CRITICAL LOWER LIMB ISCHAEMIA.

IS DISTAL REVASCULARISATION WORTHWHILE?

THESIS SUBMITTED FOR

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ABSTRACT.

Many patients with gangrene in this country are still offered amputation without any attempt at revascularisation. At Regional Vascular Services (RVS) all patients are investigated and a variety of surgical procedures performed. At many district general hospitals (DGH) the repertoire of surgical procedures is smaller. This study aims to evaluate whether it is worthwhile to apply the most sophisticated methods of revascularisation to patients with critical lower limb ischaemia.

Differences in demography are noted between patients with critical lower limb ischaemia, intermittent claudication and abdominal aortic aneurysms. Diabetes mellitus is most prevalent in patients with critical limb ischaemia. Comparing the demographic data of patients with critical ischaemia presenting to the RVS and the DGH there were no significant differences in risk factors, but, the annual presentation rate at the RVS was two and a half times greater than at a DGH in the North West Thames Region. Moreover, the RVS had more patients with distal disease.

There were no overall differences in the cumulative limb salvage and survival rates comparing the RVS and the DGH, but for patients with distal disease the cumulative limb salvage rates were 78% and 18% respectively at one year. At the RVS when revascularisation failed and major amputation was needed 72% were at the below knee level compared to 50% at the DGH.

^{31}Phosphorus magnetic resonance spectroscopy was used to study the small muscles of the foot at rest to see if the system could predict which limbs had potentially reversible ischaemia. Changes in the ^{31}P spectra were seen at rest, but proved to be of limited clinical value.

Quality of life studies demonstrated significant improvement in reduction in pain and mobility in the reconstruction group with time. Surprisingly, we were unable to demonstrate statistically significant differences between the reconstruction and amputation groups, presumably due to the small sample size.

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STATEMENT OF ORIGINALITY.

The work presented in this thesis is original, conducted and co-ordinated by myself. It was based upon an idea proposed by Professor R.M. Greenhalgh and Professor G Bydder, under whose direction I have worked.

The ^{31}Phosphorus Magnetic Resonance Spectroscopy work was presented by me at the Surgical Research Meeting in January 1991, titled

"Prediction of irreversible lower limb ischaemia using phosphorus magnetic resonance spectroscopy in the resting foot."

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ABBREVIATIONS.

ADL.	Activities of Daily Living.
ATP.	Adenosine triphosphate.
DGH.	District General Hospital.
IQR.	Inter-quartile range.
M.	Molar.
MDP.	Methylene diphosphonate.
MRS.	Magnetic resonance spectroscopy.
NHP.	The Nottingham Health Profile.
NMR.	Nuclear magnetic resonance.
31P MRS.	^{31}Phosphorus magnetic resonance spectroscopy.
Pcr.	Phosphocreatine.
PDE.	Phosphodiester.
Pi.	Inorganic phosphate.
PME.	Phosphomonoester.
ppm.	Parts per million.
RVS.	Regional Vascular Service.

CHAPTER 1.

HISTORICAL REVIEW.

DEFINITION OF CRITICAL LOWER LIMB ISCHAEMIA.

Patients presenting with lower limb ischaemia range from those with mild non-disabling intermittent claudication through to those with intractable rest pain and major tissue loss. This has led to large variations in the patency and limb salvage results published for surgical revascularisation procedures, as often series include patients with varying degrees of ischaemia. It is important that accurate definitions are provided and that limb salvage with avoidance of a major amputation is not inappropriately claimed.

One of the earliest classification in use was that described by Fontaine, Kim and Kieny. There paper published in 1954 classified patients with peripheral circulatory disorders as follows:

Stage I	Clinically symptom free occlusion.
Stage II	Ischaemia induced by exercise, clinically affecting the lower extremities as pure intermittent claudication, with absence of symptoms when at rest.
Stage III	Ischaemic symptoms even when at rest.
Stage IV	Trophic ulcers and gangrene A limited gangrene B extensive gangrene

This definition is subjective dependent upon both the patient reporting symptoms and the observer assigning the patient to the correct stage. Patients with stage III ischaemia may improve spontaneously, leading to optimistic results or deteriorate and enter stage IV. Also it lacks both objectivity and fails to predict which limbs will be lost if revascularisation is not undertaken.

The introduction of Doppler ultrasound to measure the systolic pressure in the lower limb (Strandness, McCutcheon and Rushmer) in 1966 provided for the first time an objective measure of the severity of ischaemia and in 1982 the International Vascular Symposium working party provided the first definition of critical limb ischaemia:

1. Severe rest pain that prevents the patient from sleeping and requires opiate analgesia for at least four weeks

and either:

2. Doppler ankle systolic pressure < 40 mmHg

or:

3. Doppler ankle systolic pressure < 60 mmHg in the presence of superficial tissue necrosis or digital gangrene

They stated that diabetics should be excluded from an ideal clinical study (Bell et al. 1982)

This definition of critical limb ischaemia was further modified in 1986 by the Joint Vascular Research Group:

1. Severe rest pain requiring opiate analgesia for at least four weeks

and either:

2. Doppler ankle systolic pressure < 40 mmHg

or:

3. Tissue necrosis or digital gangrene

The group also felt that the definition should exclude all diabetics, as neuropathy and sepsis, as well as ischaemia play part in the aetiology of limb loss, but in practice diabetics are included, because up to one third of patients with critical limb ischaemia are diabetic and exclusion of them from the results would lead to unnecessary bias. They also recommend that studies should not contain a mixture of patients with both critical ischaemia and intermittent claudication as patency rates and limb salvage vary depending upon the degree of ischaemia (Wolfe. 1988). This definition is more objective than the Fontaine classification (Cachovan. 1991), but still excludes a number of patients with true critical ischaemia, but whose Doppler systolic ankle pressure is above 40 mmHg.

In the USA the Ad Hoc Committee on Reporting Standards for Vascular Surgery defined critical limb ischaemia in 1986 (Rutherford et al. 1986). Acute ischaemia was defined as a clinical state that is subdivided into three classes; the limb is viable, there is threatened limb viability or there is major irreversible ischaemic change in the limb.
Chronic ischaemia was sub-divided into six categories, three refer to critical ischaemia. The presence of rest pain or tissue loss and a reduced Doppler systolic ankle or toe pressure are required: ischaemic rest pain without tissue loss and a Doppler ankle systolic pressure < 40mmHg, or minor tissue loss and a Doppler ankle systolic pressure < 60mmHg, or major tissue loss and a Doppler ankle systolic pressure < 60mmHg.

In 1989 the European Working Group on Critical Limb Ischaemia held a series of workshops and published a consensus document on critical limb ischaemia (European Consensus on critical limb ischaemia. 1989), this states that a patient with critical limb ischaemia will have had persistently recurring rest pain requiring regular analgesia for more than two weeks, or ulceration of the foot, or gangrene of the foot and a Doppler ankle systolic pressure of less than 50 mmHg (in a patient with diabetes mellitus absence of ankle pulses suffice.) Two further discussion documents were published by this group; the Second European consensus document on chronic critical leg ischaemia (1991) and the European consensus on critical limb ischaemia (1992), setting out minimum standards for the investigation and management of a patient with critical lower limb ischaemia. The definition aims to include all limbs with critical limb ischaemia, and implies that unless the limb undergoes a revascularisation procedure major limb amputation will be required. Despite these carefully defined criteria a few patients with true critical limb ischaemia will be excluded from reported series of patients with critical limb ischaemia. Also a different group of patients fulfilling the criteria for critical limb ischaemia, who are not suitable for revascularisation will maintain a useful functional limb despite no active intervention.

EPIDEMIOLOGY OF CRITICAL LIMB ISCHAEMIA.

The incidence of critical lower limb ischaemia is hard to estimate since many reported series of patients with severe ischaemia do not precisely fulfil the definition set out by the Working Party of the International Vascular Symposium (Bell et al. 1982) and thus do not have irreversible ischaemia. Most estimates of the incidence of critical limb ischaemia rely on extrapolation of the data available on the natural history of peripheral vascular disease and the amputation statistics. Prior to the widespread use of arterial reconstruction for patients with intermittent claudication and critical limb ischaemia, longitudinal studies reported on the natural history of atherosclerosis. One of the earliest of these was published by Bloor in 1961 when surgical management options were limited to lumbar ganglionectomy, amputation or tenotomy of the tendo achilles. He studied 1,508 patients between 1947 and 1953 who presented with intermittent claudication only. During that time 263 patients developed gangrene with 41 of these bilateral. One hundred and twenty one patients had a mid thigh amputation with 21 bilateral amputations. He concluded that a male patient with peripheral vascular disease surviving for five years had a seven per cent chance of a major amputation, which rose to 12 % if the patient survived ten years. (Bloor, 1961). Such information is now impossible to collect as it would be ethically impossible to randomise patients with critical limb ischaemia to undergo an attempted revascularisation or a primary major amputation.

Various studies quote the prevalence of peripheral vascular disease in the general population at between 0.3% and 7.7% (Fowkes. 1988) depending upon age, sex and the type of population studied.
Assuming that these estimates are correct and that approximately 20% of patients with symptomatic ischaemia will develop critical limb ischaemia (Jelnes et al. 1986) then the incidence of critical limb ischaemia is approximately 500-1000 per million of the population per

year of which approximately one quarter will undergo major amputation (European Consensus on critical limb ischaemia. 1989).

In 1986 nearly 5,000 new patients attended limb fitting centres in England, Wales and Northern Ireland following amputations for vascular insufficiency including Diabetes mellitus (DHSS Statistics and Research Division. 1987). This underestimates the number of major amputations performed since many patients are not referred for limb fitting due to frailty or ill health preventing mobilization or early post operative death.

With the advent of improved diagnostic skills and the widespread use of surgical revascularisation in the late 1950's (DeBakey et al. 1957) and 1960's (Hall. 1962) it was expected that the major amputation rate would fall. However this has not occurred as illustrated by a major study in Maryland, USA. (Tunis, Bass, Steinberg. 1991). Angioplasty for patients with peripheral vascular disease was accompanied by an increase in the number of bypass operations and no corresponding fall in the number of major amputations. Despite an increase in the number of revascularisation procedures, there has not been a corresponding increase in the incidence of patients with peripheral vascular disease (Kannel et al. 1970, Kannel and McGee. 1985). Prior to the widespread use of angioplasty and surgical reconstruction, many patients were treated by conservative regimes of exercise, stopping smoking and losing weight. Many centres now reconstruct early for severe symptoms in intermittent claudication and critical limb ischaemia. Failure either in the early or late post-operative period leads to further revascularisation surgery or major amputation. Therefore, many patients will have several limb salvage operations during the course of their life.

Most reports of patients with critical limb ischaemia are published from centres with a special interest in limb salvage. This thesis compares the risk factors and outcome for patients treated in both a Regional Vascular Service (RVS) and a District General Hospital (DGH). It is known that patients with critical limb ischaemia have a poor prognosis, but accurate data is hard to find. The Joint Vascular Research Group reported that one year after presenting with critical limb ischaemia 55% of patients will be alive with two legs, 25% will have had a major amputation and 20% will be dead (Wolfe, 1986).

MANAGEMENT OPTIONS IN CRITICAL LOWER LIMB ISCHAEMIA. REVASCULARISATION VERSUS PRIMARY MAJOR AMPUTATION.

Critical lower limb ischaemia and the threat of major amputation is devastating to the majority of patients. It was hoped that revascularisation - angioplasty or reconstructive surgery would reduce the total number of major amputations, this does not appear to be the case (Tunis, Bass and Steinberg. 1991). By definition all patients with critical limb ischaemia should require a major amputation if revascularisation is not undertaken early, a small number of patients are the exception. But what of the others, few patients with critical limb ischaemia have a single localised stenosis or occlusion (Harris.1987) and successful revascularisation often

requires simultaneous or serial applications of several techniques, for example; supra-inguinal angioplasty with femoro-crural vein bypass grafting. The decision to revascularise or amputate is multifactorial and all patients should be offered the opinion of a skilled vascular surgeon and the facilities of a vascular laboratory (Boontje. 1979) The factors that influence the decision to attempt revascularisation include; the severity of ischaemia with accompanying tissue loss, the site of disease, the presence or absence of autologous vein for infra-inguinal reconstructions, the distal runoff, the risk of developing intimal hyperplasia, the presence of any other medical conditions and finally cost.
Only if extensive gangrene involves the proximal foot or knee and hip flexion contractures would prevent rehabilitation should primary amputation be undertaken in preference to attempted revascularisation

The success of limb salvage procedures depends upon the site of disease, which in critical limb ischaemia is often multi-focal, 30% of patients with critical limb ischaemia have supra-inguinal disease, 40% femoro-popliteal disease and 30% femoro-crural disease (Cheshire and Wolfe. 1992). The more proximal the lesion the higher the limb salvage rate. Limb salvage rates of 85% (Crawford et al 1981) for aorto-iliac reconstructions and 60% (Myers et al. 1978b) for femoro-popliteal reconstructions make attempted revascularisation the procedure of choice in these patients. The only area where doubt exists is in patients with femoro-crural disease (Cheshire and Wolfe. 1992), especially if autologous vein is not available for infra-inguinal reconstructions. To improve the patency rates of femoral crural bypass grafts where autologous vein is in short supply a composite vein graft or a PTFE graft with either a Miller vein cuff (Miller et al. 1984)or a Taylor vein patch (McFarland and Taylor. 1988) may be used. The latter group have three year secondary patency rates of 63% for a series of 250 femoro-distal bypass grafts. In a series of patients with critical limb ischaemia Wolfe and Tyrrell (1991) advocate femoral crural grafting even with a prosthetic graft, claiming that their low primary amputation rate of 3% would rise to 24% if prosthetic femoro-distal grafts had not been used. They also state that inappropriate major amputations are due to failure to visualize distal vessels. A combination of Doppler ultrasound and pulse generated runoff can often identify patent vessels not seen on conventional arteriography (Sayers et al. 1992).

The question of attempted revascularisation or primary amputation in the medically compromised patient is relevant as the majority of these patients are elderly and have concomitant medical conditions; these include previous strokes, with resulting hemiplegia, previous myocardial infarction, diabetes mellitus, chronic obstructive airways disease and dementia. Ouriel, Fiore and Geary (1988) found that in a series of 362 medically compromised patients with critical limb ischaemia the attempted revascularisation group had a lower peri-operative mortality, shorter length of hospital stay and increased long-term survival rate than a medically matched subgroup of patients undergoing amputation. A second group of patients with critical limb ischaemia all octogenarians or nonagenarians had cumulative life table limb salvage of 84% and 74% at one and two years respectively. Seventy six percent of reconstructed patients who died with in five years did so with their previously threatened limb intact. This data supports an aggressive approach to limb salvage and advanced age should not be a contra-indication to attempted revascularisation (Scher et al. 1986).

In the current economic climate, the costs of treating critical limb ischaemia must be considered. There is general agreement that both revascularisation and amputation are expensive. Overall revascularisation costs equal major amputation costs when considering the length of hospital stay, the operative costs, physiotherapy, rehabilitation with limb fitting in the amputee and, if required, rehousing. Therefore revascularisation with limb salvage is the preferred option, but the costs for patients whose revascularisation fails, requires attempted surgical revision, but subsequently fails and needs a major amputation are highest of all (Cheshire at al. 1992, Gupta et al. 1988).

INVESTIGATION OF CRITICAL LOWER LIMB ISCHAEMIA.

Clinical evaluation of the ischaemic limb fails to accurately determine the degree of ischaemia. In the last twenty years the development of the vascular laboratory means that no patient with an ischaemic limb should have a major amputation unless he has previously been considered for limb salvage using the range of diagnostic investigations available and the opinion of a surgeon fully trained in the range of reconstructive techniques in use (Greenhalgh. 1988). For an investigation to be valuable in the assessment of the ischaemic limb it should be accurate, cheap, easily performed and as minimally invasive as possible. The following investigations are all in current use in the assessment of the limbs of patients with critical lower limb ischaemia, but none of them are able to accurately predict irreversibly ischaemia and which patients would therefore benefit from a primary amputation rather than an attempted surgical revascularisation.

Doppler systolic ankle and toe pressures.

Doppler systolic pressure measurements were developed in the 1950's and described by (Strandness, McCutcheon and Rushmer. 1966, Strandness et al. 1967, and Yao. 1970) to study the blood flow in the lower limb arteries of patients with peripheral arterial disease. Measurement of the segmental systolic pressures at four sites in the lower limb, high thigh, above the knee, below the knee and above the ankle, rely on the principle that the pressure in any point in the leg will be reduced if there is proximal disease. Four cuffs are applied around the limb at the sites described above and inflated in turn, the returning Doppler signal is detected at the ankle. A drop of greater than 30mmHg between any two points indicates a haemodynamically significant stenosis (Walker, Spence and McCollum. 1986). The absolute Doppler systolic ankle pressure is used as an index of critical limb ischaemia, it is more accurate in the detection of critical limb ischaemia than the pressure index (Oureil and Zarins. 1982). Problems are encountered using the absolute Doppler systolic ankle pressure as a measure of critical ischaemia in some patients, as it is falsely elevated in patients with calf vessels to rigid to be compressed, for example in diabetics (Vincent et al.

1982) and the pressure recorded at the ankle may not reflect the pressure recorded in the toes (Farris. 1975). To overcome these problems Doppler systolic toe pressure measurements may be performed, the site of measurement is close to the ischaemic lesion and toe vessels are not incompressible, but the reproducibility varies. Doppler flow measurements will indicate the pressure at a particular site in the arterial tree, but flow within an artery will not assure healing, as limb survival ultimately relies on cell survival.

Pulse rise time.

Green, Taylor and Greenhalgh (1987) described a method of assessing the aorto-iliac segment noninvasively using a pressure transducer placed over the common femoral artery, the examining finger often misleads and the femoral pulse may feel normal to palpation despite a significant stenosis or occlusion. Measurement of pulse rise time was thought at the time of this study to provide an objective assessment of the femoral pulse, as it was easy to use in skilled hands and thought to be more accurate than computer femoral velocity wave form analysis (Greenhalgh. 1988). Recently doubts have arisen about the accuracy of the pulse rise time measurement and its is use now limited.

Pulse generated runoff.

Demonstration of patent distal vessels, especially if the popliteal artery is occluded is unreliable using conventional arteriography. Beard et al (1988) described a new method to enhance the detection patent distal vessels using Doppler ultrasound. The pulse generated runoff machine augments a weak signal using compressed air and two separate cuffs around the upper calf, one pulsatile and one occluding. The results of using this test are preliminary, but it may allow identification of calf vessels not detected by arteriography or ankle Doppler, and can also demonstrate whether a calf vessel is in continuity with the pedal arch, an important determinant of graft patency which allows the best vessel to be chosen for the distal anastomosis in femoro-distal reconstruction.

Duplex ultrasound scanning.

This is a combination of B-mode ultrasound, linked to pulsed range-gated Doppler ultrasound with spectral analysis to sample points within the arteries may be used to assess the aorto-iliac (Langsfield et al. 1988) or femoral stenosis. The advantage of the duplex scan is that it provides both morphological and haemodynamic information about the state of the limb, it is limited in its use as it is operator dependent, difficult to use in obese patients and is time consuming. Colour Doppler imaging is the most advanced development in clinical Doppler ultrasound technology. The machines incorporate powerful computers, which enable the system to provide a real-time image of an area and also to sample simultaneously multiple, tiny volumes within that area for Doppler information. This information is then processed, and the mean frequency shift in each sample volume is then displayed as a colour code on the real-time image. Blair et al (1993) have shown that colour Doppler imaging of the aorto-iliac segment is a reliable method of assessing non-invasively the degree of stenosis in this segment of the arterial tree (Blair et al. 1993).

Arteriography.

Angiography is the gold standard for providing anatomical information about the peripheral arteries in patients in whom arterial reconstruction is contemplated. Perfemoral techniques with uniplanar views of the arterial tree do not provide accurate information about the degree of stenosis, as the atheromatous plaques are often eccentric and intra-observer correlation is poor when reviewing films as to the severity of the disease process (Slot, Strijbosch and Greep. 1981). Intra-operative angiography by direct puncture of an arterial segment provides further visualization, using a smaller volume of contrast (Scarpato et al. 1981) and may aid arterial reconstruction. The complications arising from conventional angiography include; arterial injury (haemorrhage, occlusion or trash foot), allergic reactions, nephrotoxicity of the contrast medium and fluid overload.

Digital subtraction angiography can supplement or supplant conventional angiography (Kubal, Crummy and Tunispeed. 1983). It is safer and cheaper but only shows a limited arterial segment. Good definition of the aorto-iliac segment can be obtained with intra-venous digital subtraction angiography, but definition is poor for distal arteries (Karlsson et al. 1982). This problem is overcome by intra-arterial digital subtraction angiography using a fine bore catheter with less contrast to visualize distal vessels (Kubal, Crummy and Tunipseed. 1983).

The above investigations are routinely used in vascular laboratories in the assessment of patients with critical limb ischaemia. A number of other specialised techniques have also been described for the assessment of patients with critical limb ischaemia, these include; laser Doppler flowmetry (Allen and Goldman. 1987), transcutaneous measurement of oxygen tension (White et al. 1982) photoplethysmography (van den Broek et al. 1988), xenon washout studies (Moore. 1973) and dynamic fluorescein angiography (Silverman et al. 1987), all are either time consuming to perform accurately or are more useful as a predictor of amputation healing than as a test of whether revascularisation should be undertaken.

None of these tests will accurately predict which limbs are irreversibly ischaemic and should undergo primary amputation. Nuclear magnetic resonance studies using ^{31}Phosphorus magnetic resonance spectroscopy (^{31}P MRS) may offer a non-invasive clinical test that provides information at the cellular level and prove to be a useful diagnostic test in patients with critical limb ischaemia.

Historical aspects of nuclear magnetic resonance.

Nuclear magnetic resonance was discovered experimentally in 1946 (Purcell, Torrey and Pound. 1946, Bloch. 1946, Bloch, Hansen and Packard. 1946a and 1946b). This initial pioneering work laid down the basic principles of the behaviour of the spinning atomic nucleus in an applied magnetic field and the theoretical analysis of these spins with their local molecular environment.

Improvements in magnetic field strength and the quality or homogeneity lead to the resolution of different molecular groups according to their resonant frequency. In many ways this is analogous to the optical work of Isaac Newton who showed that a glass prism can be employed to separate white light into a "spectrum" of its component colours. Nuclear magnetic resonance is described as a radiofrequency spectroscopic technique.

Nuclear magnetic resonance remained a chemist's and physicist's research tool for a decade or more during which a number of important developments were made. The application of Fourier Transform techniques led to a dramatic increase in sensitivity in what is a comparatively insensitive spectroscopic method. The development of "solid state" nuclear magnetic resonance increased the understanding of interactions between magnetic and quadrupolar nuclei allowing the deeper probing of molecular structure. By the late 1960's nuclear magnetic resonance was applied to biochemical systems (Cohn and Hughes. 1960) and later to perfused, intact systems, eg heart (Gadian et al 1976).

In 1971 Damadian observed that nuclear relaxation times recorded from neoplastic tissues were different from those found in normal tissue. In addition Lauterbur, suggested a method for localising the source of the signals and thus creation of nuclear magnetic resonance images (Lauterbur. 1973). At this point we see the origins of the technique known as magnetic resonance imaging, which developed in parallel with the observation of nuclear magnetic resonance spectra from isolated perfused limb muscle from frog and toad (Hoult et al. 1974, Dawson, Gadian and Wilkie. 1977, Dawson, Gadian and Wilkie. 1978). The early 1980's and the development of wide bore, higher field magnets, saw the first in-vivo animal studies using surface coils (Ackerman et al. 1980). By the mid-1980's the technique of magnetic resonance imaging and nuclear magnetic resonance spectroscopy, now known as MRS, converged allowing the spatial localisation of spectroscopic information in a non-invasive fashion from the intact human body.

In spectroscopic terms the field strengths routinely employed in whole body human MRS are low, with 1.5 Tesla representing the norm. Increased field strengths are desirable from a spectroscopic view point, making spectra proportionally easier to resolve, however, increased costs and the difficulties of working in strong magnetic fields limit the field strength.

MRS can be offered by many manufacturers as an extension to the imaging capabilities on their 1.5 Tesla imaging systems.

Nuclear magnetic resonance with respect to muscle and limb ischaemia.

Chronic ischaemia is difficult to produce experimentally in animal models and muscle ischaemia in most animal models is produced by acute vessel ligation (Soussi et al. 1990) and it is therefore incorrect to extrapolate these results to chronic ischaemia. Human nuclear magnetic resonance studies followed the early in-vivo animal studies, surface coils and small bore magnets were used, therefore it was mainly limbs that were studied (Chance Eleff and Leigh. 1980, Chance et al 1981, Radda. 1986). The phosphorus metabolites of muscle were readily available for study as the phosphorus nuclei possess spin, have a 100% natural abundance, a relatively high sensitivity and are present in muscle at concentrations detectable by ^{31}P magnetic resonance spectroscopy (^{31}P MRS). These early studies enabled the normal concentration of phosphocreatine (Pcr), inorganic phosphate (Pi), and adenosine triphosphate (ATP) to be determined at rest, immediately after exercise and during recovery from exercise in normal subjects (Taylor et al. 1983). ^{31}P MRS studies in patients with peripheral vascular disease followed, most of these were on patients with intermittent claudication, few studies analyse spectra from patients with critical limb ischaemia only. Studies in this field have compared patients suffering from intermittent claudication with a control group looking at gastrocnemius muscle using a whole body magnet and surface coils. At rest no significant difference in the spectra produced by the patients or the controls were seen, but following an exercise regime that reproduced their claudication pain, the patient group showed reproducible spectral changes, namely a fall in phosphocreatine, pH and a rise in inorganic phosphate. Repeat muscle spectroscopy in the patient groups following successful vascular reconstruction produced results that were comparable with the control group (Hands et al. 1986). This finding is not confirmed by Zatina and colleagues who found that despite an immediate improvement in the symptoms and non-invasive tests the return of phosphorus metabolites to normal levels took several months (Zatina et al. 1986). Studies from Oxford in patients with severe ischaemia, some with ulceration and gangrene, looked at extensor digitorum brevis muscle in the foot at rest using a whole body magnet and surface coils. This demonstrated that the resting muscle in these patients differed significantly from healthy controls, demonstrating a fall in phosphocreatine, an increase in the inorganic phosphate to phosphocreatine ratio and a rise in the inorganic phosphate (Hands et al. 1990). Lenkinski et al (1988) compared the spectra obtained from the proximal calf muscle (gastrocnemius), the distal calf (gastrocnemius) and the small muscles of the foot (flexor digitorum and abductor hallucis) and found that the small muscles of the foot are the most sensitive indicators of muscle ischaemia in patients with peripheral vascular disease.

QUALITY OF LIFE STUDIES.

As clinicians we assume that our treatment of ill patients will improve their feeling of well-being, with increasing economic constraints we are forced to justify certain expensive treatments. Illness or lack of health status is a difficult concept to define, a person may be ill, but not disabled or disabled, but not ill. A persons perception of their state of health will be affected by their social class, family and friends and physiological factors. The concept of Quality of life was first used by John F. Kennedy's presidential commission (Williams. 1991), which set goals for the USA for the year 2000. But as early as the 1940's proposals were made for changing the evaluation of health care. In 1947 the World Health Organisation defined health as " a state of complete physical, mental and social well-being and not merely the absence of disease" (World Health Organisation Constitution. 1947) and Elkington later said that quality of life should be the goal aimed for by every physician for the patient (Elkington. 1966).

If we decide to measure quality of life, we must decide what parameters to measure. What constitutes an improvement in quality of life? There is general agreement that studies on health related quality of life studies should assess functioning in a number of important domains,: physical functioning including somatic sensations such as physical symptoms and pain; psychological functioning including concentration and mood; social (including sexual) functioning: occupational status; and possibly economic status.

Methods of measurement.

One of the early quality of life studies was devised in 1949 by Karnofsky and Burchenal as part of the evaluation of new chemotherapeutic agents, they looked at survival and objective response, but also more qualitative parameters such as performance status, improved mood, reduction in symptom level and a sense of well-being. A number of established methods exist for measuring health status.

Mortality rates have the advantage that they are widely available, but lack accuracy as most death certificates are written without knowledge of post-mortem findings. They take no account of chronic illness or debility and as longevity increases in an affluent society death is often due to multicausal disease and disability. Therefore survival is a measure of quantity rather than quality.

Morbidity measures take account of a wide range of diseases, but accurate statistics are difficult to collect. Therefore, morbidity statistics have been developed in a number of ways:

1. Refined indices look at specific aspects of morbidity, for example incidence and prevalence rates for specific conditions, absence from work and duration of disability. Only people who present to health professionals enter these statistics and thus bias is introduced and disease or "lack of health" is underestimated.

2. Disability indices measure the extent that people are able to perform the essential tasks of daily living. The Activities of Daily Living scale (Katz et al. 1963) is used in the evaluation of treatment with relation to specific groups and focuses on disability in relation to those groups. It assesses independence, bathing toileting etc using an ordinal scale and has been found to be predictive of outcome in patients with stroke and hip fractures (Katz et al. 1964, Katz et al. 1966) Disability measurements have the advantage that they are graded degrees of disability, but rely on comparisons with normal populations. Such normal values vary with age, sex social roles and expectations.

3. Symptom and functional indices focus on clinical symptoms and are subjective measures of distress or disability as perceived by the affected person. An example of this is the Health Perceptions Questionnaire (Ware. 1976). This consists of statements about personal health, the response consists of five standardized categories on a true or false answer. It lacks validity on re-testing.

Well validated scores exist and in choosing a health profile it is preferable to modify an existing questionnaire rather than devise a new one. We have used the Nottingham Health Profile (NHP) as it has been well validated and used in patients with vascular disease. The NHP questionnaire was constructed by a group of workers at the University of Nottingham working between September 1975 and December 1981. Initially statements were collected from members of the general public describing the typical effects of ill-health, looking at the social effects, the psychological effects, the behavioural effects and the physical effects (Hunt, McEwen and McKenna. 1986).

The questionnaire is self-administered, but can be read out and filled in by an assessor.

Applications of quality of life assessments in surgery.

The aim of quality of life studies is to allow the making of impartial judgments leading to appropriate changes in treatment practice rather than support prejudices. It may be used to assess the outcome of treatment, not just in terms of morbidity or mortality, but to show the improvements in quality of life brought about by new technical advances, particularly when the disease is not a major cause of mortality, but imposes severe restrictions in lifestyle. Health profiles allow the comparison of differing treatment options, allowing the monitoring of health care, which is becoming increasingly important as part of clinical audit. The selection of patients for surgery may be improved by the use of quality of life studies, as some patients fare badly with a certain treatment, especially if high levels of motivation are required.

CHAPTER 2.

PREVALENCE OF RISK FACTORS IN THE VARIOUS MANIFESTATIONS OF ATHEROSCLEROSIS.

INTRODUCTION.

Atherosclerosis is a common cause of premature death (Bloor. 1961, Dormandy and Thomas. 1988), and may affect the head, the heart, the abdomen or the legs.It is known that hypertension, increased serum lipid levels, cigarette smoking, and diabetes mellitus are important precursors of atherosclerosis. The pathological processes and aetiology differ depending upon the site of disease. In 1975 Greenhalgh, Taylor and Kaye recognised that the aetiology of stenosing (intermittent claudication or critical limb ischaemia) and dilating (aneurysmal disease) differ in their aetiological risk factors. A number of studies have looked at prevalence and risk factors for developing critical limb ischaemia, intermittent claudication and abdominal aortic aneurysms and have found wide variations in prevalence depending upon the source of the data studied. For peripheral vascular disease the main sources of data have been collected from autopsy surveys, mortality statistics, hospital in-patient statistics and population screening surveys. Each of these methods of estimating prevalence has limitations, population screening potentially gives the most accurate assessment and may allow estimation of risk factors in both healthy and diseased populations.

AIM OF THIS STUDY.

This study was designed to compare risk factors for patients developing critical lower limb ischaemia, intermittent claudication and abdominal aortic aneurysms. It then investigated the difference in risk factors in patients with critical limb ischaemia who required a major amputation compared with the group who achieved successful limb salvage.

PATIENTS AND METHODS.

Three groups of patients attending the Regional Vascular Service (RVS) at Charing Cross Hospital were entered in to an observational study to determine the difference in risk factors for different manifestations of peripheral vascular disease. The first group of patients had critical lower limb ischaemia, as defined by the Critical Limb Ischaemia document (Bell et al. 1982) and comprise the group studied in detail in chapters 3 and 4.

The second group of patients with intermittent claudication, diagnosed by a history of cramping discomfort in the calf, which was clearly provoked by walking and relieved by rest, accompanied by a pressure index of less than 0.9 at rest, or a significant drop in pressure after a one minute standard exercise test (Laing and Greenhalgh. 1980). These patients were either newly referred to the RVS or attending the vascular follow-up clinic, some had undergone reconstructive surgery for intermittent claudication with no history of critical limb ischaemia.

The third group were patients presenting with abdominal aortic aneurysms, defined by an infra-renal diameter of greater than three centimetres measured by B-mode ultrasound. The patients were

either new referrals to the RVS or attending the follow-up clinic following abdominal aortic aneurysm surgery.
Data was collected from the critical limb ischaemia patients between 1st January 1989 and 31st July 1991. The data collection period for both the intermittent claudication and the aneurysm patients was between 1st September 1990 and 31st July 1991. Patients attending the clinic with peripheral arterial disease and a coincident abdominal aortic aneurysm were excluded from this analysis.

A vascular risk profile was obtained by taking a full history, performing a physical examination and non-invasive tests. Investigations included measurement of the absolute Doppler ankle systolic pressure, calculation of the ankle to brachial pressure index and a standard one minute exercise test if required. B-mode ultrasound of the infra-renal aorta was performed to detect an abdominal aortic aneurysm. Other tests included a resting E.C.G., a Duplex ultrasound scan of the carotid arteries and a fasting blood glucose level.

Diabetes mellitus was defined as either treated diabetes mellitus or a fasting venous whole blood glucose level of ≥ 7.0 mmol per litre (World Health Organisation Expert Committee on diabetes mellitus. 1980). Hypertension was defined as a history of treated hypertension or a diastolic blood pressure of greater than 115 mmHg. Ischaemic heart disease was defined as a history of a previous myocardial infarction, with corresponding ECG changes, or treated angina pectoris. The definition of a stroke encompassed four neurological conditions; an established stroke, a transient stroke, a transient ischaemic attack or amaurosis fugax. All patients with renal failure had end stage renal failure requiring dialysis or having previously undergone a renal transplantation. Smoking habit was categorised as a current smoker, an ex-smoker, someone who had not smoked in the past three months or someone who had never smoked. Pack years smoked were calculated multiplying the average number of packets of cigarettes smoked per day by the years smoked.

STATISTICAL ANALYSIS.

Statistical analysis was either by Chi squared for trend (1 degree of freedom) for categorical data or Kruskal-Wallis for continuous data. Logistic regression analysis was performed to determine independent risk factors after adjusting for age and sex.

RESULTS.

The results of the demographic data for the three groups is shown in TABLE 2.1. The median age was similar for the three groups between 70 and 72 years, but a significant difference emerged in the sex ratios for the three manifestations of peripheral vascular disease. There was a male preponderance in all groups, which was greatest in the aneurysm group. The male to female ratios were 1.3 to 1 for critical limb ischaemia patients, 2 to 1 for intermittent claudication patients and 5.3 to 1 for aneurysm patients ($p < 0.001$).

There was a significant difference in the prevalence of diabetes mellitus in the three groups, 34% of the critical limb ischaemia group had diabetes, compared with 16% of the patients with intermittent claudication and only 4% of patients with an abdominal aortic aneurysm ($p < 0.001$). A similar proportion of patients with stenosing disease (25% of patients with critical limb ischaemia and 28% of patients with intermittant claudication) were insulin dependent compared with none of the aneurysm patients.

Over one third of patients in each group were hypertensive, the prevalence being highest for patients with critical limb ischaemia (54%), with a significant trend between the groups ($p = 0.015$). Ischaemic heart disease was present in 59/153 (39%) of patients with critical limb ischaemia, compared with 45/160 (28%) of patients with intermittent claudication and only 20/101 (20%) of the aneurysm patients ($p < 0.001$).

No significant difference emerged between the groups for the prevalence of stroke ($p = 0.146$). Seventeen (11%) patients with critical limb ischaemia had renal failure, compared with none of the patients with intermittent claudication or aortic aneurysm ($p < 0.001$).

Smoking was a dominant feature in all three groups of patients, with only 19/153 (12%) of critical limb ischaemia patients, 10/160 (6%) of intermittant claudication patients and 10/101 (10%) of aneurysm patients never having smoked ($p = 0.371$). The median number of pack years smoked were similar in each group between 38 and 40 ($p = 0.956$).

Logistic regression analysis was performed comparing patients with peripheral arterial disease (critical limb ischaemia and intermittent claudication) with patients with abdominal aortic aneurysms to determine differences between risk factors. The following risk factors were examined; male sex, a median age of less than 66.8 years, a history of diabetes mellitus, ischaemic heart disease, stroke, current smoking habit and smoking pack years greater than 26. Renal failure as a factor was excluded from the analysis, since it only occurred in patients with critical limb ischaemia.

All the risk factors examined except hypertension and stroke were significant (TABLE 2.2.), the most significant being diabetes mellitus (odds ratio 2.77, 95% confidence interval 1.49 to 5.17) and being a current smoker (odds ratio 1.94, 95% confidence interval 1.44 to 2.61).

Logistic regression analysis was performed on the same independent risk factors (excluding renal failure) comparing patients with critical limb ischaemia with intermittent claudication. (TABLE 2.3.) Four independent risk factors were identified. Diabetes mellitus was the most important factor (odds ratio 1.93, 95% confidence interval 1.42 to 2.63), the other significant factors are age < 75.7 years (odds ratio 1.53, 95% confidence interval 1.15 to 2.03), being a current smoker (odds ratio 1.50, 95% confidence interval 1.14 to 1.97), and hypertension (odds ratio 1.28, 95% confidence interval 1.0 to 1.65).

Patients in the critical limb ischaemia group were further sub-divided into patients who had successful limb salvage and patients who had a major amputation. No statistically significant difference emerged between the limb salvage group and the major amputation group (TABLE 2.4.). There was no significant difference between the degree of ischaemia in the major amputation group compared with the limb salvage group ($p = 0.217$) (TABLE 2.5). Forty eight (37%) of the limb salvage group and 14/45 (31%) of the amputation group had rest pain and an ankle pressure of < 40mmHg, without tissue loss. A smaller proportion in each group (limb salvage 9/129 (7%), amputation 7/45 (16%)) had ulceration or gangrene with a Doppler systolic ankle pressure < 40mmHg. The largest group had ulceration or gangrene and a Doppler systolic ankle pressure > 40mmHg (limb salvage 72/129 (56%), amputation 24/45 (53%).

TABLE 2.1. DEMOGRAPHIC DATA FOR ATHEROSCLEROSIS.

	critical ischaemia		intermittent claudication		aortic aneurysm	
number	153		160		101	
age, yrs (median, IQR)	72 (61,78)		70 (63,77)		72 (68,77)	
sex male:female*	87:66	1.3:1	106:54	2:1	85:16	5.3:1
diabetes mellitus*	52	34%	25	16%	4	4%
DM treatment						
insulin	13	25%	7	28%	0	
drugs	24	46%	12	48%	2	50%
diet	15	29%	6	24%	2	50%
hypertension	82	54%	66	41%	39	39%
heart disease*	59	39%	45	28%	20	20%
stroke	29	19%	25	16%	12	12%
renal failure	17	11%	0		0	
smoker ever	134	88%	150	94%	91	91%
current	77	50%	67	42%	70	70%
ex-smoker	57	38%	83	52%	20	20%
never	19	12%	10	6%	10	10%
pack years (median IQR)	40 (17,56)		39 (20,57)		38 (23,59)	

* $p < 0.001$

TABLE 2.2. LOGISTIC REGRESSION ANALYSIS COMPARING PATIENTS WITH PERIPHERAL ARTERIAL DISEASE WITH ABDOMINAL AORTIC ANEURYSMS, TO DETERMINE INDEPENDENT RISK FACTORS.

Risk factors.	Odds ratio	95% confidence interval	p value
diabetic	2.77	1.49 to 5.17	<0.001
current smoker	1.94	1.44 to 2.61	<0.001
age <66.8yrs	1.87	1.35 to 2.59	<0.001
male sex	1.93	1.37 to 2.72	<0.001
heart disease	1.47	1.06 to 2.03	0.015
pack yrs >26	1.40	1.03 to 1.91	0.027

TABLE 2.3. LOGISTIC REGRESSION ANALYSIS COMPARING PATIENTS WITH CRITICAL LIMB ISCHAEMIA OR INTERMITTENT CLAUDICATION, TO DETERMINE INDEPENDENT RISK FACTORS.

Risk factors	Odds ratio	95% confidence interval	p value
diabetic	1.93	1.42 to 2.63	<0.001
age <75.7yrs	1.53	1.15 to 2.03	<0.002
current smoker	1.50	1.14 to 1.97	<0.002
hypertension	1.28	1.00 to 1.65	<0.001

TABLE 2.4. DEMOGRAPHIC DATA FOR CRITICAL LIMB ISCHAEMIA PATIENTS.

	limb salvage		amputation		p value
number	112		41		
age, yrs (median, IQR)	72	(61,78)	72	(64,78)	0.931
sex male:female	62:50	1.2:1	25:16	(1.6:1)	0.662
diabetes mellitus	35	31%	17	41%	0.323
treatment					
insulin	9	26%	4	24%	
drugs	15	43%	9	52%	0.533
diet	11	31%	4	24%	
hypertension	57	51%	25	61%	0.355
heart disease	41	37%	18	44%	0.526
stroke	18	16%	11	27%	0.204
renal failure	14	13%	3	7%	0.540
smoker ever	100	90%	34	83%	0.476
current	59	53%	18	44%	
ex-smoker	41	37%	16	39%	
never	12	10%	7	17%	
pack years median (IQR)	39	(18,54)	40	(12,80)	0.754

TABLE 2.5. INDICATION FOR STUDY ENTRY IN PATIENTS WITH CRITICAL LIMB ISCHAEMIA.

	limb salvage		amputation	
number of limbs	129		45	
rest pain and ankle pressure < 40mmHg	48	37%	14	31%
tissue necrosis and ankle pressure < 40mmHg	9	7%	7	16%
tissue necrosis and ankle pressure > 40mmHg	72	56%	24	53%

DISCUSSION.

This study compares demographic data and risk factors for the different manifestations of atherosclerosis, unlike other studies which compare a single manifestation of atherosclerosis with a normal population. It is known there is a significant difference in the prevalence of the risk factors in patients with the various manifestations of atherosclerosis; critical lower limb ischaemia, intermittent claudication, and abdominal aortic aneurysms. This has not been fully investigated or explained and for many years the term atherosclerotic aneurysm has existed. This is misleading since dilating and stenosing disease have different risk factors, which have been studied in the three patient groups.

In this study the critical limb ischaemia, the intermittent claudication and the abdominal aortic aneurysm patients have a similar median age. Males predominate in all three groups, but is most evident in the patients with abdominal aortic aneurysms, a finding confirmed in previous studies (Castleden and members of the West Australian Vascular Service. 1985, Lilienfield et al. 1987). The ratio of male to female approaches one to one for critical limb ischaemia, since the percentage of patients with peripheral vascular disease is higher in men, this suggests that female patient with critical limb ischaemia suffer a more aggressive form of the disease than the male. This would have to be confirmed by a larger investigation of patients with peripheral vascular disease.

Three populations studies have shown the prevalence of diabetes mellitus in normal populations to vary between one and two percent

(1.9%, Reid et al. 1974; 1.1%, O'Sullivan, Williams and McDonald. 1967; 1.92%, Garcia et al. 1974). Our series of patients show that the three groups of patients with atherosclerotic disease all have a higher prevalence of diabetes mellitus compared with the total population and that the percentage rises with increasingly severe stenosing disease (abdominal aortic aneurysms 4%, intermittent claudication 16%, limb salvage 31%, all critical limb ischaemia 34% and major amputation 41%). Approximately one third of patients with critical limb ischaemia also have distal disease. This implies that diabetes mellitus maybe a major factor associated with distal disease, and hence outcome of surgical management maybe influenced by diabetes. There is much information on the increase of the incidence of peripheral arterial disease in diabetics. The Framlingham study has shown that diabetics in general show an increased morbidity and mortality from all cardiovascular causes compared with a non-diabetics (Garcia et al. 1974). But little has been written about the differing prevalence of diabetes in the various manifestations of peripheral arterial disease.

The prevalence of the risk factors studied in the three population groups are higher than in the general population. Atherosclerosis is a cause of premature death. For example, Strachan. 1991 found that premature death in male aneurysm patients was associated with cigarette smoking and hypertension. A sixty year old claudicant has a life expectancy approximately half that of the general population (Hughson et al. 1978) whereas patients with a critically ischaemic lower limb have a forty to seventy percent mortality at five years (Dormandy and Thomas. 1988).

This study compares risk factors in patients with critical limb ischaemia who kept their limb with patients with critical limb ischaemia who required a major amputation. Surprisingly none of the risk factors compared achieved statistical significance, for example; 35 (31%) diabetics with critical limb ischaemia kept their limb, compared with 17 (41%) who required a major amputation ($p = 0.323$). This may be explained by small number of patients studied in each group. It would also be expected that patients requiring a major amputation have more severe ischaemia, but we have not been able to demonstrate this in the present study. Why do some limbs need major amputation despite a technically successful revascularisation, yet other limbs survive without revascularisation despite fulfilling the criteria for critical limb ischaemia (Bell et al. 1982)? Predicting which critically ischaemic limbs will require major amputation, despite an attempted revascularisation remains a difficult problem for the vascular surgeon. None of the definitions, currently in use, or investigations show both sensitivity and specificity. Therefore it remains the goal of the vascular surgeon to develop new criteria that adequately fulfil the definition of critical limb ischaemia and investigations to determine irreversible limb ischaemia.

CHAPTER 3.

DESCRIPTION OF DEMOGRAPHIC DATA FOR PATIENTS PRESENTING WITH CRITICAL LOWER LIMB ISCHAEMIA AT THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

INTRODUCTION.

In recent years increasing sophistication in non-invasive investigation and high quality angiography allowing accurate pre-operative assessment of patients with critical limb ischaemia, coupled with the expertise of specialist vascular surgeons attempting ever more complex distal revascularisation are thought to lead to increased limb salvage and survival. Patients referred to a specialist unit with an aggressive revascularisation policy should have a lower amputation rate and higher survival than patients treated in a non-specialist vascular unit.

To determine the accuracy of this view, two groups of patients with critical limb ischaemia were studied. The first group of patients were studied in the Regional Vascular Service (RVS), situated at Charing Cross Hospital, London, W.6. and compared to a group of patients with critical limb ischaemia presenting to a District General Hospital (DGH), the Lister General Hospital in Stevenage, Hertfordshire.
The RVS accepts patients both from within its local catchment area, the Riverside District, serving a population of 279,000 people and from other districts within North West Thames Region. The RVS is staffed by a Professor of Surgery and a Senior Lecturer with Honorary Consultant status, two Senior Surgical Registrars with a vascular interest and a fully equipped Vascular Laboratory.
The district hospital accepts the majority of its patients from within the district, a population of 180,000. Elective vascular surgery was performed entirely by one of the four consultant surgeons.

AIM OF THIS STUDY.

This chapter identifies the risk factors for critical limb ischaemia in two populations, the first are patients referred to the RVS and the second patients referred to the DGH. Logistic regression analysis being performed to identify differences in limb salvage and mortality between the two groups.

PATIENTS AND METHODS.

A consecutive series of patients from the RVS and the DGH with critical limb ischaemia (Bell et al, 1982) were studied. Patients with acute limb ischaemia were excluded, as were patients with proven arterial embolism, Beurger's disease and arterial trauma.

The RVS patients were recruited over a thirty one month period, from 1st January 1989 to 31st July 1991, and the DGH patients over a sixteen month period, from 1st April 1990 to 31st July 1991. All patients were entered prospectively into the study. Analysis of the two groups was made by comparing the demographic populations and their referral patterns. Age, sex and the following risk factors were analysed; diabetes mellitus, hypertension, ischaemic heart disease, stroke, renal failure and smoking status. The indication for entry into the study and the referral patterns are also analysed.

The author recruited all patients presenting to the DGH with symptoms of lower limb ischaemia and those fulfilling the criteria for critical limb ischaemia were entered prospectively into the study. The demographic data for this group were compared and contrasted with that for the RVS patients.

STATISTICAL ANALYSIS.

Statistical analysis was performed using Chi square with Yates correction and Mann-Whitney U test. Logistic regression analysis was performed to identify risk factors affecting limb salvage at the RVS compared to the DGH. The Cox Proportional Hazards Model was used to analyse any difference in mortality between the two groups.

RESULTS.

Table 3.1 lists the patient details from the RVS and the DGH. The RVS treated 153 patients with 174 critically ischaemic limbs during 31 months of recruitment from 1st January 1989 to 31st July 1991. The DGH treated 30 patients with 30 critically ischaemic limbs during their 16 month period of recruitment from 1st April 1990 to 31st July 1991. There were more male than females (RVS 1.3 to 1, DGH 2 to 1) in each group, their median age was 72 and 73 years (inter-quartile range RVS 61 to 78 years, DGH 68 to 80 years).

Listed in the table are the prevalence of risk factors for peripheral vascular disease. Both groups had a similar proportion of patients with diabetes mellitus (RVS 34%, DGH 30%), hypertension (RVS 54%, DGH 53%), ischaemic heart disease (RVS 39%, DGH 30%). Differences in prevalence occurred in patients with a history of stroke (RVS 19%, DGH 4%)and renal failure (RVS 11%, DGH 4%). Less than 20% of patients in either group had never smoked. Statistical analysis of the groups showed no statistically significant difference between the two populations.

Logistic regression analysis was performed to identify risk factors affecting limb salvage at the RVS compared to the DGH. The following independent risk factors were analysed: diabetes mellitus, hypertension, ischaemic heart disease, cerebrovascular disease, renal failure, smoking status, Doppler systolic ankle pressure and pressure index of less than 0.5. No factor was significant, the best predictive factor trend was a pressure index of less than 0.5 ($\chi^2 = 3.66$, $p = 0.056$).

Cox Proportional Hazards Model was used to analyse any difference in mortality between the RVS and the DGH, none existed ($\chi^2 = 0.50$, $p = 0.481$). But analysis of the risk factors for total mortality for patients at the RVS, using the same model, adjusted for age and sex, identified two significant risk factors: ischaemic heart disease (relative risk 2.20, 95% confidence interval 1.14 to 4.26, $p = 0.016$) and renal impairment (relative risk 2.70, 95% confidence interval 1.26 to 5.80, $p = 0.016$).

The definition of critical limb ischaemia (Bell et al. 1982) was fulfilled by all patients in both groups (table 3.2). The majority of patients (64% at the RVS and 80% at the DGH) had ulceration or gangrene to a variable extent. Patients with rest pain alone and a

Doppler ankle systolic pressure of less than 40 mmHg was present in 36% of the group at the RVS and 20% at the DGH. The median Doppler ankle systolic pressure for each patient was 39 mmHg at both the RVS and the DGH. The median ankle to brachial pressure index in patients at the RVS was 0.27 and 0.25 in patients at the DGH.

Referral patterns differed, as might be expected, between the two hospitals (Table 3.3). As a tertiary referral centre the RVS accepted 15% of referrals from other hospitals and 18% of referrals from other disciplines within Charing Cross Hospital, mainly from the Endocrine and the Nephrology departments. All referrals to the DGH came from General Practitioners (GP) (90%) or from the Care of the Elderly department within the DGH (10%), ($x^2 = 7.2$, $p = 0.027$). Referrals to the RVS came from outside the district in 37% of cases, many directly from GP's outside the district without access to a local vascular surgeon. This differed significantly at the DGH, only one (3%) patient was referred from outside the district ($x^2 = 11.4$, $p = 0.007$)

TABLE 3.1. DEMOGRAPHIC DATA OF PATIENTS WITH CRITICAL LOWER LIMB ISCHAEMIA AT THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service		District General Hospital		p value
number of patients	153		30		
number of limbs	174		30		
median age, yrs (IQR)	72 (61,78)		73 (68,80)		0.453
male:female	87:66	1.3:1	20:10	2:1	0.466
RISK FACTORS.					
diabetes mellitus	52	(34%)	9	(30%)	0.832
hypertension	82	(54%)	16	(53%)	0.997
heart disease*	59	(39%)	9	(30%)	0.455
stroke~	29	(19%)	1	(4%)	0.057
renal impairment	17	(11%)	1	(4%)	0.331
smoker ever	134	(88%)	25	(84%)	0.660
current smoker	77	(50%)	15	(50%)	
ex-smoker	57	(38%)	10	(34%)	0.733
never smoked	19	(12%)	5	(16%)	
pack years (median, IQR)	40	(17,56)	37	(11,56)	0.592

* angina pectoris, previous myocardial infarction

~ an established stroke, a transient stroke, a transient ischaemic attack, amaurosis fugax

TABLE 3.2. INDICATION FOR STUDY ENTRY AND DOPPLER INDICES FOR PATIENTS WITH CRITICAL LOWER LIMB ISCHAEMIA AT THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service		District General Hospital	
number of limbs	174		30	
rest pain and ankle pressure < 40mmHg	62	(36%)	6	(20%)
tissue necrosis and ankle pressure < 40mmHg	16	(9%)	5	(17%)
tissue necrosis and ankle pressure > 40mmHg	96	(55%)	19	(63%)
ankle pressure(mmHg) (median, IQR)	39	(30,79)	39	(35,76)
pressure index (median, IQR)	0.27	(0.20,0.43)	0.25	(0.20,0.39)

TABLE 3.3. SOURCE OF REFERRAL FOR PATIENTS WITH CRITICAL LOWER LIMB ISCHAEMIA AT THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service	District General Hospital
number of patients	153	30
referral from GP	103 (67%)	27(90%)
referral within hospital	27 (18%)	3(10%)
referral from other hospital	23 (15%)	0 *
referral from outside the district	56 (37%)	1~(3%)

* $x^2 = 7.2$, 2df, $p = 0.027$

~ $x^2 = 11.4$, 1df, $p = 0.007$

DISCUSSION.

Standardization of reporting of patients with severe lower limb ischaemia is difficult to achieve. Many series report patients with claudication and those with severe ischaemia together, although the natural history of the disease may be different. For many years clinicians used the Fontaine classification of lower limb atherosclerosis, but it is subjective and lacks any reproducible measurements. In an attempt to standardize reporting of patients with severe ischaemia the concept of critical ischaemia was introduced in 1982 by a working party of the International Vascular Symposium (Bell et al 1982). Further subsequent attempts have been made to refine this definition (Ad Hoc Committee on Reporting Standards. 1986, European Consensus documents. 1989, 1991,1992). Although it is the best measure of severe ischaemia currently available, doubts exist as to the adequacy of this definition as patients with limb or life threatening ischaemia maybe excluded (Thompson et al. 1993).

This study includes only patients with critical ischaemia as defined by the International Vascular Symposium (1982), as that was the accepted definition at the start of the study.

It is no longer possible to study the natural history of patients with critical lower limb ischaemia, as it would be considered unethical not to assess a patient for revascularisation. Most of the centres that publish their limb salvage and survival figures have a special interest in reconstruction and therefore bias may be introduced the limb salvage results on a population basis. This study differs in that it compares two centres with different approaches to patients with critical limb ischaemia within defined patient populations; the RVS, where limb revascularisation is undertaken whenever possible, and the DGH where a selective limb revascularization policy is undertaken. This chapter has described the prevalence of risk factors, the indication for study entry and the referral patterns for patients presenting to the RVS the DGH. The age and sex distribution for these patients are similar to previously published results (Cheshire et al. 1992, Hunink, Cullen and Donaldson. 1994). Within these two groups of patients the findings of widespread atherosclerosis affecting the heart, brain and kidneys has been confirmed by several authors (Scher et al. 1986, Cheshire, Noone and Wolfe. 1992). In this study no significant difference between the two groups could be demonstrated, suggesting that they are comparable and that differences in management and outcome in terms of limb salvage and survival reported in the next chapter are valid.

One third of patients in each group suffered from diabetes mellitus. This figure is comparable to other studies (Sayers et al. 1994), but higher than the general age matched population (Reid et al 1974). The International Vascular Symposium working party (Rutherford et al. 1986) and the European Working Group on CLI (European Consensus on critical limb ischaemia. 1989) suggest that patients with diabetes mellitus should be excluded from series of patients with critical limb ischaemia. However, to do so would exclude one third of these patients and thus skew the data.

The Joint Vascular Research Group found that 409 diabetic and non-diabetic patients with critical limb ischaemia had similar ankle pressures and that outcome in both groups in terms of limb salvage and survival were similar (Wolfe. 1986). This view has been confirmed by Iaksson and Lundgren (1994) who report one year limb rates of salvage of 89% and survival rates of 82% in critically ischaemic diabetic's undergoing vein bypass to the arteries of the foot.

Patients with peripheral vascular disease have increased mortality compared with the general population and die on average ten years earlier than the general population, often from myocardial ischaemia or the complications of cerebrovascular accidents (Myers et al 1978a). The Joint Vascular Research Group (Wolfe. 1986) showed that within one year of the diagnosis of critical limb ischaemia 26% of patients would become amputees and 18% would die. However, Dormandy and Thomas (1988) calculate that between 40% and 70% of patients will be dead with or without their limb within five years of presenting with critical limb ischaemia. This begs the question of whether a policy of aggressive medical therapy and attempted revascularisation improve the outcome in these patients?

Medical therapy may be aimed at treatment of hypertension, cardiac failure and ischaemic heart disease, but optimization of the patient's condition should not be undertaken at the expense of limb salvage (Bergqvist. 1994). Alternatively, medical therapy can be aimed at the ischaemic limb. The options include drugs - antiplatelet agents, anti-coagulants, vascoactive drugs and prostanoids, or manipulation of the sympathetic nervous system - sympathetic block, spinal cord stimulation or transcutaneous nerve stimulation. Iloprost, a stable prostacyclin analogue, has been used in patients undergoing femoro-distal bypass and has been found to increase graft blood flow and reduce endothelial swelling (Shearman, Hickey and Simms. 1990, Thomsom et al. 1994). This immediate effect seems to have a beneficial role on long term graft patency.

The question as to whether attempted revascularisation improves the survival rate of patients with critical limb ischaemia is discussed in Chapter 4, with reference to results of this study.

Patients from the RVS and the DGH. all fulfilling the definition of critical ischaemia, had similar indications for entry into the study. The largest proportion in each group had ulceration or gangrene (RVS 55%, DGH 63%). Thompson et al. (1993) compared two groups of patients, one with rest pain alone and one with tissue necrosis, they found no significant differences in haemodynamic measurements or limb salvage, but an increased mortality in the tissue necrosis group. Such factors may contribute to variations in outcome reported in series of patients with critical ischaemia.

The RVS is a well established tertiary centre and accepts referrals from its local catchment area and from other districts within North West Thames. This is reflected in the annual presentation rates of 59 patients to the RVS compared with 22.5 patients to the DGH. General Practitioners in the region may be referring patients directly to the RVS for assessment of their critical ischaemia if they are aware that attempts at limb salvage were more likely to be undertaken.

The patients studied at the two centres demonstrated no significant demographic differences. They tend to be elderly males with widespread atherosclerosis, current or ex-smokers. Similar proportions rest pain with or without ulceration of their leg. Without revascularisation it is expected that they would require major amputation. The next chapter analyses their outcome in terms of limb salvage rate and survival rates.

CHAPTER 4.

COMPARISON OF REVASCULARISATION PROCEDURES FOR CRITICAL LOWER LIMB ISCHAEMIA AT THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

INTRODUCTION.

Series reporting outcome for revascularisation in critical limb ischaemia tend to come from centres with an expertise in vascular surgery and may provide falsely optimistic results for patients with end stage ischaemia.
It is well recognised that patients with critical limb ischaemia often have distal vessel disease and femoro-distal revascularisation requires specialist non-invasive investigation with high quality angiography to visualize patent distal vessels. Surgeons attempting distal revascularisation require commitment to time consuming and often difficult surgery with the ever present risk of early failure and major amputation.

The Regional Vascular Service (RVS) has a policy of attempting revascularisation of a limb whenever there is a chance of saving a functionally useful limb. Previous medical disease, age or distal gangrene were not considered contra-indications to revascularisation. The policy at the District General Hospital (DGH) was more conservative, where no femoro-distal revascularisation surgery was performed. Chapter 3 dealt with the risk factors for the two populations of patients with critical limb ischaemia and showed that the two groups were well matched for age, sex and risk factors.

AIMS OF THIS STUDY.

This study compared the limb salvage rate and the survival rate at thirty days and one year at the RVS and the DGH. In addition an extended period of follow up in the RVS allowed for analysis at eighteen months and two years. Analysis was performed looking at outcome depending upon initial management. This showed a major difference in the operative management and led to separate analysis of the outcome in patients with distal disease, that is, a haemodynamically significant stenosis at or below the division of the tibio-peroneal trunk and the anterior tibial artery.

PATIENTS AND METHODS.

A consecutive series of patients from the RVS and the DGH with critical limb ischaemia as defined in the Critical Limb Ischaemia document (Bell et al. 1982) were studied. A total of 153 patients were recruited from the RVS over thirty one months, from 1st January 1989 to 31st July 1991. A total of 30 patients were recruited from the DGH patients over sixteen months, from 1st April 1990 to 31st July 1991.

The patients were divided into four groups for analysis; attempted revascularisation, major amputation, minor amputation and no immediate intervention. Revascularisation was analysed as a whole,and then further sub-divided depending upon the type and level of reconstruction. The sub-divisions comply with those recommended by the Ad Hoc Committee on Reporting Standards

(Rutherford et al .1986). The subdivisions are proximal or supra-inguinal reconstruction, femoro-popliteal reconstruction, femoro-distal reconstruction, miscellaneous comprising angioplasty, lumbar sympathectomy and embolectomy, and the final group those patients in whom revascularisation was attempted, but not technically feasible. Patients with distal disease, were analysed separately as it was known that the two centres had different management policies for these patients.

The Regional Vascular Service (RVS).

All patients referred to the RVS between the 1st January 1989 and 31st July 1991 were entered prospectively into the study. A clinical history was taken, physical examination and non-invasive investigations were performed together with a radiological assessment.

Physical examination included full assessment of arterial pulses, the presence or absence of bruits, the presence or absence of an abdominal aortic aneurysm and documentation of any digital ulceration or frank gangrene. Diabetic peripheral neuropathy was revealed by anaesthesia and loss of vibration sense in the foot. The non-invasive investigations performed were measurement of Doppler ankle systolic pressure and measurement of segmental Doppler systolic pressures in the lower limb, the high thigh, low thigh, below knee and above ankle levels. The ankle to brachial pressure index was calculated. Aorto-iliac disease was assessed using the pulse rise time method (Green, Taylor and Greenhalgh. 1987). Distal vessel run off was assessed during the latter months of the study by the pulse-generated run-off method (Beard et al. 1988).

All patients diagnosed with critical limb ischaemia underwent an arteriogram, via the femoral or brachial route. Intra-arterial digital subtraction angiography was used to demonstrate distal run off when the arteriogram was inadequate.

Management of patients was decided at a multi-disciplinary meeting of surgeons, radiologists and vascular technicians. Patients were then assigned to one of the four management groups, attempted revascularisation, major amputation, minor amputation or no immediate intervention. Revascularisation was attempted whenever possible. At the completion of the operation Doppler waveform analysis provided the opportunity for any technical errors to be corrected.

Post-operatively the limb was assessed clinically and with non-invasive monitoring of Doppler ankle systolic pressure, and towards the end of the study using colour duplex Doppler scanning (Acuson 128) of femoro-popliteal segment for distal grafts. Early re-exploration and revascularisation were undertaken for any signs of graft failure in the early post-operative period.

In patients where reconstruction was not possible, three options were considered. Patients with severe intractable rest pain and/or spreading gangrene underwent a major limb amputation. Those with limited distal gangrene (often diabetic) a minor amputation only. A small number of patients usually with limited dry gangrene or rest pain did not initially undergo any procedure, and were treated with analgesics and dressings to any areas of tissue necrosis. This sub-group was analysed separately as the "no immediate surgical intervention group". All patients in this group strictly adhered to the definition of critical limb ischaemia and later discussion highlights this point.

Assessment took place one month after entry to the study and subsequently at three months, six months, one year,eighteen months and two years.

<u>The District General Hospital (DGH).</u>

Patients were recruited over a sixteen month period from 1st April 1990 to 31st July 1991, In addition to the routine clinical assessment made in the DGH, for the purpose of this study each patient with symptoms of severe vascular disease was assessed to determine whether they complied with the definition of critical limb ischaemia (Bell et al. 1982). Only those who strictly fulfilled these criteria were included. The vascular surgeon did not have access to a vascular laboratory and his decision to reconstruct or amputate was made on clinical grounds aided by arteriography if performed.

The author took a clinical history and performed a physical examination to assess limb viability, peripheral pulses and the presence or absence or bruits. The Doppler ankle systolic pressure was measured and the ankle to brachial pressure index calculated. The arteriograms were reviewed to determine the site of disease.

None of the non-invasive tests results were known by the surgical team to avoid influencing their surgical practice. Once the surgical team had decided on the initial management the patient was assigned to one of the four management groups. The revascularisation group were examined in the immediate post-operative period for limb viability and the Doppler ankle systolic pressure measured, allowing calculation of the ankle to brachial pressure index.

Assessment at one month, three months six months and one year was performed.

STATISTICAL ANALYSIS.

Statistical analysis was performed using Chi square with Yates correction. Limb salvage and survival rates were by life table analysis using the Lee-Desu statistic.

RESULTS.

The RVS treated 153 patients with 174 critically ischaemic limbs during 31 months of recruitment. The DGH recruited 30 patients with 30 critically ischaemic limbs during their 16 month period of recruitment. Giving annual presentation rates of 59 and 22.5 patients respectively. Twenty four (16%) patients at the RVS had had a reconstruction for peripheral vascular disease prior to entering the study, two thirds of these for critical limb ischaemia. At the DGH three (10%) patients had previously had a reconstruction for critical limb ischaemia.

The initial management plans for the limbs of all patients entering the study with critical limb ischaemia are shown in TABLE 4.1. The number of limbs in each centre undergoing an attempted revascularisation differed: In the RVS 131/174 (75%) critically ischaemic limbs underwent an attempted revascularisation, compared with 13/30 (43%) at the DGH. Major amputation, as an initial procedure, was performed in 16/174 (9%) limbs at the RVS and 5/30 (17%) limbs in the DGH. Of these three patients at the RVS and one in the DGH had undergone a revascularisation prior to entering the study, therefore having a secondary amputation. By thirty days the major amputation rate at the RVS had risen to 22% a further 22 limbs requiring a major amputation, either following attempted revascularisation (21) or minor amputation (1). At the DGH two more patients had a major amputation within thirty days of entering the study, one after a failed femoro-popliteal bypass graft and one after a minor foot amputation. Therefore the major amputation rate at the DGH was 23% at thirty days.
The higher proportion of major amputations as an initial management option at the DGH did not balance the reduced proportion of attempted revascularisations, a higher proportion of limbs at the DGH had a minor amputation 4/30 (13%) or no immediate intervention 8/30 (27%) compared to the RVS 7/174 (4%) and 20/174 (12%) respectively.

Despite this differing practice the cumulative limbs salvage rate at thirty days was 80% at the RVS and 83% at the DGH. By one year the cumulative limb salvage rate was higher in patients at the RVS 74% versus 53% at the DGH (p = 0.493) (FIGURE 4.1.). These figures refer to limbs, not patients. The two year cumulative limb salvage rate at the RVS was 74%.

Cumulative survival rates were comparable at thirty days, at both centres, 88% at the RVS and 93% at the DGH, at one year cumulative survival rates had fallen to 73% at the RVS and 65% at the DGH ($p = 0.714$) (FIGURE 4.2.). These figures refer to patients.
The two year cumulative survival rate at the RVS was 63%.

<u>The revascularisation group.</u>
FIGURE 4.3. illustrates the difference in type of revascularisation between the two centres. At the RVS 43/131 (33%) patients had a femoro-crural vein bypass graft, none of the DGH patients had an anastomosis below the infra-geniculate popliteal artery ($p = 0.032$).
In keeping with an aggressive revascularisation policy seven patients at the RVS with unilateral critical ischaemia had an exploration of the distal vascular tree in an attempt to salvage the limb, but no suitable vessel was found and the procedure was abandoned.
Graft failure early or late was treated aggressively at the RVS and 30 limbs required a further revascularisation procedure, six of these required a third reconstruction. None of the DGH patients had a second revascularisation procedure.

The cumulative limb salvage rate at the RVS and DGH at thirty days was 84% and 92%. At one year this had fallen to 76% at the RVS and 55% at the DGH ($p = 0.717$), the cumulative limb salvage rate at the RVS was maintained at 76% at two years.

The cumulative survival rates at the RVS and DGH are 90% and 92% respectively at thirty days and 75% and 78% at one year ($p = 0.539$), falling to 63% by two years at the RVS.

<u>The major amputation group.</u>

At the RVS 14/153 (9%) patients had a major amputation as their initial management after entering the study. Two patients with bilateral critical limb ischaemia had bilateral amputations. Three patients, all unilateral amputees had previously undergone a surgical revascularisation for critical limb ischaemia. This compares with the DGH where five (17%) patients with unilateral critical limb ischaemia had a major amputation as their initial management, one had previously had a revascularisation for critical limb ischaemia. The RVS performed a higher percentage of below knee amputations (56%) than the DGH (40%).

Cumulative survival at one month in the RVS and DGH were 85% and 100% and at one year 63% and 67% respectively ($p = 0.521$). Two year cumulative survival rate for major amputees at the RVS was 63%

The minor amputation group.

A minor amputation only was performed as the initial management option in seven (4%) patients at the RVS and four (13%) patients at the DGH, all with unilateral critical limb ischaemia.

None of the patients had a revascularisation performed. One patient at each centre had a below knee amputation after failure to heal of a minor foot amputation. Cumulative limb salvage rates were 83% at the RVS and 75% at the DGH by one year, this level of limb salvage was maintained at two years at the RVS. Not surprisingly the majority of patients in this group at both centres were diabetic, five (71%) at the RVS and four (80%) at the DGH.

Cumulative survival rates in both centres was 100% for the duration of the study.

The no intervention group.

This group of patients all fulfilled the criteria for critical limb ischaemia (Bell et al. 1982), but, were not suitable for a surgical revascularisation and either refused or did not require a major amputation. Sixteen patients (10%) at the RVS were assigned to this group. Two patients with bilateral critical limb ischaemia and four with unilateral critical limb ischaemia died within 30 days of entering the study, the surviving ten patients kept their ischaemic limbs. At one year only six (38%) patients were alive with viable limbs, one with bilateral critical limb ischaemia.

The cumulative limb salvage rate at the RVS was 100% at thirty days and 95% at one year, this remained unchanged at two years.

Cumulative survival figures at the RVS were 63% at thirty days and 56% at one and two years.

A higher proportion of patients at the DGH had no immediate intervention, 27%, all had unilateral ischaemia. At 30 days one patient had died with an ischaemic limb, the remaining seven all kept their limbs. After one year four more patients had died and one required a below knee amputation.

The cumulative limb salvage rate at the DGH was 100% at thirty and 60% at one year.

Cumulative survival figures at the DGH were 88% at thirty days and 48% at one year.

Few patients in either centre were diabetic, at the RVS 6/16 (38%) and the DGH 1/8 (13%).

Distal disease.

The main difference in management policy between the RVS and the DGH was femoro-crural revascularisation in patients with distal disease, one third of patients undergoing an attempted revascularisation at the RVS had a femoro-crural bypass graft, none of the patients at the DGH had a femoro-crural bypass graft ($p = 0.032$). We separately analysed the limb salvage and survival rates at the RVS and the DGH for patients with a significant stenosis at or below the popliteal trifurcation.

At the RVS 62/153 (40%) patients with 68/174 (39%) ischaemic limbs had distal disease, compared with 9/30 (30%) patients at the DGH.

Slightly more patients at the RVS had diabetes mellitus 22/62 (36%) than the DGH 2/9 (22%). Patients with distal disease either had an attempted revascularisation, a major amputation or no immediate intervention. The initial management in the two centres differed. (TABLE 4.2.).

At the RVS 50/68 (74%) limbs in 47/62 patients had an attempted distal revascularisation, none of the DGH patients had a revascularisation to a femoro-crural vessel. The upper anastomosis of femoro-crural grafts were all from the common femoral artery and were vein grafts either in-situ or reverse. The distal anastomosis were to the tibio-peroneal trunk (9), the posterior tibial artery (9), the anterior tibial artery (11), the peroneal artery(10) and miscellaneous distal grafts (4). One patient had a supra-inguinal angioplasty immediately before distal grafting. In seven patients the calf was surgically explored and no suitable vessel was found to perform a distal anastomosis and revascularisation was abandoned.

Only 5/62 (12%) of patients with distal disease at the RVS had primary major amputations, in one patient the amputations were bilateral. At the DGH one third of the group with distal disease had a primary major amputation. The remaining two thirds of the DGH patients had no immediate intervention, a far higher percentage than at the RVS, but, by one year three patients had needed a major amputation.

This difference in initial revascularisation policy is reflected in the cumulative limb salvage rates at the two centres. By thirty days it is 78% at the RVS and only 53% at the DGH. By one year the salvage rates are 78% and 18% ($p = 0.025$), falling to 73% at the RVS at two years (FIGURE 4.4.). Attempted revascularisation did not compromise the level of major amputation. At the RVS 72% of amputations are at the below knee level compared to 50% at the DGH (TABLE 4.3.).

Cumulative survival figures at the RVS and DGH for 30 days are 82% and 100% respectively falling to 65% and 34% at one year ($p = 0.867$) and 55% at two years at the RVS, (FIGURE 4.5.).

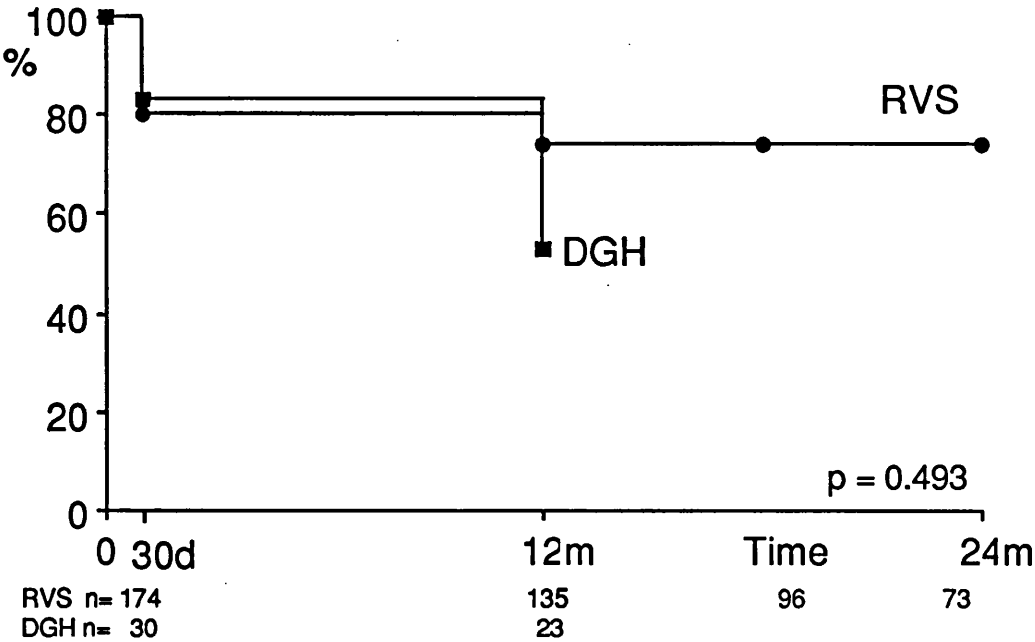


FIGURE 4.1. OVERALL CUMULATIVE LIMB SALVAGE RATE - COMPARISION BETWEEN THE RVS AND THE DGH

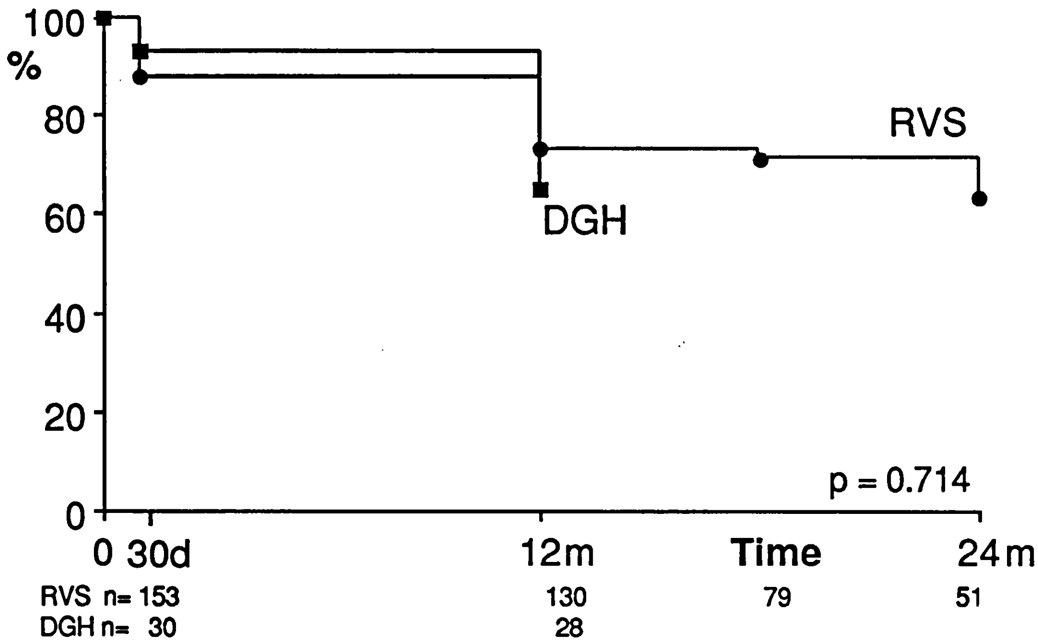
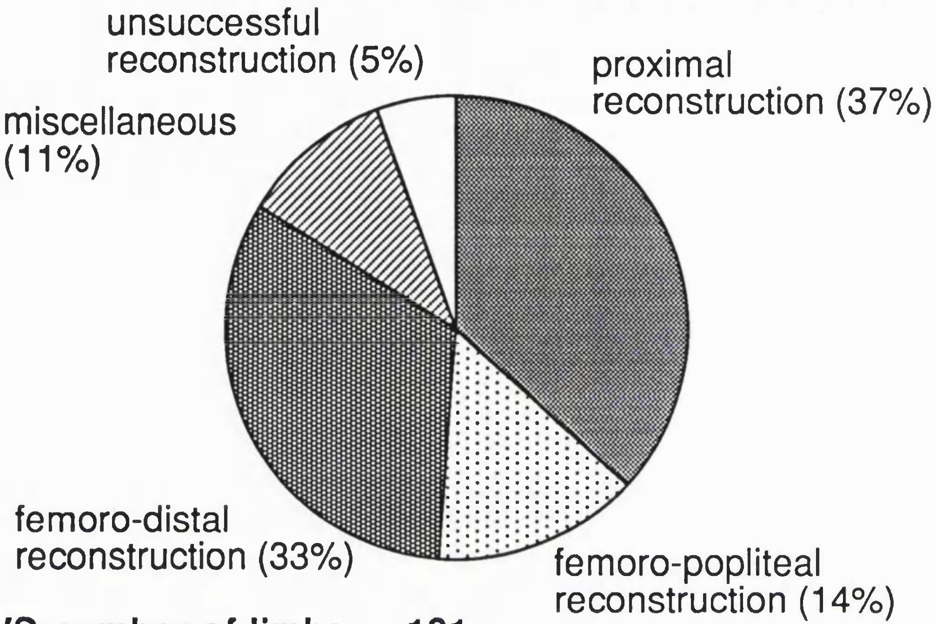
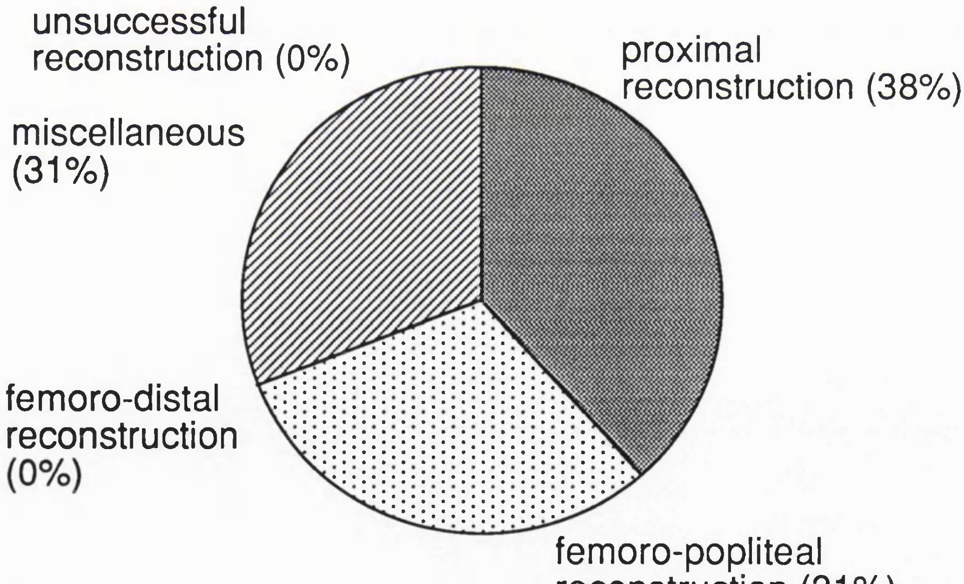


FIGURE 4.2. OVERALL CUMULATIVE SURVIVAL RATE - COMPARISON BETWEEN THE RVS & THE DGH

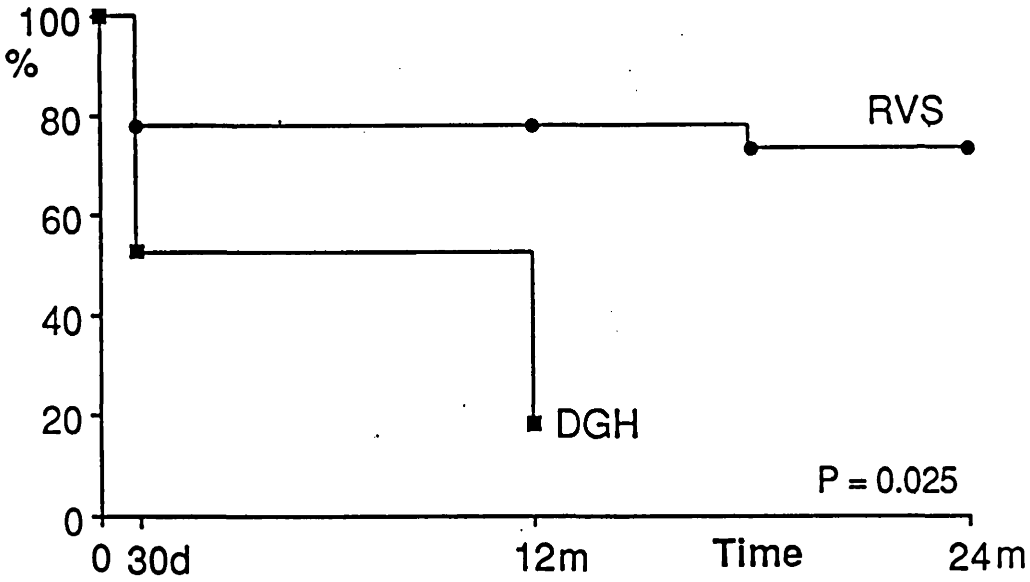


RVS number of limbs = 131



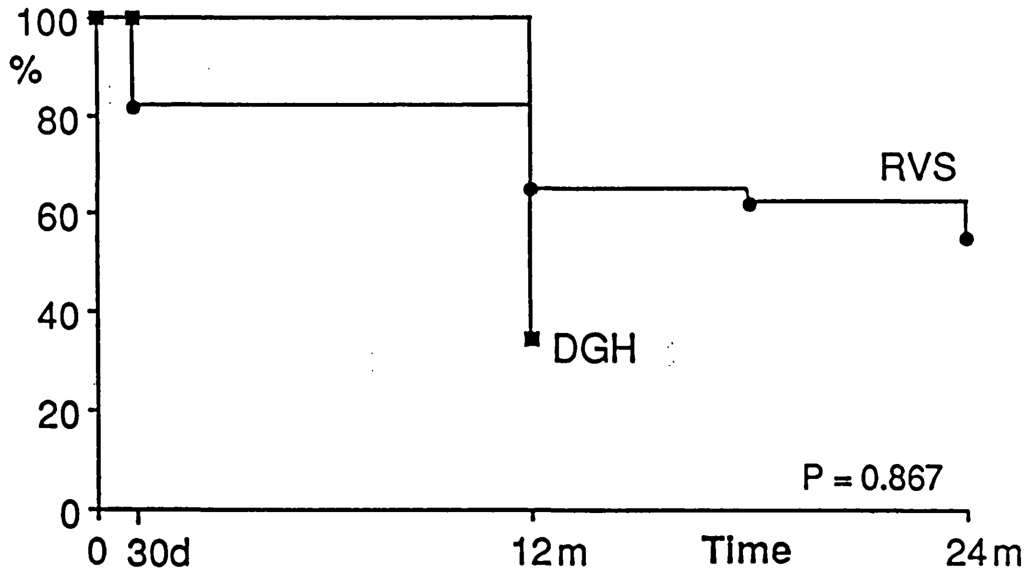
DGH number of limbs = 13

FIGURE 4.3. COMPARISON OF REVASCULARISATION PROCEDURES PERFORMED AT THE RVS & THE DGH



RVS n= 68 52 36 25
DGH n= 9 4

FIGURE 4.4. CUMULATIVE LIMB SALVAGE RATE IN PATIENTS WITH DISTAL DISEASE - COMPARISON BETWEEN THE RVS & THE DGH



RVS n= 61 49 28 16
DGH n= 9 9

FIGURE 4.5. CUMULATIVE SURVIVAL RATE IN PATIENTS WITH DISTAL DISEASE - COMPARISON BETWEEN THE RVS & THE DGH

TABLE 4.1. INITIAL MANAGEMENT OF LIMBS WITH CRITICAL ISCHAEMIA. COMPARISON BETWEEN THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service	District General Hospital
Total number of limbs	174	30
Revascularisation	131 (75%)	13 (43%)
Major amputation	16 (9%)*	5 (17%)~
Minor amputation	7 (4%)	4 (13%)
No intervention	20 (12%)	8 (27%)

* 3 secondary amputations

~ 1 secondary amputation

TABLE 4.2. INITIAL MANAGEMENT IN PATIENTS WITH DISTAL DISEASE. COMPARISON BETWEEN THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service*	District General Hospital
number of patients	62	9
number of limbs	68	9
reconstruction	50 (74%)	0
major amputation	6 (9%)	3 (33%)
no intervention	12 (18%)	6 (67%)

* Six patients had bilateral critical ischaemia in this group, 3 had a reconstruction, 1 had primary below knee amputations and two had no intervention.

TABLE 4.3. LEVEL OF MAJOR AMPUTATION IN PATIENTS WITH DISTAL DISEASE, COMPARISON BETWEEN THE REGIONAL VASCULAR SERVICE AND THE DISTRICT GENERAL HOSPITAL.

	Regional Vascular Service	District General Hospital
number patients	17	6
number limbs	18	6
above knee	1 (6%)	3 (50%)
through knee	4 (22%)	0
below knee	13 (72%)	3 (50%)

DISCUSSION.

The optimal management of patients with critical lower limb ischaemia remains controversial and will depend upon the facilities available at the centre to which the patient is referred. This may, in turn, influence the patient's limb salvage and survival. This study compares limb salvage and survival in two groups of patients - one treated in a RVS, the other in a DGH. The RVS had a vascular laboratory, good imaging and interventional radiology and a policy of aggressive revascularisation. The DGH had no vascular laboratory, limited radiological services and revascularisation to the level of the infra-geniculate popliteal artery only. These differing approaches led to 75% of patients undergoing an attempted revascularisation at the RVS, but only 43% at the DGH.

The decision to attempt revascularisation depends upon the diagnosis and assessment of critical ischaemia. Conventional pre-operative arteriography may fail to demonstrate patent calf and foot vessels, and the influence decision to perform a primary major amputation rather than attempt revascularisation (Campbell, Fletcher and Hands. 1986). At the DGH patients were assessed clinically and with arteriography, but no attempt was made to visualize distal runoff. At the RVS patients underwent intra-arterial digital subtraction angiography and during the latter months of the study pulse generated runoff assessment. Pulse generated runoff has been found to demonstrate up to 25% more patent distal vessels suitable for distal anastomosis than evidenced by arteriography or standard Doppler ultrasound (Beard et al. 1988).

Another deciding factor in the decision to reconstruct a lower limb is the choice of conduit for infra-inguinal bypass grafts. Below the knee, vein, either in-situ or reverse produces superior patency rates to prosthetic grafts. However, if insufficient vein is available a prosthetic graft with a venous cuff improves patency and limb salvage (Wolfe and Tyrrell. 1991). At the RVS careful assessment of suitable vein was made using Duplex scanning. If the long saphenous vein was inadequate or had previously been used for coronary bypass grafting, search was made for the short saphenous vein or arm veins and these used instead. Assessment of the vein was not performed at the DGH. This resulted in 33% of attempted revascularisation at the RVS being to femoro-distal vessels compared with none at the DGH.

Studies in patients with critical limb ischaemia report varying limb salvage and survival rates. Treatment options vary and London and colleagues suggested in a recent report that up to 25% of limbs with critical ischaemia may be suitable for angioplasty (London et al. 1993). They reported a two year limb salvage rate of 89% in these patients. In this present study only three (2%) limbs at the RVS had an angioplasty as their principal revascularisation. At the DGH 4 (31%) limbs had an angioplasty as the principal procedure.

The overall 30 day cumulative limb salvage and survival rates do not reflect the differences in initial management at the RVS and the DGH. One year cumulative limb salvage rates of RVS (74%) and DGH (53%), and one year cumulative survival of RVS (73%)and DGH (53%) are comparable to the findings of the Joint Vascular Research group

(Wolfe. 1986) and the Leicester group (Sayers et al. 1994). Hickey and colleagues adopted a policy of aggressive revascularisation on 369 patients over a five year period, 315 patients with 329 critically ischaemic limbs had an attempted revascularisation and at one year excellent graft patency rates of 85% and survival 82% were reported. These results were achieved using a combination of simple non-invasive Doppler ultrasonography pre-operatively and on-table pre-operative angiography to choose the most suitable recipient vessel for femorocrural bypass (Hickey et al. 1991).

It is only when the patients with distal disease were analysed separately that differences in initial management and outcome become apparent. Sixty two (40%) patients at the RVS and 9 (30%) patients at the DGH had distal disease. Seventy four percent of the RVS patients with distal disease had a femoro-distal reconstruction, resulting in a cumulative limb salvage rate of 78% and cumulative survival rate of 82% at thirty days. None of the DGH patients with distal disease had an attempted revascularisation. This resulted in a cumulative limb salvage rate of 53% and cumulative survival of 100% at thirty days. At one year the cumulative limb salvage rate at the RVS was maintained at 78%, compared with 18% ($p = 0.025$) at the DGH. The patients at the RVS had either died or had a major amputation. Cumulative survival at one year was 65% at the RVS and 34% at the DGH. This figure fails to achieve significance ($p = 0.0867$) presumably because the sample size at the DGH was small, only nine patients with distal disease.

The low primary amputation rate (7%) at the RVS compares well with that from St Mary's Hospital, London (3%). The group at St Mary's hospital found that their primary amputation rates would have risen to 24% if prosthetic femoro-crural grafts had not been used (Wolfe and Tyrell. 1991). In this series the primary amputation rate at the DGH, where no femoro-crural grafts were performed was lower at 13%. Debate exists about whether bypass grafting jeopardises the healing of a subsequent below knee amputation if the graft fails (Kazmers, Satiani and Evans. 1980). We did not find this. Seventy two percent of amputations for distal disease at the RVS were below knee and our experience is similar to Tsang and colleagues who found that failed femoro-crural reconstruction did not prejudice amputation level (Tsang et al. 1991).

The minor amputation group had a high proportion of diabetics, as might be expected. Surprisingly the groups at both centres had a 100% survival for the duration of the study, but some patients in both groups came to major amputation. None of the patients in either centre required a revascularisation, suggesting that they patients had small vessel diabetic disease (Myers et al. 1978b). Diabetics with critical ischaemia who have stenoses or occlusions in the infra-geniculate popliteal arteries may have one or more patent vessels at the level of the ankle. A recent study from Sweden suggested that good limb salvage can be achieved in elderly diabetics by vein bypass surgery to foot and that limb salvage will only be achieved by searching for a patent vessel at the ankle or in the foot (Isaksson and Lundgren. 1994).

Most reports of patients with critical limb ischaemia concentrate on those who have a revascularisation or a major amputation, 27% of patients at the DGH had no immediate intervention, a much higher proportion than at the RVS (10%) or in reported series from centres with an aggressive limb salvage policy. This group fared badly at the DGH with a cumulative survival rate of only 48% at one year. RVS patients in the attempted revascularisation group but for whom revascularisation was not technically possible also did badly. Their cumulative limb salvage rate at thirty days was 29%, with a one year cumulative one year survival of 43%.

In this study, we have attempted to demonstrate differences in limb salvage and survival by comparing management of critical ischaemia in a specialist vascular unit with a district general hospital. Two recent studies have analysed the impact of altering vascular services within an area. Lindholt and colleagues in Denmark retrospectively studied patients with critical limb ischaemia, before and after the establishment in 1988 of a Department of Vascular Surgery. They found that the number of patients assessed by a vascular surgeon prior to amputation rose from 19% to 49% in the second study period and that there was a significant 25% reduction in the amputation rate (Lindholt et al. 1994). Pedersen studied the amputation rate in a hospital before and after the introduction of infra-popliteal vein bypass grafts in 1988. He documented a 50% reduction in major amputation in the three year period following the introduction of infra-inguinal bypass (Pedersen et al. 1994). My study has also found that in patients with distal disease referral to a specialist vascular service leads to increased limb salvage and one year survival.

Failure to investigate patients with critical ischaemia may result in inadequate identification of distal runoff and failure to identify a single patent crural or pedal vessel. Denying the patient the option of attempted revascularisation and possible limb salvage. Therefore, referral to a specialist vascular unit should be mandatory in all except the moribund patient. Revascularisation of critically ischaemic limbs results in limb salvage. Costs for both revascularisation and major amputation are high, but primary arterial reconstruction is substantially cheaper than amputation (Gupta et al. 1988). Revascularisation to crural vessels may require re-intervention to maintain graft patency Cheshire and colleagues show that primary arterial reconstruction, even to crural vessels is cheaper than primary amputation. Re-intervention increases expenditure and may even exceed primary amputation cost. But secondary amputation is most expensive (Cheshire et al. 1992.)

CHAPTER 5.

ASSESSMENT OF THE CRITICALLY ISCHAEMIC LOWER LIMB USING ^{31}PHOSPHORUS MAGNETIC RESONANCE SPECTROSCOPY.

INTRODUCTION.

In patients with a critically ischaemic lower limb, the lack of a diagnostic test to accurately predict limb viability means that a number of limbs undergo attempts at revascularisation each year and should more appropriately have undergone a primary major amputation.

Tissue survival in the ischaemic limb ultimately depends upon cell survival within muscle, but current methods of assessment of tissue viability concentrate on the macrocirculation. Doppler systolic pressure studies (Strandness. 1966, Yao. 1970), pulse rise time (Green, Taylor and Greenhalgh. 1987) and pulse generated run off studies (Beard et al. 1988), therefore have a poor predictive value. Additional investigations such as transcutaneous oxygen tension measurements (White, et al. 1982), laser Doppler flowmetry (Allen and Goldman. 1987), photoplethysmography (van den Broek et al. 1988), xenon washout studies (Moore. 1973) and dynamic fluorescein angiography (Silverman et al. 1987) assess the microcirculation of the skin, but not that of muscle. It is muscle viability at the cellular level that determines limb survival. In chronic ischaemia muscle fibres atrophy and the number of capillaries multiply to increase oxygen utilisation. Adaptation also occurs at the cellular level the number of mitochondria increase and the concentration of the substrates and metabolites alters.

NUCLEAR MAGNETIC RESONANCE.

Nuclear magnetic resonance (NMR) deals with the interaction of electromagnetic radiation with the magnetic nuclei of elements. Electromagnetic radiation can be regarded as consisting of discreet packets or quanta of energy that travel with the speed of light. The interaction of an atomic nucleus with radiation involves the absorption or emission by the nucleus of a quantum of radiation which is accompanied by a transition from one energy level to another. NMR frequencies lie in the radiofrequency region of the electromagnetic spectrum (1 - 500 MHz).

Many elements occurring in nature have at least one magnetic isotope, these include hydrogen (^{1}H), carbon (^{13}C), fluorine (^{19}F), sodium (^{23}Na), and phosphorous (^{31}P).The usefulness of certain isotopes in clinical applications is limited by their natural abundance, their sensitivity and their abundance in-vivo.

The most abundant isotope of hydrogen (^{1}H, 99.98%) is given a relative sensitivity of one and has been of clinical relevance in producing magnetic resonance images. It must be remembered that these images are produced from the water and lipid components of tissue of high concentration (50 - 110 Molar (M)). If these dominant ^{1}H signals are suppressed or reduced in amplitude, then further "spectroscopic" signals of metabolites can be observed, for example, creatine, phosphocreatine, choline and N-acetyl-aspartate. These signals have concentrations of 50mM and below, in the range 10^{3} to 10^{4} lower than water and lipid signals.

The phosphorus isotope, ^{31}P, is 100% naturally abundant and relative to hydrogen has a sensitivity of 6.63 x 10^{-2}. In-vivo concentrations of common phosphorus containing compounds and metabolites are known to lie in the 20-30mM range. ^{31}P magnetic resonance spectroscopy (^{31}P MRS) is employed to provide information on the relative concentration of the phosphorus metabolites in muscle.
In contrast the ^{19}F isotope of fluorine is 100% naturally abundant, but is not naturally occurring within the body, therefore its use is limited. It can be used as a magnetic marker for tracer experiments with fluorine, labelled materials used include polypeptides, proteins, cytotoxic agents and anaesthetic agents.

Only a nucleus with an odd number of protons can display magnetic resonance. Nuclei with an odd number of protons possess the property of "spin", when placed in static magnetic field (B_0) the nuclei act as tiny bar magnets and align themselves along its axis of rotation. At equilibrium a small nuclear magnetization is produced which is aligned along B_0. If a transient magnetic field (B_1) is now introduced at right angles to B_0, it perturbs this equilibrium magnetization. When B_1 disappears, the nuclei re-emit the absorbed resonant energy as the preferred magnetization orientation is re-established and a receive coil detects this signal. The signal or free induction decay takes the form of a voltage decaying with time. (FIGURE 5.1a). This free induction decay signal is fed into a computer where it is processed to obtain the relative contributions of each frequency. This processing, involving the mathematical process of Fourier Transform, results in output of signal as a function of frequency - a spectrum (FIGURE 5.1b). The peaks are due to phosphocreatine (Pcr), α, β, phosphorus nuclei of adenosine triphosphate (ATP) and methylene diphosphonate (MDP). The various metabolites of phosphorus are resolved and lie at well defined frequencies of varying amplitude. The phosphocreatine resonance is often taken as the reference for each line in the spectrum and the frequency is written as a parts per million scale (ppm). Resonances to the left of the phosphocreatine line (FIGURE 5.1b) are labelled as positive chemical shifts and those to the right as negative .

Most of the metabolites detected by ^{31}P MRS have chemical shifts which depend to some extent upon the pH of their environment. In the pH range 6 - 7.5, the resonances of -ATP, inorganic phosphate, the phosphomonoesters and the sugar phosphates shift substantially. Inorganic phosphate has been found to be the most useful metabolite for pH estimation, because of its high sensitivity to pH changes, low sensitivity to metal-ion concentration, adequate tissue concentration in a variety of metabolic states and intrinsic single peak profile.

Intracellular pH can be can be determined from the chemical shift difference between the phosphocreatine and inorganic phosphate signals (Hoult et al. 1974, Taylor et al. 1983).

The calibration curve used is

$$pH = 6.75 + \log(\delta - 3.27) / (5.69 - \delta)$$

where δ is the chemical shift in parts per million between the inorganic phosphate and phosphocreatine signals.

PRACTICAL ASPECTS OF A MAGNETIC RESONANCE SPECTROSCOPY.

The ischaemic foot is placed in a strong homogeneous magnetic field. In this work the magnet presents an approximate 60cm access bore which can accommodate the whole body and operates at a field of 1.6 Tesla (FIGURE 5.2.). A radiofrequency transmitter coil is placed around the foot, which produces a radiofrequency pulse of short duration. For this work a 200µsec pulse is sufficiently narrow to irradiate equally all resonances known to exist in the ^{31}P spectra. The transmitter coil itself is large enough to envelope the ischaemic limb in order to produce a spatially homogeneous radiofrequency field over the whole relevant volume of tissue. As such all nuclei across the width of the spectrum and spatially over the limb are irradiated equally. This allows easier comparison of signals or resonances that may be spatially resolved over the ischaemic region. After the pulse, the nuclei re-emit the absorbed resonant energy and the specially designed receive coil (FIGURE 5.3.) detects this signal. The signal must be sampled correctly and in these studies this required sampling for a period of 200ms.

An important aspect of clinical magnetic resonance spectra data acquisition is to obtain the required information in the minimum time and with the least discomfort to the patient. Important factors that affect the time required to obtain adequate results include metabolite concentration, the degree of spatial localisation required, radio frequency noise and interference, the spin-lattice relation time T1, the radio frequency flip angle, and the delay between the successive pulses TR. Although the metabolite concentrations and the spin-lattice relaxation times of in-vivo tissue metabolites are not normally under the operators control, it is normally possible to have a direct influence on the other factors mentioned above.

Signal localisation is important to allow the operator to define the shape, size and location of the tissue volume from which the spectrum is acquired. The selected volume should have sharply defined boundaries and the signal from outside this volume should make a negligible contribution to the final spectrum. Localisation techniques often sample from a small area, reducing the signal to noise ratio, thus requiring a longer sampling time. Many spectra are poorly resolved and are complicated by overlapping peaks, making interpretation difficult.

The processed signal or spectrum can be resolved into separate and distinct frequencies that can be matched to the important metabolites present in phosphorus. Resolution is improved by increasing the period of sampling. However resolution cannot be increased indefinitely since there are practical and theoretical limits to the duration of the time domain signal. The quality of the local magnetic field is the principal practical limit to the length of signal. In turn this may be due to the intrinsic quality of the magnet or alternatively to degradations due to the tissue itself. The latter known as a susceptibility effect. In cases where these are not the limiting factors and this is rarely the case, then the natural linewidth of each resonance (which may be different for each line) ensures the time domain signal does not persist. Signal amplitude depends upon the number of nuclei producing the signal, therefore the relative size of the signals from the sample are a measure of the relative molecular concentration. But signal intensity modified by other factors, these include; spin-lattice relaxation time T1, spin-spin coupling T2, and the more practical aspects of field quality.

THE BIOCHEMISTRY OF ^{31}P MAGNETIC RESONANCE SPECTROSCOPY.

The major source of energy within the cell is adenosine triphosphate (ATP). ATP is generated by three main pathways, the breakdown of phosphocreatine stores within the cell, glycolysis and oxidative phosphorylation. Under normal conditions in resting muscle ATP is generated by oxidative phosphorylation, the limiting factor being an adequate oxygen supply. In situations of increasing energy demand the ATP is maintained by mobilization of phosphocreatine stores. In chronic ischaemia the oxygen delivery to the cell is reduced and ATP formation by anaerobic glycolysis is increased. ATP releases its energy by forming Pi and adenosine diphosphate (ADP). In normal resting muscle the relative concentration of Pcr to Pi in 32 : 2 mmols. In situations of high energy demand within the cell the relative concentration of Pi rises.

Short-term (anaerobic) energy sources.

$$\text{ATP} \longrightarrow \text{ADP} + \text{Pi} + \text{ENERGY}$$

$$\text{ADP} + \text{Pcr} \longrightarrow \text{ATP} + \text{creatine}$$

$$\text{glycogen} + \text{ADP} + \text{Pi} \longrightarrow \text{ATP} + \text{lactic acid}$$

Long-term (aerobic) energy sources.

glucose/glycogen + ADP + Pi + O_2

$$\longrightarrow ATP + H_2O + CO_2$$

fatty acids + ADP + Pi + O_2

$$\longrightarrow ATP + H_2O + CO_2$$

AIMS OF THIS STUDY.

This study aims to use ^{31}Phosphorus magnetic resonance spectroscopy as a non-invasive clinical test to assess irreversible muscle ischaemia in the foot of patients presenting to the Regional Vascular Service at Charing Cross Hospital, London W6 8RF, with critical lower limb ischaemia.

The hypothesis tested are as follows;

A. that ^{31}P MRS in patients with critical limb ischaemia will show spectral changes in the small muscles of the foot at rest.

B. that ^{31}P MRS can be used to define which patients will benefit from a revascularisation procedure and which patients have irreversible muscle ischaemia and therefore require an early major amputation.

C. that a follow-up ^{31}P MRS scan after revascularisation will be able to demonstrate whether or not surgical revascularisation has been successful and therefore predict limb salvage.

PATIENTS AND METHODS.

Patients.

Thirty two patients were studied, having been recruited from the Regional Vascular Service at Charing Cross Hospital between 1st January 1989 and 31st December 1990, all these patients make up part of the critical limb ischaemia series in chapters 3 and 4 in this work. ^{31}P MRS studies were attempted on three patients, but the studies were abandoned as the patients were unable to lie with their foot in the magnet due to ischaemic pain (two male patients) or due to claustrophobia (one female patient). Patients were excluded from this study if any of the following condition were applicable, the patient had a pacemaker, the patient had a metallic implant, the patient was undergoing renal dialysis, the patients haemoglobin was below 9.5 or above 14 gm per 100 ml or the patient had a platlet count greater than 6×10^5 mm^3.

Forty spectroscopy examinations were performed adequately on 29 patients, eight patients were studied on one or more occasions after revascularisation surgery. There was a male preponderance, 19 male to 10 females, their mean age was 65 years (range 43 - 91 years). Risk factors for peripheral vascular disease were as follows, nine patients (31%) had diabetes mellitus, nine (31%) had a history of hypertension, seven (24%) had a history of angina pectoris or had a myocardial infarction in the past, three (10%) had a stroke and 27 (93%) had been or were current smokers. (TABLE 5.1.)

All patients had ischaemic rest pain, 15 with an ankle systolic pressure of < 40mmHg without tissue loss, 14 patients had ulceration or gangrene. Seven of the latter group had an ankle systolic pressure < 40mmHg and seven an ankle systolic pressure of > 40mmHg (TABLE 5.2).

Controls.

Twelve healthy volunteers without symptoms of peripheral vascular disease, ie no intermittent claudication or rest pain and no history suggestive of rest pain acted as controls. All had normal Doppler ankle systolic pressures before and after a one minute exercise test (Laing and Greenhalgh. 1980) Twelve control subjects, had 14 MRS studies performed. The control subjects mean age was 56 years, range 32 to 79 years,with a slight female preponderance, seven (58%).

They had no clinical evidence of hypertension, ischaemic heart disease or cerebrovascular disease, but five were smokers. Two of these subjects (both female, aged 50 and 56 years) were studied before, and within one month after varicose vein surgery.

Clinical Investigation.

The patient series studied using ^{31}P MRS patients had non-invasive investigations in the Vascular Laboratory, at Charing Cross Hospital, London W6. Physical examination of peripheral pulses, testing for peripheral neuropathy by noting loss of sensation and vibration sense and identification of tissue loss or gangrene was noted. Non-invasive investigations included measurement of the Doppler ankle systolic pressure using a hand held 5 MHz probe and calculation of the ankle to brachial pressure index. Pulse rise time calculation and measurement of segmental systolic pressures at high thigh, low thigh, below knee and above ankle were performed. Angiography was undertaken in any patient whose clinical condition warranted attempted revascularisation.

Patients underwent either an attempted revascularisation or a major amputation this was decided upon by the vascular consultant surgeons at the RVS without knowledge of the ^{31}P MRS results. Revascularisation was attempted in 21 patients, and primary major amputation in eight.

The ^{31}P MRS studies were performed at the Nuclear Magnetic Resonance (NMR) Unit at the Hammersmith Hospital, London W8. Patients were consented for the study before travelling from Charing Cross Hospital by car to the Hammersmith Hospital. This was a limiting factor in selecting patients for study, as only those patients mobile enough to travel could be studied.

Spectroscopy.

Spectroscopy was performed using an Oxford Magnet 2.0 Tesla whole body magnet operating at 1.6 Tesla, 27.53 MHz for phosphorus Sagittal ^{1}H images of the foot in the plane of maximum muscle bulk, were acquired for localisation (FIGURE 5.4.), unlocalised spectra were acquired at repetition times of 1000 ms and 5000 ms to assess saturation effects.

The radiofrequency pulse angle at the centre of the transmitter coil was 45°, to reduce the partial saturation effects, maintain signal and reduce sampling time.

Two dimensional chemical shift imaging was performed in the long axis of the foot at 2 cm intervals (Brown, Kincaid and Ugurbil. 1982). In addition to Fourier transformation additional filtering functions were employed to improve spectral appearance. Localised spectra were obtained and for all data presented here peak area ratios were analysed from the plane containing maximum muscle bulk. In each case the tissue concentration of a particular metabolite is proportional to the area under the curve.

STATISTICAL ANALYSIS.

Statistical analysis was performed comparing the controls and the patients with critical lower limb ischaemia using the Mann-Whitney U-test. Statistical analysis of the results before and after surgery in the limb salvage group was by Wilcoxon matched pairs.

RESULTS.

Spectral patterns in normal and ischaemic feet.

Spectra acquired from the whole volume of the resting foot at a repetition time of 5000 ms from a 57 year old male patient (limb salvage group) and a male control subject are illustrated in FIGURE 5.5a. and 5.5b. The peaks are due to phosphocreatine (Pcr), inorganic phosphate (Pi), $\alpha, \beta,$,phosphorus nuclei of adenosine triphosphate (ATP), the phosphomonoesters (PME) and the phosphodiesters (PDE). The spectrum from the patient is noisier, which could be as a result of reduced metabolite concentration, but could also be due to a number of other experimental reasons. Resonances from P^{cr} and P_i are both reduced when compared to the βATP signal, when the patient study is compared to the control. Furthermore the ratio of P_{cr} to P_i is 4.4 in the normal control compared with 2.4 in the patient.

The spectrum from a 78 year old male patient prior to amputation is shown in FIGURE 5.6a. In this example the spectra are considerably noisier than in the control (FIGURE 5.6b) and the previous example. Both the P^{cr} and P_i are very much reduced in comparison with the βATP. An accurate quantitative assessment of the P^{cr} to P_i ratio is more difficult given the level of noise, but in this example will lie in the range 1.0 - 1.2.

Patients were divided into two groups for analysis, those patients who had a functioning limb at six months from entry into the study, ie limb salvage (16 patients), and those patients undergoing a major amputation, either as a primary procedure or after an attempted revascularisation (13 patients) (TABLE 5.3.).

The revascularisation performed in the limb salvage group are as follows; six supra-inguinal bypass grafts, four femoro-popliteal grafts, four femoro-distal bypass grafts, one angioplasty and one patient in whom no revascularisation was feasible, but who kept a viable limb for at least one year. The five patients who had a failed revascularisation necessitating a major amputation within one month of surgery had the following operations performed; one femoro-popliteal bypass graft, three femoro-distal bypass grafts, and one in which no reconstruction was technically possible.

The intensity of a particular resonance is proportional to the quantity of the metabolite present, but will also depend upon the relaxation time T_1 of the contributing molecules. The latter has been assessed by the acquisition of two different unlocalised spectra at different repetition times T_R (1000 and 5000ms). In table 5.4 the peak height ratios for the principal resonances for the two different T_R are summarised. It is clear that P_{cr} and P_i both increase in intensity by a factor of two when increasing the T_R from 1000ms to 5000ms. This demonstrates that the T_1 of both these resonances is larger than 1000ms, but more importantly they are both partially saturated to the same extent at 1000ms.

As a result of the changes observed in the spectra of patients with critical ischaemia are likely to be changes in the concentration of these metabolites. Furthermore the metabolite ratios in table 5.5 show distinct variation between control and patient groups.

In patients with critical limb ischaemia the amplitude of the phosphocreatine peak fell, with an accompanying increase in the inorganic phosphate peak, this resulted in a fall in the phosphocreatine to inorganic phosphate ratio. The phosphocreatine to inorganic phosphate ratio was significantly lower in the amputation group compared with the control group ($p = 0.0002$). Statistical significance was also achieved comparing the limb salvage group with the control group ($p = 0.023$) and the limb salvage with the amputation group ($p = 0.030$). The importance of these results is diminished as there is a wide overlap between inter-quartile ranges of the groups (FIGURE 5.7.).

The phosphomonoester to βATP ratio, rose with increasing severity of critical limb ischaemia (limb salvage group 0.45, amputation group 0.60). Statistical significance is achieved comparing the control group with both the limb salvage group ($p = 0.026$) and the major amputation group ($p = 0.0006$) (FIGURE 5.8).

The phosphodiester ratio to βATP ratio rose with increasing levels of ischaemia, this reached statistical significance only when comparing the control and major amputation groups ($p = 0.0067$) (FIGURE 5.9.)

The phosphocreatine to βATP level fell as the degree of ischaemia increased (control 2.5, limb salvage 2.0, amputation 1.4), achieving statistical significance comparing the control and the amputation group ($p = 0.0219$), but failed to reach significance comparing the control group to the limb salvage group ($p = 0.449$) (FIGURE 5.10.)

The median pH became progressively more alkaline with increasing levels of ischaemia, but failed to reach statistical significance comparing the control group with the limb salvage group ($p = 0.276$) and the amputation group ($p = 0.303$) (FIGURE 5.11.).

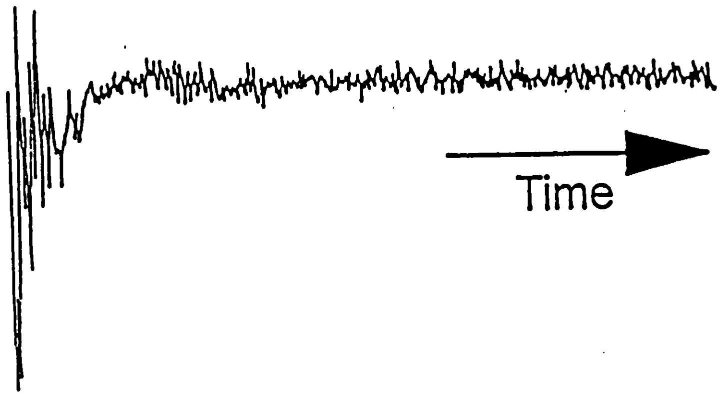
The effects of surgery on spectral patterns.

In all cases there was an immediate clinical improvement in the patients limb and the post-operative Doppler ankle systolic pressure improved by at least 40mmHg. Therefore surgery was considered successful in these patients. All patients in the limb salvage group had viable limbs six months after revascularisation. FIGURE 5.12. shows the phosphocreatine to inorganic phosphate ratios (muscle plane) from the eight patients studied before successful revascularisation and within two months after surgery. In all patients despite successful surgery, the phosphocreatine to inorganic phosphate ratio from the small muscles of the foot fell from 3.00 (2.23-3.68) pre-operatively to 1.80 (1.30-3.20) post-operatively ($p = 0.018$) (FIGURE 5.12).

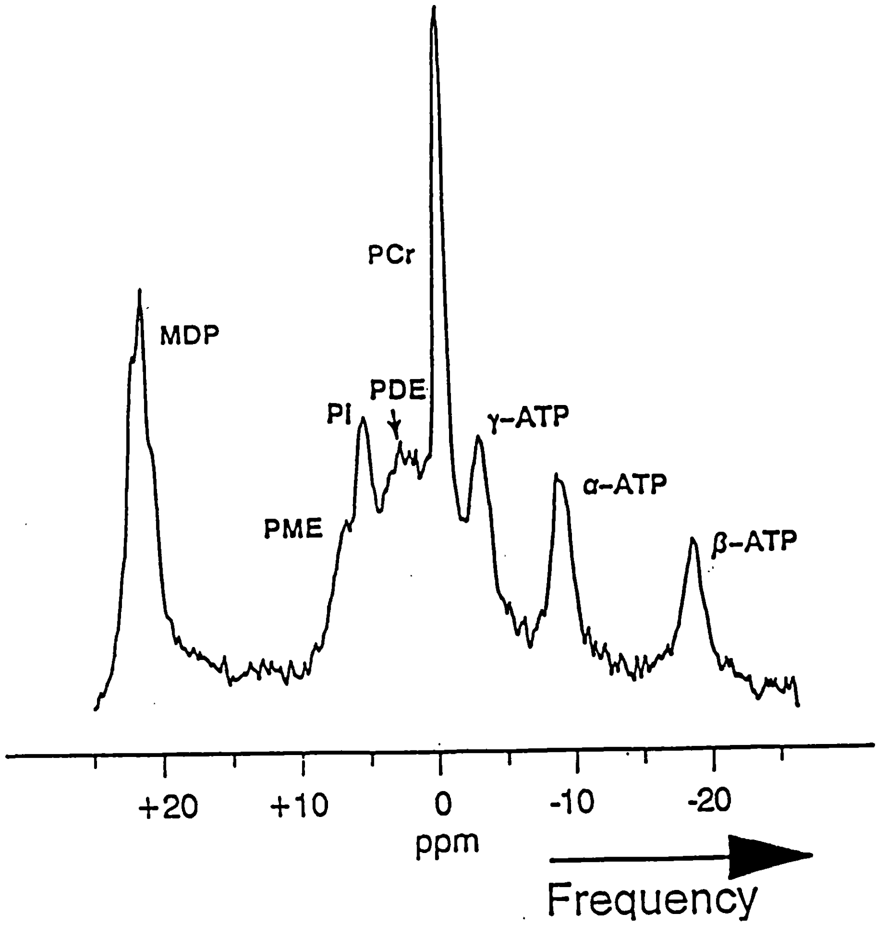
Two control subjects were studied before and after varicose vein surgery. Both had normal ankle pressures before and after surgery. The phosphocreatine to inorganic phosphate ratio did not fall after surgery and in one of the control subjects actually improved (FIGURE 5.13).

Comparison of the phosphomonoester to βATP ratio, the phosphodiester to βATP ratio, the phosphocreatine to βATP ratio and the pH before and after surgery in the limb salvage group did not achieve statistical significance.

To monitor the phosphocreatine to inorganic phosphate ratio and determine how quickly it returned to its pre-operative level one patient, a 57 year old female, was studied before revascularisation and on four subsequent occasions. Her limb immediately improved clinically and her limb remained viable during the study. Despite an early rise in the Doppler ankle systolic pressure the phosphocreatine to inorganic phosphate ratio had not risen to the pre-surgery level after twelve months (FIGURE 5.14.).



F5.1a. A ^{31}P FREE INDUCTION DECAY OBTAINED FROM NORMAL RESTING SMALL MUSCLES OF THE FOOT.



F5.1b. THE ^{31}P SPECTRUM DERIVED FROM THE FREE INDUCTION DECAY BY FOURIER TRANSFORMATION.

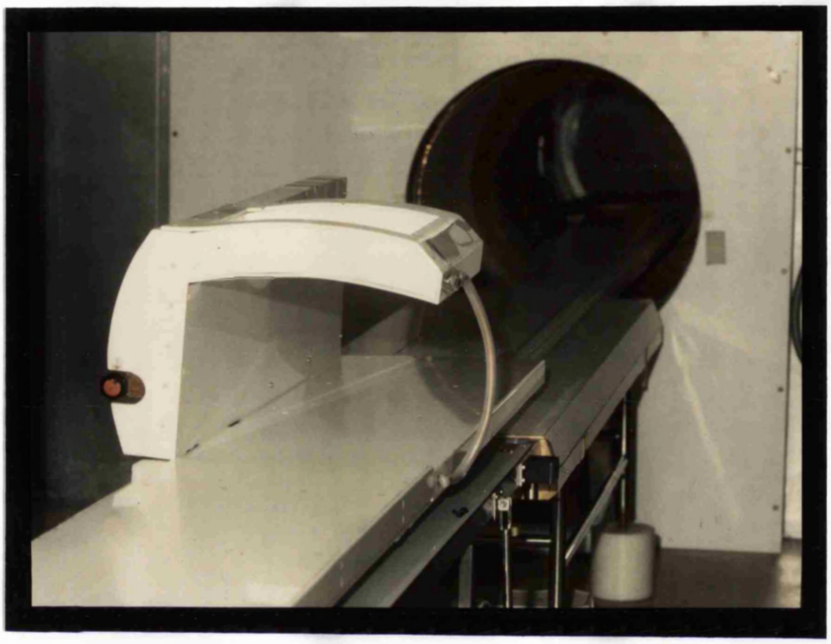


FIGURE 5.2. THE WHOLE BODY MAGNET.

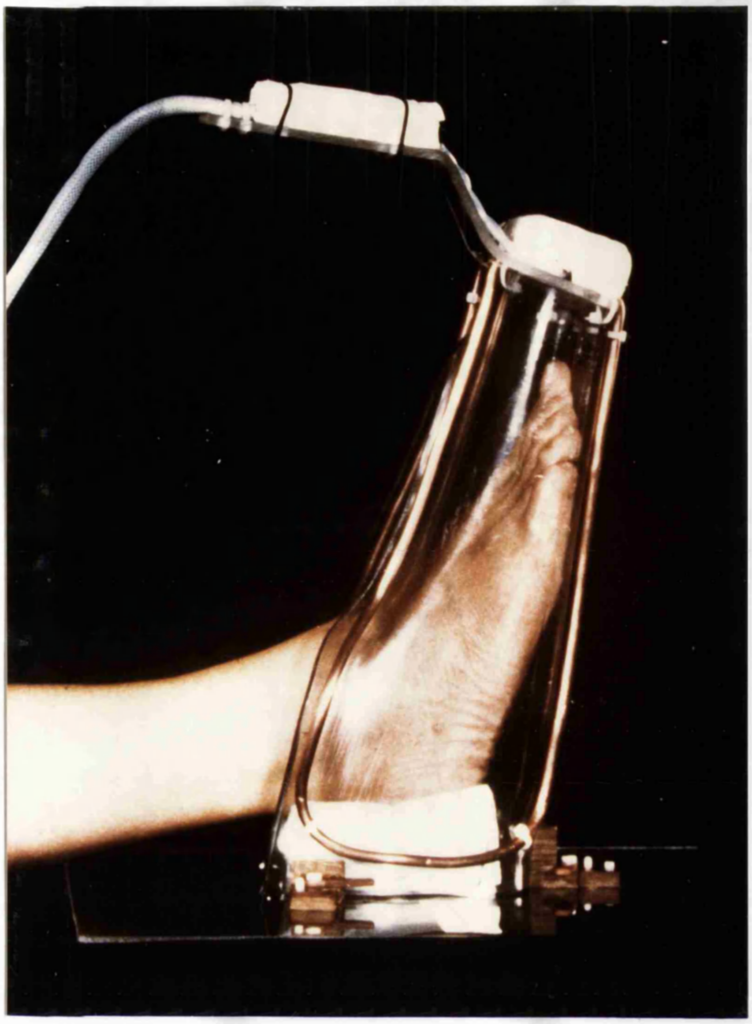


FIGURE 5.3. THE SPECIALLY DESIGNED SADDLE RECEIVE COIL.

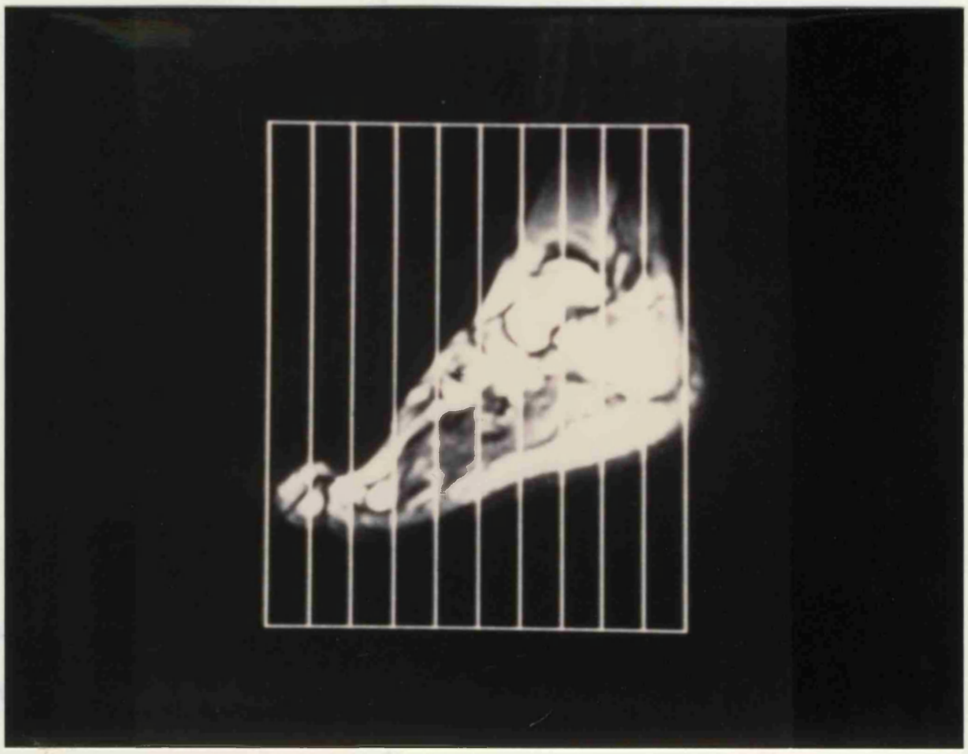
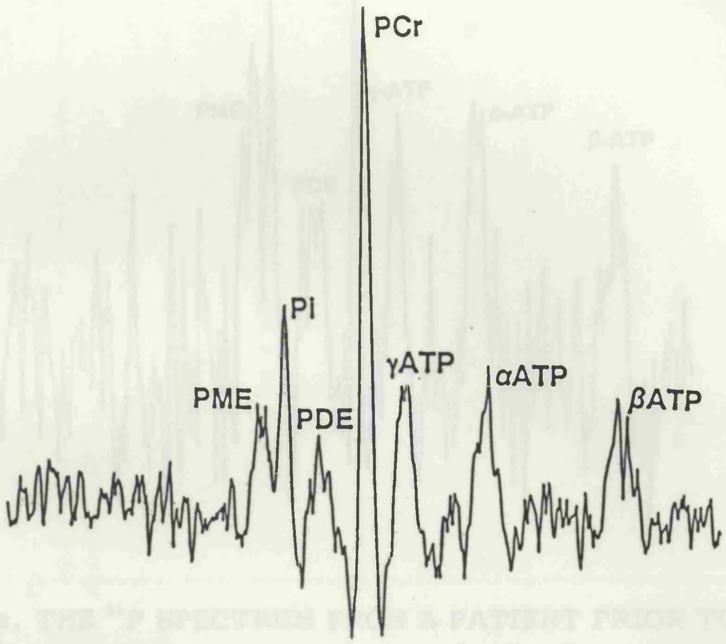
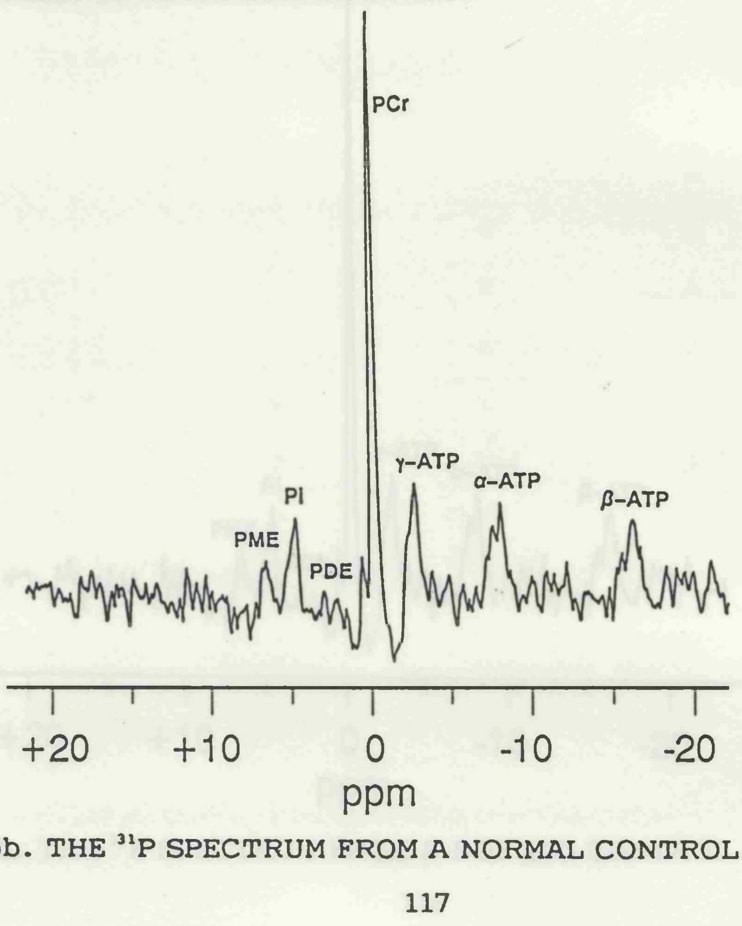


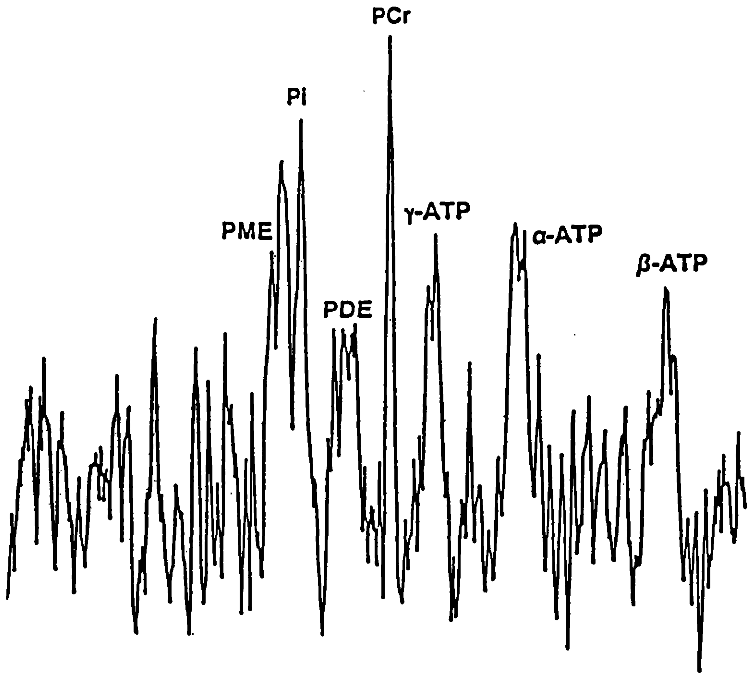
FIGURE 5.4. A SAGITTAL IMAGE OF A FOOT WITH THE GRID IN-SITU.



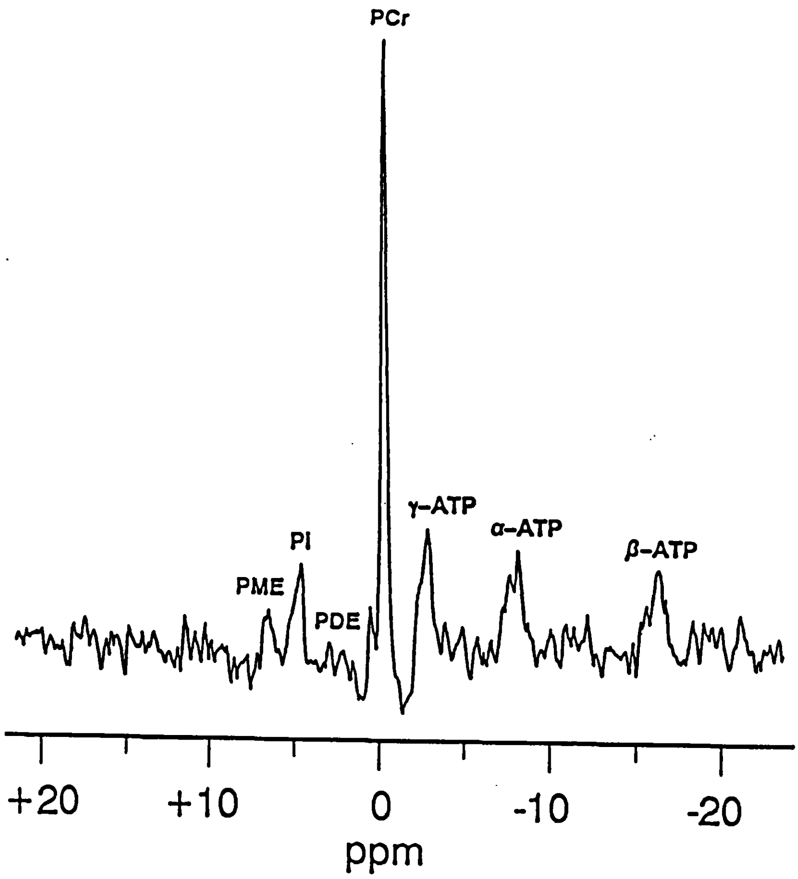
F5.5a. THE INITIAL ^{31}P SPECTRUM FROM A PATIENT WHO HAD A SUCCESSFUL REVASCULARISATION.



F5.5b. THE ^{31}P SPECTRUM FROM A NORMAL CONTROL.



F5.6a. THE ^{31}P SPECTRUM FROM A PATIENT PRIOR TO A MAJOR AMPUTATION.



F5.6b. THE ^{31}P SPECTRUM FROM A NORMAL CONTROL.

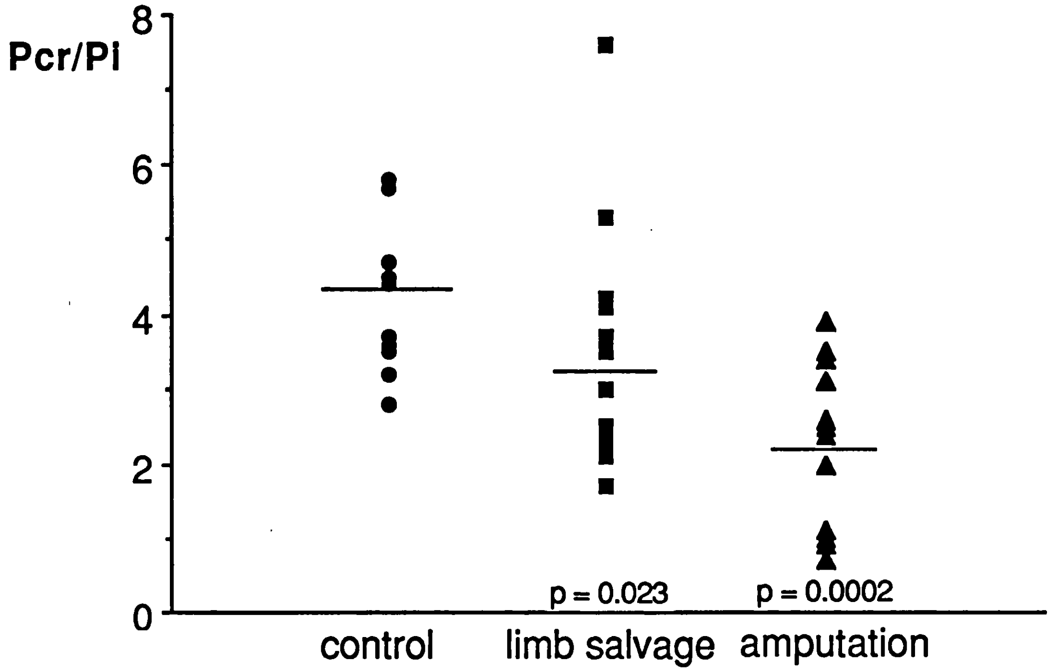


FIGURE 5.7. GRAPH OF THE Pcr/Pl RATIO

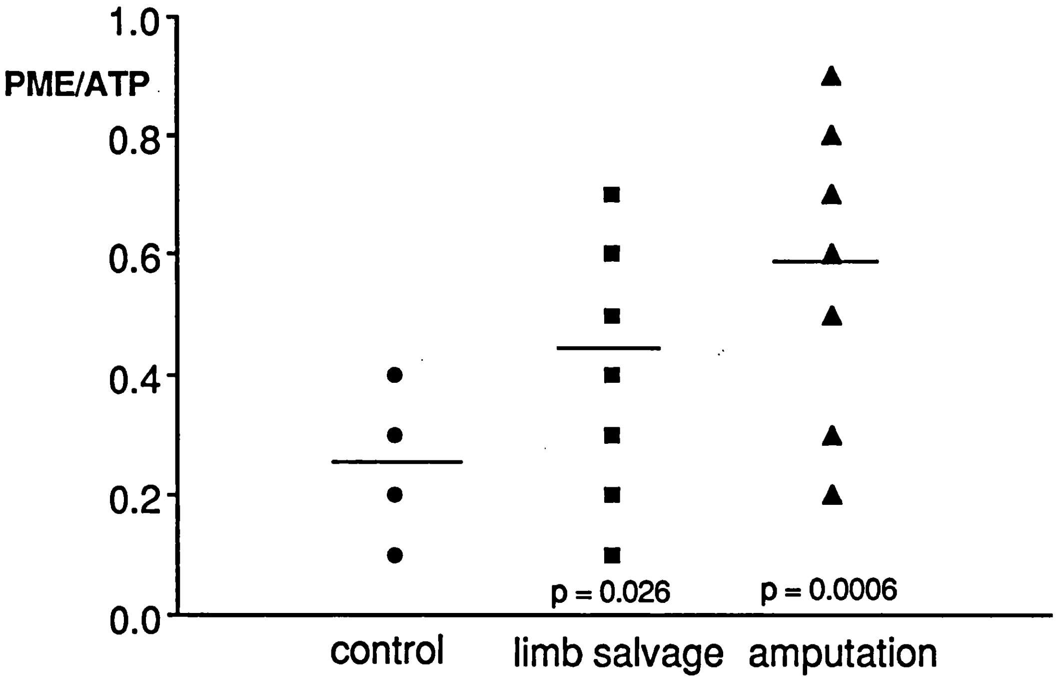


FIGURE 5.8. GRAPH OF THE PME/ATP RATIO

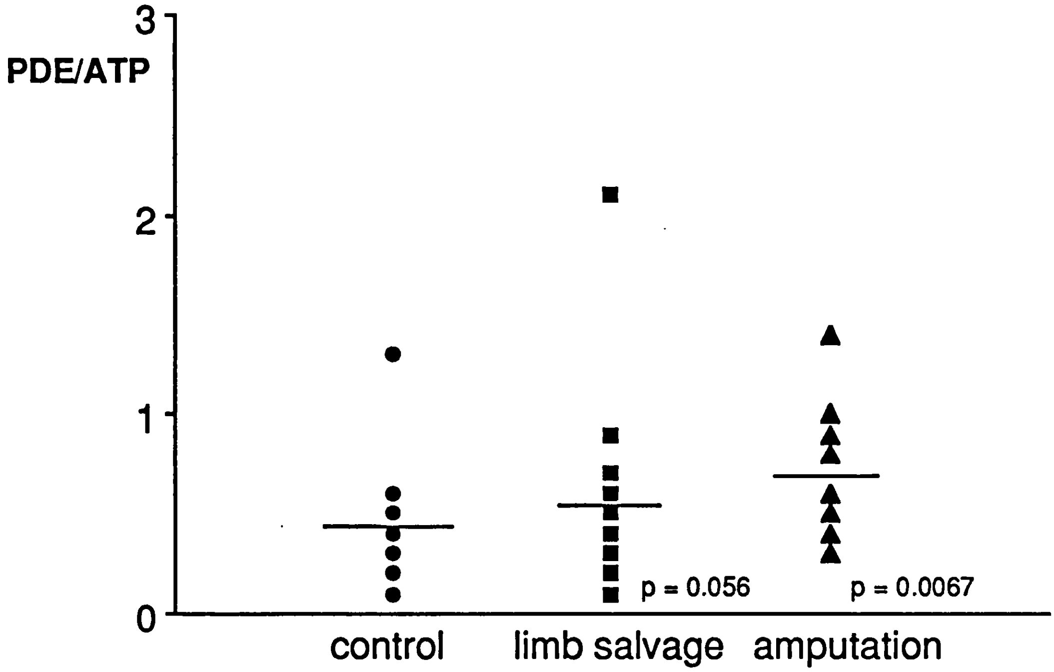


FIGURE 5.9. GRAPH OF THE PDE/ATP RATIO

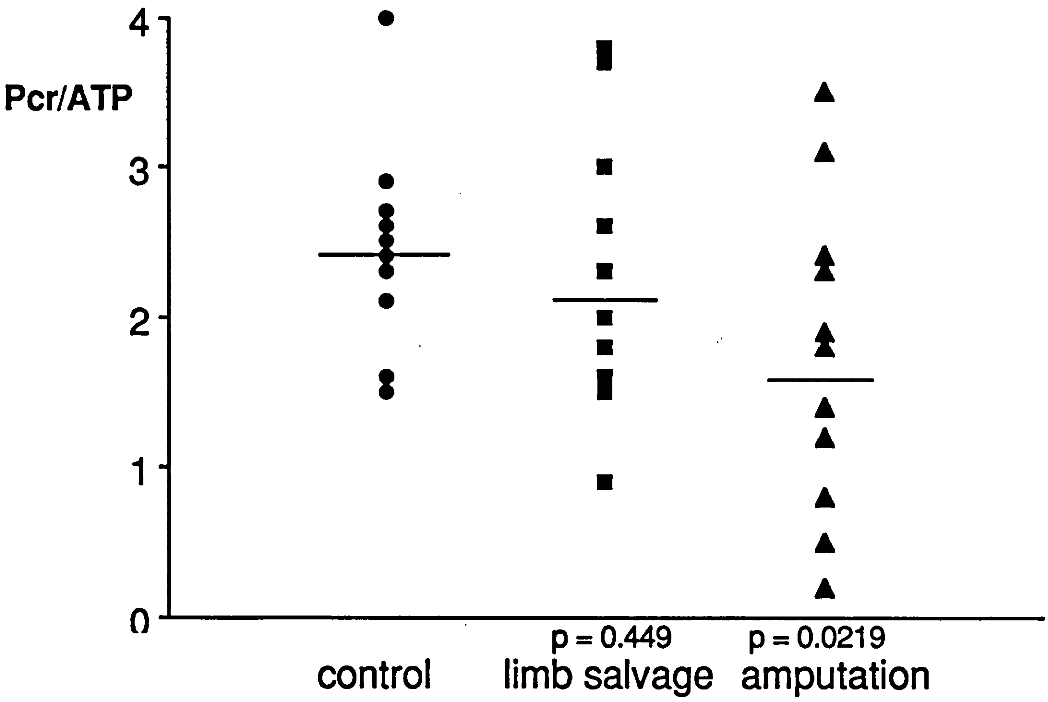


FIGURE 5.10. GRAPH OF THE Pcr/ATP RATIO

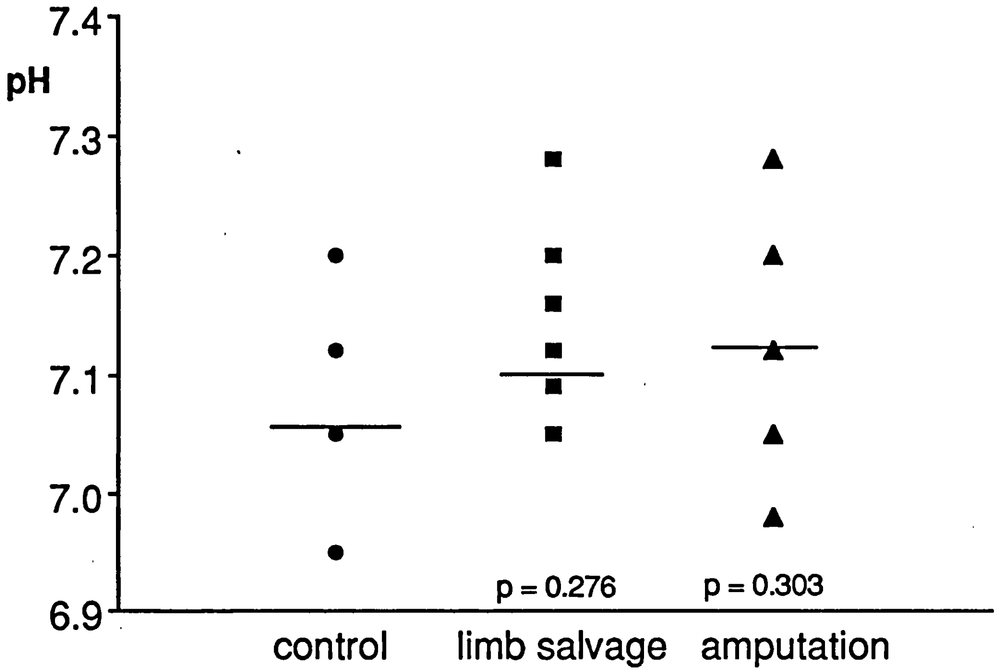


FIGURE 5.11. GRAPH OF THE pH RATIO

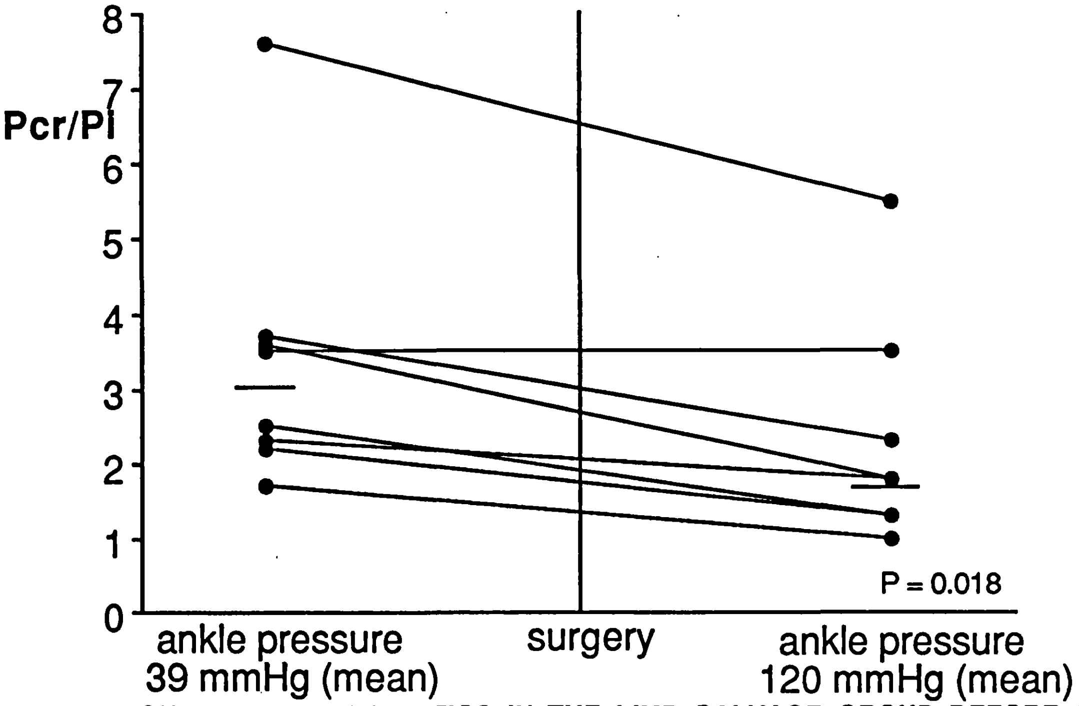


FIGURE 5.12. Pcr/PI RATIOS IN THE LIMB SALVAGE GROUP BEFORE & AFTER SURGERY

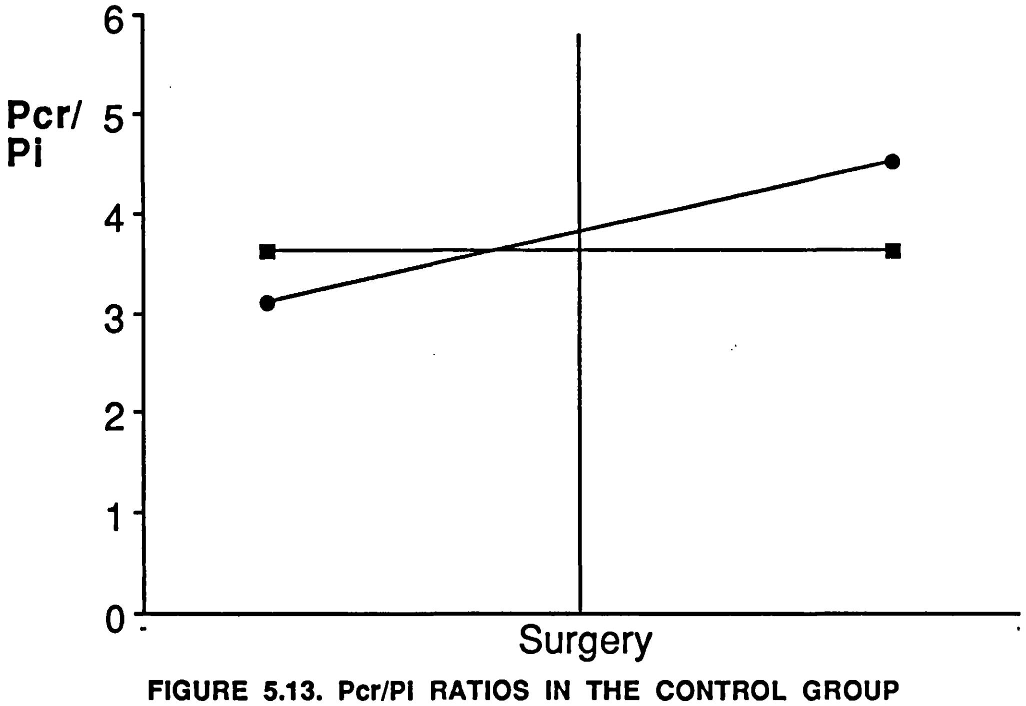


FIGURE 5.13. Pcr/PI RATIOS IN THE CONTROL GROUP BEFORE & AFTER SURGERY

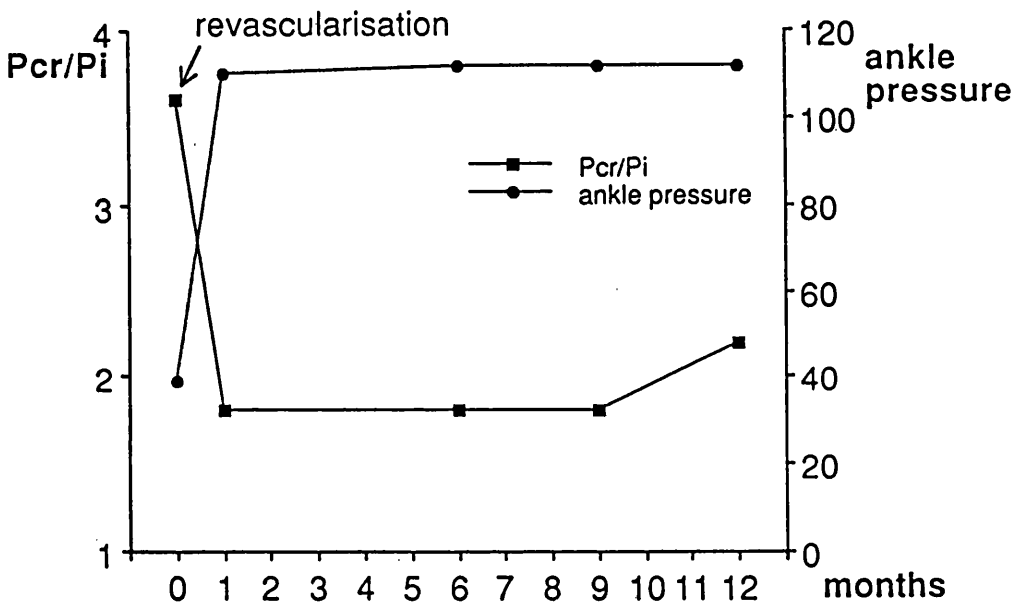


FIGURE 5.14. GRAPH OF Pcr/Pi RATIO IN ONE PATIENT AFTER SUCCESSFUL REVASCULARISATION

TABLE 5.1. DEMOGRAPHIC DETAILS AND RISK FACTORS FOR PERIPHERAL VASCULAR DISEASE IN PATIENTS AND CONTROLS.

	Controls		Critical limb ischaemia	
number	12		29	
age, yrs (range)	52	(32-79)	65	(43-91)
male:female	5:7	1:1.4	19:10	1.9:1
Diabetes mellitus	0		9	(31%)
Hypertension	0		9	(31%)
heart disease	0		7	(24%)
stroke	0		3	(10%)
smoker	5	(42%)	27	(93%)

TABLE 5.2. INDICATIONS FOR ENTRY INTO THE ^{31}P MRS STUDY.

	Controls	Critical limb ischaemia
number	12	29
rest pain and ankle pressure < 40mmHg	0	15 (52%)
tissue loss and ankle pressure < 40mmHg	0	7 (24%)
tissue loss and ankle pressure > 40mmHg	0	7 (24%)

TABLE 5.3. ALLOCATION TO LIMB SALVAGE OR MAJOR AMPUTATION GROUP IN PATIENTS STUDIED BY ^{31}P MRS.

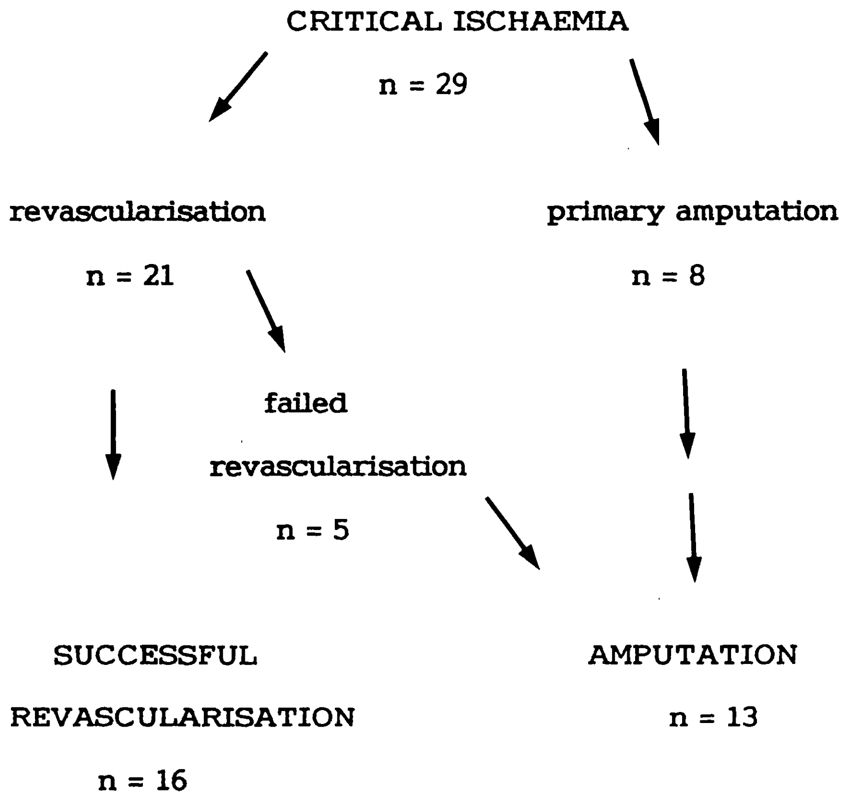


TABLE 5.4. SIGNAL HEIGHT RATIOS FOR CONTROL AND PATIENT GROUPS AT 5000 AND 1000 ms.

	Controls	Limb salvage	Amputation
number	12	16	13
Phosphocreatine	2.1 ± 0.1	2.1 ± 0.2	2.0 ± 0.1
Inorganic phosphate	2.1 ± 0.2	2.0 ± 0.1	2.0 ± 0.1
Phosphomonoester	1.8 ± 0.2	1.8 ± 0.1	1.8 ± 0.1
Phosphodiester	1.8 ± 0.2	2.0 ± 0.2	1.4 ± 0.1
β Adenosine tri-phosphate	1.8 ± 0.2	1.6 ± 0.2	1.7 ± 0.1

(mean ± standard error of the mean)

TABLE 5.5. METABOLITE RATIOS AND pH FROM THE PLANE CONTAINING THE MAXIMUM MUSCLE BULK FOR CONTROL AND PATIENT GROUPS.

	Controls	Limb salvage	Amputation
number	12	16	13
Pcr / Pi	4.45 (3.52,4.70)	3.25 (2.22,4.00)	2.40 (1.05,3.25)
PME / ATP	0.25 (0.12,0.30)	0.45 (0.27,0.60)	0.60 (0.40,0.75)
PDE / ATP	0.30 (0.12,0.47)	0.50 (0.30,0.70)	0.60 (0.40,0.90)
Pcr / ATP	2.50 (2.10,2.70)	2.00 (1.60,3.00)	1.40 (0.80,2.35)
pH	7.05 (7.05,7.12)	7.10 (7.05,7.20)	7.12 (7.05,7.24)

Pcr phosphocreatine,
Pi inorganic phosphate,
PME phosphomonoester
PDE phosphodiester,
ATP adenosine tri-phosphate.

(median, inter-quartile range)

DISCUSSION.

The detection of irreversible ischaemia of the lower limb remains a clinical problem to the vascular surgeon, as no gold standard currently exists. ^{31}P MRS offers the opportunity of non-invasively investigating the energy status of the ischaemic limb by observing the high energy phosphates within the muscle. A number of previous studies (Chance et al. 1981, Hands et al. 1986, Zatina et al. 1986, Lenkinski et al. 1988, Hands et al. 1990) have demonstrated that significantly differing metabolic profiles could be obtained from normal limbs and the limbs of patients with varying degrees of ischaemia.

Zatina and his colleagues demonstrated that normal limbs and those with moderate ischaemia could be distinguished from limbs with severe ischaemia on the basis of the NMR index $P_i / (P_{cr}+P_i)$ derived from gastrocnemius muscle. Furthermore they showed that a simple exercise protocol, performed away from the confines of the magnet, would allow this same index to distinguish significantly between these three groups. A measure of recovery of the muscle after exercise also showed a significant distinction between varying degrees of ischaemia. Following surgical revascularisation the immediate and expected improvement in the clinical condition of the leg and systolic ankle Doppler pressure was not accompanied by the re-establishment of a normal muscle metabolism, even over a period of several months (Zatina et al. 1986).

Hands at Oxford have also investigated the gastrocnemius muscle at rest, during and after exercise. In this study the exercise was carried out within the bore of the magnet (Hands et al. 1990). There was agreement with Zatina in the exercise stage of the protocol, when recovery of the NMR index P_i / $(P_{cr}+P_i)$ and the pH were significantly impaired in the most severely ischaemic limbs. However, at rest Hands found only the measured pH to be significantly elevated (by 0.05 pH units) with respect to the control limb, in contrast to Zatina who showed that metabolite ratios also varied.

Lenkinski and colleagues studied the ^{31}P spectra at three different positions in the limb, the proximal calf, the distal calf and the foot. They found that elevated levels of inorganic phosphate could be detected in the foot prior to any changes occurring in the proximal or distal calf. In this preliminary report a correlation between the phosphocreatine to inorganic phosphate ratio and the degree of symptomatic improvement after treatment was beginning to emerge (Lenkinski et al. 1988).

The work described in this thesis differs from the studies previously mentioned as all the patients had critical limb ischaemia (Bell et al. 1982). The small muscles of the foot were studied using ^{31}P MRS with a spectroscopic imaging method to select the area of maximum muscle bulk, hoping to detect small variations in the degree of ischaemia in a limb. A separate transmitter coil and specially designed saddle receiver coil were used in order to improve the signal to noise ratio of the data collected.

The findings in my study are in agreement with previous studies. There is a statistically significant fall in the phosphocreatine to inorganic phosphate ratio for both the limb salvage ($p = 0.023$) and amputation ($p = 0.0002$) groups compared to the control group and also comparing the limb salvage and amputation groups ($p = 0.030$). Previous studies have only demonstrated changes comparing severely ischaemic limbs with normal controls. The importance of the findings in this study are reduced by the large overlap between the three groups of patients studied, preventing the establishment of a reference range for each of the control, limb salvage and amputation groups. In contrast with Hands, but in agreement with Zatina, no significant change was observed in pH in these critically ischaemic limbs at rest.

Increases in phosphomonoester to adenosine triphosphate ratios reached statistical significance for both the limb salvage ($p = 0.026$) and the amputation ($p = 0.006$) groups. The extent of this elevation is more than that observed by Hands and this may reflect the severity of limb ischaemia in the patients studied in this thesis. The sugar phosphates, labelled as the phosphomonoester peak, are intermediate by-products of glycolysis and the phosphomonoester to adenosine triphosphate ratio may be a useful indicator of anaerobic metabolism with the cells of ischaemic muscle.

The increased level of cell damage and corresponding phospholipid breakdown have been noted before (Hands et al. 1990) and are evident by increased levels of phosphodiester in the ^{31}P spectra. The phosphodiester to adenosine triphosphate ratios are significantly increased in the amputation group ($p = 0.0067$), but there is a large overlap with control and limb salvage groups.

The benefits of increased spatial localisation are not readily apparent in this study. Subdividing the total ^{31}P signal when localising has the immediate effect of decreasing the signal-to-noise ratio and increasing the spread in NMR derived parameters. This is alleviated to some extent by a purpose built receiver coil, but does not provide the complete solution. The overall level of ^{31}P is apparently much reduced in the ischaemic limb, this is demonstrated in the spectra shown in Fig 5.6a.

This study highlights the difficultly encountered in investigating patients with critical limb ischaemia. The patients are elderly, often frail and find that to lie with their ischaemic limb horizontally in a whole body magnet is difficult. In this study the whole body magnet was located at a different site, transporting immobile patients to and from the magnet was difficult and time consuming. The development of a small magnet approx 30cms long, of approx 50cm diameter and sufficient field strength (approx 1.5 Tesla) to encase just the ischaemic limb in a dependent position may make such studies feasible. It is now possible to build such a magnet, but it would cost approx £200,000 and need to be situated in a magnetic spectroscopy unit in a hospital with a specialist vascular unit.

The future of magnetic resonance as applied to critical lower limb ischaemia would be enhanced by a fully integrated approach between magnetic resonance imaging and magnetic resonance spectroscopy.

The former would provide information on the muscle bulk in the foot and could also provide data on oxygen delivery to the muscle via the measurement of blood flow and perfusion (Chance. 1989, Kerr et al. 1991). Magnetic resonance spectroscopy, as applied in this study, can provide observable metabolic changes in the varying severity of ischaemia, but these changes would be clearer by close attention to the absolute quantitation of all observable ^{31}P resonances. In combination with magnetic resonance imaging data a more complete and clinically useful result may well be obtained.

CHAPTER 6.

QUALITY OF LIFE STUDIES COMPARING REVASCULARISATION WITH MAJOR AMPUTATION IN PATIENTS WITH CRITICAL LIMB ISCHAEMIA.

INTRODUCTION.

Health is a concept of tremendous importance to us all, but difficult to define. The World Health Organisation (1947) defines health as "a state of complete physical, mental and social well-being and not merely an absence of disease."

Patients with critical limb ischaemia represent the extreme of peripheral vascular disease and suffer a severe degree of ill health. Quantifying this is difficult and various well validated health profiles exist. This study has used the Nottingham Health Profile (NHP) to measure; physical functioning including somatic sensations such as physical symptoms and pain; psychological functioning including concentration and mood; social (including sexual) functioning and occupational status. The NHP has been well validated and previously used in patients with vascular disease.

The Nottingham Health Profile.

The questionnaire was constructed by a group of workers at the University of Nottingham working between September 1975 and December 1981. Initially statements were collected from members of the general public describing the typical effects of ill-health, looking at the social effects, the psychological effects, the behavioural effects and the physical effects.

The questionnaire is self-administered, but can be read out and filled in by an assessor.

PART I.

For Part I initially 2,000 statements were collected these were narrowed down to 138. Pilot studies undertaken between 1976 and 1978 used various combinations of these 138 statements refining them to 82 statements. These statements were re-selected to ensure that the following criteria were adhered to; there were no negative expressions, the statements were easy to answer, easy to understand and unambiguous, the statements were answered by a yes or no response and the language conformed to the standard of the minimum reading age.

Thirty eight statements that fulfilled these criteria were then divided into six categories; energy levels, pain, emotional reactions, sleep disturbance, feelings of social isolation and mobility problems (APPENDIX 3). The various statements in each section vary in severity and have been weighted to reflect this. The weighted score in each section totals 100. A yes answer receives the weighted score, a no answer scores zero. The higher a score on a particular section the greater the perceived health problem in that area. The statement is answered as it applies at the time of response.

PART II.

The format for these questions was gained from analysis of interviews with patients, overall seven areas were most commonly mentioned as being affected by health; occupation, ability to look after the home, social life, personal relationships including sex, holidays, interests and hobbies. Each question is answered by a yes or no answer. An affirmative answer sores one. The higher the percentage of positive answers the greater the perceived health problem.

Validation studies.

The N.H.P. was validated for face, content, and criterion validation. It was found to be a highly satisfactory measure of subjective health status in the physical, social and emotional domains, and a useful guide to the extent to which health problems restrict normal physical and social activities. For validation, ten groups were studied, these included 158 firemen, 60 fit elderly people selected from Gp records and 93 patients with peripheral vascular disease attending an outpatient clinic. The total number of people studied for validation was 5086.

Reliability studies.

Reliability studies involved testing the consistency of the questionnaire over time. The principle of test, re-test was used. Two groups of patients who were expected to have high scorers were sent the questionnaire initially and then again eight weeks later. The two groups used were 58 patients with osteoarthritis and 93 patients with peripheral vascular disease.

The higher the score, the greater the perceived health problems in that area. The "fit elderly" group had low mean scores for the questions in Part I ranging from 0.68 to 4.06. Those people with a chronic condition had higher mean scores, for example those with peripheral vascular disease scored a mean of between 9.2 and 30.3.

It was found that the scores tended to rise with age and that women consistently scored higher than men.

Advantages of the Nottingham Health Profile.

The NHP has a number of advantages these include; its useful in a wide range of clinical situations, its high reliability rate and good validation, its easy and cheap to administer, is short to complete and has a good acceptance rate by patients, is easy to score and compute and the results can be compared graphically.

The NHP has previously been used in patients with vascular disease. The Coronary Artery Surgery Study (CASS. 1983) failed to find significant differences in mortality, survival or myocardial infarction rates, but demonstrated that coronary artery bypass graft surgery significantly improved the patients quality of life. Similarly, a prospective study of 100 patients undergoing coronary artery bypass grafting showed an improvement in quality of life following surgery (Caine et al. 1991). The NHP has been used in patients with severe heart disease to identify the levels of acceptance for entry onto a heart transplantation programme, either provisional or definite (Evans et al. 1984). Patients who were identified as provisional were only accepted onto the programme if their condition deteriorated further. A strong correlation was found between the NHP scores and clinical judgments. In patients selected to undergo transplantation the questionnaire demonstrated significant improvement in quality of life. The NHP has also shown that patients with peripheral vascular disease had significantly impaired quality of life scores in their ability to enjoy their hobbies and interests and in the performance of household task and their work compared to two control groups aged over 55 years who were well and not attending a doctor. But little disturbance in their personal relationships and in feeling of social isolation (Hunt et al. 1982).

AIMS OF THIS STUDY.

This study was set up to determine if critical lower limb ischaemia patients undergoing attempted revascularisation have a better quality of life than patients undergoing a major amputation. The NHP was used as it previously been used in patients with peripheral vascular disease and shown to be well validated in this type of patient (Hunt et al. 1982).

PATIENTS AND METHODS.

This study recruited patients from both the Regional Vascular Service (RVS) and the District General Hospital (DGH) who had critical limb ischaemia (Bell et al.1982), they were allocated to either the attempted revascularisation group or the major amputation group as the initial management strategy (see Chapter 4). Patients were entered prospectively into the study between the 1st April 1990 and 31st July 1991. Eighty six patients undergoing an attempted revascularisation were given the questionnaire prior to surgery. Sixty four were able to complete it satisfactorily for analysis, giving a response rate of 76%. Seven of the eighty six patients given the

questionnaire had a failed revascularisation and subsequently had a major amputation. There were fewer patients undergoing a primary amputation in this study and 24 were given the questionnaire to complete. Seventeen were able to complete it satisfactorily, a response rate of 71%. Incomplete questionnaires were from patients who felt they were too ill or in too much pain to fill in the form.
The median age of the revascularisation group was 71 years (inter-quartile range 63 to 76 years) and the amputation group 72 years (inter-quartile range 68 to 78 years). As might be expected of patients with peripheral vascular disease there were more males than females in each group, 44 males in the revascularisation group and 10 in the major amputation group. These figure are only the patients whose questionnaires were suitable for statistical analysis.

STATISTICAL ANALYSIS.

The data for the first part of the questionnaire are presented as median with the inter-quartile range for each of the follow-ups. The Kruskal Wallace test was used to determine whether there were significant differences between follow-up for the individual groups with time. For a comparison between the reconstruction and the major amputation groups the data was fitted to a regression line and the slope of the two lines compared, with a Students t-test.

For the second part of the questionnaire the data are presented as the percentage of positive respondents whose life is affected by the area of health questioned. Analysis is by Chi trend to examine the trend within each group of observations and by the Mantez-Haenszel Chi square test which compares the two groups over the period of follow-up.

RESULTS.

PART I.

Energy.

Both the attempted reconstruction group and the major amputation group had low levels of energy (median score = 24), initially, three months and six months after entry into the study. This improved at one year in the reconstruction group (median score = 0), unlike the major amputation group (median score = 30), despite this improvement in energy levels, neither group demonstrated a significant difference with time (attempted reconstruction group $t = 2.644$, $p = 0.450$, major amputation group $t = 0.169$, $p = 0.982$). Comparison between the two groups showed no significant difference in energy levels during follow-up ($t = 1.29$, $p = 0.199$) (FIGURE 6.1.).

Pain.

Pain levels in both groups were high pre-operatively, with median scores of 59 in the attempted reconstruction group compared with 71 in the major amputation group. Significant improvement in pain levels occurred in both groups by three months (attempted reconstruction group $t = 44.05$, $p < 0.0001$, major amputation group $t = 19.25$, $p = 0.0002$). The reduction in pain levels occurred earlier in the major amputation group, but at one year the attempted revascularisation group had a median score of zero unlike the major amputation group who had a median score of 8. Comparison of the attempted reconstruction and the major amputation group failed to demonstrate any differences between the two ($t = 0.26$, $p = 0.798$) (FIGURE 6.2.).

Emotional reactions.

In the attempted reconstruction group the perceived disturbance of emotional well-being was high (median score = 24) pre-operatively, following reconstruction this improved, but did not reach statistical significance ($t = 6.97$ $p = 0.073$,). Emotional well-being had a lower pre-operative score in the major amputation group (median score = 10) and improved following major amputation, but once again failed to achieve statistical significance ($t = 0.58$, $p = 0.902$). No significant difference occurred between the two groups ($t = 0.47$, $p = 0.636$) (FIGURE 6.3.).

Sleep patterns.

The disturbance of sleep patterns was high in both groups pre-operatively (median score 20), and improved with time, possibly due to the reduction in pain in the ischaemic limb. In the reconstruction group this improvement in sleep pattern just failed to reach significance ($t = 7.19$, $p = 0.066$), no statistically significant improvement with time was shown in the amputation group ($t = 1.27$, $p = 0.952$). Comparison between the sleep patterns of the attempted reconstruction and major amputation groups failed to demonstrate a significant difference ($t = 0.06$, $p = 0.952$) (FIGURE 6.4.).

Social isolation.

Median scores in both groups were zero, (range 0 to 23). No significant difference was shown with time in either group (attempted reconstruction group t = 1.42, p = 0.700, major amputation group t = 1.91 , p = 0.592) or when comparing the two groups (t = 1.57, p = 0.119) (FIGURE 6.5).

Mobility.

Scores in both groups pre-operatively were high, reflecting the degree of immobility imposed by critical ischaemia. This was worse in the major amputation group (median score 67) compared with the attempted reconstruction group (median score 46). Both groups demonstrated a significant improvement in mobility with time (attempted reconstruction t = 17.67, p < 0.0005, major amputation t = 11.56, p < 0.009). Mobility between the two groups differed over follow-up, but failed to reach statistical significance (t = 1.85, p = 0.067) (FIGURE 6.6.).

PART II.

Table 6.1. shows the percentage of positive respondents for each of the seven areas most commonly mentioned as being affected by health; occupation, ability to look after the home, social life, personal relationships including sex, holidays, interests and hobbies.

Job.

The ability of both groups to work was limited in a maximum of one third of patients in both the amputation and reconstruction groups, this may reflect the fact that many of these patients were elderly and retired. Chi (trend)for both groups did not improve to statistical significance with time ((trend) = 0.42, p = 0.514 for the reconstruction group and (trend) = 0.46, p = 0.499 for the amputation group). Comparison of the two groups with time also failed to achieve statistical significance (^{2} = 0.03, p = 0.865).

<u>Looking after the home.</u>

Both groups had a high number of positive respondents who felt that their illness prevented then from looking after their home, both groups improved with time, but this achieved significance only in the reconstruction group (reconstruction (trend) = 5.29, p = 0.021, amputation (trend) = 2.94, p = 0.094). No difference was demonstrated between the two groups (^{2} = 1.05, p = 0.305).

<u>Social life.</u>

The trends in the reconstruction and the major amputation groups differ with respect to the effect of their illness on their social life. Thirty five percent of the reconstruction group are initially affected, with time this percentage increased and achieved statistical significance ((trend) = 5.58, p = 0.018). Fifty percent of the amputation group were initially affected, but improved with time, statistical significance is not reached ((trend) = 1.95, p = 0.162), possibly due to the small sample size. No significant difference was demonstrated between the two groups (^{2} = 1.05, p = 0.305).

Home life.

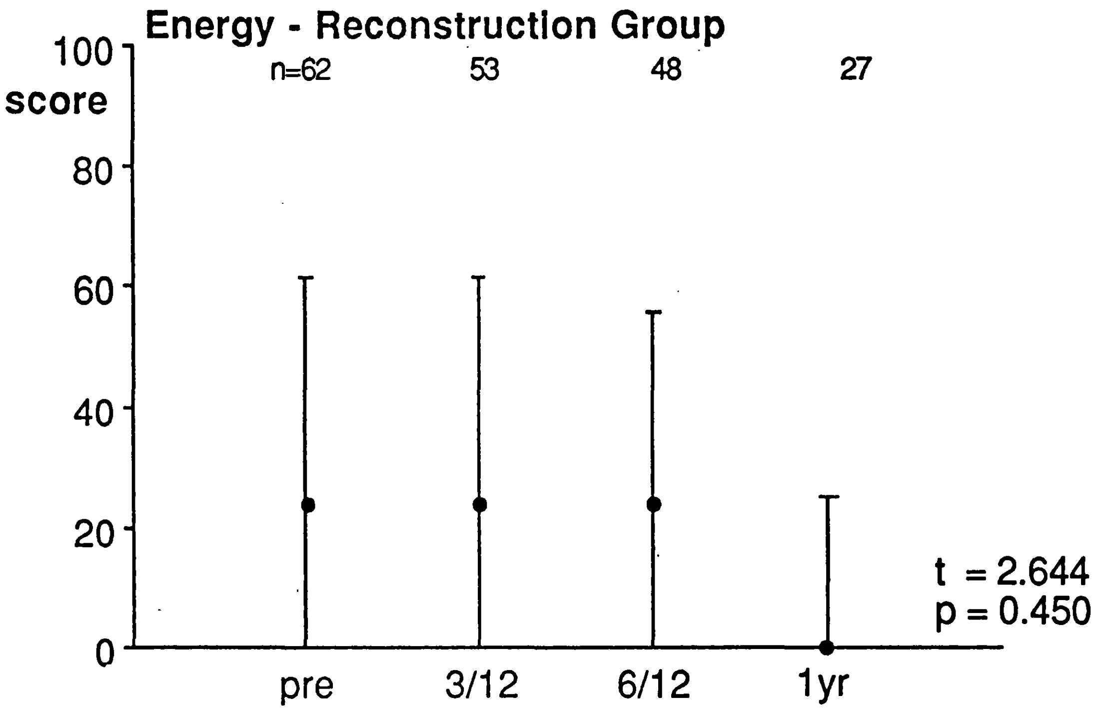
Twenty four percent of patients initially felt that their illness had a major effect on their home life in the reconstruction group, compared to 6% in the amputation group. No significant improvement with time is demonstrated in either group (reconstruction (trend) = 0.366, p = 0.545, amputation (trend) = 0.028, p = 0.867). Comparison of the two groups showed a statistically significant difference (^{2} = 5.28, p = 0.022).

Sex life.

This group of elderly patients show little disruption of their sex life by critical limb ischaemia and consequently neither comparison of each group with time or comparison of the two groups demonstrated a significant difference (reconstruction (trend) = 0.026, p = 0.963, amputation (trend) = 0.841, p = 0.359, Mantel-Haenszel ^{2} = 0.31, p = 0.101).

Hobbies and holidays.

Both groups perceived much disruption in their hobbies and holidays, initially over 50%in both groups. Only the reconstruction group demonstrated a statistically significant improvement with time, hobbies (reconstruction (trend) = 6.52, p = 0.011, amputation (trend) = 0.57, p = 0.448) and holidays (reconstruction (trend) = 5.85, p = 0.016, amputation (trend) = 2.89, p = 0.497). Comparison between the reconstruction and amputation groups failed to reach significance (^{2} = 2.89, p = 0.089).



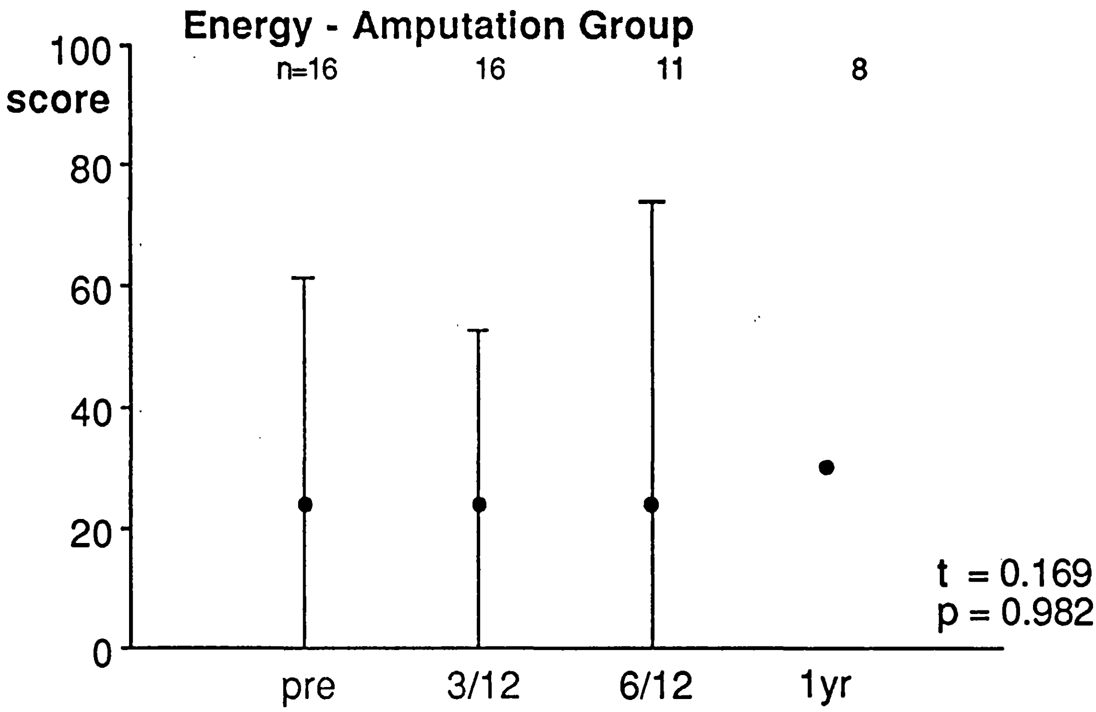
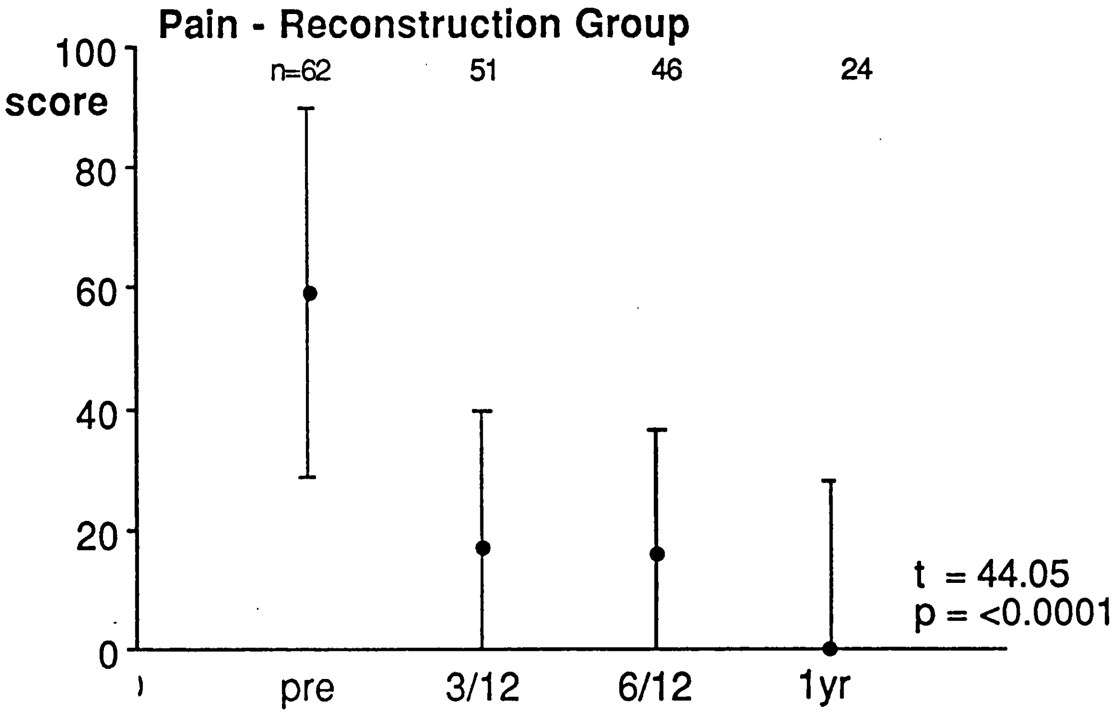


FIGURE 6.1. MEDIAN & INTERQUARTILE RANGE SCORES FOR ENERGY LEVELS



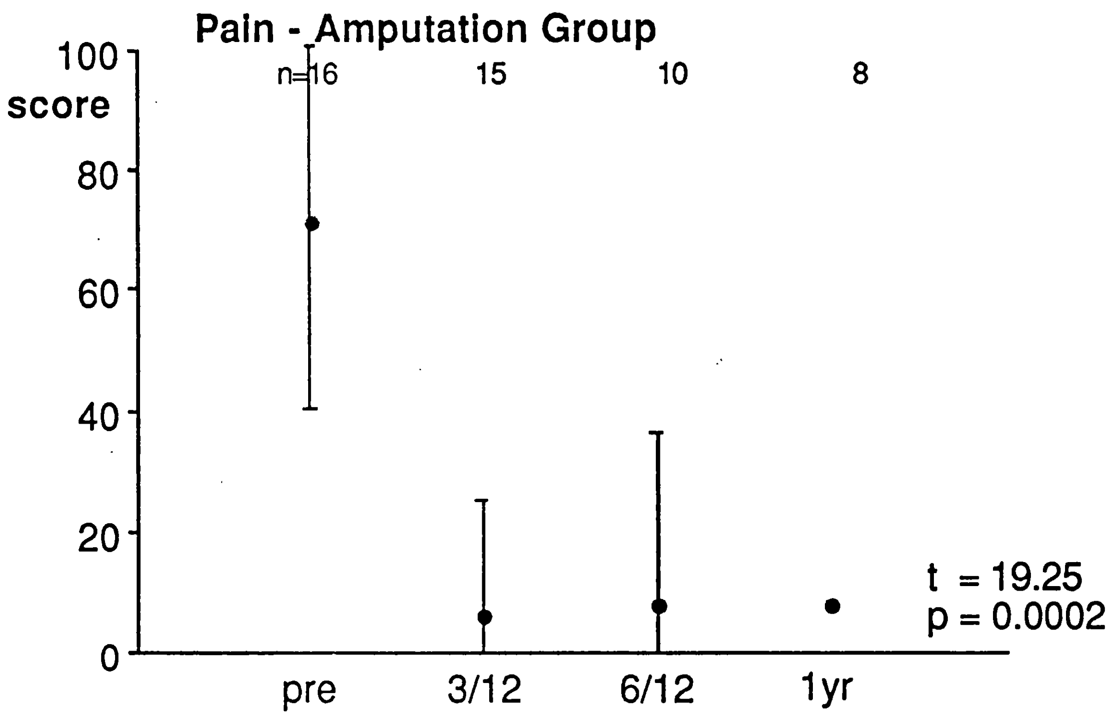
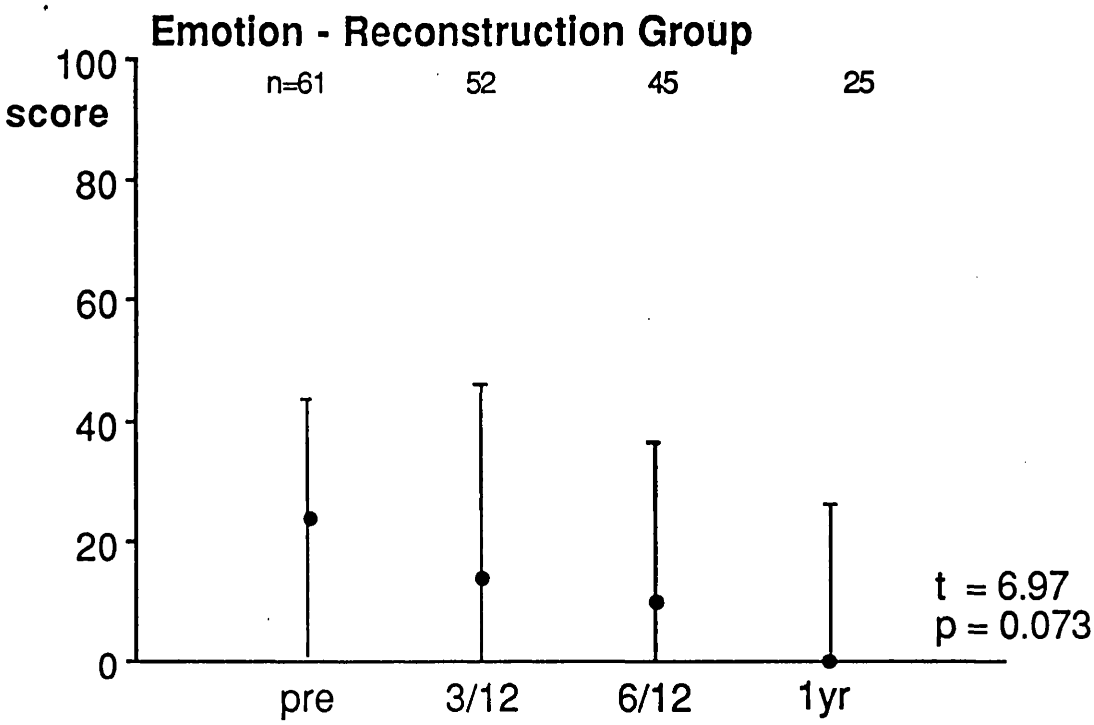


FIGURE 6.2. MEDIAN & INTERQUARTILE RANGE SCORES FOR PAIN



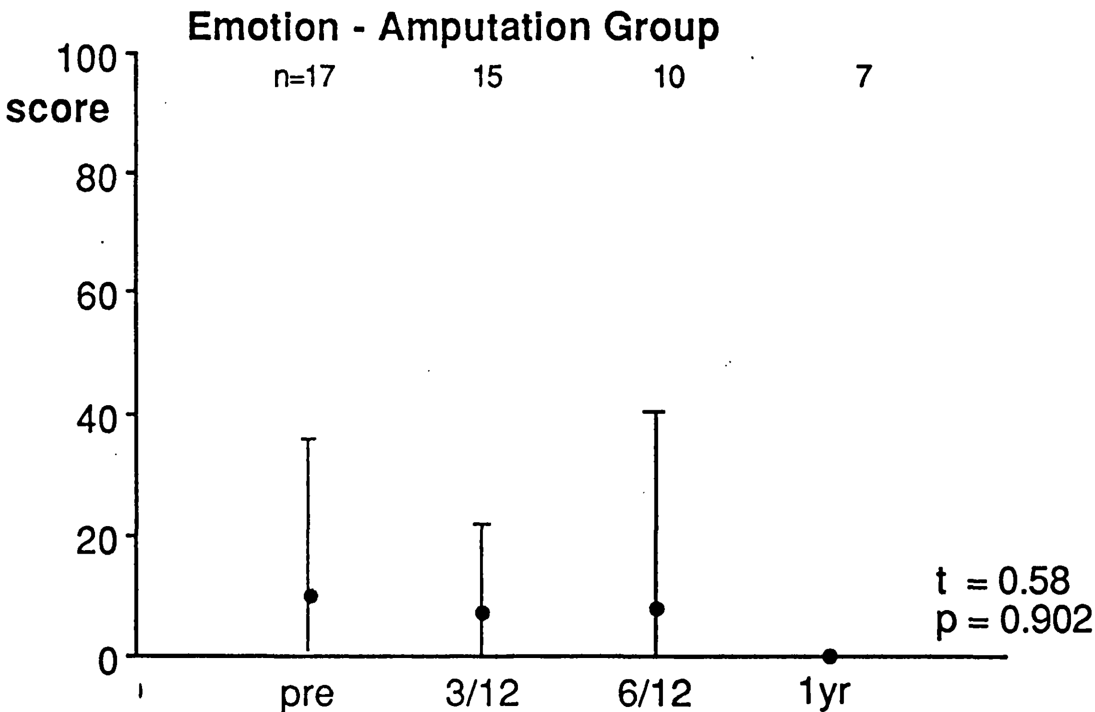
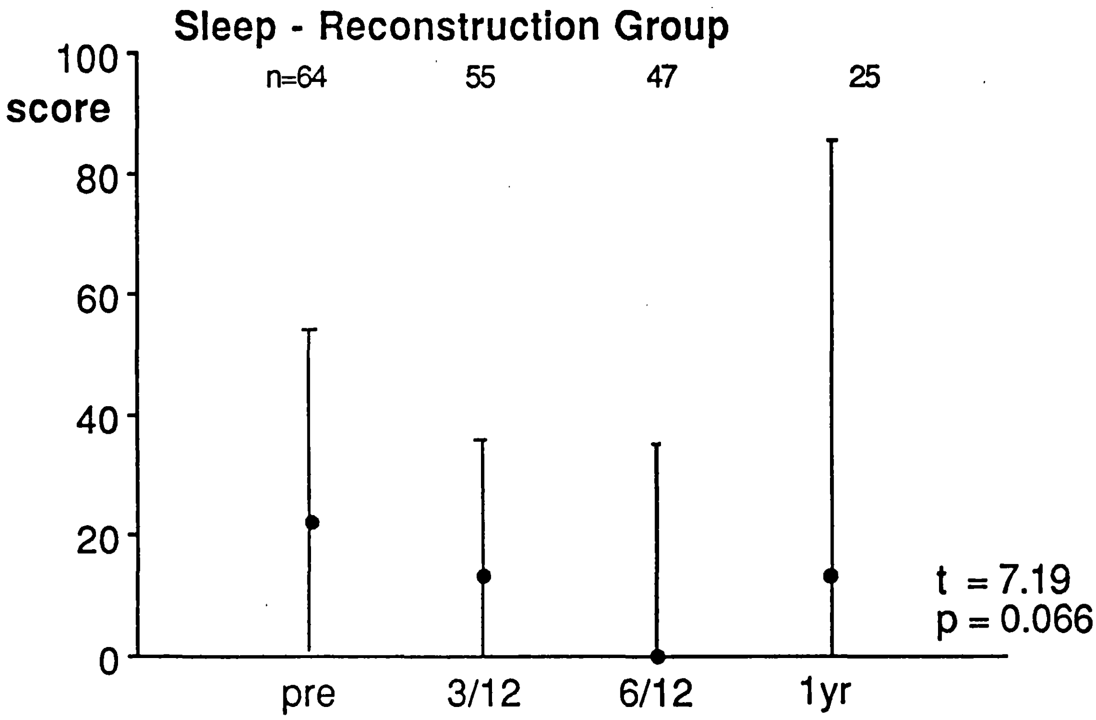


FIGURE 6.3. MEDIAN & INTERQUARTILE RANGE SCORES FOR EMOTIONAL REACTIONS



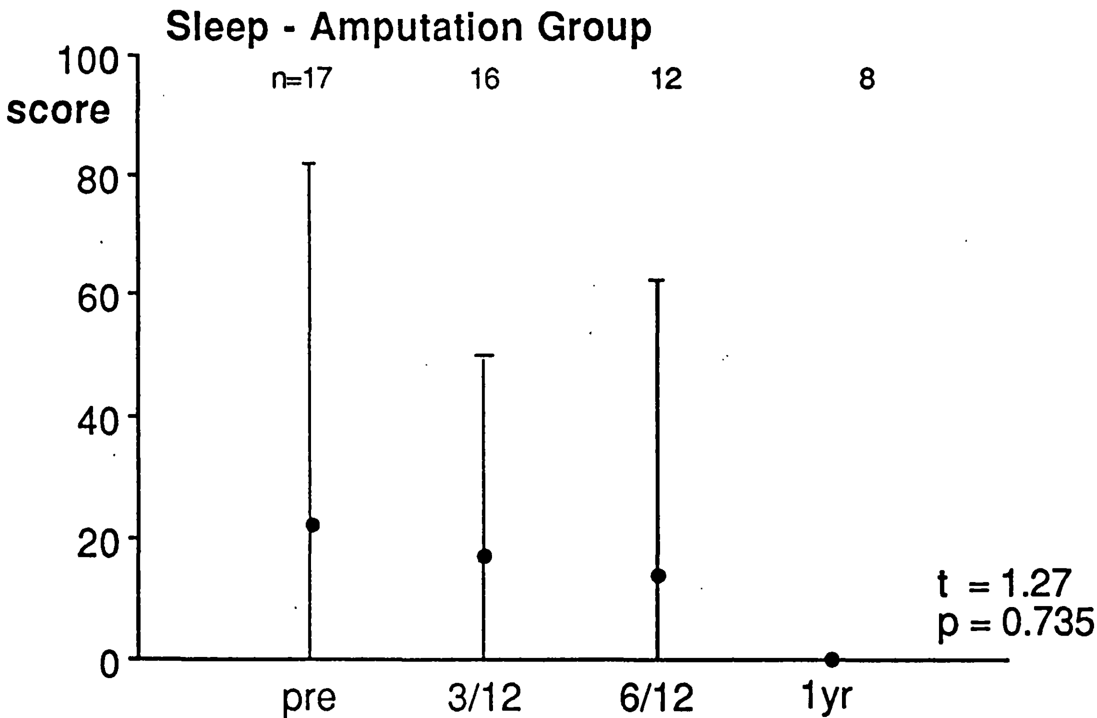
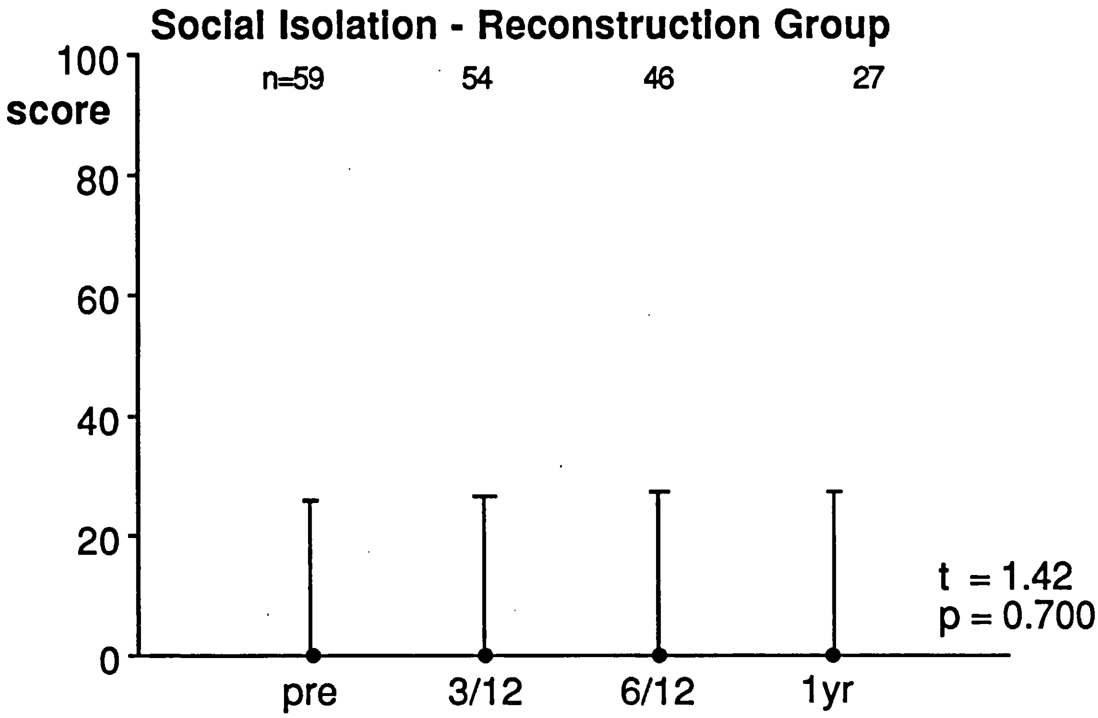


FIGURE 6.4. MEDIAN & INTERQUARTILE RANGE SCORES FOR SLEEP DISTURBANCE



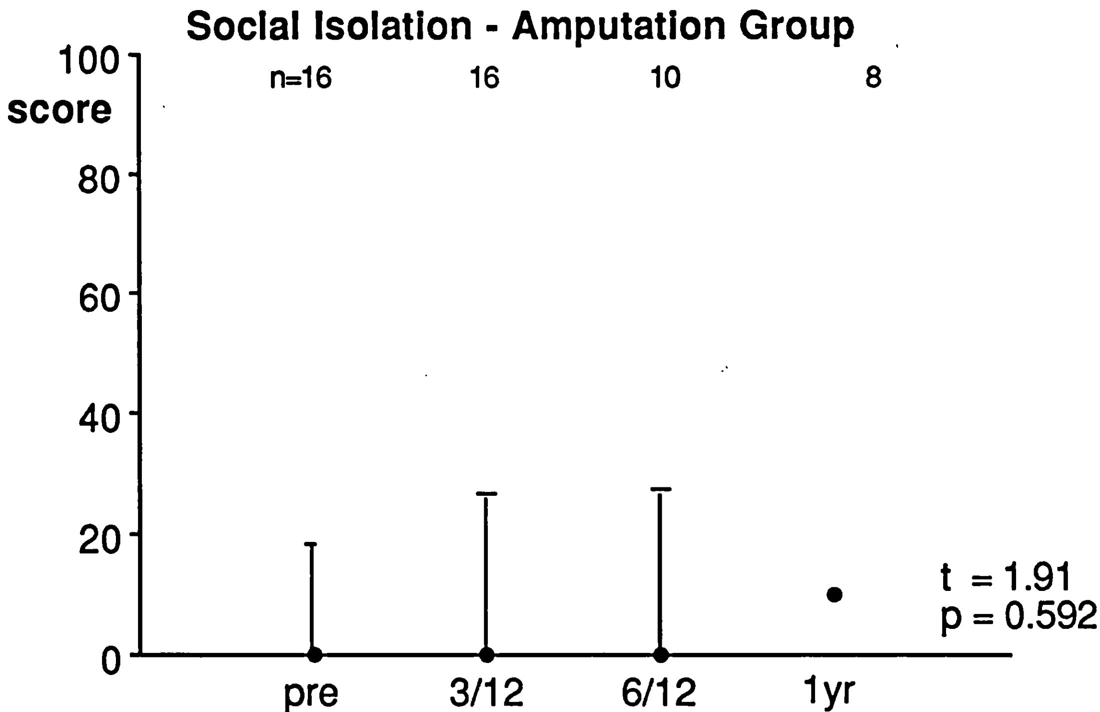
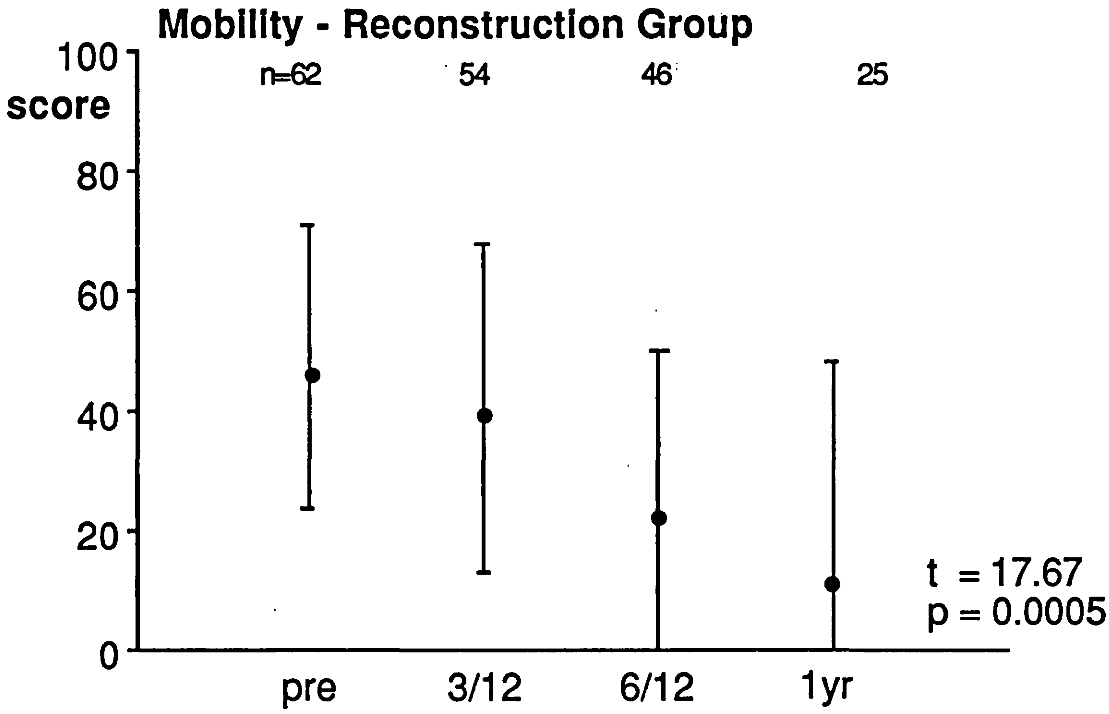


FIGURE 6.5. MEDIAN & INTERQUARTILE RANGE SCORES FOR FEELINGS OF SOCIAL ISOLATION



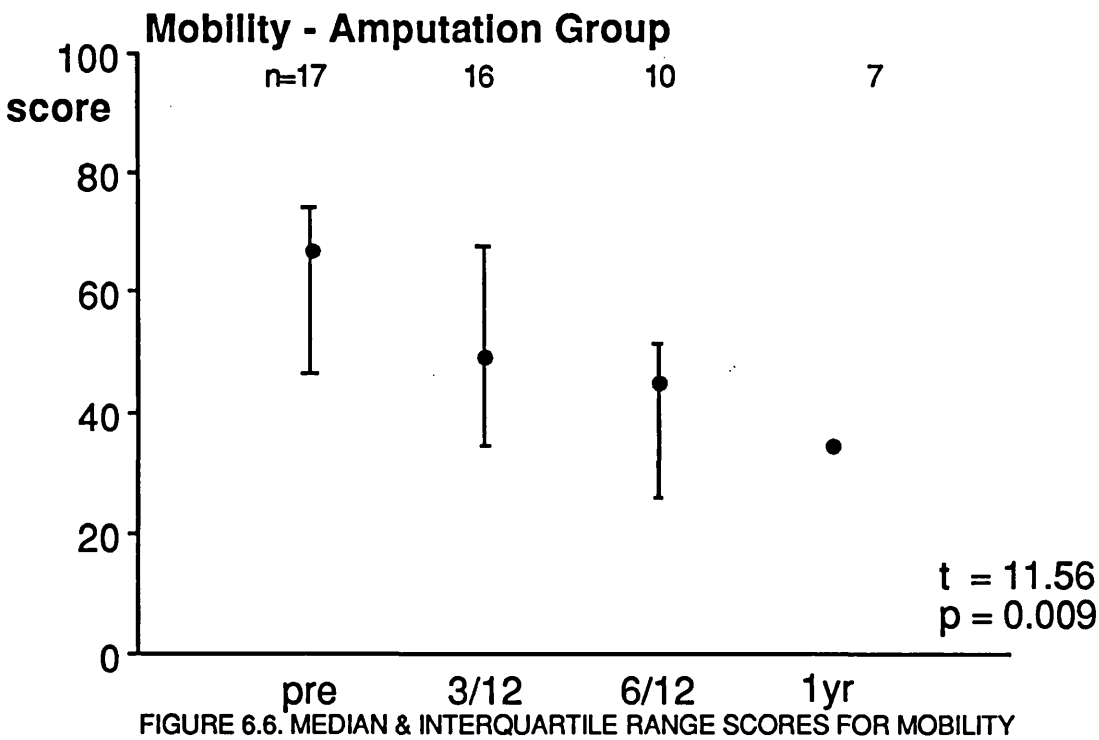


FIGURE 6.6. MEDIAN & INTERQUARTILE RANGE SCORES FOR MOBILITY PROBLEMS

TABLE 6.1a. NOTTINGHAM HEALTH PROFILE. PART II.

86 reconstructions, 24 major amputations.

		Reconstruction	Amputation
JOB			
Pre		22/69 32%	5/17 30%
3/12		18/58 31%	5/16 31%
6/12		15/48 10%	4/13 23%
1 yr		6/26 23%	1/8 13%
LOOKING AFTER THE HOME			
Pre	*	45/68 66%	12/18 67%
3/12		38/57 67%	13/16 81%
6/12		23/49 47%	9/13 69%
1 yr		13/27 48%	2/8 25%

* Chi (trend) = 5.29, p = 0.021.

		Reconstruction	Amputation
SOCIAL LIFE			
Pre	^	24/69 35%	9/18 50%
3/12		26/63 41%	6/17 35%
6/12		33/49 67%	6/13 46%
1 yr		12/27 44%	1/8 13%

^ Chi (trend) = 5.58, p = 0.018.

TABLE 6.1b. NOTTINGHAM HEALTH PROFILE. PART II.

		Reconstruction		Amputation	
HOME LIFE					
Pre		16/66	24%	1/18	6%
3/12		14/59	24%	1/16	6%
6/12		10/48	21%	2/13	15%
1 yr		5/26	19%	0/7	0%
SEX LIFE					
Pre		11/67	16%	1/16	6%
3/12		9/55	16%	2/15	15%
6/12		8/47	17%	0/12	0%
1 yr		4/26	15%	0/7	0%
HOBBIES					
Pre	+	42/67	63%	9/17	53%
3/12		36/59	61%	12/16	75%
6/12		22/49	45%	7/13	54%
1 yr		10/26	39%	3/8	38%

+ Chi (trend) = 6.52, p = 0.011.

HOLIDAYS					
Pre	"	34/68	50%	9/18	50%
3/12		28/59	48%	8/16	50%
6/12		15/49	31%	7/12	58%
1 yr		8/27	30%	5/8	62%

" Chi (trend) = 5.85, p = 0.016.

DISCUSSION.

Measurement of patient satisfaction with treatment is becoming increasingly important in surgical practice. Many quality of life studies have been conducted on patients with cancer (Mor,V. 1987), but fewer on patients with peripheral vascular disease. When setting out to measure quality of life for a particular condition, it is important to define the aspect of health and life to be tested. In patients with critical limb ischaemia the following may be considered important, freedom from pain, mobility and the ability to live independently. A number of quality of life questionnaires are already in existence. It is probably better to use one of them or adapt one since they are well validated and reliable.

In choosing a quality of life questionnaire we considered several, including, the index of Activities of Daily Living (Katz et al. 1963), the Rosser classification and scoring (Rosser and Watts, 1974), Scales for measuring general health perceptions (Ware. 1976), Spitzer QL index (Spitzer. 1987). We felt however that the NHP was preferable as it had previously been used in patients with vascular disease with good repeatability (Hunt et al. 1982).
The NHP was extensively validated on 4826 people over a wide range age groups and social classes, both with and without disease. It was found to be a highly satisfactory measure of subjective health status in the physical, social and emotional domains. It was also a useful guide to the extent by which health problems restrict normal physical and social activities. The test, re-test technique was

performed in two groups of patients expected to be high scorers and was found to be highly reliable.

Patients with critical limb ischaemia represent the extreme of patients with peripheral vascular disease. The majority have been long term smokers, one third are diabetic and often suffer the other manifestations of peripheral vascular disease, viz,ischaemic heart disease, stroke, renal failure and chronic obstructive airways disease. Not surprisingly, their perceived health problems are high. This study confirmed that in both groups there was significant impairment of pre-operative function, including low levels of energy, pain, high levels of sleep disturbance and severely restricted mobility. Feelings of social isolation and emotional well-being were less affected. These results compare well with the results of a group of patients with less severe peripheral vascular disease (Hunt et al. 1982).

The NHP has been found sensitive to changes with time in groups with on going disease and useful in monitoring treatment outcomes. The reconstruction group showed reductions in scores with time in each of the parameters measured, and this reached significance for pain (p . 0.0001) and mobility ($p = 0.0005$). A similar result was found in the major amputation group, it is somewhat surprising that mobility improves significantly in this group, presumably because immediately before amputation most of the patients are confined to their bed or chair. Mobility scores initially were very high in the amputee group (median 67), compared to the reconstruction group (median 46). With time both groups showed a fall in the score of a similar proportion (after twelve months the median score of the amputation group was 34, and the reconstruction group 11) Vascular amputees are considered to achieve poor levels of mobility even when fitted with a prosthesis (Dormandy and Thomas 1988). The level of pre-operative sleep disturbance in both groups was high, as patients with critical limb ischaemia have rest pain, which is an important cause of sleep disturbance.

Social isolation was not considered a problem by patients in this study. This agrees with the findings of Hunt et al (1982) who suggest this may be explained by the fact that a high proportion of patients with peripheral vascular disease are male and usually cared for by female companions. On closer analysis, within that group, they found that the question which received the greatest number of positive answers was "I feel I am a burden to people".

Few surgeons would minimise the impact of a major amputation upon the elderly patient, especially those who have an above knee amputation. Few vascular amputees return to an active independent life and many spend a considerable percentage of their remaining short life in hospital, often requiring re-housing and /or nursing care. Despite these facts, in Part I of the NHP questionnaire, no significant difference emerges between the attempted reconstruction group and the major amputation group. In Part II the only section to demonstrate a statistically significant difference between the two groups was the effect of their illness on their home life (^{2} = 5.28, $p = 0.022$). Although levels of interference on their home life were higher in the reconstruction group pre-operatively, these went down over time. However, there was no clear pattern for the amputation group.

I have no doubt that limb salvage is preferable in patients with critical limb ischaemia, as every patient prefers to keep their own limb, rather than have an artificial one. The lack of difference between the two treatment groups is surprising and disagrees with other studies in this field (Shearman et al. 1990, Albers, Fratezi, DeLuccia. 1992, Humphreys, Evans. 1992, Humphreys, Evans, Williams. 1993, Smith, Morgan, Gwynn. 1994). I believe that the size of the amputation group, only eight patients completed the quality of life questionnaire at one year, is of major importance in failing to demonstrate an improved quality of life in the reconstruction group. A study in Birmingham retrospectively identified 60 patients following reconstruction and age matched them with primary amputees. They found that significantly more patients in the reconstruction group could walk, use public transport, had less problems coping with household activities and less incidence of depression (Shearman et al. 1990). A study from Brazil used Spitzer's QL index to prospectively study 61 patients with severe limb ischaemia. They concluded that quality of life could be confidently assessed and would improve during the first year if major amputation was avoided. Unfortunately interpretation of their results is difficult as patients were initially assigned to one of three treatment groups and then reassigned to a further group if reconstruction or amputation was required (Albers, Fratezi, DeLuccia. 1992).

It is widely acknowledged by vascular surgeons that reconstruction is the preferred option to major amputation, but, I have been unable to substantiate this in respect of the patients' perceived health status given by the NHP during the first twelve months after surgery. We must critically appraise my study to identify whether there is a true lack of difference between the two groups or a problem associated with the methodology used. A major concern about this and all studies with negative findings is "does no difference really exist between the groups or were the tests not sensitive or specific enough to detect the differences, or was the sample size too small (the type II error)"? The NHP has been successfully used in patients with peripheral vascular disease (Hunt et al. 1982), suggesting that the findings in this study are valid. Patients in this study undergoing a reconstruction had a significant improvement in their mobility and reduction in pain levels by three months. However, the scores in both groups remained higher than the values for the "fit elderly controls" in the NHP validation studies (Hunt, McEwen, McKenna. 1986).

Significance may have achieved with a larger sample, only mobility between the groups is nearing a significant level ($p = 0.066$). This may be important since a study in Edinburgh comparing amputees with age and sex matched normal "fit" controls found that mobility was the only independent difference between the two groups. When adjusted for this factor, and differences observed on univariate analysis in the NHP scores were cancelled out, their findings led to the conclusion that "mobility was the only significant independent factor after matched logistic regression analysis and that more effort should be put into the rehabilitation of the patient with respect to improving mobility" (Pell et al. 1993).

Although vascular surgeons consider that revascularisation is worthwhile in patients with critical limb ischaemia, there is doubt as to whether this is so worthwhile in patients with femoro-crural disease (Cheshire, Wolfe. 1992). To deny a patient an attempt at revascularisation for the purposes of a randomised quality of life study would be unethical, but lack of randomisation introduces systematic bias into studies of this nature. Clearly the amputation group is not identical to the reconstruction group since the severity their disease, the nature of the lesion or severe concomitant medical disease, (for example severe hemiplegia) may make mobilization impossible.

Vascular reconstruction is expensive and time consuming surgery and the clinical view is that the patients' own limb is preferable to a prosthesis. At the outset of this study it was expected that significant improvements in quality of life in patients with limb salvage would occur and we have been able to show this. However, what we have not been able to show is significant differences between this group and the patients undergoing primary amputation, probably because of the small size of the amputation group. A larger study is clearly indicated from these results. To obtain the sample size and the necessary power for this study, several centres must combine their results. A collaborative approach with a multiple centres would appear to be the way to answer the question of reconstruction versus amputation in a definitive way.

CHAPTER 7.

CONCLUSIONS.

Critical lower limb ischaemia, is the most severe form of peripheral vascular disease, as by definition, the limb is imminently threatened. This thesis initially compared the demographic data for patients with critical limb ischaemia, intermittent claudication and abdominal aortic aneurysms. To assess the independent risk factors associated with each manifestation of atherosclerosis, diabetes mellitus (odds ratio 2.77, 95% confidence interval 1.49 to 5.17) and smoking (odds ratio 1.94, 95% confidence interval 1.44 to 2.61) were the most important. The prevalence of diabetes in the groups studied was 4% for abdominal aortic aneurysm patients, 16% for patients with intermittent claudication and 34% for patients with critical limb ischaemia, rising to 41% in the sub-group of critical limb ischaemia patients who required a major amputation. Less than 20% in each group had never smoked. This study highlights the importance of diabetes mellitus in peripheral vascular disease, especially critical limb ischaemia. Future studies on larger series of patients with critical limb ischaemia may further demonstrate the importance of diabetes mellitus.

Patients referred to a specialist unit with an aggressive revascularisation policy should have a lower amputation rate and a higher survival rate than patients treated in a non-specialist unit. To determine the accuracy of this view two groups of patients with critical limb ischaemia were studied. The Regional Vascular Service (RVS) accepted patients from both its local population and tertiary referrals from within the region. All patients at the RVS underwent a revascularisation if it was feasible. The District General Hospital (DGH) only accepted patients from its local catchment area and had a conservative approach to attempted revascularisation. Despite the difference in recruitment patterns both populations had similar risk factors for peripheral vascular disease. Over one third in each group had diabetes mellitus, at least fifty percent had hypertension and one third heart disease. This data demonstrates that most of these patients have some other form of vascular disease and management must include the relevant treatment of diabetes, heart disease and hypertension as well as the ischaemic limb.

The current definitions relating to critical lower limb ischaemia do not accurately predict irreversible ischaemia, despite several revisions since the introduction of the first definition in 1982 (Bell et al). The area in which most controversy exists is in patients with diabetes mellitus. Some authors feel that diabetics should be excluded from critical limb ischaemia patient series. One third of patients in both groups were diabetic, to exclude them from critical lower limb ischaemia series would bias the data. Separate analysis of diabetics may overcome this problem in future work.

The results of this study comparing the RVS and the DGH are presented as cumulative limb salvage rates and cumulative survival rates. No difference in limb salvage or survival was seen comparing the two groups, until separate analysis was made of patients with distal disease. Forty percent of patients at the RVS had distal disease and 74% of these had an attempted revascularisation, none of the patients at the DGH had a distal revascularisation. There was a significant difference in the limb salvage between the two groups (p = 0.025), but not survival (p = 0.867) at one year. At the RVS failed reconstruction did not result in a higher level of major amputation.

In patients with a critically ischaemic limb, the lack of a diagnostic test to accurately predict limb viability means that a number of limbs undergo attempts at revascularisation each year and should more appropriately have undergone a primary amputation. This study aimed to see if ^{31}P magnetic resonance spectroscopy could detect irreversible muscle ischaemia. ^{31}P MRS does show spectral changes in the small muscles of the foot at rest, there is a reduction in the phosphocreatine peak, an increase in the inorganic phosphate peak and a rise in the intracellular pH. Analysis of the data showed statistically significant differences do exist between the limb salvage and amputation groups, but much overlapping of the inter-quartile ranges exists.

Spectral changes do occur in the limb salvage group in the post-operative scan, but unexpectedly, the phosphocreatine to inorganic phosphorus ratio fell. This study has shown that ^{31}P MRS can be used in patients with critical limb ischaemia. Unfortunately, it remains a research tool as difficulties encountered in getting patients to lie with their critically foot horizontal in the magnet and the complexities of acquiring spectra for analysis mean that many patients are unable to undergo ^{31}P MRS studies. If small bore limb magnets become freely available, allowing the limb to be dependent, and many of the technical difficulties associated with data collection are solved ^{31}P MRS may be a useful addition to the tests currently in use to assess critical lower limb ischaemia.

Increasingly studies are being performed to assess changes in the patient's perceived health status, and interference by health in daily activities. The threat of limb loss to patients with critical lower limb ischaemia is devastating and surgical revascularisation is considered by patients and health care workers as the preferable option. This study set out to confirm that patients undergoing attempted reconstruction had a better quality of life than patients undergoing a major amputation.

The Nottingham Health Profile (NHP) was chosen as it is a well validated health questionnaire and has been used in patients with vascular disease. The questionnaire is divided into two parts, In Part I six categories are looked at; energy levels, pain, emotional reactions, sleep disturbance, feelings of social isolation and mobility problems. This study showed that patients with critical lower limb ischaemia have significant impairment of functioning, demonstrated by high scores for energy, pain, sleep disturbance and restricted mobility. These parameters improve with time following both revascularisation and major amputation, but This study did not find a statistically significant difference between the two groups. There was a difference in mobility between the reconstruction and amputation groups over time, but this failed to achieve statistical significance ($p = 0.067$). This result raises many questions, not least of which is whether a larger sample size would have detected a difference between these groups or whether the lack of significance truly reflects no difference between the two treatment groups. The second part of the NHP looked at areas most commonly mentioned as being affected by health. These are; occupation, ability to look after the home, social life, personal relationships including sex life, holidays, interests and hobbies. No statistically significant difference emerged between the two groups in Part II, the reconstruction group improved with time only in the areas of home life ($p = 0.022$), hobbies ($p = 0.011$) and holidays ($p = 0.016$). I have no doubt that sample size in the amputee group is a major factor in failing to demonstrate a statistically significant difference between the revascularisation and amputation groups.

This study has raised many issues and could be considered a suitable pilot for a major investigation of the two treatment options in these patients recruiting more patients into the study. A multicentre trial recruiting from several hospitals may be the only way to collect sufficient data for a large enough trial to answer these questions.

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APPENDIX 1.

CRITICAL LOWER LIMB ISCHAEMIA DATA.

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA.

ALL GROUPS.

	Regional Vascular Service no of limbs	salvage	District General Hospital no of limbs	salvage
30/7	174	80%	30	83%
1 year	135	74%	23	53%
18/12	96	74%		
2 years	73	74%		

p = 0.493

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

ALL GROUPS.

	Regional Vascular Service no of patients	survival	District General Hospital no of patients	survival
30/7	153	88%	30	93%
1 year	130	73%	28	65%
18/12	79	71%		
2 years	51	63%		

p = 0.714

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA.

REVASCULARISATION GROUP.

	Regional Vascular Service no of limbs	salvage	District General Hospital no of limbs	salvage
30/7	131	84%	13	92%
1 year	109	76%	12	55%
18/12	74	76%		
2 years	56	76%		

$p = 0.717$

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

REVASCULARISATION GROUP.

	Regional Vascular Service no of patients	survival	District General Hospital no of patients	survival
30/7	116	90%	13	92%
1 year	104	75%	12	78%
18/12	61	73%		
2 years	40	63%		

$p = 0.539$

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA. REVASCULARISATION GROUP, BY REVASCULARISATION TYPE AT THE REGIONAL VASCULAR SERVICE.

	n	30/7	1 yr	18/12	2 yrs
all	131	84%	76%	76%	76%
supra-ing	48	92%	85%	85%	85%
fem-pop	19	89%	84%	84%	84%
fem-distal	43	79%	72%	72%	72%
misc	14	85%	86%	86%	86%
failed	7	29%	14%	14%	14%

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA. REVASCULARISATION GROUP, BY REVASCULARISATION TYPE AT THE REGIONAL VASCULAR SERVICE.

	n	30/7	1 yr	18/12	2 yrs
all	116	90%	75%	73%	63%
supra-ing	43	89%	75%	75%	66%
fem-pop	16	93%	75%	75%	75%
fem-distal	39	87%	80%	77%	72%
misc	11	91%	91%	91%	91%
failed	7	86%	43%	43%	43%

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

MAJOR AMPUTATION GROUP.

	Regional Vascular Service no of patients	survival	District General Hospital no of patients	survival
30/7	14	85%	5	100%
1 year	10	63%	5	67%
18/12	4	63%		
2 years	3	63%		

$p = 0.521$

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA.

MINOR AMPUTATION GROUP.

	Regional Vascular Service no of limbs	salvage	District General Hospital no of limbs	salvage
30/7	7	100%	4	75%
1 year	7	83%	4	75%
18/12	7	83%		
2 years	7	83%		

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

MINOR AMPUTATION GROUP.

	Regional Vascular Service no of patients	survival	District General Hospital no of patients	survival
30/7	7	100%	4	100%
1 year	7	100%	4	100%
18/12	7	100%		
2 years	7	100%		

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA.

NO INTERVENTION GROUP.

	Regional Vascular Service		District General Hospital	
	no of limbs	salvage	no of limbs	salvage
30/7	20	100%	8	100%
1 year	12	95%	7	60%
18/12	7	95%		
2 years	6	95%		

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

NO INTERVENTION GROUP.

	Regional Vascular Service		District General Hospital	
	no of patients	survival	no of patients	survival
30/7	16	63%	8	88%
1 year	10	56%	7	48%
18/12	6	56%		
2 years	5	56%		

CUMULATIVE LIMB SALVAGE IN CRITICAL LIMB ISCHAEMIA.

DISTAL DISEASE GROUP.

	Regional Vascular Service		District General Hospital	
	no of limbs	salvage	no of limbs	salvage
30/7	68	78%	9	53%
1 year	52	78%	4	18%
18/12	36	73%		
2 years	25	73%		

p = 0.025

CUMULATIVE SURVIVAL IN CRITICAL LIMB ISCHAEMIA.

DISTAL DISEASE GROUP.

	Regional Vascular Service		District General Hospital	
	no of patients	survival	no of patients	survival
30/7	62	82%	9	100%
1 year	49	65%	9	34%
18/12	28	62%		
2 years	16	55%		

P = 0.867

APPENDIX 2.

^{31}P MAGNETIC RESONANCE SPECTROSCOPY DATA.

INITIAL SCAN DATA - CONTROL GROUP (plane).

number	Pcr/Pi	PME/ATP	PDE/ATP	Pcr/ATP	ph
1	3.1	0.3	1.3	2.9	6.95
2	3.6	0.3	0.3	1.6	7.05
3	3.5	0.3	0.2	2.5	7.12
4	3.7	0.2	0.3	2.1	7.05
5	4.7	0.1	0.5	--	7.05
6	5.8	0.4	0.2	4.0	7.20
7	4.7	0.4	0.1	2.7	7.12
8	4.5	0.2	0.1	2.3	7.05
9	4.4	0.3	0.6	2.6	7.12
10	2.8	0.1	0.1	1.5	7.20
11	3.2	0.1	0.4	2.4	7.05
12	5.7	0.2	0.3	2.5	7.05

POST OPERATIVE SCAN DATA - CONTROL GROUP (plane).

number	Pcr/Pi	PME/ATP	PDE/ATP	Pcr/ATP	pH
1	4.5	0.6	0.3	2.3	7.12
2	3.6	0.2	0.3	1.6	6 .98

INITIAL SCAN DATA - LIMB SALVAGE GROUP (plane).

number	Pcr/Pi	PME/ATP	PDE/ATP	Pcr/ATP	pH
1	7.6	0.4	0.2	3.8	7.09
2	3.5	0.5	0.4	1.6	7.05
3	2.5	0.6	0.5	1.8	7.16
4	1.7	0.1	0.9	0.9	7.05
5	2.3	0.4	0.1	1.5	7.12
6	2.2	0.2	2.1	1.8	--
7	3.6	0.1	0.4	1.8	7.05
8	3.7	0.3	0.7	3.7	7.05
9	3.0	0.5	0.6	3.0	7.12
10	2.1	1.1	0.7	2.0	7.28
11	5.3	0.6	0.6	2.2	7.2
12	3.5	0.3	0.3	1.7	7.28
13	3.0	--	--	2.0	7.10
14	4.2	0.3	0.2	2.3	7.05
15	4.1	0.5	0.6	2.6	7.05
16	2.1	0.7	0.5	2.3	7.20

POST-OPERATIVE SCAN DATA - LIMB SALVAGE GROUP (plane).

number	Pcr/Pi	PME/ATP	PDE/ATP	Pcr/ATP	pH
1	5.5	0.2	0.1	2.8	7.12
2	3.5	0.4	0.3	1.6	7.28
3	1.3	0.2	0.7	0.8	7.05
4	1.0	0.4	0.3	0.7	7.20
5	1.8	0.4	0.5	2.1	7.12
6	1.3	0.8	1.2	1.8	7.20
7	1.8	0.2	0.9	1.9	7.12
8	2.3	0.3	1.1	1.7	7.16

INITIAL SCAN DATA - MAJOR AMPUTATION GROUP (plane).

number	Pcr/Pi	PME/ATP	PDE/ATP	Pcr/ATP	pH
1*	3.1	0.6	0.3	2.3	7.12
2	2.0	0.7	0.9	1.8	7.05
3	1.0	0.8	0.8	0.8	7.28
4*	0.9	0.5	1.0	0.8	7.12
5	3.4	0.3	0.5	2.4	7.28
6*	1.1	0.5	0.3	0.2	7.05
7	0.7	0.2	0.4	0.5	7.2
8	3.5	1.4	0.8	3.5	6.98
9	1.1	0.7	0.9	1.2	7.05
10*	2.6	0.3	1.4	1.4	7.20
11	2.5	0.9	0.6	1.9	7.28
12*	3.9	0.6	0.4	3.1	7.05
13	2.4	0.6	0.6	0.8	7.05

* Failed surgical revascularisation.

All other patients were scanned just before major amputation.

INITIAL SCAN SIGNAL HEIGHT RATIOS - CONTROL GROUP (plane).

number	Pcr	Pi	ATP	PME	PDE
1	1.7	1.6	1.3	2.5	1.7
2	2.2	2.5	1.5	1.4	2.0
3	1.9	1.7	1.5	2.0	1.4
4	2.0	1.3	1.6	1.7	3.0
5	1.9	2.0	1.5	1.8	1.3
6	1.7	2.5	1.9	1.6	1.9
7	2.5	1.9	1.4	2.2	1.6
8	1.8	2.3	2.0	1.4	1.0
9	2.9	2.4	3.3	1.5	3.0
10	2.3	2.4	2.1	1.8	1.8
11	2.4	2.5	1.7	1.7	1.3
12	1.9	2.2	1.8	2.0	1.6

POST OPERATIVE SCAN SIGNAL HEIGHT RATIOS - CONTROL GROUP (plane).

number	Pcr	Pi	ATP	PME	PDE
1	2.4	2.0	2.0	1.6	1.0
2	2.4	1.8	2.0	2.0	1.7

INITIAL SCAN SIGNAL HEIGHT RATIOS - LIMB SALVAGE GROUP (plane).

number	Pcr	Pi	ATP	PME	PDE
1	2.0	1.7	2.0	2.0	2.0
2	1.8	2.4	1.5	2.2	2.4
3	2.2	1.8	1.8	1.8	2.7
4	3.0	2.1	2.2	1.6	2.1
5	1.9	2.0	0.7	---	2.0
6	1.9	2.0	0.7	---	1.0
7	2.3	2.1	1.0	2.1	2.8
8	2.0	2.4	1.9	1.5	2.0
9	1.8	2.1	1.1	---	---
10	2.2	1.7	1.7	1.9	1.2
11	2.3	2.3	2.2	1.7	2.3
12	2.2	1.7	1.1	1.0	2.4
13	1.9	2.0	2.2	2.2	2.4
14	2.2	1.9	1.8	1.7	---
15	2.4	1.7	2.0	2.1	2.9
16	2.1	2.2	1.7	1.6	1.8

POST OPERATIVE SCAN SIGNAL HEIGHT RATIOS - LIMB SALVAGE GROUP (plane).

number	Pcr	Pi	ATP	PME	PDE
1	2.6	2.9	1.6	3.0	1.8
2	2.0	1.7	2.2	1.5	1.4
3	2.1	1.8	1.5	2.5	1.5
4	1.9	2.2	1.7	1.9	1.6
5	1.7	1.4	1.6	1.4	1.4
6	2.2	2.0	1.7	1.4	1.2
7	1.9	2.0	1.4	2.7	1.2
8	2.2	2.3	1.3	2.0	1.3

INITIAL SCAN SIGNAL HEIGHT RATIOS - MAJOR AMPUTATION GROUP (plane).

number	Pcr	Pi	ATP	PME	PDE
1	1.7	1.9	2.2	2.2	1.2
2	2.0	1.9	---	1.8	1.1
3	1.6	1.9	---	1.5	1.7
4	2.1	2.0	1.3	1.8	1.6
5	2.3	1.8	1.9	2.0	1.4
6	2.6	---	2.3	1.4	1.8
7	2.2	2.0	2.0	2.0	---
8	1.9	1.8	1.9	2.0	1.3
9	2.0	2.4	1.5	---	1.9
10	1.6	1.9	2.3	1.7	1.5
11	1.9	2.4	2.0	1.4	1.1
12	2.3	2.3	1.4	2.1	1.2
13	1.8	1.7	1.6	1.7	1.0

APPENDIX 3.

QUALITY OF LIFE QUESTIONNAIRE AND DATA.

		FOR CODING
I.D. NUMBER	|__|__|__|__|__|	1.-5

HOW WOULD YOU DESCRIBE YOUR HEALTH AT PRESENT?

VERY GOOD	|__|	
GOOD	|__|	
FAIR	|__|	
POOR	|__|	
VERY POOR	|__|	|_ _|6

WE WOULD LIKE YOU TO THINK ABOUT ACTIVITIES IN YOUR LIFE WHICH MAY BE AFFECTED BY HEALTH PROBLEMS.

IN THE LIST BELOW, TICK **YES** FOR EACH ACTIVITY IN YOUR LIFE WHICH IS BEING AFFECTED BY YOUR STATE OF HEALTH. TICK **NO** FOR EACH ACTIVITY WHICH IS NOT BEING AFFECTED, OR WHICH DOES NOT APPLY TO YOU.

IS YOUR PRESENT STATE OF HEALTH CAUSING PROBLEMS WITH YOUR......

	YES	NO	
1. JOB OF WORK	|__|	|__|	|_ _|7
2. LOOKING AFTER THE HOME (EG CLEANING AND COOKING, REPAIRS,ODD JOBS)	|__|	|__|	|_ _|8
3. SOCIAL LIFE (EG GOING OUT,SEEING FRIENDS,GOING TO THE PUB ETC)	|__|	|__|	|_ _|9
4. HOME LIFE (THAT IS RELATIONSHIPS WITH OTHER PEOPLE AT HOME)	|__|	|__|	|_ _|10
5. SEX LIFE	|__|	|__|	|_ _|11
6. INTERESTS AND HOBBIES (EG SPORTS, ARTS AND CRAFTS,DO-IT-YOURSELF)	|__|	|__|	|_ _|12
7. HOLIDAYS (EG SUMMER OR WINTER HOLIDAYS,WEEKENDS AWAY)	|__|	|__|	|_ _|13

BELOW ARE LISTED SOME PROBLEMS PEOPLE MAY HAVE IN THEIR DAILY LIFE. LOOK DOWN THE LIST AND PUT A TICK IN THE BOX UNDER **YES** FOR ANY PROBLEM YOU HAVE AT THE MOMENT. TICK THE BOX UNDER **NO** FOR ANY PROBLEM YOU DO NOT HAVE. PLEASE ANSWER EVERY QUESTION. IF YOU ARE NOT SURE WHETHER TO ANSWER **YES** OR **NO**, TICK WHATEVER ANSWER YOU THINK IS MORE TRUE AT THE MOMENT.

	YES	NO	
I'M TIRED ALL THE TIME	|__|	|__|	|_ _|14
I HAVE PAIN AT NIGHT	|__|	|__|	|_ _|15
THINGS ARE GETTING ME DOWN	|__|	|__|	|_ _|16
I HAVE UNBEARABLE PAIN	|__|	|__|	|_ _|17
I TAKE TABLETS TO HELP ME SLEEP	|__|	|__|	|_ _|18
I'VE FORGOTTEN WHAT ITS LIKE TO ENJOY MYSELF	|__|	|__|	|_ _|19
I'M FEELING ON EDGE	|__|	|__|	|_ _|20
I FIND IT PAINFUL TO CHANGE POSITION	|__|	|__|	|_ _|21
I FEEL LONELY	|__|	|__|	|_ _|22
I CAN ONLY WALK ABOUT INDOORS	|__|	|__|	|_ _|23
I FIND IT HARD TO BEND	|__|	|__|	|_ _|24
EVERYTHING IS AN EFFORT	|__|	|__|	|_ _|25
I'M WAKING UP IN THE EARLY HOURS OF THE MORNING	|__|	|__|	|_ _|26
I'M UNABLE TO WALK AT ALL	|__|	|__|	|_ _|27
I'M FINDING IT HARD TO MAKE CONTACT WITH PEOPLE	|__|	|__|	|_ _|28
THE DAYS SEEM TO DRAG	|__|	|__|	|_ _|29
I HAVE TROUBLE GETTING UP AND DOWN STAIRS/STEPS	|__|	|__|	|_ _|30
I FIND IT HARD TO REACH FOR THINGS	|__|	|__|	|_ _|31

REMEMBER, IF YOU ARE NOT SURE WHETHER TO ANSWER **YES** OR **NO** TO A PROBLEM, TICK WHICHEVER ANSWER YOU THINK IS MORE TRUE AT THE MOMENT.

	YES	NO	
I'M IN PAIN WHEN I WALK	|__|	|__|	|_ _|32
I LOSE MY TEMPER EASILY THESE DAYS	|__|	|__|	|_ _|33
I FEEL THERE IS NOBODY I AM CLOSE TO	|__|	|__|	|_ _|34
I LIE AWAKE FOR MOST OF THE NIGHT	|__|	|__|	|_ _|35
I FEEL AS IF I'M LOSING CONTROL	|__|	|__|	|_ _|36
I'M IN PAIN WHEN I'M STANDING	|__|	|__|	|_ _|37
I FIND IT HARD TO DRESS MYSELF	|__|	|__|	|_ _|38
I SOON RUN OUT OF ENERGY	|__|	|__|	|_ _|39
I FIND IT HARD TO STAND FOR LONG (EG AT THE KITCHEN SINK, WAITING FOR A BUS)	|__|	|__|	|_ _|40
I'M IN CONSTANT PAIN	|__|	|__|	|_ _|41
IT TAKES ME A LONG TIME TO GET TO SLEEP	|__|	|__|	|_ _|42
I FEEL I AM A BURDEN TO PEOPLE	|__|	|__|	|_ _|43
WORRY IS KEEPING ME AWAKE AT NIGHT	|__|	|__|	|_ _|44
I FEEL THAT LIFE IS NOT WORTH LIVING	|__|	|__|	|_ _|45
I SLEEP BADLY AT NIGHT	|__|	|__|	|_ _|46
I'M FINDING IT HARD TO GET ON WITH PEOPLE	|__|	|__|	|_ _|47
I NEED HELP TO WALK ABOUT OUTSIDE (EG A WALKING AID OR SOMEONE TO SUPPORT ME)	|__|	|__|	|_ _|48
I'M IN PAIN WHEN GOING UP AND DOWN STAIRS/STEPS	|__|	|__|	|_ _|49
I WAKE UP FEELING DEPRESSED	|__|	|__|	|_ _|50
I'M IN PAIN WHEN I'M SITTING	|__|	|__|	|_ _|51

|_1_|_2_| 79-80

NOW PLEASE GO BACK TO THE BEGINNING AND MAKE SURE YOU HAVE ANSWERED **YES** OR **NO** TO EVERY QUESTION.

PART 1. Questions as grouped into six sections.

ENERGY.

I soon run out of energy.

Everything is an effort.

I am tired all the time.

PAIN.

I am in pain when going up and down stairs or steps.

I am in pain when I am standing.

I find it painful to change position.

I am in pain when I am sitting.

I am in pain when I walk.

I have pain at night.

I have unbearable pain.

I am in constant pain.

EMOTIONAL REACTIONS.

The days seem to drag.

I am feeling on edge.

I have forgotten what it is like to enjoy myself.

I loose my temper easily these days.

Things are getting me down.

I wake up feeling depressed.

Worry is keeping me awake at night.

I feel as if I am loosing control.

I feel that life is not worth living.

PART 1. Questions as grouped into six sections (cont).

SLEEP.

I am waking up in the early hours of the morning.

It takes me a long time to get to sleep.

I sleep badly at night.

I take tablets to help me sleep.

I lie awake for most of the night.

SOCIAL ISOLATION.

I am finding it hard to get on with people.

I am finding it hard to make contact with people.

I feel there is nobody I am close to.

I feel lonely.

I feel I am a burden to people.

PHYSICAL MOBILITY.

I find it hard to reach for things.

I find it hard to bend.

I have trouble getting up and down stairs.

I find it hard to stand for long

(e.g. at the kitchen sink, waiting for a bus).

I can only walk about indoors.

I find it hard to dress myself.

I need help to walk about outside

(e.g. walking aid or someone to support me).

I am unable to walk at all.

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

RECONSTRUCTION GROUP.

	n	median(IQR)	
ENERGY			
Pre	62	24 (0 - 61)	
3/12	53	24 (0 - 61)	t = 2.644
6/12	48	24 (0 - 55)	p = 0.450
1 year	27	0 (0 - 24)	
PAIN			
Pre	62	59 (30 - 90)	
3/12	51	17 (0 - 38)	t = 44.05
6/12	46	15 (0 - 36)	p < 0.0001
1 year	24	0 (0 - 29)	
EMOTION			
Pre	61	24 (0 - 42)	
3/12	52	14 (0 - 45)	t = 6.97
6/12	45	10 (0 - 35)	p = 0.073
1 year	25	0 (0 - 28)	

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

RECONSTRUCTION GROUP.

	n	median(IQR)	
SLEEP			
Pre	64	22 (0 - 55)	
3/12	55	13 (0 - 35)	t = 7.19
6/12	47	0 (0 - 34)	p = 0.066
1 year	25	13 (0 - 44)	
SOCIAL ISOLATION			
Pre	59	0 (0 - 23)	
3/12	54	0 (0 - 23)	t = 1.42
6/12	46	0 (0 - 23)	p = 0.700
1 year	27	0 (0 - 23)	
MOBILITY			
Pre	62	46 (22- 69)	
3/12	54	39 (11- 67)	t = 17.67
6/12	46	22 (0- 48)	p = 0.0005
1 year	25	11 (0- 51)	

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

AMPUTATION GROUP.

	n	median(IQR)	
ENERGY			
Pre	16	24 (0 - 61)	
3/12	16	24 (0 - 52)	t = 0.169
6/12	11	24 (0 - 76)	P = 0.982
1 year	8	30 ----	
PAIN			
Pre	16	71 (40 -100)	
3/12	15	6 (0 - 23)	t = 19.25
6/12	10	8 (0 - 32)	p = 0.0002
1 year	8	8 -----	
EMOTION			
Pre	17	10 (0 - 34)	
3/12	15	7 (0 - 21)	t = 0.58
6/12	10	8 (0 - 40)	p = 0.902
1 year	7	0 ----	

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

AMPUTATION GROUP.

	n	median(IQR)	
SLEEP			
Pre	17	22 (0 - 81)	
3/12	16	17 (0 - 47)	t = 1.27
6/12	12	14 (0 - 62)	p = 0.735
1 year	8	0 ----	
SOCIAL ISOLATION			
Pre	16	0 (0 - 17)	
3/12	16	0 (0 - 23)	t = 1.91
6/12	10	0 (0 - 23)	p = 0.592
1 year	8	10 ----	
MOBILITY			
Pre	17	67 (46- 76)	
3/12	16	49 (34- 68)	t = 11.56
6/12	16	22 (0- 48)	p = 0.009
1 year	7	34 ----	

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

86 reconstructions, 24 major amputations.

	RECONSTRUCTION		AMPUTATION		
	n	median(IQR)	n	median(IQR)	
ENERGY					
Pre	62	24 (0 - 61)	16	24 (0 - 61)	t = 1.290
3/12	53	24 (0 - 61)	16	24 (0 - 52)	p = 0.199
6/12	48	24 (0 - 55)	11	24 (0 - 76)	
1 yr	27	0 (0 - 24)	8	30 (----)	
PAIN					
Pre	62	59 (30- 90)	16	71 (40-100)	t = 0.256
3/12	51	17 (0 - 38)	15	6 (0 - 23)	p = 0.798
6/12	46	15 (0 - 36)	10	8 (0 - 32)	
1 yr	24	0 (0 - 29)	8	8 (----)	
EMOTION					
Pre	61	24 (0 - 42)	17	10 (0 - 34)	t = 0.474
3/12	52	14 (0 - 45)	15	7 (0 - 21)	p = 0.636
6/12	45	10 (0 - 35)	10	8 (0 - 40)	
1 yr	25	0 (0 - 28)	7	0 (----)	

QUALITY OF LIFE STUDIES. Part 1.

NOTTINGHAM HEALTH PROFILE.

86 reconstructions, 24 major amputations.

	RECONSTRUCTION		AMPUTATION		
	n	median(IQR)	n	median(IQR)	
SLEEP					
Pre	64	22 (0 - 55)	17	22 (0 - 81)	t = 0.061
3/12	55	13 (0 - 35)	16	17 (0 - 47)	p = 0.952
6/12	47	0 (0 - 34)	12	14 (0 - 62)	
1 yr	25	13 (0 - 84)	8	0 (----)	
SOCIAL ISOLATION					
Pre	59	0 (0 - 23)	16	0 (0 - 17)	t = 1.565
3/12	54	0 (0 - 23)	16	0 (0 - 23)	p = 0.119
6/12	46	0 (0 - 23)	10	0 (0 - 23)	
1 yr	27	0 (0 - 23)	8	10 (----)	
MOBILITY					
Pre	62	46 (22 - 69)	17	67 (46 - 76)	t = 1.846
3/12	54	39 (11 - 67)	16	49 (34 - 68)	p = 0.066
6/12	46	22 (0 - 48)	10	45 (24 - 48)	
1 yr	25	11 (0 - 51)	7	34 (----)	