent claudication in Quebec men from 1974-1986; The Quebec Cardiovascular study; Clin Invest Med 1991, 14: 93-100.

40-Newman AB, Siscovick DS, Manolio TA, et al: Ankle-arm index as a marker of atherosclerosis in the cardiovascular health study. Circulation 1993, 88: 837-845.

41-Vogt MT, Cauley JA, Newman AB, et al: Decreased ankle-arm pressure index and mortality in elderly women. JAMA 1993, 270:465-469.

42-Kannel WB, McGee DL: Update on some epidemiological features of intermittent claudication. J Am Geriatr Soc 1985; 33: 13-18. (Framingham study)

43-Mc Allister FF: The fate of patients with intermittent claudication management non-operatively. Am J Surg. 1976, 132: 593-595.

44-Houghson WG, Mann JI, Garrod A: Intermittent claudication; prevalence and risk factors. BMJ. 1978, 1:1379-81.

45-Houghson WG, Mann JI,Tibbs DJ, et al: Intermittent claudication factors determining outcome. BMJ 1978, 1: 1377-1379.

46-Jelnes R., Gaardsting O, Hougaard JK, et al: Fate of intermittent claudication; outcome, and risk factors. BMJ 1986, 293: 1137-40.

47-Cronenwett JL, Warner KG, Zelenock GB, et al : Intermittent claudication; current results of non-operative management. Arch Surg 1984; 119: 430-436.

48-Jonason J, Ringqvist I: Factors of prognostic importance for subsequent rest pain in patients with intermittent claudication. Acta Med cand 1985; 218:27-33.

49-Imparato AM, Kim GE, Davidson T, et al: Intermittent claudication; its natural course. Surgery1975; 78:795-799.

50-O'Riordain DS, O'Donnell JA: Realistic exceptions for the patients with intermittent claudication., Br.J.Surg.,1991;78:861-863.

51-Juergens JL, Barker NW, Hines EA: Arteriosclerosis obliterans: Review of 520 cases with special reference to pathogenic and prognostic factors. Circulation 1960; 21:188-195.

52-McDaniel MD, Cronenwett JL: Basic data related to the natural history of intermittent claudication. Ann Vasc Surg 1989;3: 273-277.

53-Dormandy JA, MurrayGD: The fate of the claudicants; a prospective study of 1969 claudicants. Eur J Vasc Surg; 1991; 5:131-3.

54-Taylor MS, Calo MR: Atherosclerosis of arteries of lower limbs. B.M.J 1962;24: 507-19.

55-Begg TB, Richards RL: The prognosis of intermittent claudication. Scott Med J 1962; 7: 341-52.

56-Bloor K: Natural history of atherosclerosis of the lower extremities. Ann Roy Coll Surg Eng 1961; 28: 36-51.

57-Dormandy J, Mahir M, Ascady G et al : Fate of patient with chronic leg ischaemia. J Cardiovasc Surg 1989; 30: 50-57.

58-Myers KA, King RB, Scott DF et al : Surgical treatment of the severely ischaemic leg; Survival rate; Br. J. Surg., 1987;65: 460-4.

59-Dormandy J., Stock G.: Definition and epideimiology of chronic critical limb ischaemia-European Working Group on Critical leg Ischaemia. In critical leg ischaemia; its pathophysiology and management., Springer-Verlag Berlin Heidelberg-Germany 1990 pp 1-5.

60- Wolfe JN. Defining the outcome of critical ischaemia: a one year prospective study. Br J Surg., 1986; 73: 321

61-Griffith CDM, Callum KG: Limb salvage surgery in a district hospital; Factors affecting outcome. Ann Coll Surg Eng 1988; 70: 95-8.

62- Veith FJ, Gupta SK, Samson RH, et al: Progress in limb salvage by reconstructive arterial surgery combined with new or improved adjuvent procedures. Ann Surg. 1981;194:386-401.

63-Hickey NC, Thomson IA, Shearman CP, Simms MH: Aggressive arterial reconstruction for critical limb ischaemia. Br.J.Surg.,1991;78:1476-8.

64- Dormandy JA, Stock G: Critical leg ischaemia, its pathophysiology and management European Consensus Document on Critical leg Ischaemia; March 1989; in Berlin, springer-verlag, 1990; X111.

65-Allen DR, Smallwood J, Johnson CD. Intra-arterial thrombolysis should be the initial treatment of acutely ischaemic limb. Ann Coll Surg Eng 1992;74: 106-11.

66-Beard J.: Recommendations for the management of chronic critical lower limb ischaemia. Eur J Vasc Endovasc Surg 1996; 12, 131-135.

67-Kelly PJ, Janes JM: Criteria for determining the proper level of amputation in occlusive vascular disease. A review of 323 amputations. J Bone Joint Surg 1957; 39: 883-91

68- Scott S, Wolma FJ, Flye MW: Factors affecting the results of below knee amputation in patients with and without diabetes. Surgery, Gynaecology & Obstetrics, 1982, 155: 513-18.

69-Dowd G.: Predicting stump healing following amputation for peripheral vascular disease using transcutaneous oxygen monitor. Ann Coll Surg Eng 1986; 68: 31-4.

70-Kihn RB, Warren R, Beebe GW: The geriatric amputatee. Ann Surg. 1972; 176: 305-14.

71-DeWeese JA, Rob C.: Autogenous vein grafts ; ten years later. Surgery 1962, 6:775-84.

72-Malone JM, Moore WS, Goldstone J: Life expectancy following aortofemoral arterial grafting. Surgery1977; 81:551-5.

73-Hughson WG, Mann JI, Garrod A: Intermittent claudication; prevalence and risk factors. BMJ 1978; 1:1379-81.

74-Szilagyi DE, Hageman JH, Smith RF et al: Autogenous vein grafting in femoropopliteal atherosclerosis; The limits of its effectiveness. Surgery 1979; 86:836-51.

75-Crawford ES, Bomberger RA, Glaeser DH et al: Aortoiliac occlusive disease: Factors influencing survival and function following reconstructive operation over twenty-five year period. Surgery 1981, 1981; 90:1055-67.

76-Hertzer NR: Fatal myocardial infarction following lower extremities revascularisation: Two hundreds and seventy three patients followed six-eleven postoperative years. Ann Surg. 1981;193: 492-8.

77-Vecht RJ, Nicolaides AN, Brandao E, et al: Resting and treadmill electrocardiographic findings in patients with intermittent claudication. Inter. Angio. 1982; 1:119-21.

78-Hertzer NR, B even EG, Young GR, et al: Coronary artery disease in peripheral vascular patients- a classification of 1000 coronary angiograms and results of surgical management. Ann Surg. 1984; 199:223-33.

79-Brewster DC, Okado RD, Strauss HW, et al: Selection of patients for preoperative coronary angiogram: use of Dipyridamole stress-thallium myocardial imaging. J. Vasc. Surg. 1985, 2:504.

80-Turnipseed WD, Berkoff HA, Belzer FO: Post operative stroke in cardiac and peripheral vascular disease. Ann Surg 1980; 192: 365-8.

81-Hennerici M, Aulich A, Sandeman W, Freund H-J: Incidence of asymptomatic extracranial arterial disease. Stroke 1981; 12: 750-8.

82-Klop RBJ, Eikelboom BC, Taks ACJM: Screening of the internal carotid arteries in patients with peripheral vascular disease by colour-flow duplex scanning. Eur J Vasc Surg 1991; 5: 41-5.

83-Missouris CG, Buckenham TM, Cappucio FP, et al: Renal artery stenosis : A common and important problem in patients with peripheral vascular disease. Am J Med 1994; 96: 10-14.

84-Choudhri AH, Cleland JGF, Rowlands PC et al: unsuspected renal artery stenosis in peripheral vascular disease. BMJ1990; 301:1197-8.

85-Murray K, Hawkins F: Angiography of the lower extremities in atherosclerotic vascular disease; Current technique. Surgical Clinic of North America 1992; Vol 72, No 4: 767-789.

86-Doppler CA: Ueber das farbige licht der doppelsterne und einiger anderer gistirne des himmels. Abhandl d Konigl Bohmischen Gesselschaft der Wissenschaften. 1843; Sers.2: 465-482.

87- Polak JF: Doppler Sonography: An overview. In peripheral vascular sonography: A Practical Guide, A Waverly company 1992; Chapter(1): 1-47.

88-Nichols W., O'Rourke M.:The Physics of ultrasound In McDonald's Blood Flow In arteries. Third Ed Thomson Press Ltd. India. 1990; pp 196-199

89-Keidel WD: Uber eine neue methde zur regisrierung der volumver anderungen des herzens am menschen. Ztschr fuer Kreilaufforschung 1950; 39: 257-271.

90-Satomura S: Study of the flow pattern in peripheral arteries by ultrasonic. J. Acoust Soc Jpn 1959; 15: 151-158.

91-kaneko Z: First steps in the development of the Doppler flowmeter. Ultrasound Med Biol 1986; 12: 187-195.

92-Olinger CP: Ultrasonic carotid echoarteriography. Am J Roentger Rad. ther Med. 1969; 106: 282-295.

93-Thiele B., Strandness DE.: Accuracy of angiographic quantification of peripheral atherosclerosis. Progress in cardiovascular diseases, Vol XXVI 1983; 3 : 223-235

94-Polak JF: Doppler Sonography: An overview. In peripheral vascular sonography: A Practical Guide, A Waverly company 1992; Chapter(1): 1-47.

95-Bernstein E: Doppler ultrasound technique in vascular disease, In Vascular diagnosis, 4th Ed 1993 by Mosby Year Book, Inc. USA. pp 67-74.

96- Kremkau FW: Principle and pitfalls of real-time colour flow imaging. In Vascular diagnosis, 4th Ed 1993 by Mosby Year Book, Inc. USA. pp 90-105

97-Merritt C.: Introduction for ultrasound, In Doppler colour imaging. Churchill Livingstone 1992, pp 1-6.

98-Nicolaides A, Renton SC: Duplex scanning; The second sight of vascular surgeon. Eur J Vasc Surg 1990; 4:445-447.

99- Nichols W., O'Rourke M.: The Physics of ultrasound In Mc Donald's Blood Flow In arteries. Third Ed Thomson Press Ltd. India. 1990; pp 199-201

100-Polak JF: Doppler Sonography: An overview. In peripheral vascular sonography: A Practical Guide, A waverly company 1992; Chapter

101-Nichols W., O'Rourke M.: The Physics of ultrasound In Mc Donald's Blood Flow In arteries. Third Ed Thomson Press Ltd. India. 1990 pp: 201-209

102-Kremkau F.: Principle and instrumentation of ultrasound. In Doppler colour imaging. Churchill Livingstone 1992, pp 7-60.

103-Faris I., McCollum P., Mantese V., Lusby R.: Investigation of the patient with atheroma. Surgical management of vascular disease. Ed by Bell P., Jamieson C., C. Ruckley, 1992 W.B. Saunders Company Ltd pp 131-196.

104- Seldinger S.: Catheter replacement of the needle in percutaneous arteriography: a new technique. Acta Radiol. 1953; 39:368-376.

105-Kohler T., Nance D., Cramer M., et al: Duplex scanning for diagnosis of aortoiliac and femoro-popliteal disease. Circulation 1987; 76: 1074-80

106-Koelemay MJW, Hartog D, Prins MH, et al: Diagnosis of arterial disease of the lower extremities with duplex ultrasonography. Br.J.Surg, 1996; 83: 404-409.

107-Cossman D., Ellison J., Wagner W., et al: Comparison of contrast arteriography, to arterial mapping with colour flow duplex imaging in lower limbs extremities. J Vasc Surg 1989; 10: 522-29.

108-Moneta GL, Yeager RA, Antonovic R, et al: Accuracy of lower extremity arterial duplex mapping. J Vasc Surg 1992; 15: 275-83.

109- Jager KA, Philips DS, Martin RL, et al: Non invasive mapping of lower limb arterial lesions. Ultrasound Med Biol 1985; 11:516-21.

110-Moucka J., Jager K.: Rational approach to peripheral arterial occlusive diseases. Schweiz-Rundsch-Med-Prax. 1990; 79(50):1553-9

111-Langsfeld M, Nepute J, Hershey FB, et al: The use of deep duplex scanning to predict heamodynamically significant aortoiliac stenosis. J Vasc Surg 1988; 7:395-9.

112-Legemate D., Ackerstaff R., Eikelboom B.: Duplex scanning in cerebral, abdominal, and peripheral arterial disease. Eur J Vasc Surg 1989; 3: 287-295.

113-Legemate DA, Teeuwen C, Hoeneveld H, et al: The potential of duplex scanning to replace aorto-iliac and femoro-popliteal angiography. Eur J Vasc Surg 1989; 3: 49-54.

114-Legemate DA, Teeuwen C, Hoeneveld H, et al: Value of duplex scanning compared to angiography and pressure measurement in assessment of aorto-iliac and femoro-popliteal arterial lesions. Br. J. Surg., 1991; 78: 1003-8.

115-Legemate DA, Teeuwen C, Hoeneveld H, et al: Spectral analysis in duplex scanning of aorto-iliac and femoro-popliteal arterial disease. Ultrasound Med Biol 1991; 17: 769-76.

116-Elsman BHP, Legemate DA, Van Der Heijden Fhwm, et al: Impact of ultrasonographic duplex scanning on therapeutic decision making in lower-limb arterial disease. Br. J. Surg., 1995; 82: 630-3.

117-Vashisht R, Ellis MR, Skidmore C, et al: Colour-coded duplex ultrasonography in selection of patients for endovascular surgery. Br .J. Surg., 1992; 79:1030-1.

118-Allard L, Cloutier G, Durand LG, et al: Limitations of ultrasonic duplex scanning for diagnosing lower limb arterial stenosis in the presence of adjacent segment disease. J Vasc Surg 1994; 19: 650-7

119-Koennecke HC, Fobbe G, Hamed MM, et al: Diagnottik Arterieller Gefaberkrankungen der unteren Extremitaten. Vasa Suppl 1991; 32: 154-6.

120-Whelan J., Barry M., Moir J.:Colour flow Doppler Ultrasoungraphy: Comparison with peripheral arteriography for investigation of peripheral arterial disease. J Clin Ultrasound 1992; 20:369-374.

121-Polak JF, Karmel MI, Mannick JA, et al: Determination of the extent of lower-extremity peripheral arterial disease with colour-assisted duplex sonography: comparison with angiography. AJR Am J Roentgenl 1990; 155: 1085-9.

122- Hatsukami TS, Primozich JF, Zierler RE, et al: Colour Doppler imaging of infrainguinal arterial occlusive disease. J Vasc Surg 1992; 16: 527-31.

123-Baxter G., Polak J.: Lower limb colour flow imaging: a comparison with ankle :brachial measurement and angiography. Clin Radiol 1993; 47: 91-5

124-Davis A, Magee T., Parry R, et al: Duplex ultrasonography and pulse-generated run-off in selecting claudicants for femoro-popliteal angioplasty. Br. J. Surg 1992; 79:894-6

125-Whyman M., Gillespie I., Ruckley CV. Allen P., Fowkes F: Screening patients with claudication from femoro-popliteal disease before angioplasty using Doppler colour flow imaging. Br. J Surg 1992; 79:907-9

126-Landwehr P., Lackner K.:Farbkodierte duplexsonographie vor und nach PTA der arterien der unteren extremitat. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 1990; 152: 35-41

127-Baumgarner I., Koch M., Maier S.: Duplex-sonographie magnetresononanz (MR) -arteriographie und konventionelle Verschlubkrankheit. Vassa Suppl 1991; 33:303.

128-Heijden V., Legemate DA, Teeuwen C et al: Value of duplex scanning in the selection of patients for percutaneous transluminal angioplasty. Eur J Vasc Surg 1993; 7: 71-76.

129- Bergamini T., Tatum C., Marshall C .et al: Effect of multilevel sequential stenosis on lower extremities arterial duplex scanning. Am J Surg 1995 169: 564-566

130-Whiteley M., Harris R., Horrocks M.: Aortoiliac segment examination with colour flow duplex- A pilot study using Klean prep. to improve the image quality. Eur. J Vasc Surg. 1995; 10(2) :192-197.

131-Winters K., Busch D: Adobe photoshop principles. In Photoshop 3.0, A Subsidiary and Co Inc. first Ed. 1995 (USA) PP: 41-59.

132-Wegener O.: Mathematical principles of the image. In whole body computed tomography. Blackwell scientific publications. Boston 1992 second Ed. pp 3-4.

133:Wegener O.: Image reconstruction. In whole body computed tomography. Blackwell scientific publications. Boston 1992 second Ed. pp 5-8

134-Winters K., Busch D:Image resolution. In Photoshop 3.0, A Subsidiary and Co Inc. first Ed. 1995 (USA) PP: 259-281.

135-Stranden E., Slagsvold E., Morken B., Alker H., Bjordal J.: Three dimensions visualisation of peripheral arterial disease. In Vascular imaging for surgeons. Ed by Greenhalgh R.W.B. Saunders Company Ltd UK. 1995 PP: 71-80

136-Einenkel D, Bauch KH, Benker G: Treatment of juvenile goitre with levothyroxine, iodide, or a combination of both; the value of ultrasound grey scale analysis. Acta Endocinol Copenh. 1992;127(4) 301-6.

137-Becker W, Frank R, Borner W: The importance of quantitative grey scale analysis of the sonogram in diffuse thyroid disease. ROFO-Fortschr Geb Rontgenstr Nuklearmed 1989;150(1): 66-71.

138-Huber S, Delorme S, Knopp MV, et al: Breast tumours; computer-assisted quantitative assessment with color Doppler US. Radiology 1994; 192(2):797-801.

139-Zendel W, Wakat P, Fischer G, et al: A comparison of the quantified determination of the echogeneity of the liver by ultrasound and the density of the liver by CT. Rontgenblatter 1989; 42(3):114-7.

140-Hess CF, Wolf A, Kolbel G, et al: Subjective evaluation and quantitative grey scale analysis in the sonographic diagnosis of diffuse changes in the liver parenchyma. Fortschr Geb Rontgenstr Nuklearmed 1986;145(2): 140-4.

141-Lusby R.: Plaque characterisation: Does it identify high risk group? In Cerebral re-vascularisation Ed by Bernstein E., Callow A., Nicolaides A., Shifrin E., By Med-Orion publication company, 1993 pp:93-107

142-Lusby R, Farrell L, Ehrenfeld W, et al: Carotid plaque haemorrhage: Its role in production of cerebral ischaemia. Arch Surg 1982; 117: 1479-1488.

143-Fisher M.: Occlusion of internal carotid artery: Arch. Neurol Psychiatry 1951; 5: 346.

144-Fisher M., Ojemann R., : A clinico-pathologic study of carotid endarterectomy plaques. Rev Neurol 1986; 142:573.

145-Fisher M.: The use of anticoagulants in cerebral thrombosis. Neurology 1958; 8: 311.

146-Leahy A, Grouden M, Mcbride K, et al: Duplex scanning for assessment of both carotid luminal diameter and atheromatous plaque morphology. Ann Vasc Surg 1986; 1:465.

147-Moore WS., Ziomek S., Baldrich WJ., Et al: Can clinical evaluation and non-invasive testing substitute for arteriography in evaluation of carotid artery disease? Ann Surg 1988; 208: 91.

148- Moore WS., Hall AD, :Ulcerated atheroma of carotid artery : A cause of transient cerebral ischaemia. Am J Surg 1968; 116: 237.

149- Moore WS., Boren C., Malone JM: Natural history of non-stenotic asymptomatic ulcerative lesions of the carotid artery. Arch Surg 1978; 113: 1352.

150- Hollenhorst R: Significance of bright plaque in the retinal arterioles. JAMA 1961; 178: 23.

151-Bock R, Gray-Weale A, Mock P, et al: Natural history of asymptomatic carotid artery disease. J Vasc Surg 1993; 17: 160-171.

152-Grey-weale AC, Graham JC, Burnett JR, et al: Carotid artery atheroma: Comparison of preoperative B-mode ultrasound appearance with carotid endartectomy specimen pathology. J Cardiovasc Surg 1988; 29: 676-681.

153-Geroulakos G, Sonecha T, Nicolaides A, et al: The management of patients with asymptomatic carotid stenosis. In Bernstein E, Callow A, et al ed. Cerebral re-vascularisation. London Med Orion. 1993; 565(b).

154-Langsfeld M. Gray-Weale AC, Lusby RJ: The role of the plaque morphology and diameter reduction in the diameter of new symptoms in asymptomatic carotid arteries. J.Surg 1989; 9: 548.

155-Langsfeld M., Lusby RJ: The spectrum of carotid artery disease in asymptomatic patients. J Cardiov Surg 1988; 29: 687.

156-El-Barghouty N, Geroulakos G, Nicolaides A, et al : Computer-assisted carotid plaque characterisation. Eur J Vasc Surg 1995; 9(4) 389-93.

157- Dotter CT: Cardiac catheterization and angiographic techniques of the future. Cesk Radiol 1965; 19: 217-36.

158-Dotter CT, Judkins MP: Transluminal treatment of arteriosclerotic obstruction: Description of a new technique and a preliminary report of its application. Radiology 1989;172:904-920.

159-Porstmann W: Ein neuer Korsett-balloonkatheter zur transluminalen Rekanalisation nach Dotter unter besondere Berucksichtigung von Obliterationen an den Beckenarterien. Radiol Diagn(Berl) 1973;14: 239.

160-Gruntzig A, Hopff H: Perkutane Rekanalisation chronischer arterieller Verschlusse mit einem neuen Dialationskatheter: Modification der Dotter-Technik. Dtsch Med Wochenschr 1973; 99: 2502-2505.

161-Deutsch L.: Technique of PTA including aortoiliac and femoropopliteal system: indications, results, and complications. In Endovascular surgery Ed by Ann S., Moore W. W.B.Saunders Company 1992; pp: 166-211.

162-Block PC, Myler RK, Stertzer S, et al: Morphology after transluminal angioplasty in human beings. N Engl J Med 1981; 305:382-385.

163-La delia V, Rossi PA, Sommers S, et al: Coronary histology after percutaneous transluminal coronary angioplasty. Tex Heart Institute J 1988; 15: 113-116.

164-Castaneda-zuniga WR, Formanek A, Tadavarthy M, et al: The mechanism of balloon angioplasty. Radiology 1980; 135:565-571.

165-Deutsch L.: Technique of PTA including aortoiliac and femoropopliteal system: indications, results, and complications. In Endovascular surgery Ed by Ann S., Moore W. W.B.Saunders Company 1992; pp: 166-211.

166-Zarins CK, Lu CT, Gewertz BL, et al: Arterial disruption and remodelling following balloon dilation. Surgery 1982; 92:1086-1095.

167-Post MJ, Borst C, Pasterkamp G, et al: Arterial modelling in atherosclerosis and restenosis: a vague concept of a distinct phenomenon. Atherosclerosis 1995; 118: 115-123.

168-Eikelboom B., Odink H, Valois J: Percutaneous transluminal angioplasty. In Surgical management of vascular disease. Ed by Bell P., Jamieson C., C. Ruckley, 1992 W.B. Saunders Company Ltd pp: 469-490

169-Rutherford R: Standards for evaluating results of interventional therapy for peripheral arterial disease. Circulation 1991; 83:(suppl I) I-6-I-11.

170- Rutherford R., Becker G.: Standards for evaluating and reporting the results of surgical and percutaneous therapy for peripheral arterial disease. Journal of vascular and interventional radiology (JVIR) 1991; 2: 169-174.

171-Privatdozent D, Zeitler E, Schoop W, et al: The treatment of occlusive arterial disease by transluminal catheter angioplasty. Radiology 1971; 99:19-26.

172-Wierny L, Plass R, Prostmann W: Long term results in 100 consecutive patients treated by transluminal angioplasty. Radiology, 1974; 112: 543-548.

173-Calapino RF, Harries-Jones EP, Johnston KW: Percutaneous transluminal dilation and re-canalisation in the treatment of peripheral vascular disease. Radiology 1980; 135: 583-587.

174-Freiman DB, Spence R, Gatenby R, et al: Transluminal angioplasty of the iliac and femoral arteries: Follow up, results without anticoagulation. Radiology 1981; 141: 347-350.

175-Greenfield AJ: Femoral, popliteal, and tibial arteries: Percutaneous transluminal angioplasty. AJR 1980; 135:927-935.

176-Martin E, Frankuchen E, Karlson K, et al: Angioplasty for femoral artery occlusion: Comparison with surgery. AJR 1981; 137: 915-919.

177-Kaufman SL, Barth H, Kadir S, et al: Haemodynamic measurements in the evaluation and follow up of transluminal angioplasty of the iliac and femoral arteries. Radiology 1982; 142:329-336.

178-Ckien-Tia L, Zarins CK, Yang CF, et al: Percutaneous transluminal angioplasty for limb salvage. Radiology 1982; 142: 337-341.

179-Russel H S, Sprayregen S, Veith FJ, et al: Management of angioplasty complications; unsuccessful procedures and early and late failures. Ann Surg 1984; vol 199 No 2, 234-240.

180-Krepel VM, Van Andel C, Van Erp WFM, et al: Percutaneous transluminal angioplasty of the femoro-popliteal artery: Initial and long-term results. Radiology 1985;325-328.

181-Johnston W, Rae M, Johnson SAH, et al:5 Year results of a prospective study of Percutaneous transluminal angioplasty. Ann Surg 1987; Vol 206 No 4: 403-13.

182-Brewster DC, Cambria RP, Darling C, et al: Long term results of combined iliac balloon angioplasty and distal surgical re-vascularisation. Ann Surg 1989;Vol 210 No 3: 324-331.

183-Capek P., McLean G., Berkowitz H: Femoro-popliteal angioplasty: Factors influencing long term success. Circulation Suppl. 1991 Vol 83; No 2:70-80

184-Jeans WD, Danton RM, Baird RN, Horrocks M: A comparison of the costs of vascular surgery and balloon dilatation in lower limb ischaemic disease. Br J Radiol 1986; 59: 453-456

185-Sudhir K, Fitzgerald PJ, Yoch PG: Intravascular ultrasound: Technical advances and clinical applications. In Endovascular surgery 2nd Ed; 132-144.

186-Geber TC, Erbel R, Gorge G, et al: Classification of morphological effects of Percutaneous transluminal coronary angioplasty assessed by intravascular ultrasound. Am J Cardiol 1992; dec 15; 70(20):1546-54.

187-Amendt K, Schomig A, Wilhelm C: Intravascular ultrasound in patients with peripheral arterial occlusive disease. Vasa 1992; 21(1): 27-38.

188-Everitt BS: Cross over designs. In Statistical methods for medical investigators. Oxford University Press New York1989; pp: 68-82

189-Cox DR: Statistical significant tests. Br J Clin Pharmac 1982;14: 325-331.

190-Armitage P, Berry G.: Kappa measurement of agreement. In Statistical methods in medical research 3 th Ed. Blackwell scientific publication 1994; pp: 443-447

191-Altman D G: Inter-rater agreement. In Practical statistics for medical research. Chapman and Hall 1991; 403-409.

192- Hirsch R., Riegelman R.: Applying probabilities, Diagnostic testing. In Statistical operations, Blackwell Science1996; pp:1-39.

193-Jekel J., Elmore J., katz D.: Receiver operating characteristics curve. In Epidemiology biostatistics and preventive medicine. Saunders text and review series 1996: 93-97

194-Bodily K., Buttorff J., Nordesgaard A., Osborne R.: Aortoiliac reconstruction without arteriography. Am.J Surg 1996; vol 171: 505-507.

195-Orron D, Kimm D, Kramer J, Shifrin E: The role of arteriography in the evaluation of extracranial cerebrovascular artery disease. In cerebral re-vascularisation Ed by Bernstein E, Callow A, Nicolaides A, Shifrin E. MED-ORION, 1993; 110-147.

196-Wiliam P, Warwick R, Dyson M, Bannister L: The arteria profunda femoris in Gray anatomy textbook 3th Ed. 1989; 783.

197-Lusby R: Plaque characterisation: Does it identify high risk group. In cerebral re-vascularisation Ed by Bernstein E, Callow A, Nicolaides A, Shifrin E. MED-ORION 1993; 93-107

198-Pemberton M, Nydahl S, Harshorne T, et al: Can lower limb vascular reconstruction be based on colour duplex image alone. Eur. J Vasc Surg 1996;12(4): 452-4

199-Egglin T, O'Moore P, Feinstein A,et al: Complication of peripheral arteriography: a new system to identify patients at risk. J Vasc. Surg 1995; 22:787-794.

200-Karasch T., Rieser R., Grun B., et al: Determination of the length of the occlusion in extremity arteries- colour duplex ultrasound versus angiography. Ultraschall-Med. 1993; 14:247-254.

201-Bell P, London N: Surgical treatment of critical ischaemia. Critical ischaemia 1992; 2:15-23.

202-Mewissen M., Kinney E., Dennis F., et al: The role of duplex scanning versus angiography in predicting outcome after balloon angioplasty in the femoro-popliteal artery. J Vasc Surg 1992; 15: 860-6.

203-Cluley S., Brener B., Hollier L., et al: Transcutaneous ultrasonography can be used to guide and monitor balloon angioplasty. J Vasc Surg 1993; 17: 23-31.

204-Edwards J., Coldwell D., Coldman M., et al: The role of duplex scanning in selection of patients for transluminal angioplasty. J Vasc Surg 1991; 13: 69-74.

205-Collier P., Wilcox G., Brooks D., et al: Improved patient selection for angioplasty utilising color Doppler imaging. Am J Surg 1990; 160:171-174.

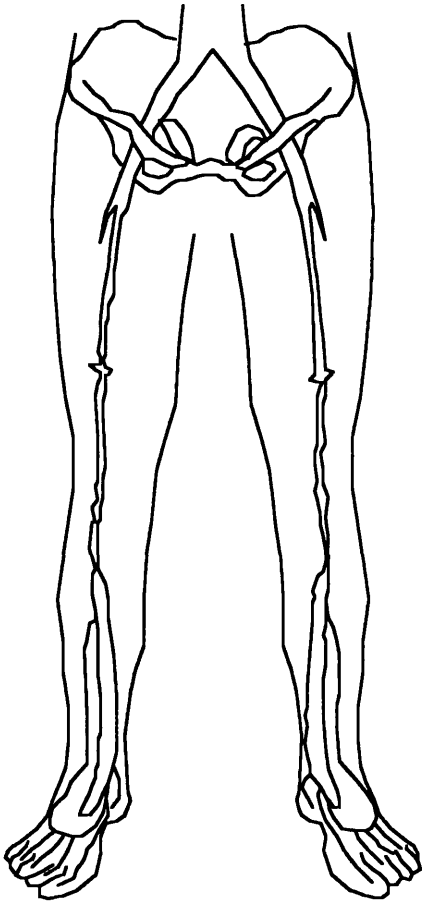
206-Andersen H., Maeng M., Thorwest M., Falk E.: Remodeling rather than neointimal formation explains luminal narrowing after deep vessel wall injury. Circulation 1996; Vol 93 No 9: 1716-24

207-Carter A., Laird J., Farb A., Kufs W., Wortham D., Virmani R.: Morphological characteristics of lesion formation and time course of smooth muscle cell proliferation in a porcine proliferative restenosis model. JACC 1994; Vol 24, No 5: 1398-1405.

Part V : Appendix -1-

Duplex scanning in assessment of peripheral arterial disease:

Personal details:
Patient's name
Age
Hospital No
Smoking Status



Cardiac status
-
-
-

Cerebrovascular status:
-
-

-Peripheral arterial disease History:
Duration
History
-
-

History of intervention (Surgery/ Angioplasty):
-
-

Medication

Current status

Claudication Distance

Rest Pain Site
Way of control

Ulceration Site

Blue toe syndrome

General assessment

Local assessment
-

Duplex scanning

Report

Appendix-2- Angioplasty trial form:

Angioplasty

Patient's name
Age
Hospital No
Smoking Status

Cardiac status

-
-
-

Cerebrovascular status:

-
-
-

Peripheral arterial disease History:

Duration
History

-
-
-
-

History of intervention (Surgery/ Angioplasty):

-
-
-

Medication

Current status

Claudication	Distance	
Rest Pain	Site	Way of control
Ulceration	Site	
Blue toe syndrome		

General assessment

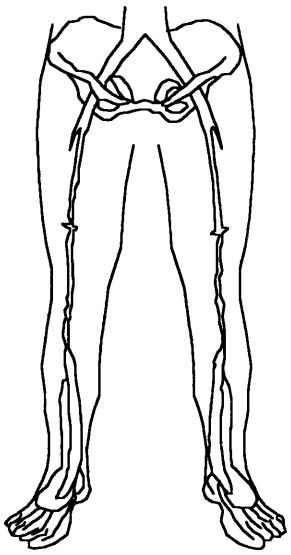
-
-

Local assessment

-
-
-

Duplex scanning

Report



Initial visit

24 hours post balloon

3 weeks

3months

6 months

1 years

more

MILD Classification

M:	**Echolucent**	**Mixed**	**Echogenic**
I	**Smooth**	**Ulcerated**	
L	**< 5 cm**	**5-10cm**	**>10cm**
D	**Insignificant(<50%)**	**Significant(>50%)**	**Occluded**
Total			

Appendix -3: List of original articles:

1-A comparison of duplex imaging and arteriography in the evaluation of peripheral arterial disease of lower limb.

S. Aly, K. Sommerville, M. Adiseshiah, M. Rafeal, PD Coleridge Smith, C C R Bishop. accepted for publication in Br J Surg. 1997.(in press)

2-Duplex scanning and clinical management of lower limb arterial disease.

S. Aly, C C R Bishop, PD Coleridge Smith.

3-Effect of multisegmental arterial disease on duplex accuracy.

S. Aly, M. Jenkins, C C R Bishop, PD Coleridge Smith..

4-Computer-assissted technique in atherosclerotic plaque characterisation. work-shop.

S. Aly, H.Al Adaileh, C C R Bishop, PD Coleridge Smith.

5-Criteria of arteriography following duplex scanning of lower limb arterial disease.

S. Aly, PD Coleridge Smith, C C R Bishop.

6-Value of computer-assisted image analysis in plaque atherosclerotic plaque characterisation. S. Aly, PD Coleridge Smith, C C R Bishop.

7-An objective classification for peripheral arterial disease of lower limb arterial disease.

S. Aly, C C R Bishop, PD Coleridge Smith.

8-Value of atherosclerotic plaque characterisation on the outcome of balloon angioplasty in lower limb arteries.

S. Aly, PD Coleridge Smith, C C R Bishop.

List of presentations from this thesis:

1-Duplex scanning in assessment of peripheral arterial disease.

S Aly, K.sommerville, PD Coleridge Smith, C C R Bishop.

Abstract accepted and published in ESRS as poster 1995

2-Currents aspects in evaluation of chronic ischaemia of lower extremities.

S Aly, K.sommerville, C C R Bishop, PD Coleridge Smith.

Abstract accepted and presented in the Antylious society in September 1994

3-Why duplex not arteriography in routine assessment of peripheral arterial disease of lower limbs?

S Aly, K.sommerville, PD Coleridge Smith, C C R Bishop.

Abstract accepted for presentation and published in Royal Society of Medicine June 1996

4-Duplex ultrasound scanning is another diagnostic modality for assessment of PVD.

S Aly, K.sommerville, PD Coleridge Smith, C C R Bishop. Presentation in Research meeting at Whittington Hospital 1996.

5-Effect of multisegmental disease on duplex accuracy.

S Aly, M. Jenkins, C C R Bishop, PD Coleridge Smith. Abstract accepted as a poster in First international ultrasound meeting in Malmo Sweden 1996

6-Duplex ultrasonography assessment in aortoiliac and femoro-popliteal arteries.

S Aly, K.sommerville, PD Coleridge Smith, C C R Bishop. Abstract accepted for presentation in First international ultrasound meeting in Malmo Sweden 1996

7-Clinical decision based on duplex ultrasonography compared to IA DSA.

S Aly, K.sommerville, PD Coleridge Smith. Presented in the visitor professor research annual meeting at UCLMS 1997.

8-An Objective classification for peripheral arterial disease.

S Aly, PD Coleridge Smith, C C R Bishop. Abstract accepted for presentation Surgeon association for Great Britain and R. Ireland -Bournemouth 1997, and published in the Br J Surg. May 1997

9-Will duplex ultrasonography replace arteriography in routine assessment of peripheral arterial disease.

S Aly, K.sommerville, PD Coleridge Smith, C C R Bishop

Abstract presented in the Midland Vascular Society Meeting- Norwich in 1996

10-Middlesex classification is an objective classification for lower limb arterial disease.

S Aly, PD Coleridge Smith, C C R Bishop. Presented in the Antylious Vascular Society 1996

11-Criteria for arteriography following lower limb duplex scanning. Vascular Surgical Society, November 1997.

S. Aly, P.D. Coleridge smith,. C C R Bishop.

12- Value of atherosclerotic plaque characterisation and its effect on balloon angioplasty. Vascular Surgical Society, November 1997.

S. Aly, P.D. Coleridge smith, C C R Bishop. (BJS prize)