Studies on Skin Blood Flow Measurement with Particular Reference to Amputation Level Selection

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Being a thesis submitted for the degree of
Doctor of Medicine
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Dedicated to Patricia and Victoria

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Declaration

These studies were carried out whilst I was a registrar in the department of Peripheral Vascular Surgery in Glasgow Royal Infirmary.

I declare that I am the sole author of this thesis. The patient investigations and data collection were concieved, planned, and performed by myself. Analysis of clearance data was performed with the assistance of Dr W Angerson, physicist in the University Department of Surgery.

Much of this work has been presented at scientific meetings including:

The use of isotopes to determine skin blood flow.
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SUMMARY.

In the United Kingdom over 75% of lower limb amputations are performed as a consequence of ischaemia, and in excess of 80% of these patients are over the age of 60 years. Unfortunately, failure of amputation healing is a common problem, because of the nature of the underlying disease process, and the surgeon's endeavour to perform the amputation at the most distal level possible. Primary amputation failure has disastrous consequences; mortality is increased following revision; subsequent independent mobility is jeapordised; hospitalisation is prolonged with adverse effects on the well-being of the patient, and in addition there are the financial implications of decreased efficiency in terms of hospital bed usage.

Because of acknowledged difficulties in the selection of the correct amputation level using clinical criteria, a variety of laboratory techniques to supplement clinical examination have been devised. The number of techniques available however is a confusing testimony to the inadequacy of these methods, for to date none has provided an accurate means of pre-operative prediction of the chances of healing at a given amputation level. In Chapter 2 the development of philosophies for selection of amputation level, and the current methods for assessing blood flow are discussed. In particular, the problems which one

encounters when attempting to adapt such methods into clinical practice are highlighted.

Chapter 3 describes a retrospective analysis of 171 patients with peripheral vascular disease requiring amputation. Two hundred and twenty five amputations were studied with respect to wound healing. Factors such as previous vascular surgery, age, and diabetes mellitus, and their influence on healing were evaluated. The overall healing rate for all amputations was 66%. Although the optimal healing rate (78%) was achieved following above knee amputation, this was at the expense of a high mortality (14%). For foot amputation the primary healing rate was only 51%. The mean hospital stay was 45 days (range 2 - 180) which was a direct result of a combination of poor healing in distal amputations, and difficulties with mobilisation, and subsequent disposal in patients with proximal amputations. The long term survival was extremely limited with a cumulative survival of only 27% after 3 years. This retrospective analysis thus established the need for an objective method to select the appropriate amputation level in these patients.

Part 11 of this thesis is concerned with the method used for the measurement of skin blood flow (SBF). In Chapter 4 the methodology for the measurement of SBF blood flow in this study, based on the clearance of an intradermal deposit of 125-I-iodoantipyrine is described. In Chapter 5 studies on the methodology proved isotope clearance to be flow dependent and reproducible.

Part 111 of the thesis examines SBF in a number of clinical situations. In Chapter 6 the correlation between 125-I-iodoantipyrine clearance and various clinical and laboratory parameters currently used to assess the degree of vascular disease present is investigated, and found to be poor, basically because SBF is a dynamic measurement, in comparison to clinical examination, Doppler blood pressure measurement, and arteriography, all of which are capable of providing limited information only.

In Chapter 7 the technique of 125-I-iodoantipyrine clearance is employed to assess the response of patients following surgery aimed at improving distal blood flow. Direct arterial reconstruction caused a significant increase in SBF, but these changes were not apparent following lumbar sympathectomy (Chapter 8). The validity of sympathectomy as a procedure to increase nutritional blood flow in the foot of patients with severe peripheral vascular disease is questioned, and may explain the variable clinical response following sympathectomy in clinical practice.

Part IV of the thesis describes the use of the isotope method to select the appropriate level of amputation in

patients with end stage peripheral vascular disease.

In Chapter 9 a clinical study to assess the relationship of Doppler ankle blood pressure (DABP) and the healing of amputations in the foot is presented. There was no difference in mean DABP in healing (DABP = 89 +/- 8 mmHg) and non-healing (DABP = 91 +/- 12 mmHg) groups. This observation was independent of the presence of diabetes. Pre-operative infection did not influence amputation failure, although sepsis was often a factor responsible for non-healing. Amputation failure was observed in the ranges of Doppler pressure which have previously been considered to be compatible with healing, and the converse, healing at levels considered incompatible was also observed. DABP is not sufficiently reliable for the identification of patients for forefoot amputation.

In Chapter 10 a prospective study of the relationship of pre-operative SBF and amputation healing is described. Eighty patients were included in the study. The selection of amputation level was made purely on clinical grounds. When the healing at all levels of amputation was considered, primary healing was achieved in 65% with amputation failure in 23%. There was a significant difference in pre-operative skin blood flow between healing (12.1 +/- 0.6 ml/100g/min),

and non-healing (5.8 +/- 1.0 ml/100g/min) groups, but it was not possible to define a precise value to discriminate between healing and non-healing. This was principally due to the inclusion of amputations at the below knee level where healing ocurred at low flows after prolonged periods. However when the patients with foot amputations were selected, a value for SBF of 7 ml/100g/min emerged as the critical flow for healing. At SBF values below this level, failure was inevitable, primarily because of the combination of ischaemia and sepsis.

In general therefore, it is concluded that a need exists for a means of accurate pre-operative selection of the appropriate amputation level. The use of 125-I-iodoantipyrine clearance appears to be a simple and reproducible means of measuring skin blood flow. Although there is a significant difference in skin blood flow between healing and non healing amputations, it is only in the forefoot that skin blood flow measurement is capable of providing a value which appears to be critical for healing. With this technique available the identification of patients suitable for conservative foot amputation should be possible, allowing mobility without the use of a prosthesis. It should now be possible to reduce failure of forefoot amputations, and so reduce the hospital occupancy of these patients, free bed use for other categories of patients with peripheral vascular disease, and partially reduce the economic burden that these patients impose on the Health Service.

PART I : GENERAL INTRODUCTION.

CHAPTER 1

General Introduction

A century ago it was uncommon to live beyond the age of 50, the major causes of death being tuberculosis, infection, and malnutrition. Improvements in public health since the turn of the century have led to an increase in the size of the elderly population in developed countries, which, together with the habit of cigarette smoking, and possibly dietary changes have resulted in an increase in the number of patients presenting with the clinical manifestations of peripheral arterial disease.

In the past 30 years direct operations on arteries have become possible with the introduction of autografts and arterial prostheses for the treatment of degenerative arterial disease. However, despite such relatively recent innovations, one of the greatest remaining problems which faces the vascular surgeon is the patient with non reconstructible end stage ischaemia where amputation of the limb is the only solution. In the United Kingdom 80% of lower limb amputations are performed as a consequence of ischaemia, and more than 80% of these patients are over the age of 60 (Hamilton and Nichols 1972; Department of Health and Social Security 1972,1983; Murdoch 1975).

Unfortunately the outlook for many amputees is poor, with high early and late mortality (Weaver and Marshall 1973; Harris et al 1974), frequent problems with stump healing, (Warren and Kihn 1968; Couch et al 1977; Porter et al 1981), and difficulties with rehabilitation (Chilvers and Browse 1971; Malone et al 1979). The primary objective of amputation is to remove gangrenous tissue and relieve pain. In doing so however, the surgeon must ensure primary healing.

Proximal amputations are at less risk of healing failure requiring revision to a higher level (Figure 1.1). Above knee and through knee amputations are more likely to heal than below knee amputations (Warren and Kihn 1968; Weale 1969; Greene et al 1972; Newcombe and Marcuson 1972; Barnes et al 1976; Tracy 1982). This is not surprising as ischaemia is more severe distally, and section of a limb through its more proximal part means that healing is more likely in an area of relatively greater vascularity. However, although amputations through the thigh heal well, the mortality following surgery is between 10 and 40% (Gilchrist 1961; Warren and Record 1967), and of those patients who survive the operation only about one third will ever use a prosthesis (Couch et al 1977).

In patients with cerebrovascular or cardiac manifestations of the underlying arteriopathy, where it is not possible to contemplate rehabilitation, there would

Figure 1.1.

Early wound failure due to ischaemia at the amputation site in a below knee amputation.

seem to be little point in striving for a distal amputation and primary healing must be the cardinal objective (Jamieson and Hill 1976). However, in the majority of patients, with encouragement and an intensive programme of physiotherapy, rehabilitation can be successfully achieved.

There is no doubt that an amputation at the below knee level offers a better chance of rehabilitation (Kihn Warren and Beebe 1972; Little 1973). Studies of energy expenditure (Bresler and Berry 1951; Ralston 1958; McCollough et al 1971) have shown that following an above knee amputation, energy expenditure while walking on a prosthesis increases by some 70% compared to only a 10% increase after a below knee amputation. Many of the elderly patients are unable to adapt to this increased energy demand. In addition, in certain circumstances where ischaemia is confined to the forefoot (figure 1.2), it may be possible to preserve the limb by performing conservative amputation in the foot. It is obvious that in these circumstances rehabilitation is not a problem.

As the average life expectancy following an amputation is less than three years (Little et al 1973; Finch et al 1970), it is imperative that the rehabilitation of amputees is as rapid as possible, and the advantages of preserving limb length must be balanced against the increased morbidity that is inevitable if the amputation breaks down as a result of ischaemia.

Figure 1.2.

Localised forefoot ischaemia; an ischaemic ulcer in a diabetic patient.

If one reviews the techniques currently used to select amputation level, it becomes apparent that all are associated with problems due to inaccuracy, lack of reproducibility, complexity, non availability, and lack of specificity (Nicholas et al 1982; Cooperman et al 1977). Such selection criteria include clinical pre-operative assessment (Barnes 1976; Malone 1979; DeCossart 1983), Doppler pressure studies (Cooperman 1977; Creaney 1981; Pollock 1980), plethysmography (Barnes 1981), segmental pressures (Barnes 1981; Lepartelo et al 1982), skin pressures (Holstein et al 1979; Chavastaz et al 1975), skin oxygen tension (Burgess et al 1982), fluorescein angiography (Tanzer and Horne 1982; McFarlane and Lawrence 1982), muscle pH (Young et al 1978), and thermography (Spence et al 1978; Henderson and Hackett 1978).

Although the merits of each method have been defined and will be discussed fully in a subsequent chapter, none of them provides a clear cut end point above or below which the healing of an amputation can be predicted with confidence.

CHAPTER 2.

Literature Review

Historical Aspects of Amputation Surgery.

Amputations (derived from Latin - Amputare - to cut away) have been practised since the beginning of mankind. Archaeological evidence dates to the Neolithical period knifes and saws of bone and stone of this period have been found with skeletal remains with amputated bone stumps.

The history of amputation is closely related to the development of surgery itself. The earliest scientific account of amputation appears in the Hippocratic treatise 'On Joints' (Rang and Thomson 1981), in the fifth century BC, which recommended that the amputation be performed through the devitalised tissue at a site where the vessels were thrombosed to assure that no bleeding occurred, and the stump subsequently healed by granulation tissue formation.

By the beginning of the first century AD, Aulus Cornelius Celcus had advanced beyond Hippocratic doctrine to performing the amputation at the line of demarcation between normal and gangrenous tissue, but again at this point the majority of the vessels had thrombosed. He stated that it was preferable that "some of the sound part be cut away than any of the diseased part be left behind." (cited by Harvey 1929).

By 100 AD, Archgenes had advocated primary ligation of blood vessels proximal to the level of gangrene (cited by Beasley 1982). These techniques and recommendations were followed by Galen in the second century AD, but with the subsequent fall of the Roman Empire there was a decline in civilisation including education, culture, the arts, religion, and especially medicine and surgery.

During the first half of the middle ages there was a steady decline in amputation technique that eventually resulted in the abandonment of the use of the ligature with increasing dependence on the use of cautery with hot irons or boiling oil to control haemostasis.

Towards the latter part of the middle ages the need for amputation increased greatly. This was in part due to the devastating effects of leprosy and ergotism, and in part to the introduction of gunpowder and firearms. Cannon shot was first introduced at the battle of Crecy in 1346 and half pound gunshot in 1364 at Perugia. The wounds inflicted by these weapons were often so mutilating that amputation was necessary. It was Ambrose Paré, the great French military surgeon, who made the most significant contributions to amputation surgery. He reintroduced ligatures for the control of bleeding and condemned the use of cautery. Paré emphasised the removal of all devitalised tissue in an amputation for gangrene, and was responsible for the recognition of appropriate site selection with respect to future prosthetic use. Indeed Paré described the re-amputation of an officer's leg that had been shot off by a musket ball because the healed stump was too long for use with a prosthesis (cited by Wilson 1972). This was the first recorded revision of an amputation for prosthetic reasons, and was surely a formidable undertaking in the pre-aseptic and pre-anaesthetic era for a non life threatening condition.

Peter Lowe, the founder of the Royal College of Physicians and Surgeons of Glasgow, is credited with the first description published in English reporting the use of ligatures to control bleeding in an amputation in 1596. However, when infection was present, Lowe resorted to cautery, a practice that was continued until the nineteenth century.

The discovery in 1616 of the circulation of the blood by Harvey led to the introduction of more effective tourniquets resulting in amputation with minimal blood loss. This in turn permitted the surgeon to use flap methods to achieve better tissue coverage, and a more acceptable stump for use with a prosthesis.

The major cause of mortality at this time was sepsis. In

1842 the mortality for all amputations was 39% rising to 62% for those performed through the thigh. Lister's observations published in 1867 on antisepsis profoundly altered surgical science, and in particular the mortality following amputation. The discovery of effective anaesthetic agents also enabled the surgeon to perform the amputation painlessly and without haste. With such improvements, surgeons could focus their attention on improved method and site selection. By the end of the nineteenth century, surgeons had all but abandoned the guillotine method, and the techniques used by Symes, Pirigoff, Gritti, Lisfranc, and Stokes, recognising the importance of appropriate flap and stump design, are still in use today.

By the turn of the twentieth century, with the decline in the number of deaths from tuberculosis, infection, and malnutrition, the problems of an ageing population presenting with degenerative vascular disease emerged. In times of peace, gangrene secondary to advanced occlusive vascular disease became the primary indication for lower limb amputation, the preferred level of amputation being above the knee. The frequency of infection with its grave danger to life and limb discouraged attempts to amputate at a lower level. In 1939 Homans was voicing contemporary surgical opinion concerning atherosclerosis of the lower limb when he wrote "Amputations below the knee can almost never be expected to offer a healthy stump".

Over the following decade, however, the introduction of antibiotics, and the better understanding and treatment of peripheral vascular disease led to a better prognosis for both life and limb, and the management of patients with gangrene, ulceration, and infection of the lower limb became more conservative with successful amputation at the below knee, transmetatarsal, and forefoot level possible in many cases (McKittrick et al 1949; Warren et al 1952; Silbert 1948; Silbert and Haimovici 1950). This conservative trend has continued with the emphasis now placed on amputation at the most distal level which is compatible with healing (Edwards and Linton 1953; Schumaker and Moore 1951; Smith 1953; Silbert and Haimovici 1954; Kendrick 1956).

Previous Methods Used to Determine Amputation Level

(i) Clinical Methods

Introduction

In current practice the selection of the appropriate level of amputation is based mainly upon the judgement and experience of the surgeon. Although the status of the arterial circulation is a major determinant of amputation wound healing, objective criteria such as level of distal pulse, skin temperature, and angiographic patterns of disease have not provided a clear cut guide which accurately predicts the most distal level at which an amputation can be expected to heal (Romano and Burgess 1971; Browse 1973). Reported rates of below knee healing when clinical assesment alone is used are of the order of 70% (Kendrick 1956; Condon and Jordon 1970; Chivers et al 1971.).

Pulse Pattern

Burgess et al (1971) stated that the absence of a popliteal pulse does not contra-indicate a below knee amputation, demonstrating satisfactory and lasting wound healing in the absence of a popliteal pulse. Warren and Kihn (1968) also conceded that the absence of a popliteal pulse should not be considered a contra-indication to below knee amputation. Such opinions reflected the philosophies of the previous decades that the level of choice was at mid thigh unless there were circumstances in which a more distal amputation could be considered. Cranley and associates (1969) suggested that the absence of a common femoral pulse in the presence of gangrene of the foot was an indication for primary above knee amputation. However, Barnes (1976) reported healing of below knee amputation in two of three patients without femoral pulses.

Nicholas et al (1982) found that 45% of patients with successful below knee healing had had a popliteal pulse present, whereas only 14% of those amputations that failed had a palpable popliteal pulse. If one combines the results reported by Barnes (1976) and Nicholas (1982), failure of below knee amputation occurred in only 3% of those patients with a popliteal pulse present, while failure of healing occurs in 22% of those with an absent popliteal pulse. Therefore it appears that a popliteal pulse allows one to feel confident that below knee amputation will heal successfully. However the converse of this statement is not true, and it would obviously be inadvisable in certain circumstances to sacrifice the knee joint where the popliteal pulse is absent.

Palpable pulsations reflect major arterial flow but not collateral circulation, which, in the ischaemic limb is the major determinant of whether the patient develops symptoms, and reflects the healing potential following amputation.

Skin Appearance

In the absence of any other reliable criteria the selection of the appropriate level for amputation based solely on the condition of the skin is of value. Atrophy, cyanosis, and loss of hair may be ignored where there is a skin capillary flush following release of digital pressure. Ulceration, sepsis, severe pallor, and coolness are indications for amputation at a higher level (Burgess and Romano 1971). Such criteria however are highly subjective, and do not quantify a critical end point for prediction of healing. Skin temperature has been considered too non-specific as a determinant of appropriate amputation level (Barnes et al 1976).

Operative Bleeding

Although the relationship of the arterial supply to the skin and wound healing has been emphasised, operative bleeding does not correlate well with subsequent amputation wound healing. A 'trial incision' at the proposed level of amputation has been used as a test for adequate blood supply (Schumaker and Moore 1951), but the value of this approach has not been confirmed. Kihn et al (1972) stated that absent or minimal skin bleeding at the time of the incision should not be considered a definitive contra-indication to below knee amputation. Furthermore, when the degree of bleeding at operation was graded there was no statistically significant difference in the healing rates between the patients with various grades of bleeding. This observation had been reported earlier by Cranley and co-workers (1969) who found no correlation between wound healing and the highly subjective status of operative wound bleeding.

Angiography

Tolstedt and Bell (1961), reporting a 29% failure rate for below knee amputations, suggested that femoral arteriography might be a valuable aid in determining the site of amputation, allowing a below knee amputation in the presence of patent superficial femoral and popliteal arteries. Baddeley and Fulford (1964) advocated the use of arteriography to select the level of amputation. Femoral arteriography allowed them to predict a successful outcome correctly in 23 of 26 below knee amputations. They suggested that below knee amputation was not appropriate in patients with marked disease of the superficial femoral artery and occlusion of the popliteal artery.

Lim et al (1967), reviewing their experience with below knee amputation, found that the degree and pattern of disease in the superficial femoral, profunda femoris, popliteal, and trifurcation arteries did not differ significantly between those patients with successful and those with unsuccessful below knee amputations. In particular they claimed that neither patency nor occlusion of the popliteal or tibial stem vessels correlated with successful healing. They clearly showed that below knee amputation was feasible in both the absence of a popliteal pulse and occlusion of the popliteal artery on angiography. In the presence of occlusion of the superficial femoral and popliteal arteries, provided the profunda femoral remains patent, sufficient collateral circulation may be available to permit a below knee amputation. Burgess et al (1971) were also unable to demonstrate a constant relationship between the severity of angiographic disease and the failure of a below knee amputation to heal. A policy based solely on angiography as the determinant between below and above knee amputation is at risk of sacrificing the knee joint unnecessarily in a significant number of individuals.

For conservative foot amputation in diabetic patients Baddeley and Fulford (1964) found that when the degree of run-off was good and satisfactory collateral circulation was present, toe or mid-tarsal amputations were generally achieved. Occlusion of one or more tibial vessels did not exclude foot amputation as long as the collateral circulation was good. They found that it was possible to forecast the level of amputation in this way in 71.6% of limbs, and when radiography was combined with the clinical appearance this figure was raised to 88.1%. However as this work was carried out exclusively in diabetics with the pattern of distal disease typical of the diabetic, it has not been reproduced in patients with atherosclerotic occlusive disease.

According to Murdoch (1967) the disadvantage of arteriography is its inability to demonstrate the true vascular picture, underestimating the functional disease present. This assertion was supported by Warren (1967) who added that arteriography demonstrates the pattern of collateral circulation, but likewise does not quantify it.

The major objection to amputation selection based purely on clinical observations is therefore that no single clinical criteria provides a dependable and reproducible basis since none are quantitative and all lack a sharp end point (Moore et al 1968; Lim 1967; Romano and Burgess 1971). The failure of such clinical criteria led to the development of two extreme approaches for amputation level selection. One approach (Jamieson and Hill 1976) advocated performing the most distal amputation that circumvented the disease process, provided that the surgeon was willing to carry out progressively higher amputation revisions until primary healing occurred. The opposite extreme was to assume that patients with vascular disease were unlikely to have sufficient nutritional blood flow to heal amputations at conservative levels, and therefore all amputations were performed at the above knee level as an expedient way to obtain healing. Both these methods of level selection are unsatisfactory. Using the first method, repeated anaesthetics and revision amputations put the patients' life in jeopardy, and often result in an amputation at a higher level than might have been possible had the proper level been selected in the first instance (Moore et al 1981). The second approach, while resulting in a satisfactory rate of primary healing produces maximal disability and reduces the likelihood for satisfactory prosthetic rehabilitation (Moore 1974).

Laboratory Methods

Introduction

The development of non-invasive tests to assess the functional integrity of the arterial supply to the limb has made the vascular laboratory an integral part of the diagnostic work-up of the patient with peripheral vascular disease. The most important application of the non-invasive laboratory is determining the appropriate operation for an individual patient and its chances of success. A number of these non-invasive tests have been applied to the patient with non-reconstructible disease in an attempt to determine the appropriate level of amputation.

(ii) Doppler Ultrasound.

In 1959 Satomura and Kaneko (1959) using an electronic blood rheograph based on the principal of the Doppler effect, first described a non-invasive method of studying changes in blood flow in human peripheral arteries. Later Strandness et al (1966), and Yao et al (1969) popularised the use of transcutaneous Doppler flow measurement to study peripheral vascular disease.

The most widely used Doppler diagnostic procedure is the measurement of the segmental lower extremity systolic pressure with or without comparison to the brachial pressure (Yoa 1970; Mannick 1983.). In the continuous wave Doppler, the ultrasound beam is produced continuously by exciting a piezo electric crystal. Depending on the character of the crystal, an ultrasound beam of 2, 5, or 10 mc/s (mhz) can de emitted from a ceramic crystal following excitation by an electrical oscillator. Two crystals, one transmitting the other receiving, are mounted on a small transducer. Using a water soluble gel as a coupling agent, the transducer is placed over the artery to be examined at an angle of insonation of approximately 60 degrees. Ultrasound reflected from moving red cells in the blood vessel is shifted in frequency by an amount proportional to the flow velocity of the red cells. The back scattered sound is detected by the receiving crystal mounted adjacent to the transmitting crystal, and a signal whose pitch is proportional to the velocity of the blood flow within the vessel is produced within the audible range. When compared to the electro- magnetic flowmeter (EMF), the Doppler instrument is capable of measuring flow velocity to within 5% of that recorded by the EMF (Shoor et al 1979).

Segmental pressure measurements are performed using a Doppler blood velocity detector and a pneumatic blood pressure cuff and sphygmomanometer. The cuff is inflated to occlude flow in the segment under study. The pressure at which flow returns on gradual deflation of the cuff can be expressed as an absolute value or as an index related to brachial pressure (Yao and Bergan 1974; Yao et al 1969). The accuracy of this technique correlates well with intra-arterial pressure measurement (Kazimias et al 1971.). The pressure index is useful in grading the degree of ischaemia. In normal individuals the pressure index is equal to or greater than 1.0. A calcified artery which the cuff cannot compress tends to produce a falsely high reading; the pressure index or absolute pressures are more reliable in non-diabetic patients (Yao and Bergan 1984).

Barnes et al (1976) studied the relationship between Doppler ultrasound assesment of below knee pressure and the healing of subsequent below knee amputations for advanced ischaemia in 50 patients. They demonstrated that healing did not occur in patients with no detectable Doppler arterial signal (and thus no pressure) below the knee. When the pressure at this level was less than 70 mmHg, there was failure of healing after below knee amputation in 25% of the patients. When the pressure was greater than 70 mmHg, healing of below knee amputation was universally successful. They concluded that Doppler ultrasonic assessment of below knee arterial signals and pressures was a simple haemodynamic determinant of healing and non-healing following a below knee amputation, and suggested that the absence of a detectable below knee signal might be an indication for primary above knee amputation. However, they qualified these observations by stating that the ability to detect an arterial blood pressure, however low should not be a contraindication to a below knee amputation "if other clinical factors are favourable to such a procedure", thus once more introducing the imprecision of clinical assessment. Dean et al (1975) studied the predictive value of ultrasonically derived blood pressure for determining the optimal amputation level, and suggested that when there is no detectable flow in the popliteal artery an above knee amputation is advisable. On the other hand when there was detectable flow in the popliteal artery they were able to measure the thigh pressure by proximal occlusion. They concluded that in those situations where the thigh pressure exceeded 50 mmHg, a below knee amputation should be attempted as the chance of successful healing is high. The presence of an audible signal in the posterior tibial or dorsalis pedis arteries was associated with successful below knee amputation.

Lee et al (1979) found Doppler pressures similar to those reported by Barnes (1976) and Dean (1975), in that healing of below knee amputation was associated with thigh pressures in excess of 70 mmHg.

Pollock and Ernst (1980) described the value of Doppler ultrasound for the selection of patients for below knee amputation, and reported satisfactory healing in 82% of below knee amputations where the below knee pressure exceeded 70mmHg.

Similarly, Creaney et al (1981) used the Doppler ultrasound to measure the below knee pressure and the pressure index in 46 below knee amputations, and found a statistically significant difference between preoperative values in the healed and non-healed groups. When the below knee pressure exceeded 70mmHg, all below knee amputations healed satisfactorily, and in only one patient with a pressure below 70 mmHg was healing successful. These authors concluded that the below knee ultrasound pressure was of value in determining the level of amputation about the knee joint.

Pressure measurement using Doppler techniques has also been employed in an attempt to predict the healing potential of ischaemic ulcers, and the healing of conservative amputations at digital and transmetatarsal level. Carter (1973) studied the relationship between ankle blood pressure and the healing of skin lesions in the foot, and found that at pressures of less than 50mmHg, healing did not occur. Other studies indicate that in the diabetic an ankle pressure greater than 90 mmHg is generally associated with the healing of arterial lesions in the foot with conservative measures alone (Raines et al 1976; Strandness and Sumner 1972).

For successful digital and transmetatarsal amputation healing Carter (1973) suggested that a minimum ankle pressure of 35 mmHg was necessary.

Gibbons et al (1979) reported the value of Doppler ultrasound in forefoot amputation in diabetics. In the patients whose amputations healed, 36% had ankle pressures of less than 70mmHg. In patients with failed amputations, 27% had pressures of less than 70 mmHg, and 64% of this group had pressures of between 70 and 200 mmHg. The inability of Doppler ultrasound to define healing and non-healing groups led these workers to conclude that no patient should be denied a forefoot amputation solely on the basis of unfavourable Doppler ankle pressures.

In comparison, Verta et al (1976) state that in the absence of invasive infection, forefoot perfusion pressure is the single most important factor in determining the outcome of minor foot amputation. At ankle pressures of less than 35 mmHg, they demonstrated that salvage of the foot by such measures appeared to be futile, with universal amputation failure. In this series, the presence or absence of diabetes had no noticeable effect on the outcome following amputation.

In the small series reported by Baker and Barnes (1977), the authors were unable to document healing of forefoot amputations at pressures of less than 60 mmHg. Although there were only four patients with pressures of this level in the study, the authors suggested that these patients would have been preselected on clinical grounds for a primary below knee amputation. No explanation was offered to explain the discrepancy between their conclusions and those of Verta et al (1976) whose patients were able to heal amputations in the presence of such low pressures. In a later study, Barnes (1981) demonstrated healing at pressures of lower than 60 mmHg, and concluded, in variance with his experience of four years previously, that Doppler ultrasound is fallible.

Bone and Pomajzl (1981) found that the mean Doppler ankle pressure in limbs with healing of forefoot amputation did not differ significantly from the pressure in those that failed to heal.

The measurement of ankle blood pressure is an imprecise index of the outcome of amputation, particularly at forefoot level. The use of ankle systolic pressure alone must be interpreted with extreme caution. A high ankle pressure does not necessarily guarantee amputation success, as the pressure level at the ankle may not reflect the status of perfusion of the toes or forefoot. This is particularily true in diabetics in whom the ankle pressure is unreliable (Schwartz 1982). Most studies indicate that about one half of diabetic men over the age of 40 years will have mural calcification in the arteries of the leg (Morrison and Boyen 1929; Hanssen 1946; Ferrier 1964; Ferrier 1967.). According to Raines et al (1976), diabetes completely prevents cuff compression of the ankle vessels in 5-10% of patients with this condition.

(iii) Plethysmography

Blood flow measurement using the air filled rubber cuffed plethysmograph described by Dahn (1965) has been used extensively in physiology as well as in the study of arterial insufficiency (Concordila, Koroxenidis and Shepherd 1964; Siggaard-Andersen 1970). Venous occlusion plethysmography records the increase in volume of the limb from which the venous outflow is temporally occluded while the arterial inflow is left intact. During the first few seconds after venous occlusion, the volume increase may be assumed to be proportional to the arterial inflow which can thus be calculated in ml/100g/min. Applied to a calf segment, the results obtained reflect primarily the muscle blood flow (Hillestad 1962; Siggaard-Anderson 1965; Dahn 1965· Sumner and Strandness 1969). The digits of the hand and feet are assumed to consist essentially of skin and bone. Thus a volume change induced in a digit by occlusion of its venous outflow is taken as a volume change in skin. The rate of change of the volume of the skin, if steady, may be taken to represent the unimpeded rate of arterial inflow. Foot plethysmography thus chiefly illustrates skin blood flow (Whitney 1953; Mune 1967; Schraibman and Ledingham 1969; McEwan and Ledingham 1971). However, plethysmographic techniques can only estimate cutaneous blood flow in a semi-quantitive or qualitive fashion, as complicated subtraction procedures must be applied to correct for blood flow in the subcutaneous tissue and muscle.

(iv) Pulse Volume Recording.

The pulse volume recorder (PVR) is a quantitative segmental air plethysmograph that utilises cuffs placed around the thigh, calf, and ankle (Darling et al 1972; Raines et al 1976.). The PVR is calibrated so that a 1 mmHg fluctuation in each cuff causes a 20 mm deflection on a chart recorder. The amplitude of the pulse volume recording is related to the local blood pressure, segmental arterial compliance, and the number of arterial vessels in the involved segment, as well as to the degree of arteriosclerotic occlusive disease present. The amplitude of the calibrated PVR tracing has been shown to be related to the degree of peripheral arterial occlusive disease, and the published data suggest that there is a relationship between the pulse volume and the likelihood that arterial lesions in the skin of the foot will heal spontaneously (Raines et al 1976). The combination of systolic Doppler ankle pressure and thigh, calf, and ankle PVR appears to be of particular value for predicting the success following below knee amputation (Raines et al 1976).

Gibbons et al (1979) assessed the use of the PVR to predict the outcome following forefoot amputations in diabetic patients. They demonstrated that segmental PVRs were sequentially predictive in 49% when the outcome was successful, although in 51% the measurement was not of value in predicting the success of the amputation. A flat or only slightly positive PVR was present in 90% of the failed forefoot amputations. However 50% of the successful amputations had flat or only slightly positive recordings. They concluded that a strongly positive forefoot trace was the best non-invasive predictor for successful amputation healing especially when compared with favourable clinical signs.

(v) Digital Plethysmography.

Toe blood pressure measurement can be determined indirectly by an infrared photoelectric transducer as a flow detector, placed distally to a small pneumatic occlusion cuff which encircles the base of the toe (Bone and Pomajzl 1981). Hirai and Kawai (1977) demonstrated that measurements obtained by the photoelectric plethysmographic technique corresponded closely to those obtained by the less convenient method of strain guage plethysmography.

The photoplethysmograph contains a light emitting diode, operating in the near infrared position in the spectrum, and a phototransistor detector. Light emitted by the diode is reflected from the underlying micro-circulation. Changes in the reflected light induced by variations in the blood flow can be detected by the phototransistor and the resultant signal can be amplified and recorded. A pneumatic cuff is applied on the toe, proximal to the sensor. Systolic pressure in the toe is then measured by noting the point at which arterial pulsations reappear during deflation of the cuff.

Using this technique, Bone and Pomajzl (1981) documented a significant difference between the toe pressures of those forefoot amputations which healed and those that did not heal. Failure of amputation healing occurred in all limbs with toe pressures of less than 45mmHg and in 25% of those with pressures of between 45 and 55 mmHg. When the toe pressure was 55mmHg or above, primary healing was universally achieved, suggesting that toe pressure measurement may be a useful haemodynamic correlate of the healing potential of a forefoot amputation.

Digital photoplethysmography has also been used by Barnes (1979) who, in contrast to Bone and Pomajzl, observed healing of toe and forefoot amputations with toe blood pressures as low as 10 mmHg. However, the technique used by Barnes differed in several important aspects and may have precluded accurate measurement of pressure below

40mmHg.

In 1981 Barnes presented further work relating digital plethysmography to the healing of digital and foot amputations in both diabetic, and non-diabetic patients. The mean digital systolic blood pressure in patients with healed amputations was significantly higher than in those in whom foot amputations failed. Healing of foot amputations was found consistently if the digital pressure was above 10 mmHg in non diabetics, and above 25 mmHg in diabetics.

Wagner and Briggs (1978) found toe amputation healing to be possible whenever toe pressures exceeded 50mmHg. None of their patients with lower pressures than this healed toe amputations.

Digital blood pressure measurement by photoplethysmography has not however been commonly employed in clinical practice due, perhaps, in part to the tediousness of obtaining this measurement when compared to the more traditional methods such as Doppler ultrasound. However, the published data to date suggests that toe pressure measurements may be a useful guide to the healing potential of a forefoot amputation, although there would appear to be a considerable overlap, without a precise discriminant value to predict healing with certainty.

(vi) Skin blood pressure

Various methods exist to measure skin blood pressure. A simple method, devised by Chavastas and Jamieson (1974), employed a transparent sphygmomanometer cuff and a histamine induced flare. The sphygmomanometer was inflated with the cuff over the area of the flare, and the pressure at which blanching of the skin disappeared, as the cuff was deflated, was the skin occlusion pressure. Neilsen, Poulsen, and Gyntelberg (1973) used a similar technique, but detected occlusion pressure by placing a photocell beneath the sphygmomanometer cuff. Nilsen et al (1967) used an intracutaneous deposit of Xenon-133 beneath an occlusion cuff, and noted the point at which clearance was arrested by cuff inflation. This they referred to as the skin blood pressure. This technique was refined by Lassen and Hostein (1974) who arrested the local clearance of an intracutaneous deposit of 131-I-iodoantipyrine by counterpressure in a sphygmomanometer cuff.

Holstein (1982) studied amputation healing correlated to skin blood pressure using this method. When the skin blood pressure was above 30mmHg, 97% of below knee amputations healed. When the skin blood pressure was between 20 and 30 mmHg healing failed in 54%, and when the skin blood pressure was below 20mmHg, there was failure of healing in 89%. However, no mention was made of this technique at levels other than below knee,

(vii) Fluorescein angiography

The ultimate non-invasive test should be capable of providing regional blood flow information. The techniques of fluorescein angiography and infrared thermography have great potential, but as yet they lack the necessary quantification, and in the case of thermography, there are interpretative difficulties in relation to flow through specific vessels of the dermal microvasculature. Tissue fluorescence is regarded as a function of nutritional blood flow because, following an intravenous injection of fluorescein, the dye accumulates in the extracellular fluid by passage across capillary walls. Exposure of a skin site to ultaviolet light highlights the extent of yellow green fluorescence in the dermal tissue. In ischaemic areas fluorescein concentration is impaired relative to normal skin and a quantification of this relative index is possible (Silverman et al 1980).

(viii) Thermography and temperature measurement techniques

Thermographic mapping of regional skin temperature gradients is ideally non-invasive. However, the contributions of heat flux from specific segments of the dermal vasculature is uncertain, although it is clear that the capillaries and venules act as the greatest heat exchangers. The ability of the venules to act as a reservoir of large volumes of slow moving blood has the most significant impact on heat exchange in the cutaneous layers of the skin. In addition, the density and type of arterio-venous anastomoses moderate heat exchange because of their ability to short circuit large volumes of blood into the superficial venous plexus. These shunts are abundant in the hands and feet and they have such a significant effect on heat exchange that a thermogram from an acral part of the body is almost entirely dominated by the tone of these vessels. An effective transfer of heat can also be maintained in ischaemic feet because, despite extensive arterial occlusions, a normal or even raised volume of blood can be held under the skin surface (Conrad 1968). However, it should not be assumed that this apparently good blood flow will adequately perfuse the tissues (McEwan and Ledingham 1971), and it is this discrepancy between volume flow and perfusion which makes foot thermograms difficult to interpret, although the value of thermal gradients at the below knee level is more readily apparent in terms of nutritional blood flow (Spence and Walker 1984). This is because there are few arterio-venous anastomoses in the skin of the lower leg and, in ischaemic conditions, the control of blood flow is essentially pressure dependent due to suppression of autoregulatory and temperature sensitive mechanisms.

Lee et al (1979) assessed the use of skin thermistor thermography and other non-invasive techniques for selection of amputation level. They showed that skin thermistor thermography exhibited a well formed line of temperature demarcation consistent with wound healing in below knee amputations. With above knee amputations, or distal amputations which failed and required revision to below knee level, thermistor thermography failed to provide an accurate line of temperature demarcation. These authors concluded that skin thermistor thermography is of little use in patients with extensive severe ischaemia of the leg.

Emission Thermography has been used extensively in the past comparing angiographic patterns of vascular disease with the thermographic images (Soulen et al 1972, Siltonen et al 1971, McLaughlin and Rawsthorne 1973, Lovisatti et al 1975).

However, thermography has not been adopted as a convenient method of assessing tissue viability although the possible use of the technique in selecting the optimal site for amputation has been expressed on several occassions.

Thermography is based on the established fact that matter above zero absolute temperature emits a wide spectrum of electromagnetic radiation. Infrared and microwave radiation are two narrow bands of such spectrum. Any buried heat sources in the body (tumour or blood vessels) are more active in the production of this electromagnetic power. The lower frequency components of this radiation are more likely to escape from within the body surface than higher frequency components depending on the depth of the source and the surrounding tissue type.

Spence et al (1978) investigated the value of infrared thermography for assessing the optimal site of amputation in ischaemic limbs. The examinations were carried out in a draught free environment at 20 degrees centigrade using an EMI thermoscan with a cadmium-mercury-telluride detector to obtain thermograms of the limbs. Their results demonstrated that the thermographic method is a reliable indicator of the level of major limb amputations, with correct prediction of healing at the above knee, through knee, and below knee levels of 88%. These results compared favourably with those of Henderson and Hacket (1978). However, Spence (1978) found that the thermographic classification of distal amputations proved to be less precise. Fourteen patients in their study had a successful partial foot amputation when thermography would have predicted non-healing. They explained such incorrect predictions on excessive foot hyperaemia due to the presence of infection, demonstrating that thermography is not appropriate in the presence of an inflamed, ischaemic foot. Because the frequency of the infrared emissions are at the upper end of the spectrum of electromagnetic radiations, infrared thermography can only give thermal information from the skin surface (Lyoyd-Williams 1964). However microwave thermography is able to detect the lower frequency emissions from subcutaneous tissues as well (Monson et al 1985). Although the thermal picture obtained by infrared reflects temperature changes deep to the skin, this picture is dependent on the subcutaneous tissue thermal conductivity, and the thermal balance at the air/skin boundary. Microwave thermography attempts to overcome this problem by observing directly the source tissue thermal radiation. Microwave thermography has thus a major advantage over infrared thermography in patients with peripheral vascular disease, and although it has yet to be used to predict amputation healing, the ability to assess deeper tissue viability is a potential advantage.

(ix) Transcutaneous oxygen tension measurement.

The ability to measure the partial pressure of tissue oxygen by transcutaneous means is a recently developed non-invasive test of tissue perfusion. Although the technique, using a miniaturised Clark electrode was described over a decade ago by Huch and colleagues (1972), and Eberhard and colleagues (1972), transcutaneous oxygen tension measurement did not make a major impact on the vascular surgeon until its application was described by Matsen et al (1982), Franzeck et al (1982), and White et al (1982).

Transcutaneous oxygen tension measurement involves the application of heat to the skin, producing localised hyperaemia and oxygen excess. Oxygen then diffuses along a concentration gradient from the capillaries to the tissues, and if still present in excess of skin requirement, may diffuse across the skin where it is electro-chemically reduced and measured by a Clark electrode. The Clark electrode consists of a silver ring anode, and a large gold cathode containing a heating resistor and two calibrated precision thermistors. The sensor is prepared by applying a special electrolyte solution and a precut membrane (Graham and Kenny 1980). The amount of oxygen available for diffusion across the skin depends on the oxygen delivery which is a function of arterial oxygen content and the blood flow (Eickhoff and Jacobson 1980).

Transcutaneous oxygen tension has been shown to be a sensitive and specific test for arterial insufficiency (Hauser and Shoemaker 1983, Byrne et al 1984). The technique has been applied to predict amputation wound healing in patients with severe peripheral vascular disease.

Burgess et al (1982) evaluated segmental transcutaneous pO2 in patients requiring below knee amputation. When the transcutaneous pO2 was above 40mmHg, all amputation wounds healed. At pO2 levels of below 40mmHg, the healing rate was less predictable. When the pO2 was zero, all amputations failed. Their data did not therefore identify a sharp threshold value.

Katsamouris et al (1984) confirmed this observation. They showed that although an absolute value of 40 mmHg was predictive of success, conversion of the absolute value to a transcutaneous oxygen index, by division of the value by the corresponding value obtained from the anterior chest wall, appeared to offer better discrimination. The use of the index allowed greater separation, with a threshold index for healing of 0.59, between healing and non-healing amputation groups.

Both Burgess and Katsamouris agreed that more data were necessary to establish the role of transcutaneous oxygen tension measurements for the selection of the optimal level of amputation. However, their results indicate that the technique has certain advantages. Transcutaneous p02 measurement can be made at any point in the limb of the patient. The measurements can be obtained in limbs without distal pulses or Doppler signals. Transcutaneous p02 responds rapidly to changes in local circulation. The technique is simple to perform and does not require a controlled temperature environment. Furthermore, the technique is of use in the presence of painful lesions which may exclude other methods of assessment. A point of controversy however, is whether transcutaneous p02 reflects impaired blood flow produced by the underlying arterial insufficiency. Both systemic and local factors affect percutaneous diffusion of oxygen, including skin thickness, capillary density, inflamation, oedema, and the oxygen consumption of the skin (Byrne 1984). Systemic factors which may influence transcutaneous p02 measurement are those which affect the arterial oxygen content and those that affect blood flow. Arterial oxygen content is affected by ventilation and haemoglobin concentration. Blood flow depends on cardiac output and perfusion distribution. These factors however, are unlikely to change during individual measurements.

(x) Muscle pH.

Muscle pH has been shown by Couch et al (1971) to be a sensitive index of muscle perfusion in clinical and experimental hypovolaemia. O'Donnell et al (1977) have shown that the pH of calf muscles falls with increasingly severe atherosclerotic ischaemia.

Young et al (1978) correlated healing and muscle pH in 20 patients following below knee amputation. Muscle pH was measured intra-operatively using a glass pH electrode and a pH meter. They showed that a muscle pH of above 7.0 did not correlate with the outcome of the amputation, although when the pH was below 7.0, healing was never achieved. Glinz (1970) described a series of 23 patients with ischaemia who underwent above knee or below knee amputation. In each patient the pH in three muscle groups at each of the two possible amputation levels was measured percutaneously prior to operation. Of eight below knee amputations performed as the primary operation 4 healed and 4 did not. Muscle pH values recorded in the healed group ranged from 7.28 to 7.45; those in the unhealed group from 7.03 to 7.25. Although he suggested that the muscle pH had good predictive accuracy there were too few patients for the results to reach statistical significance. Furthermore his results also show that six of eleven patients who had an above knee amputation as the primary procedure had a mean below knee pH that was higher than 7.28 but above knee amputation was judged on clinical grounds to be appropriate. Had below knee amputation been performed, healing might not have been attained, and the apparent predictive accuracy of pH measurement might have been invalidated.

In both these studies it is apparent that a below knee amputation can heal in the presence of moderate muscle ischaemia (pH 7.0-7.3). Provided underperfused muscle does not become infected, it seems the muscle atrophies and does not jeapordise the outcome.

(xi) Radioactive microspheres.

A constant component of the healing process is capillary proliferation. In 1972 Gardner et al (1972) suggested that the intra-arterial injection of radioactive microspheres could be used to measure the degree of capillary proliferation in ischaemic leg ulcers, and that this measurement could in turn be used to indicate the likelihood of spontaneous wound healing. Johnson and Patten (1977) used this technique with radio-active albumin labelled microspheres in a prospective study in 26 patients with ischaemic ulceration of the foot to assess the predictive ability of the technique with regard to spontaneous healing. There was a significant difference in the 'ulcer activity' (the uptake of the ulcerated area indicating active capillary proliferation) in those ulcers which went on to heal. This method has not been applied prospectively to select amputation level as yet.

Skin Blood Flow

(i) Introduction

There are many techniques which are available for the study of cutaneous blood flow, although much of the current knowledge relating to skin circulation has been derived from plethysmographic studies and temperature measurements directed mainly at obtaining digital blood flow, and defining the role of cutaneous blood flow in thermoregulation (Burton 1939, Goetz 1946). These methods are largely based on the concept that total digital flow reflects skin blood flow and skin temperature. This relationship between temperature and volume flow has led to the concept that the skin circulation has a heat exchanging, non nutritional role, as its potential maximal flow is well in excess of its nutritional requirements. This means that the nutritional skin blood flow of the finger can be a small fraction of the total blood flow at high flow rates, and so volume flow measurement is an insensitive indicator of nutritional blood flow. Although there are these two functionally separate flow components in the skin, the nutritional blood flow is the more important component because skin ischaemia may occur despite the potential for excessive flow rates.

The measurement of nutritional blood flow has not proved simple, mainly because it has been difficult to separate the skin flow into its relative components.

(ii) The anatomy of the microcirculation of the skin.

The blood vessels of the skin microvasculature demonstrate considerable variation in size, mural thickness, and geometrical arrangement, with many vessels in parallel or in series with each other. There are four main categories of vessels; arterioles, capillaries, venules, and arterio-venous shunts, but the definition of a particular vessel can be made only in terms of its position and function rather than its physical appearance (Weidman 1963). The nutritive vessels are the thin walled capillaries consisting of a single layer of endothelium for the effective fluid interchange between blood and tissue. The effective capillary surface area is under the control of the precapillary sphincters acting as regulators of resistance. At the efferent end of the capillary network there are the venules which with their thin walls and scant collagen content, may be indistinguishable from an exchange vessel.

Arterio-venous shunts bypass the capillary network and may exhibit considerable variation in their extent, size, and structure, depending on their location. These shunts are under thermoregulatory control and when open have the ability to redistribute large volumes of blood from the arterial to the venous circulation with significant consequences for the heat loss from the skin. These shunts contribute 'non nutritional ' flow to the skin.

Alterations in the haemodynamics of skin blood flow are influenced primarily by arteriolar and venous tone. The arterioles are the resistance vessels of the terminal vascular bed, whereas the volume flow at a given moment is determined by the venules which act as capacitance vessels. These two mechanisms are primarily responsible for controlling the continually variable blood flow and pressure which are characteristic of the nutrient capillaries. Capillary pressure is the major determinant of fluid exchange across the capillary wall, and the relationship between this pressure, the perfusion, and outflow pressures, and the relation of the pre- and post-capilary resistance is

$$\frac{Rv}{Ra}(Pa - Pc) = (Pc - Pv)$$

Where

Pa, Pc, and Pv are arterial, capillary, and venous pressures,

and

Ra and Rv are the pre- and post-capillary resistances

The pre- and post-capillary resistances are under many influences including myogenic activity and neurogenic reflexes. As there is little evidence of any consistent distribution of terminal nerve fibres in the smallest arterioles, capillaries, or venules, it seems reasonable to postulate that blood tissue hormonal factors will dominate the regulation of flow through the vascular bed

(Zweifach 1973).

In contrast, arterio-venous shunts are densely innervated and this accounts for their greater activity and autonomy of action.

This simplified concept of microvascular haemodynamics demonstrates that the nutritional requirements may be controlled despite fluctuations in arterial pressure. The autoregulatory mechanisms responsible for this control could be mediated by a deficit in nutritional supply, or by an increased concentration of waste products of metabolism. Although the ability to overcome increasing hypoperfusion is limited, the phenomena of reactive hyperaemia and local hyperthermia induced vasodilatation demonstrates a significant potential for increased flow.

Previous methods of measuring skin blood flow

The ultimate factor which determines whether or not a patient develops symptoms with arterial occlusion is the amount of blood delivered to the tissue in question, and the particular metabolic requirements of that tissue. In clinical examination of patients with peripheral arterial disease of the lower limbs, attention is primarily devoted to studying skin and muscle blood flow, as circulatory insufficiency appears to affect these tissues in the first instance.

Many methods for quantifying skin blood flow have been described, but unfortunately quantitative measurement is not easily obtained. The main problem involves separation of cutaneous blood flow from that of the underlying subcutaneous tissue, and previous techniques have all been beset with serious sources of error because of this problem.

(iii) Early methods

The heat clearance method described by Hensel (1959) has been used on the surface of the skin to estimate blood flow quantitively but was considered incapable of yielding absolute values for cutaneous blood flow (Sejrsen 1969). This is due to the high diffusibility of heat through skin, resulting in flow values which reflect both cutaneous and subcutaneous tissue perfusion (Sejrsen 1971).

Hardy and Soderstom (1938) had earlier utilised heat loss measurements from the body surface in man to estimate peripheral blood flow. This principle is fundamentally similar to that of Hensel and therefore a quantitative evaluation of skin blood flow alone is not possible for the same reasons.

A similar heat loss technique used by Stewart and Evans (1943) suffered from the same theoretical problems.

Helium uptake through the skin on the extremities and trunk was studied by Behnke and Willmon (1940). However, it was later recognised that there is a diffusion barrier to helium in the skin. This results in a serious under estimation of the cutaneous blood flow (Sejrsen 1969).

(iv) Isotope techniques for the measurement of skin blood flow

Blumgarth and Yens (1927) were the first to use a radio-isotope technique for the study of blood circulation. They measured the arm to arm circulation time after an intravenous injection of 24-NaCl dissolved in sterile water.

Studies of the circulation in the lower limbs of normal persons and of patients with obliterative atherosclerosis were originally performed by Smith and Quimby (1945; 1947), again using 24-NaCl. They were the first to apply this investigation to the study of patients who required amputation of the leg. In a crude manner they were able to determine whether conditions in a gangrenous leg would permit an amputation at calf level in preference to an amputation at thigh level.

Friedell et al (1949) used 32-Phosphorus to study the circulation in the legs of patients with peripheral vascular disease. They monitored the increase in radio-activity in the leg following an intravenous injection of 200 microcuries of 32-P (in the form of phosphoric acid or Sodium Phosphate) and were able to document greater deposits of the isotope in the distal limb of those patients with advanced atherosclerosis than in the limbs of normal young persons. It would appear that this method was not measuring actual peripheral circulation, but that the increased deposition of 32-P in the tissue was a manifestation of hypoxic capillary damage.

The major disadvantage of these early techniques however was the relatively large amounts of radioactivity to which the patients were exposed. A further problem posed by the administration of the tracer substance into the general circulation was the mathematical analysis required to extrapolate blood flow values from the saturation curves, with subtraction techniques to account for the variety of tissues with differing independent blood flows. This drawback was partially overcome by Smith and Morales (1944) by the use of radioactive Krypton, and the assumption in their analysis that the arterial concentration of the tracer remained constant, allowing the approximation of quantitative values for skin blood flow. When however the arterial curve is variable, as in the case with intravenous administration of 24-Na, mathematical analysis becomes almost hopelessly complex, and requires at best a complicated integration involving the arterial curve obtained from serial blood samples. These methods therefore could only be acceptable as a qualitative test of peripheral circulation. Further disadvantages of these techniques were the time involved for a single measurement, and the inability to demonstrate rapid serial changes in blood flow.

These difficulties were overcome in 1949 when Kety (1949) proposed that the diffusible tracer substance, instead of being administered into the general circulation, be introduced directly into the tissue whose blood flow was to be studied. The decline of radioactivity, or clearance, from the tissue will depend on and be a measure of the local circulation of that tissue. Kety's principle was soon applied in studies of peripheral vascular disease by Cooper et al (1949) who measured local muscle blood flow following intramuscular administration of 10 microcuries of 24-NaCl in a volume of 0.2 ml. The error of this technique however was considerable. According to McGirr (1952) muscle clearance data obtained by this technique were liable to vary by more than 80% in the same individual. Reese et al (1951) found even greater variation in muscle blood flow of as much as 185% using this technique. Moreover, no significant difference in resting blood flow could be established between persons with normal circulation and patients with occlusive arterial disease in the legs. However, when the studies were repeated during exercise a difference in muscle blood flow between normals and claudicants was apparent (Reese et al 1951).

Barron and Veal (1952) adopted the isotope clearance method for studies of the skin circulation.

in clinical practice in plastic surgery. Recording the disappearance of the radioactivity in a subcutaneous deposit of 24-Na in physiological saline, they found that the blood supply in 2nd and 3rd stage pedicle grafts became satisfactory within 4-10 days. In situations where the flow remained low for longer than 10 days, they were alerted to technical problems in the graft itself, for example haematoma formation at the pedicle attachment.

Walder (1958) demonstrated with 24-NaCl clearance that there was a reduced blood flow in calf muscle during exercise in patients with arterial disease in the limb and reported a prolonged post exercise hyperaemia in these patients.

Harris, Martin, and Williams (1952) used isotope clearance for the simultaneous investigation of the blood supply in the subcutaneous tissue of the hand and the interosseous muscle in the foot. Readings from these two sites were made simultaneously with two separate detectors. They were able to demonstrate a significant increase in skin clearance following body heating; no change in muscle blood flow was observed in association with body heating.

Barany (1955) investigated skin blood flow in diabetic patients using intracutaneously injected 24-Na into the skin of the heel. He established that the flow increase after blockade of the posterior tibial nerve was significantly less in diabetic patients than in normal controls.

Valdes and Pecorini (1962) used 22-Na to investigate the subcutaneous circulation in the calf in normal persons and in patients with intermittent claudication. They found that the clearance of the isotope was significantly faster in normal individuals compared to those patients with arterial disease.

Wahlberg (1965) measured the cutaneous clearance of radio-active labelled metallic compounds. He found that the clearance was influenced not only by the state of the circulation, but also by the individual chemical nature, and metabolic handling of the compounds.

(v) Inert gas clearance

In 1951 Kety reported the advantages of using inert gases, in particular Xenon, in studies of the circulation (Kety 1951). Lassen et al (1964) adapted Kety's technique of Xenon clearance for measuring the muscle blood flow in the anterior tibial compartment at rest and after ischaemic work. In contrast to the technically similar 24-Na injection method, Xenon clearance gave absolute values for local blood flow, allowing for the first time a reliable, clear cut differentiation between legs with normal circulation, and those with occlusive vascular disease.

Xenon clearance from intramuscular injected deposits became the standard technique for investigating skeletal muscle blood flow, both at rest and during exercise (Holyman et al 1962; Lindbjerg 1964; Lassen et al 1964; Tonnesen 1964). Inert gas clearance for measuring blood flow has also been applied to the heart, (Bassingthwaighte et al 1968; Herd et al 1962; Ross et al 1964), the kidney (Pomeranz et al 1968; Thorburn et al 1963) the intestine (Kampp and Lindgren 1968; Kampp et al 1968), and the brain (Lassen and Munck 1955; Harper et al 1964).

Although techniques for isotope clearance applied to the study of peripheral vascular disease were primarily directed at muscle blood flow (Lassen 1964; Lassen et al 1965; Lindbjerg 1967), other workers were developing similar methods for the determination of skin blood flow.

In 1967 the techniques originally described by Lassen et al (1964) using Xenon were modified by Sejrsen (1967 i) who studied skin blood flow by the epicutaneous diffusion of a high concentration of gaseous Xenon-133 introduced into a 1 ml reservoir beneath an adhesive polythene or mylar membrane. The Xenon was allowed to diffuse into the skin over a period of 10 minutes and the subsequent clearance measured. The advantage of this method was the avoidance of the need to introduce the isotope by injection, and thus prevent any injection artefact which may influence clearance of the isotope. Sejrsen found however that the method was not practical because of what he termed as 'subcutaneous refixation' which delayed clearance of the isotope, and required a prolonged observation period. Furthermore, because this epicutaneous technique also labels subcutaneous tissue, which has a greater affinity for Xenon than dermis due to the high lipid content of subcutaneous tissue, mathematical curve stripping techniques were required to eliminate the slow component of subcutaneous washout, thus impairing the clinical usefulness of the technique (Sejrsen 1971; Kostuik et al 1976).

Sejrsen (1967 ii) also described the use of an intracutaneous injection of a histamine/Xenon mixture in an attempt to measure skin blood flow under standardised maximal cutaneous vasodilatation.

Further work by Sejrsen (1968) uncovered some additional properties of Xenon. Although he showed that in areas of the skin where the circulation was arrested by a proximal tourniquet, the loss of 133-Xenon by diffusion back through the dermis was negligible, he found that there was a significant loss of the isotope through sweat, accounting for between 10 and 25% of the fraction cleared by blood flow under these conditions.

The actual intracutaneous technique using Xenon differs from the 24-Na method of Kety, merely in the choice of radio-active indicator. Lassen (1964) however, felt that this was of great significance; the 24-Na ion is a hydrophilic particle which does not cross cellular membranes readily. Hence one could not be certain that the 24-Na was evenly distributed within the local 'sodium space'. In contrast, 133-Xenon is lipophilic and the lipid cell membrane does not constitute a barrier to diffusion of the gas. This results in a much more even distribution of the tracer within the tissue. Where the tracer diffuses so freely between the tissue and capillary blood, diffusion equilibrium is practically maintained regardless of the rate of blood flow. For these tracers therefore, it is the rate of blood flow that is the limiting factor in the removal of the locally injected deposit ('flow limited' tracer). Small ionised tracer molecules pass on the other hand more slowly across the capillary membrane. This means that during maximal hyperaemia it is predominantly the capillary diffusion capacity (ie the permeability) which determines the rate of removal by the blood. Such tracers are thus mainly 'diffusion limited' during hyperaemia. However at the very low flow rate which may prevail in patients with peripheral vascular disease, the small ions may be assumed to reach close to diffusion equilibrium between tissue and blood. Hence in these situations, even these tracers are predominantly flow limited.

Chimoskey (1972) correlated skin blood flow measurements obtained by 133-Xenon clearance with flow measurements obtained by venous occlusion plethysmography. Twenty-five observations in fourteen subjects gave a positive correlation coefficient of 0.95. Chimoskey concluded that such positive correlation with venous occlusion plethysmography had validated the Xenon clearance technique.

Further experience with the use of subcúticular 133-Xenon was reported by Carr et al (1972) who used the technique to assess the skin blood flow before and after vascular surgery.

The distribution of 133-Xenon in various tissues has been investigated by Conn (1961), and Anderson and Ladefoged

(1967). They suggested that the increased solubility of Xenon in fat involves certain disadvantages because a high content of subcutaneous fat delays the elimination of Xenon. Under such circumstances the clearance of Xenon is complex because of multicompartmental clearance with a resultant multiexponential time/activity curve being generated, with an initial fast component and a later slower component. Tonesen and Sejrsen (1970), in a study of the clearance of 133-Xenon from muscle, concluded that the local clearance is not representative of the mean blood flow at rest, whether calculated from the initial fast component, or from the slower tail of the clearance curve. The initial slope corresponds to a flow which exceeds that directly measured from the muscle by 100 - 300%, whereas the tail of the curve of activity against time corresponds to only 40 - 80% of directly measured venous outflow from the muscle.

To calculate flow from the clearance curve it is necessary to know the tissue/blood partition coefficient, that is, the equilibrium value of the ratio of the relative concentration of the indicator in tissue and blood. A further criticism of the use of Xenon for measurement of skin blood flow is that it is not possible to extrapolate a partition coefficient for Xenon in skin from its partition coefficient in muscle. Studies of the partition coefficient of the isotope in skin have failed to confirm previous assumptions (Neilson 1972i,ii; Larsen et al 1976; Lindbjerg 1967) regarding this property, and demonstrated that the partition coefficient for Xenon in skin varies widely between individual subjects (Bjerre-Jepson et al 1982), concluding that the partition coefficient for Xenon is dependent on the fat content in subcutaneous tissue in individual subjects. The variable partition coefficient associated with Xenon may therefore explain the paradoxically high 133-Xenon clearance rates observed in patients with severe occlusive arterial disease (Ahlstrom and Westling 1971, Henricksen 1974).

In comparison to Xenon, radio-active iodine labelled antipyrine (125-I-iodoantipyrine, 125-I-IAP) clearance from the dermis is faster, and as the clearance is independent of fat content because of low lipid solubility of antipyrine, the clearance gives a more representative expression of the blood flow in areas where the fat content is high (Kovamees 1968).

Binder, Jorgensen and Neilsen (1967) used the technique to demonstrate that insulin labelled with 125-I-IAP disappeared twice as quickly from the skin on the back compared to the thigh. Munck, Anderson and Binder (1967) followed up this observation by examining the elimination rate of 125-I-IAP in the subcutaneous tissue in different parts of the body. They found different rates of clearance in different areas of the body, and explained this observation on different absorption rates due to differences in local blood flow.

The partition coefficient for 125-I-IAP in skin has been recorded in vitro, by determination of the olive oil/water solubility ratio, to range between 1.0 and 1.5 ml/g (Epstein 1958). In tissues with a low fat content such as myocardium, Krasnow (1963) reported a partition coefficient value of 1.0 ml/g. Since the fat content of the subcutaneous tissue in the calf and foot is low, the partition coefficient for antipyrine in these situations is very close to 1.0 ml/g (Bjerre-Jepson et al 1982).

Alternative radiotracers which have been used to evaluate skin blood flow in the limbs have included macroaggregated albumen particles tagged with 99m-Technetium, 201-Tl, and 133-Xenon (Tauxe et al 1970; Seigal et al 1975; Seigal and Seimsen 1978). The major disadvantages of the tagged particle methods are the need for intra-arterial injections and the comparative, rather than the quantitative, nature of the data obtained. Although 201-Tl may be given intravenously, there are similar disadvantages, in that relative changes in limb perfusion are observed rather than absolute perfusion measurements. A further limitation to these techniques is that they do not allow isolated study of the skin independent of other tissues.

Skin Blood Flow and Amputation Level Selection.

Skin blood flow measurements have been used in the past to determine amputation level. In 1973 Moore (1973) reported preliminary results using 133-Xenon clearance in an attempt to correlate the healing of below knee amputations with pre-operative skin blood flow. In 33 below knee amputations, skin blood flow on the anterior aspect of the incision was measured. The three amputations which failed to heal had the lowest blood flows, indicating at that time that skin blood flow was a promising technique for pre-operative selection of amputation level.

Subsequent use of the technique led to further reports (Moore 1974; Roon, Moore, and Goldstone 1977), and the prospective use of Xenon clearance to establish the healing potential at the below knee level. Where the flow was greater than 2.6ml/100g/min, amputation healing was observed, while a flow of less than 2.0 ml/100g/min was incompatible with amputation healing. In 1981 Moore adapted his technique for use with a gamma camera enabling measurement of multiple points simultaneously, thereby increasing accuracy, and also reducing the time taken for sequential flow determinations.

Silberstein and co-workers (1983) evaluated intracutaneous 133-Xenon using a similar technique.

Although they were able to demonstrate satisfactory healing when the flow was in excess of 2.4ml/100g/min, at flow values of less than 2.2 ml/100g/min satisfactory healing occurred in over 50% of cases.

Although these results tend to suggest that the Xenon clearance method is of value, both studies are open to a number criticisms both in study design and technique. The physico-chemical properties of Xenon, in particular its lipid solubility results in intracellular diffusion of Xenon and subsequent multicompartmental clearance. Both Moore and Silberstein calculated the skin blood flow from the initial monoexponential component of the clearance curve which may not reflect overall flow. A further methodological criticism which may have influenced the results, is the use of a partition coefficient for skin which was derived from the partition coefficient of Xenon for skeletal muscle. In view of the different lipid content in muscle and skin, such an assumption is not appropriate for skin because of its significant and variable lipid component. This criticism does not entirely invalidate the work, since as the partition coefficient is a first order function in the Kety Schmit equation, it alters the relative numerical value for blood flow. The only influence therefore that this may have is in the absolute numerical value which would alter the absolute flow value, and therefore absolute flows derived from this method cannot be compared to those derived from other methods. Certainly the flow values quoted by Moore are significantly less than the flows obtained in the current studies. This may simply be a matter of partition coefficient, but may also be related in part to relatively slower clearance of Xenon due to its lipid solubility.

Holloway and Burgess (1978) using a similar technique to Moore were unable to produce meaningful results, and concluded that the technique was incapable of providing such clear cut differentiation between healing and non healing categories as reported by Moore.

Acceptance of the Xenon clearance method for amputation level selection has not been universal owing mainly to the difficulty in interpretation of the clearance data and poor reproducibility.

HYPOTHESIS.

Of the variables which influence successful healing of an amputation, the most important are the blood supply at the amputation site, and the care with which the surgeon creates a tension free suture line so as not to compromise the blood supply to the wound post-operatively (Kacy 1982). If skin blood flow is a major determinant of subsequent amputation healing, then pre-operative measurement of skin blood flow at the proposed level of amputation should be a helpful guide in determining the chance of healing of the amputation at that particular level.

AIM

The aims of the present studies were :

1. To undertake an analysis of amputation wound healing within the context of a peripheral vascular surgical unit serving a population with a high incidence of degenerative arterial disease to establish the magnitude and nature of the problems associated with amputation wound healing

2. To validate a method to measure skin blood flow using a local isotope clearance technique in patients with peripheral vascular disease.

3. To define the relationship between skin blood flow assessed by this method with other clinical and laboratory methods for assessing severity of ischaemia.

4. To employ the method in clinical practice to study the responses of skin blood flow in patients undergoing arterial reconstruction, and to assess the effect of lumbar sympathectomy on skin blood flow.

5. To assess critically the role of Doppler ankle systolic blood pressure as a means of amputation level selection in patients with localised ischaemia in the forefoot.

6. To employ the local isotope clearance method for measuring skin blood flow in a clinical context to determine tissue viability pre-operatively in patients undergoing lower limb amputation in order to evaluate the technique as a means of amputation level selection.

CHAPTER 3.

Healing following Amputation for Peripheral Vascular Disease.

A Retrospective Analysis.

Introduction.

Distal bypass grafts have gained wide acceptance as limb salvage procedures in advanced atherosclerotic disease of the lower limb. Favourable graft patency and limb salvage rates, combined with a relatively low operative mortality rate have led to the aggressive use of femoro-popliteal and femoro-tibial grafts to preserve ischaemic limbs threatened with amputation (LoGerfo et al 1977; Naji et al 1978; Myers et al 1978). However, many arterial occlusions in the lower extremities are irredeemable, and there are many such legs that cannot be salvaged. In addition, many series report an eventual amputation rate of between 30 and 40% despite initial successful grafting (Couch et al 1977; O'Donnel et al 1977; Reichle et al 1977.).

The Department of Health statistics indicate that there were 6400 major lower limb amputations performed in the United Kingdom in 1983, the majority of these amputations due to vascular disease in a geriatric population (DHSS 1983). The figure for amputations in North America is nearer 60 000 per year with a similar prevalence in the elderly (Warren and Kihn 1968; U.S. Dept of Health 1983). The incidence of lower extremity amputation increases progressively each year and has far reaching socio-economic implications. With the cost of hospitalisation approaching £200 per day in the United Kingdom, it is incumbent upon surgeons to continue to explore means of reducing the period of hospitalisation.

Dale (1961) reported a series of amputations carried out in the previous decade. The majority of amputations in this series were carried out at the above knee level and the operative mortality was 11%. The healing rate for below knee amputations was 60%.

In 1963, Eraklis and Wheeler evaluated lower limb amputation, noting that in terms of rehabilitation, especially in older patients, the below knee procedure was the operation of choice. Stahlgren and Otteman (1965) reported a series of amputations in which 29% were below the knee; 32% of these subsequently required amputation to a higher level.

Cameron (1964) reported a 71% primary healing rate with equal numbers of amputations above and below the knee. However, all patients in this series were diabetic which undoubtedly influenced the tendency to distal amputation, but resulted in a mortality of 35%.

Warren and Kihn in 1968 evaluated 453 amputations from fourteen Veterans Administration Hospitals throughout North America; they noted that although the rate of healing for above knee amputations (64% of the procedures performed) was better than that of below knee amputations, the mortality was greater for above knee than for below knee procedures (28% versus 10.3%). Success in ambulation after operation was greater for below knee than for above knee amputees. Patients with below knee amputations also walked sooner than those with above knee amputation. (13 weeks versus 6 weeks).

Other reported series of amputations quote mortality figures ranging from 20-40% with the majority of amputations at the above knee level (Otteman and Stahlegren 1965; Eidemuller et al 1968; Siverstein and Kadish 1973).

In recent years there has been a definite trend towards more distal amputations, with a reduction in operative mortality, although significant problems with wound healing persist, particulary when the amputation is carried out at the below knee level (table 3.1). Although the literature is replete with reports of specific categories of amputation, there are only sporadic reports describing the total experience of a single department in the recent surgical literature. If the total experience of a single institution is not reported one cannot accurately evaluate the results of a

Author	BK	BK/AK ratio	Primary BK healing (%
Kendrick (1956)	51	6.3:1	63
Dale (1961)	77	0.3:1	60
Cameron (1964)	29	1.0:1	71
Burgess (1971)	157	5.6:1	26
Barnes (1976)	67	1.5:1	58
Potts (1979)	48	0.8:1	87
Finch (1980)	61	0.9:1	75
Castronuovo (1980)	50	1.4:1	77
Porter (1981)	88	1.0:1	85

Table 3.1.

The ratio of below (BK) to above knee (AK) amputation and subsequent healing rates of below knee amputations where stated in recently published papers.

single category of amputation, or the impact that improved selection methods have had on healing. For example, a high rate of successful below knee amputation healing might simply reflect the fact that more distal amputations, some of which may have healed, were not attempted. The healing rate at a specific site alone may give a false impression of the success of an amputation policy, as it takes no account of the number of amputations performed at that level in relation to the total number of amputations performed at all levels. Therefore, the evaluation of recent approaches to amputation and their results are only valid if they are presented for each category of amputation in relation to all other categories, that is, by presenting the relative numbers and healing rates for each level of amputation.

To establish the demography of the population of patients requiring amputation, and illustrate the medical and social problems that these patients present, I undertook a retrospective study of all amputations performed for ischaemia in the Department of Peripheral Vascular Surgery at Glasgow Royal Infirmary over a recent four year period. The Glasgow Royal Infirmary serves a population in the east side of the City of Glasgow where the incidence of peripheral and coronary artery disease is high. Concern with the current overall risk of amputation in terms of morbidity as well as mortality prompted this survey of current practice to establish both the nature of the problem and the need, if any, for corrective measures. In addition, an attempt was made to identify the factors which affect the immediate and long term results of an amputation in terms of morbidity and mortality.

Methods.

All patients undergoing amputations for ischaemia between 1978 and 1982 in the department of Peripheral Vascular Surgery at Glasgow Royal Infirmary were included in the study. Ischaemic rest pain with or without accompanying tissue loss, with non reconstructible vascular disease were the indications for amputation.

A total of 255 amputations were performed on 171 patients during this period, consisting of 162 single limb and 9 bilateral amputations. Numbers refer to amputations and not the number of individual patients. A patient may be entered more than once if a higher amputation on the ipselateral limb, or if an amputation on the contralateral limb was required during the period of review.

All the patients were considered for arterial reconstruction prior to amputation. Angiography was performed if indicated and reconstruction carried out where clinically and anatomically feasible. If the distribution of disease on the angiogram was considered not suitable for reconstruction, the level of amputation was selected by one of three consultant surgeons, on the basis of clinical judgement alone, with a view to obtaining primary healing at the most distal level of amputation possible. In elderly bed bound patients an above knee amputation was performed to ensure healing at the expense of limb length. Bed rest, control of diabetes when present, and the use of antibiotics and drainage to control sepsis were important aspects of treatment prior to definitive amputation. All patients were given routine antibiotic prophylaxis with penicillin (1 megaunit) and metronidazole (500 mg) given intravenously on induction of anaesthesia. Three further doses were administered in the first 24 hours post-operatively.

Amputations were classified as partial foot, below knee, and above knee. Partial foot amputations included both trans-phalangeal and trans-metatarsal amputations of one to all five toes. For partial foot amputations, incisions were kept on the dorsal surface of the foot where possible. The incisions were closed primarily unless there was clinical evidence of sepsis with cellulitis on the dorsum of the foot, in which case the wound was left open to allow free drainage. When below knee amputation was necessary, the long posterior flap method described by Bickel and Ghormley (1943), and more recently by Condon and Jordan (1970), and Burgess and Romano (1968) was used. Skin was closed using fine interrupted monofilament sutures without tension. Above knee amputations were performed with short equal length anterior and posterior skin flaps.

Primary healing was defined as healing obtained without revision, with the presence of a dry non-inflamed wound by the 14th post -operative day. Delayed healing occurred when healing was achieved at the initial level after a period of greater than 14 days, perhaps requiring surgical revision, but without progression to a higher level of amputation. Recurrence of ischaemic necrosis at the amputation site or uncontrollable sepsis were indications for revision to a more proximal level, which was defined as non-healing or amputation failure. Operative mortality was defined as death within 30 days of primary amputation.

Data are expressed as mean +/- one standard deviation unless otherwise stated. For unpaired data statistical significance was determined using the Mann Whitney U test. Values for p were calculated from the z value. When $p < 0.05$ the results were interpreted as statistically significant. For comparison between 2 groups of data, Fisher's exact test was used. Late mortality was calculated using the life table analysis method to plot the survival curve.

Results.

(i) Patient Population.

There were 96 males and 75 females. The mean age of the males was 64 years and of the females 72 years. The age and sex distribution is shown in figure 3.1. One hundred and forty four patients (82%) were cigarette smokers, and 85 (49%) had a previous history of, or biochemical evidence of diabetes mellitus. There was no significant difference in the mean age of diabetic (67.2 +/- 11.1 SD years) and non-diabetic patients (66.9 +/- 12.1 SD years; p = NS Mann Whitney).

(ii) Previous Vascular Surgery.

Angiography was performed with a view to possible limb salvage prior to amputation in 121 patients (71%). Vascular reconstruction was attempted in all cases where anatomically possible. Ninety-nine patients had had previous vascular procedures (Table 3.2). Thirty two of the procedures were performed immediately prior to amputation in an attempt to salvage the limb. In the 42 patients who had undergone sympathectomy, the wound failure rate was 19% compared to 21% in non sympathectomised patients (p = NS; Fisher's exact test). In 6 patients in whom a below knee amputation was

Figure 3.1.

Age and Sex Distribution of 171 patients undergoing amputation for end-stage peripheral vascular disease in the Glasgow Royal Infirmary.

Procedure performed	n	no. of patients wit functioning graft
Aorto-iliac reconstruction	14	12
Femoro-popliteal bypass	10	4
Femoro-tibial bypass	16	5
Embolectomy	17	2
Sympathectomy - operative	12	-
chemical	30	-

Table 3.2

Nature of vascular procedures performed on 99 patients in an attempt to salvage the limb prior to amputation.

performed immediately following a failed below knee reconstruction, there was subsequent non-healing in two patients. In these two patients the presence of the recent below knee wound was considered a contributory cause of the amputation failure.

(iii) Level of Amputation.

Table 3. 3 shows the levels at which the 225 amputations were performed.

(iv) Immediate Outcome Following Amputation.

Eleven patients (4.8%) died following amputation. The operative mortality for above knee amputation was 13.5% which was significantly higher than that for below knee amputation. ($p < 0.001$; Table 3. 4). Five of the deaths occurred in elderly bed ridden patients who underwent primary amputation at the above knee level. The cause of death in these patients was bronchopneumonia in four, with a cerebro-vascular accident in one patient. The remaining five deaths in patients after above knee amputation followed failed embolectomy. These five patients presented late with a non-viable limb.

The overall primary healing rate for all amputations was 66% with failure requiring revision to a higher level in

Level of amputation	n		no. of diabetic patients
Digit and forefoot	84	(33%)	52
Below knee	97	(38%)	24
Above knee	74	(29%)	9
Total	225	(100%)	85

Table 3.3

Site of amputation for 225 amputations and number of diabetic patients in each specific category of amputation.

Amputation level	Outcome			
	Primary healing	Delayed healing	Healing failure	Operative mortality
Digit/foot	43 (51%)	15 (18%)	26 (31%)	-
Below knee	67 (69%)	12 (13%)	17 (18%)	1
Above knee	58	3 (4%)	3 (4%)	10
Total	168	30	46	11

Table 3.4

Outcome of amputation healing, and operative mortality for forefoot, below knee, and above knee amputations

18%. Healing rates for each category of amputation are given in Table 3.4. The poor healing after partial foot amputations reflects the higher incidence of diabetes and associated infection experienced in these patients.

Several factors were evaluated to ascertain their effect on healing. No difference was noted in primary healing rates between patients over the age of 60 (64.3%) and those under 60 (67.0%). Diabetes did not significantly influence the primary healing rate with wound failure in 16.2% of diabetic and in 19.1% of non-diabetic patients. Prior arterial reconstruction did not influence the eventual healing rate.

(v) Hospital Stay.

Mean hospital stay for all patients was 45 days with a range of 2 to 180 days (Figure 3.2). The duration of hospitalisation was independent of the level of amputation with a mean hospital stay of 41 +/- 10, 42 +/- 14, and 47 +/- 14 days for foot, below knee, and above knee amputations respectively. Difficulty in mobilisation and previous failure of a more distal amputation was the major factor responsible for the prolonged stay in below knee and above knee amputation patients. In foot amputation, delay and failure of healing were the two most important factors contributing to the delayed discharge from hospital.

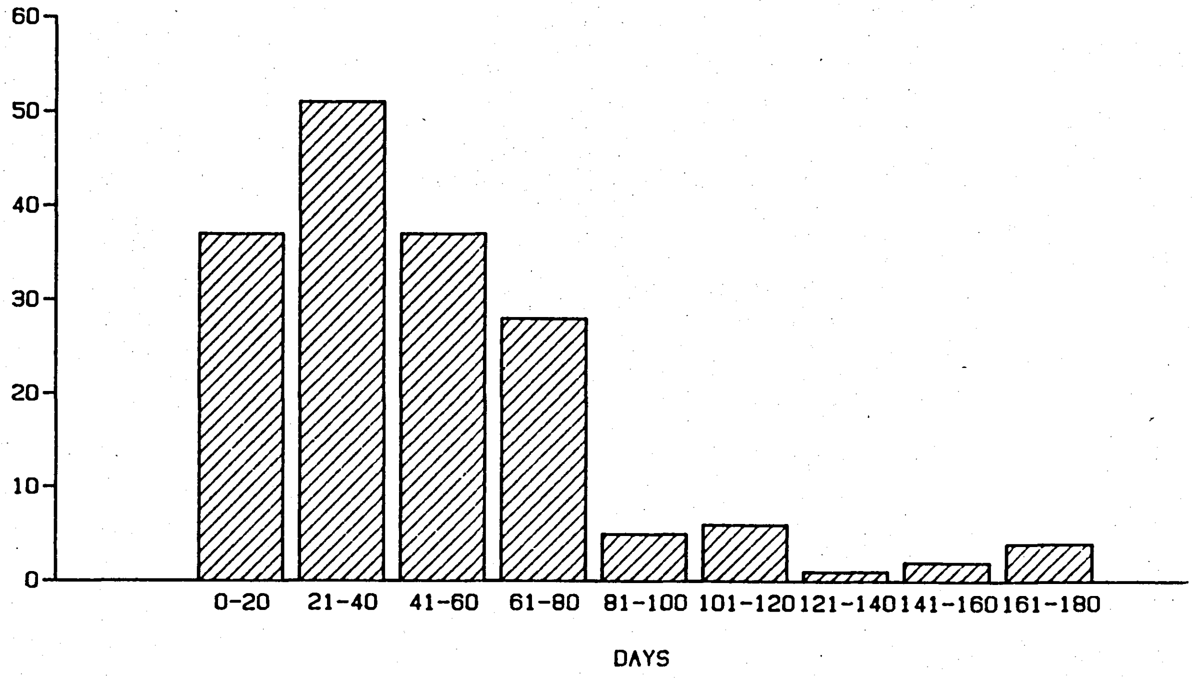

Figure 3.2.

Hospital bed occupancy of 171 patients following amputation for end-stage peripheral vascular disease in the Glasgow Royal Infirmary

(vi) Long Term Outcome Following Amputation.

Progression of disease following foot amputation was apparent in 18 of the 58 patients (31%) in that initial successful healing was followed by higher amputation at a mean period of 17.4 +/- 8.2 (sd) months. In the healed below knee amputations subsequent higher amputation was necessary in 9 of 79 patients (11%) at a mean interval of 14 +/- 7.1 (sd) months.

At one year the survival was 64%; by four years it was only 16% (Figure 3.3)

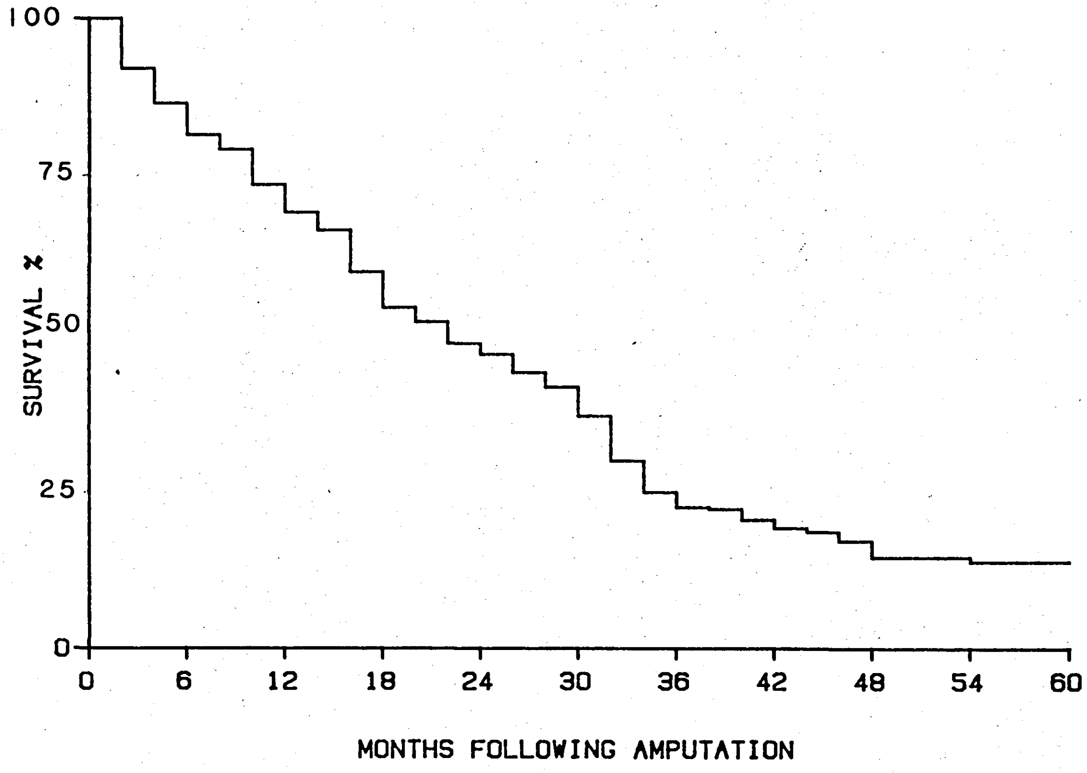

Figure 3.3.

Long term survival in 171 patients following amputation by life table analysis.

Discussion.

The interpretation of clinical results regarding amputation healing is fraught with difficulties, and an attempt to assess the outcome may be jeopardised by many variables, including different surgeons, different wound and patient management, the incidence of diabetes mellitus, and changing policies in limb salvage surgery. By evaluation of amputations at all levels, attention is focussed on the proportion of the total amputation group at each operative level. The ratio of above knee to below knee amputations, in particular the number of prosthesis free amputations (ie forefoot), and the healing rates at each level are sensitive indices of current practice. This information can be derived only by evaluating the results of all amputations, as acceptable rates of primary healing may simply reflect an unwillingness to attempt a more distal amputation.

This survey has confirmed that patients requiring lower limb amputation as a consequence of ischaemia are generally elderly with widespread vascular disease, and this is reflected in the high mortality and compromised long term survival rates. A high mortality with a direct relationship between age and mortality rate has been previously reported by Eliason and Wright (1926), Carp (1953), Dale and Jacobs (1962), and Schlitt and Serlin (1960). Otteman et al (1965) reported a hospital mortality rate of 39%. Even with modern improvemnents in anaesthetic techniques and postoperative care, Harris et al (1974) reported a hospital mortality in excess of 30%, rising to 60% in patients over the age of 80 years. This exceptionally high figure is probably related to the high incidence (68.3%) of above knee amputation in this series. Roon et al (1977) had no mortality at 30 days, although 3 patients died during a prolonged course of hospitalisation

Complications following an amputation for peripheral vascular disease are predominantly related to manifestations of vascular insufficiency, in contrast to those amputations carried out for trauma, malignancy, or deformity. The high mortality would seem at least partially attributable to a combination of age and the basic pathological entity in the patient whose vessels have deteriorated to the point of providing inadequate blood supply to an extremity. The high mortality in the above knee amputee also reflects the general state of the circulation in these patients compared to the below knee or more distal amputee. The inverse relationship between overall mortality and length of the remaining extremity has been noted by Kim et al (1976).

Holden (1947) reviewed the records of 57 above knee amputees and reported that a thigh amputation which had been preceded by an unsuccessful distal amputation was associated with an increased mortality.

Although the patient numbers in each group in the present series are too small to draw any firm conclusions in this respect, it would seem obvious that repeated failed amputation in these already demoralised patients, together with physical frailty and prolonged pain, contribute to the development of hydrostatic pneumonia which is often the principal cause of death. In addition to a high early mortality, the long term survival of patients following an amputation is limited. This once again demonstrates the widespread nature of the atherosclerosis. The major causes of late mortality are cardiovascular and cerebrovascular accidents (Browse 1973), but in addition peptic ulcer (Bouhoutsos et al 1973), and malignancy (Irvine et al 1972) are also reported to be higher in this group of patients. In most series, patients surviving after successful arterial reconstruction have a lower mortality rate than amputees (Eastcott 1973). Weaver and Marshall (1973) reported that few of their amputees were alive three years following amputation. More recently, Finch et al (1980) reported accumulated survival figures showing a 45% mortality within 2 years of amputation, with only 25% alive at four years. The present series with 84% mortality at four years confirms the expectations of limited survival in this extremely poor risk group of patients. Since the life expectancy is so limited it is important that rehabilitation of vascular amputees is as rapid as possible. In the present series the mean period of hospitalisation of 45 days was related to failure of distal amputation, and to the difficulties associated with mobilisation in patients with proximal amputations. Thus the advantages of conserving the foot and the knee joint must be balanced against the increased morbidity that will inevitably occur if primary healing of the stump is not achieved. It may be argued that when primary healing of a stump is not obtained, the level of selection was not correct. However when healing occurs by secondary intention, or following a local wedge resection,it follows that the tissues are not ischaemic. For healing to occur at the level of selection, albeit by secondary intention, sufficient local blood flow must exist (McCollum et al 1984). The failure of primary healing is also influenced by extrinsic factors such as infection, or operative technique. If these factors can be controlled, the use of a more objective method than clinical judgement may allow the surgeon to select the most distal level of amputation possible.

PART II : METHODS USED IN THE STUDY

CHAPTER 4

Method Used in Current Study.

(i) Introduction.

The choice of method used in the current study was dictated by the necessity of obtaining objective quantitative data on skin blood flow. The choice was further restricted by the need to use a method which was reliable and reproducible in patients with peripheral vascular insufficiency. As was discussed in Chapter 2, the use of radio-active isotope clearance measurements in the skin under standard conditions fulfil these requirements and are relatively simple and quick to perform.

(ii) Chemical nature and properties of 125-I-iodoantipyrine

Radio-isotopes are isotopes in which the nuclei of the atom contains either more or fewer neutrons than are present in the naturally occurring stable isotope of the element. Such nuclei are unstable and they tend in time to change into more stable configurations by various processes known collectively as radio-active decay. The primary radio-active decay process is by the emission of a charged particle (alpha, beta, or gamma), or by the capture by the nucleus of an orbital electron. These processes change the electric charge on the nucleus, thus giving a product nucleus which is chemically a different element. The product nucleus also invariably has a lower energy content than the parent radio-active nucleus, and the difference in energy appears as the energy of different types of radiations which are emitted. These radiations consist of the charged particles accompanied in many cases by electromagnetic radiation in the form of gamma-rays or X-rays.

The tracer substance used in the study was 125-iodine labelled antipyrine, 125-I-IAP, (4-iodo,2,3,-dimethyl,1-phenyl,3-pyrazolone); figure 4.1.

125-I-IAP has been used in many laboratories as a label for organ or total body water, and for the estimation of

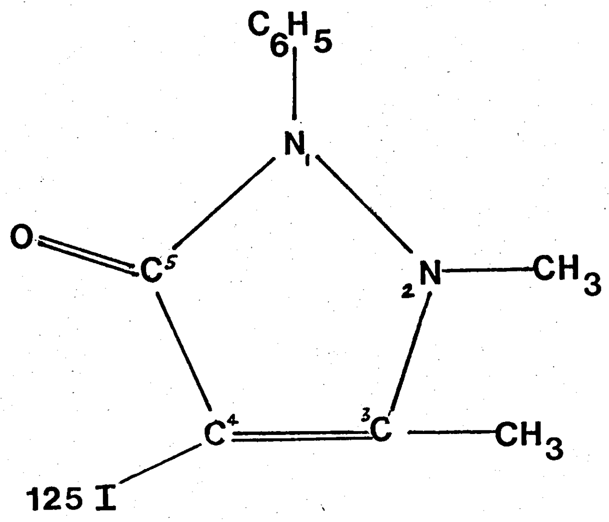

Figure 4.1.

The chemical structure of 125-I-iodoantipyrine

4-iodo.2,3-dimethyl,1-phenyl,3-pyrazole.

organ blood flow using uptake or washout techniques. As stated in the previous chapter, the advantage of radiolabelled iodoantipyrine over other freely diffusible indicators is the lack of dependence of its tissue/blood partition coefficient on tissue fat content (Lassen 1971). The radio-active moiety of this compound, Iodine 125 is produced by neutron irradiation of Xenon. The use of 125-I has certain advantages over 131-I. 125-I decays by the process of electron capture with associated low energy gamma- and X-irradiation, and unlike 131-I which is radiolytically oxidised to iodate and periodate, the radiolytic effect is much less with 125-I. Solutions of iodine 125-I can therefore be stored for some weeks in the absence of reducing agents without significant oxidation. Iodine-125 can be measured efficiently using crystal scintillation counting. The physical data on 125-I is given in Table 4.1.

125-I-IAP was obtained from the Radiochemical Centre, Amersham, UK. The isotope is supplied as a neutral aqueous solution with an initial activity of 75 microcuries/ml. Commercially prepared 125-I-IAP is not however in general use for the measurement of local blood flow because of the presence of significant quantities of free 125-I which, because of its property of restricted diffusibility, do not allow an accurate determination of local blood flow.

Half life	60 days
Type of Decay	electron capture
Gamma energy MeV	0.035 - 7%
	0.027 - 138%
Internal conversion	93%
Production process	124-Xe(n, γ) 125-Xe $\xrightarrow[18h]{\beta}$ 125-I

Internal conversion is the number of transitions between energy states

Table 4.1.

125-Iodine - Physical Data

Source: The Radiochemical Manual; The Radiochemical Centre, Amersham.

(iii) The chemical stability and purification of 125-I-IAP.

Introduction.

Munck and Andersen (1967) observed that up to 26% of the 125-I label became detached from 125-I-iodoantipyrine particularly after dilution in saline. A similar study by Lindbjerg (1967) reported that the free 131-I content of commercially produced 131-I-IAP varied from between 6 and 21%. Hope et al (1976) found that the free iodine content of a solution of 124-I-IAP greatly exceeded the manufacturers' quoted value. All the above authors found it necessary to purify the compound before clinical use by passing it through a gel filtration column. The method used for purification was similar to that described by Robinson and Lee (1976), and later modified by Forrester and colleages (1980). Applying their methods 4 mg of 4-IAP was labelled with 1 mCi 125-I with labelling efficiences of between 50 and 70% giving an average specific activity of 150 microCi/mg.

Yipintsoi, Gustafson, and Braithwaite (1971) documented that up to 22% of the activity of the sample was present as free 125-I. They also showed that the fraction of free iodine in the sample was dependent on the material of the storage container, and the nature of the diluent, being greatest for plastic containers and dilution with saline. A significant fraction of iodine which is not bound to antipyrine may cause important changes in the solubility of the indicator, thus affecting its tissue/blood partition coefficient. A further potential source of error arises on account of the different clearance rates of free 125-I and 125-I-IAP.

When 125-I-iodoantipyrine is used to measure skin blood flow it is imperative that the isotope radicle is firmly attached to the parent compound since the tissue permeability of free halides is high compared to that of antipyrine. Prior to use it was necessary to determine the radiochemical purity of 125-I-IAP following purification to remove free iodine in an ion exchange column. The presence of unbound 125-I was also tested at intervals during the use of 125-I-IAP in the study.

Methods.

The separation of bound and unbound 125-iodine in solution was performed using thin layer chromatography. Tests of purity were carried out on receipt of each vial of purified isotope, and also during the storage of the sample. Thin layer chromatography was carried out on pre-coated silica gel plates. The solvents used were either Ethyl acetate/toluene (1:1) or Chloroform/butanol (1:1).

Results.

(a) Immediately following purification.

Thin layer chromatography carried out following purification revealed a negligible concentration of free 125-I in the sample of all samples tested.

(b) During storage.

Assessments were carried at a mean time of 7 weeks following purification. Although one sample showed a concentration of 125-I of almost 20%, the mean concentration of free Iodine in the samples tested was less than 10%

Discussion.

Thin layer chromatography has been described as a satisfactory method of estimating the percentage of free iodine in 125-I-iodoantipyrine (Yipintsoi, Gustafson, and Basingthwaighte 1971). It has been shown that an increase in unbound iodine occurred with dilution in saline and with storage in plastic containers. (Yipintsoi et al 1971). In Munck and Andersons' study (Munck and Anderson 1967) the free iodine content increased to as high as 14.4% after a period of only 4 days dilution in saline.

This experiment confirms that the storage of 125-I iodoantipyrine in glass containers at 4° C does not appreciably effect the degradation of aqueous compound, even after a prolonged period. In only one sample was the concentration of free iodine in the sample significantly raised. However, because of the slow gradual degradation it is necessary to monitor the concentration of free iodine in the sample at frequent intervals.

Forrester et al (1980) showed that the stability of the 125-I iodoantipyrine was reduced by storage in temperatures of 20° C and 37° C. It is reasonable to assume that that a free iodine impurity concentration of less than 10% will not significantly affect the freely diffusible properties of the indicator 125-I iodoantipyrine.

(iv) Confirmation of Sterility of the Isotope Solution.

125-I-IAP is supplied as a non sterile aqueous solution. Prior to clinical use, the solution of the isotope was sterilised by filtration through a prefilter (Millipore type AP 2001000) and a filter (Millipore type GSWP 01300) to remove any particulate matter or bacteria.

Sterility was checked following filtration and during the shelf life of the isotope. A sample containing 0.05mls was incubated on nutrient agar broth for 48 hrs. Samples were also taken for anaerobic culture. In none of the samples was there any evidence of aerobic or anaerobic growth. Furthermore, in none of the patients studied was there any evidence of septic complications following the use of the isotope.

The filtration technique is therefore a satisfactory method of ensuring sterility of the solution, although it is probable that the level of radiation in the solution is sufficient to inhibit bacterial growth.

(v) Calculating blood flow using isotope clearance

Kety (1949) recognised that if a diffusible tracer substance, instead of being administered into the general circulation and following the subsequent saturation curve into the tissue under study, be introduced directly into the tissue in question, it is apparent that its clearance from the tissue will depend on, and be a measure of the local tissue circulation. He described a mathematical model for determining the clearance of radioactive sodium from its site of injection in a tissue.

The change in concentration (dQ) of a tracer in time dt is

$$dQ = Fa.Ca.dt - Fv.Cv.dt - Fl.Cl.dt$$

where Fa, Fv, and Fl are the arterial, venous, and lymphatic flow, and Ca, Cv, and Cl are the respective concentrations in arterial and venous blood, and lymph.

As the tracer is introduced locally, the arterial concentration is virtually zero. Therefore,

$$\frac{dQ}{dt} = -Fv.Cv - Fl.Cl$$

However, $Cv = mCs$

and $Cl = nCs$,

Where m and n are constants between 0 and 1 expressing the extent to which capillary blood and lymph come into equilibrium with the tissue concentration of the tracer (Cs)

Therefore,

$$\frac{dQ}{dt} = -Fv.mCs - Fl.nCs$$

$$= -Cs(mFv + nFl)$$

but since $Cs = \frac{Q}{S}$ (the sodium space)

then $$\frac{dQ}{dt} = - Q \frac{mFv}{s} + \frac{nFl}{s}$$

which, solved for Q

$$Q = Qo^{e-kt}$$

where Qo represents the initial amount of tracer

and $$k = \frac{mFv}{s} + \frac{nFl}{s}$$

or the sum of the effective venous blood and lymph flow per volume of extracellular water of the tissue in question.

Since Fv and Fl are both constant fractions (r, and 1-r) of Fa under any one set of physiological conditions then,

$$k = \frac{m.r.Fa + n.(1-r).Fa}{s} = Fa\theta$$

Where $$\theta = \frac{m.r + n(1-r)}{s}$$

θ therefore represents the net effectiveness of the circulation as a renewal mechanism.

If the counts per minute c1 and c2 are plotted semilogarithmetically at times t1 and t2 and a straight line drawn through the points then the slope of this line gives the value for k,

$$k = \frac{\log c1 - \log c2}{0.4343\ (t1 - t2)} = Fa\theta$$

Where k is the clearance constant for an exponential clearance and is equal to the effectiveness of the arterial circulation.

Blood flow to the skin can be generally divided into two compartments, capillary (nutritional) blood flow and blood flow short circuited through arterio-venous communications. Only the capillary blood flow is effective in providing the nutritional requirements of the skin and measurement of this parameter is therefore of value when assessing the healing potential of the skin.

Capillary blood flow can be measured by I-125-IAP clearance because IAP is a freely diffusible substance whose only mechanism for removal from an injected deposit is by passive transport across the capillary cell membrane. Diffusion equilibrium is maintained regardless of the rate of blood flow. Blood flow is therefore the limiting factor for the removal of IAP. The rate of IAP transport across the capillary cell membrane is proportional to the differential concentration (the partition coefficient) on both sides of the membrane and. therefore, directly related to the rate of blood flow through the capillary system. Capillary flow can therefore be calculated from the Kety-Schmidt equation,

$$F = \frac{100.\lambda . k}{p} \quad ml/100g/min$$

Where

F = perfusion in ml/100g/min
λ = the blood tissue partition coefficient
k = the clearance constant of the washout slope
= 0.639/t1/2
p = the specific gravity of the skin

This equation simplifies to

$$F = \frac{Logn2.\lambda. 100}{t1/2} \quad ml/100g/min$$

Where t1/2 is the half time for a complete clearance. Where the clearance is biexponential t1/2 is the faster component of the biexponential resolution of the clearance curve.

For cutaneous tissue a λ value for IAP of 1.0 is used, λ being the partition coefficient in ml/g (Epstein 1958, Krasnow 1963, Bjerr-Jepsen et al 1982).

(vi) Procedure during isotope clearance studies.

In order to achieve maximum vasodilatation and hence standardise conditions, all skin blood flow measurements were carried out in a constant temperature room with the thermostat set at 28 degrees centigrade. Thirty minutes prior to examination the subject is given 60mg of potassium iodide by mouth to block the uptake of any free 125-I by the thyroid gland. The subject lies in a supine position for 30 minutes before commencing the clearance study, to equilibrate with the high environmental temperature. The isotope I-125-IAP was used undiluted. 0.05 ml of I-125-IAP with an activity of approximately 2 microcuries was injected intracutaneously using a tuberculin syringe with 0.01ml graduations and a 25 guage hypodermic needle with a length of 25 mm and an external diameter of 0.5 mm. The exact position of the injected deposit within the skin is of crucial importance. As the thickness of the skin varies in different areas of the limb under study, a standardised injection depth with a stop guard on the needle could not be used. The following injection technique was therefore used throughout the study. The needle was inserted at an angle of 10 degrees through the skin until its tip reached the subcutaneous tissue. Thereafter, the tip was directed upwards and the needle advanced, the skin in front of the tip being depressed lightly. The needle was thus directed tangentially towards the surface of the skin until the tip was just visible within the dermis through the epidermis.

The injection was usually made 2cm from the point of puncture of the skin. On injection, a small bleb would be raised when the needle was in the correct position. On withdrawal of the needle, negative pressure was maintained on the syringe. Any blood or fluid appearing at the point of puncture was removed with a moist swab. All injections were made at standard sites on the limb. When skin blood flow and amputation healing were studied, the site of isotope injection corresponded to the proposed site of the incision used for the subsequent amputation.

The clearance of the injected intracutaneous deposit of the isotope was monitored using a 2 inch diameter collimated sodium iodide crystal scintillation detector connected to a multichannel ampliflier. The scintillation detector was held at 15 cm from the skin surface, and coupled via a pulse counting interface to a microcomputer (Cromenco Z-2D) which read the count rate at one second intervals. For monitoring purposes a chart recorder driven by the computer showed the clearance curve on a semilogarithmic scale as it was recorded. The clearance of the isotope was followed for 30 minutes after which the data were stored on floppy disk for subsequent analysis. The equipment in use is illustrated in figure 4.2.

Figure 4.2.

Equipment for measurement of radioactive isotope clearance in the temperature controlled room. A is the collimated sodium iodide scintillation detector, B is the computer with video display and keyboard, C is a multichannel amplifier, and D is a pen recorder.

For analysis the clearance curve was displayed by the computer on a video diplay in a low resolution, character position graphics format, to allow selection of the fast component of the clearance curve for calculation. Most curves showed an initial plateau whilst the injected fluid was absorbed into the tissue and partition equilibrium established. Following this initial period the clearance was essentially mono-exponential for at least two half-lifes. A slowing of the rate of the clearance sometimes became apparent towards the end of the recording period, but in these circumstances the activity at this point was often less than 10% of the initial activity.

The rate constant (k) for the mono-exponential phase of the clearance was obtained from the logarithmically transformed data by linear regression. This was multiplied by the tissue/blood partition coefficient taken to be 1 ml/g for I-125-IAP to yield blood flow expressed in units of ml/100g/min.

(vii) Consent

All subjects and patients included in the studies using radio-isotopes were informed of the nature of the study and informed consent was obtained. Approval was also sought and obtained from the hospital ethical committee. Authorisation for the adminstration of radio-active isotopes was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) in compliance with The Medicines (Radioactive Substances) Order 1978.

(vii) The temperature controlled room.

When measuring skin blood flow it is essential that any factors which may influence skin blood flow should be maintained as constant as possible. Environmental temperature has a major effect on skin blood flow, as part of the temperature regulation mechanism in mammals is dependent on heat loss through the skin by alteration in blood flow.

In order to reduce the effect of environmental temperature on skin blood flow, all measurements were performed throughout the study in a controlled temperature environment. The controlled temperature room is a purpose built room contained within the Fraser Vascular Laboratory in the University Department of Surgery of Glasgow Royal Infirmary. The room is fully insulated with a fan-assisted heating/cooling system allowing the room to be maintained at any temperature between 0 and 50 degrees centigrade. The temperature is monitored by a wall mounted thermometer and controlled by a Honeywell thermostat. The room has electricity and water supply with a sink approved for the disposal of radioactivity. The overall dimensions of the room are 3 metres by 5 metres which accommodates the subject, examination couch, and all the necessary equipment with ease.

(viii) Appearance of Skin Clearance Curves.

Analyses were made of the various components of the skin clearance curves obtained under the standard experimental conditions already described. After injection there is an initial slow phase of variable duration, usually lasting up to 4 minutes (Figure 4.3). The initial slow component may be wholly absent in areas where the clearance rate is high (Figure 4.4). This slow initial phase was assumed to correspond to the absoption phase of the injectate into the tissue and the establishment of partition equilibrium. Kovamees (1968) has shown that intradermal injection causes local initial vasoconstriction which may explain this appearance. The second phase of rapid clearance is monoexponential (Figure 4.5). After 20 minutes when the remaining radioactivity is <10% of the initial dose, there may be a slower phase (Figure 4.6). This final slow phase is unaffected by changes in flow and is related to injection artefact resulting from residual local isotope within the needle tract which is cleared at a much slower rate. When the skin is traumatised, regardless of the nature of the trauma, a reaction occurs which was described by Lewis (1927) as the triple response. There is a question as to how extensive this response is, and to what degree it affects the normal physiological function of the skin. Holloway (1980) studied the effect of injection trauma on the skin blood flow using laser Doppler velocimetry. He showed a significant increase in resting

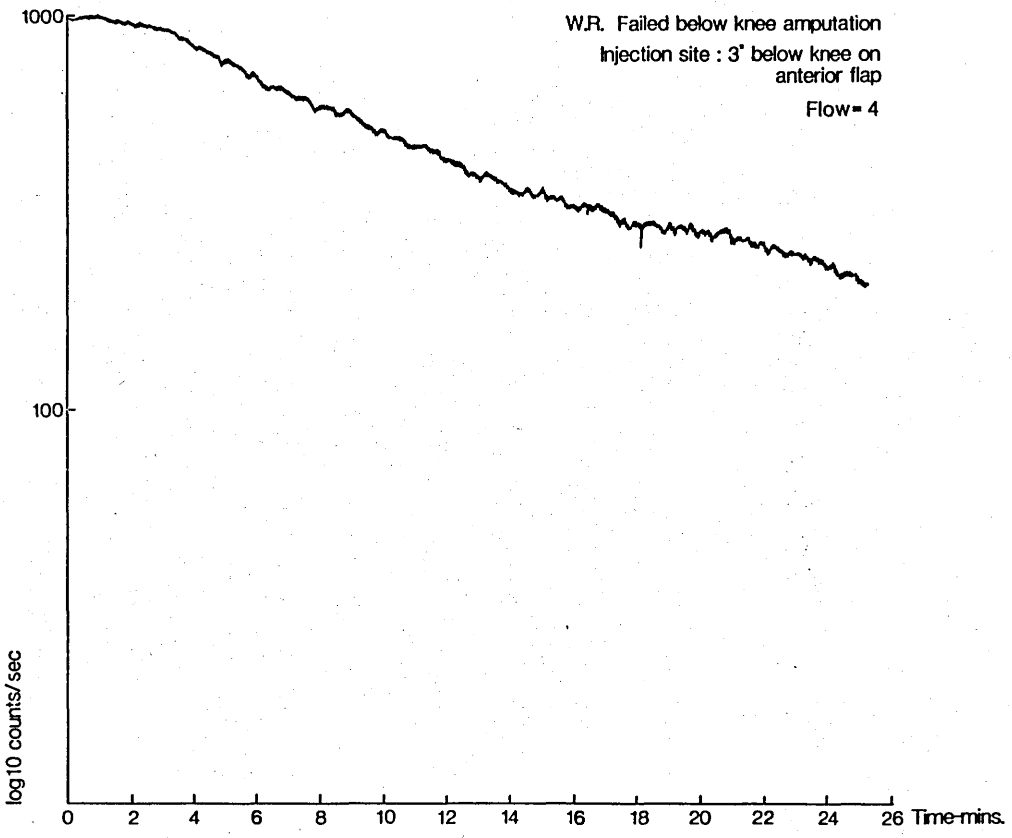

Figure 4.3.

Clearance curve for 125-I-IAP showing initial plateau.

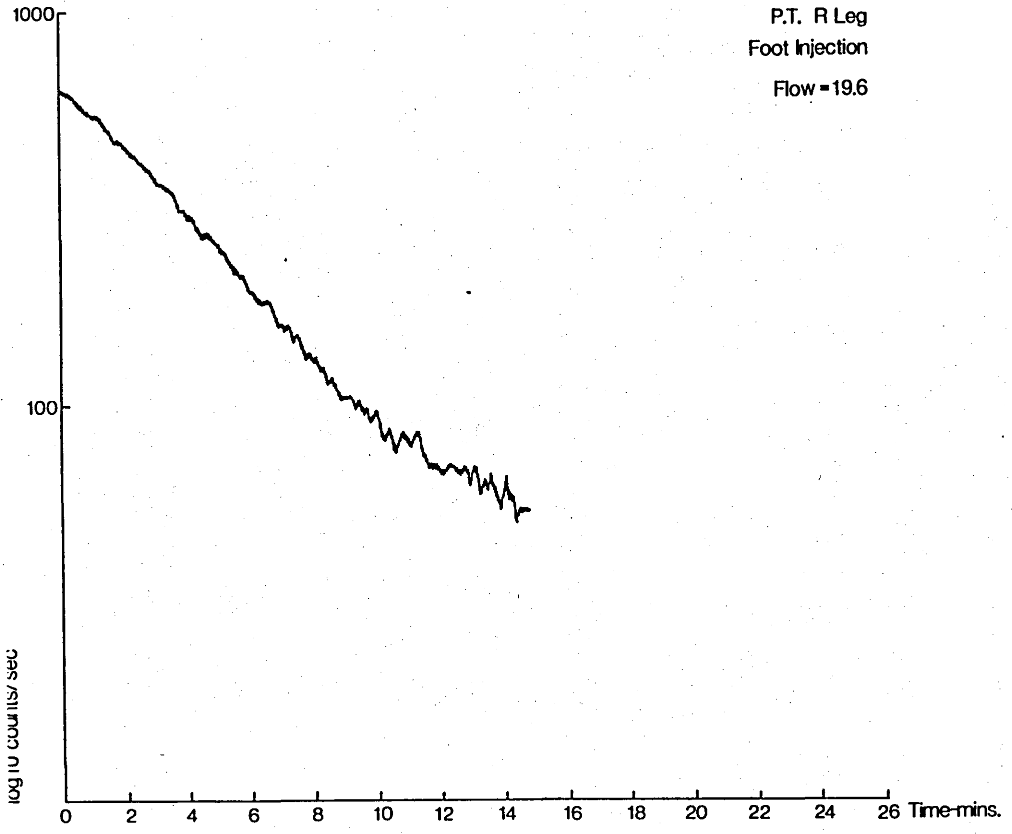

Figure 4.4.

Clearance curve for 125-I-IAP. Rapid clearance showing absence of initial plateau.

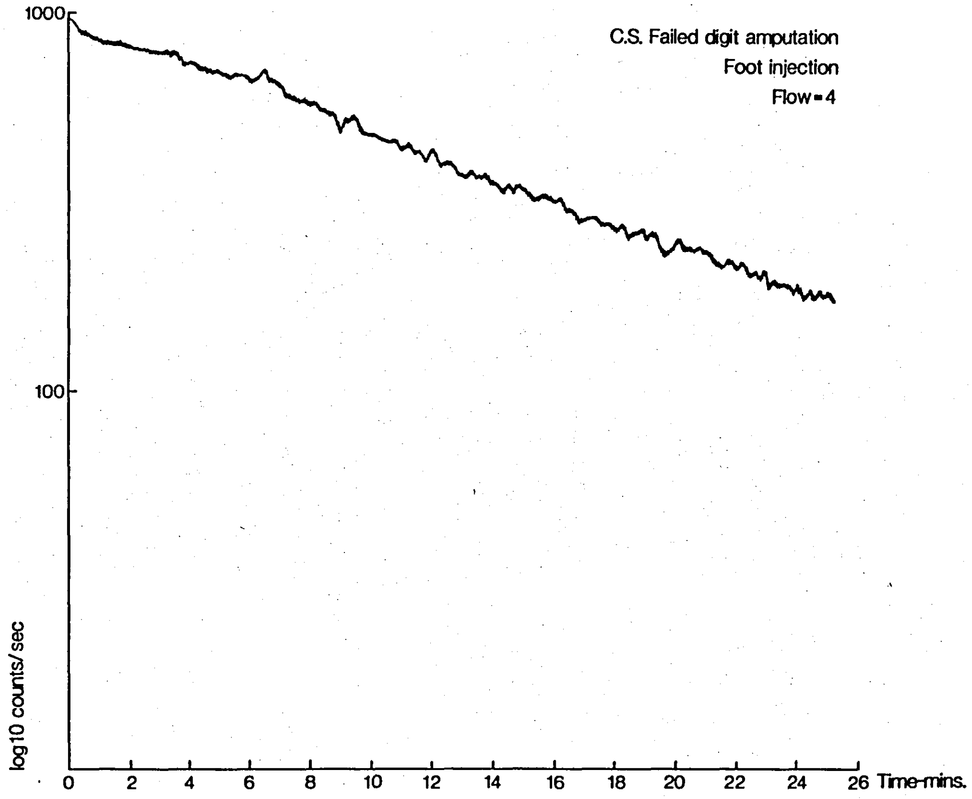

Figure 4.5.

Clearance curve for 125-I-IAP. Monoexponential clearance.

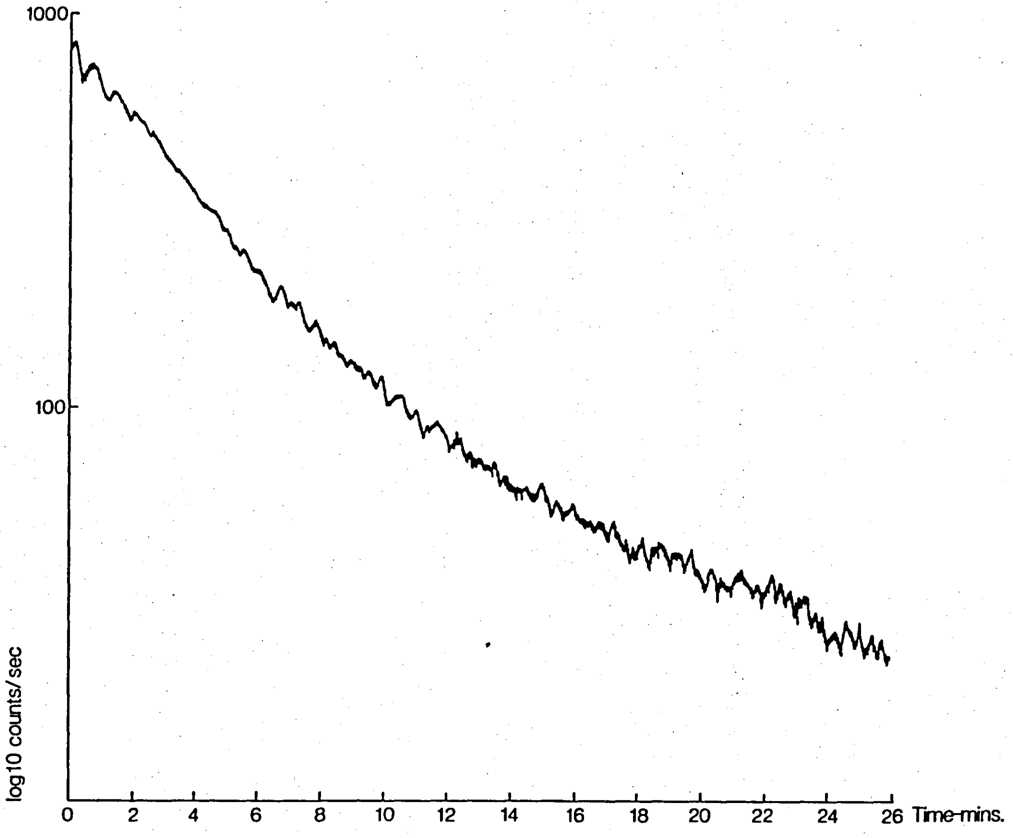

Figure 4.6. Clearance curve for 125-I-IAP. showing biphasic pattern due to decreased clearance with time resulting in a slow 'tail' phase.

injection into the skin, but these responses however were progressively less marked as baseline flow levels were increased. Throughout the studies, cogniscence was taken of the possible effect of injection trauma on skin blood flow. However, measurements were obtained at maximal flow achieved by increased environmental temperature in an effort to reduce this effect. For calculation of skin blood flow the fast monoexponential component was used in all cases as representing maximal blood flow at that point.

(ix) Statistical methods.

As for any biological measurement skin blood flow tends to be skewed in distribution. Therefore non-parametric statistical tests were used throughout the study.

A Wilcoxon matched pairs signed rank test was used for paired data, and a Mann-Whitney U test where the data were unpaired. Calculations were performed using the University Department of Surgery statistics package run on an Apple micro-computer. The p value was derived from the z score using statistical tables (Cohen and Holliday 1982). Results were interpreted as significant at $p < 0.05$, and highly significant where $p < 0.001$.

Correlation between skin blood flow and other parameters was sought using linear regression analysis with a correlation coefficient (r) derived by the method described by Moroney (1951), with data processing on an Apple Europlus computer.

CHAPTER 5

Studies on the isotope clearance method.

(i) Introduction.

Since little information is available on the reproducibility of skin clearance using 125-I-iodoantipyrine, and on variables which may influence clearance, the present study was extended to investigate certain methodological aspects of skin blood flow measurement.

The following methodological problems were investigated:

1 The reproducibility of the technique

2 The effect of perfusion pressure on clearance

3 The effect of ambient environmental temperature on skin blood flow

4 The amount and effect of background radiation and recirculation

(ii) Reproducibility

For a technique to be of clinical value it must be shown to be reproducible under similar conditions in the same subject.

Methods

The reproducibilty of 125-I-IAP clearance from the skin was investigated by repeating the examination on consecutive days in 12 limbs in 9 subjects. The subjects were chosen to include healthy control limbs (3) and limbs with symptomatic peripheral vascular disease in order to test the reproducibility over as wide a range of values as possible. In two limbs intermittent claudication was the major problem, in four limbs there was evidence of tissue loss, and in the remaining three limbs rest pain was the predominant feature. The standard protocol for measurement of clearance and skin blood flow described in Chapter 4 was followed. Clearance measurements were from the skin on the dorsum of the foot and were repeated at the same site after a period of 24 hours. Variables such as relationship to meals and time of day were maintained as standard.

Results

The results are shown in table 5.1. Run 1 and Run 2 are the skin blood flow results at the same site at 24 hr

PATIENT	LIMB	PRESENTATION	ABPI*	RUN 1	RUN 2
JT	R	NORMAL	1.1	18.2	18.4
	L	NORMAL	1.0	14.0	16.0
PC	R	CLAUDICATION	0.8	19.2	19.6
	L	NORMAL	1.0	22.1	13.9
JH	R	CLAUDICATION	0.7	12.9	7.5
	L	ULCER	0.2	9.6	9.8
RD	R	GANGRENE TOE	0.4	10.6	10.8
JC	R	GANGRENE TOE	0.3	21.0	19.7
HS	R	GANGRENE FOOT	0.0	1.5	1.0
JD	R	REST PAIN	0.2	12.8	10.9
EK	R	REST PAIN	0.0	1.8	1.0
HK	L	REST PAIN	0.2	8.1	7.3

* ABPI is the ankle brachial pressure index, the ratio of the ultrasonically derived brachial blood pressure to the higher pressure obtained in the anterior or posterior tibial arteries.

Table 5.1

Results of Reproducibility Studies

intervals. Skin blood flow for Run 1 was 12.6 +/- 6.5 (mean +/- SD) ml/100g/min, compared to a value for Run 2 of 11.2 +/- 5.9 (mean +/- SD) ml/100g/min. This difference was not statistically significant, and linear regression analysis (figure 5.1) shows a linear relationship (r = 0.908) between Runs 1 and 2.

Discussion

This experiment demonstrates that the technique is reproducible although the difficulty in obtaining two identical injections in the same individual should not be ignored. This difficulty offers an explanation for the discrepancy between Run 1 and Run 2 observed in two of the limbs during this experiment. Both of these results were obtained from individuals with flows at the upper range of normal, and may also demonstrate the great variability of skin blood flow in normal individuals.

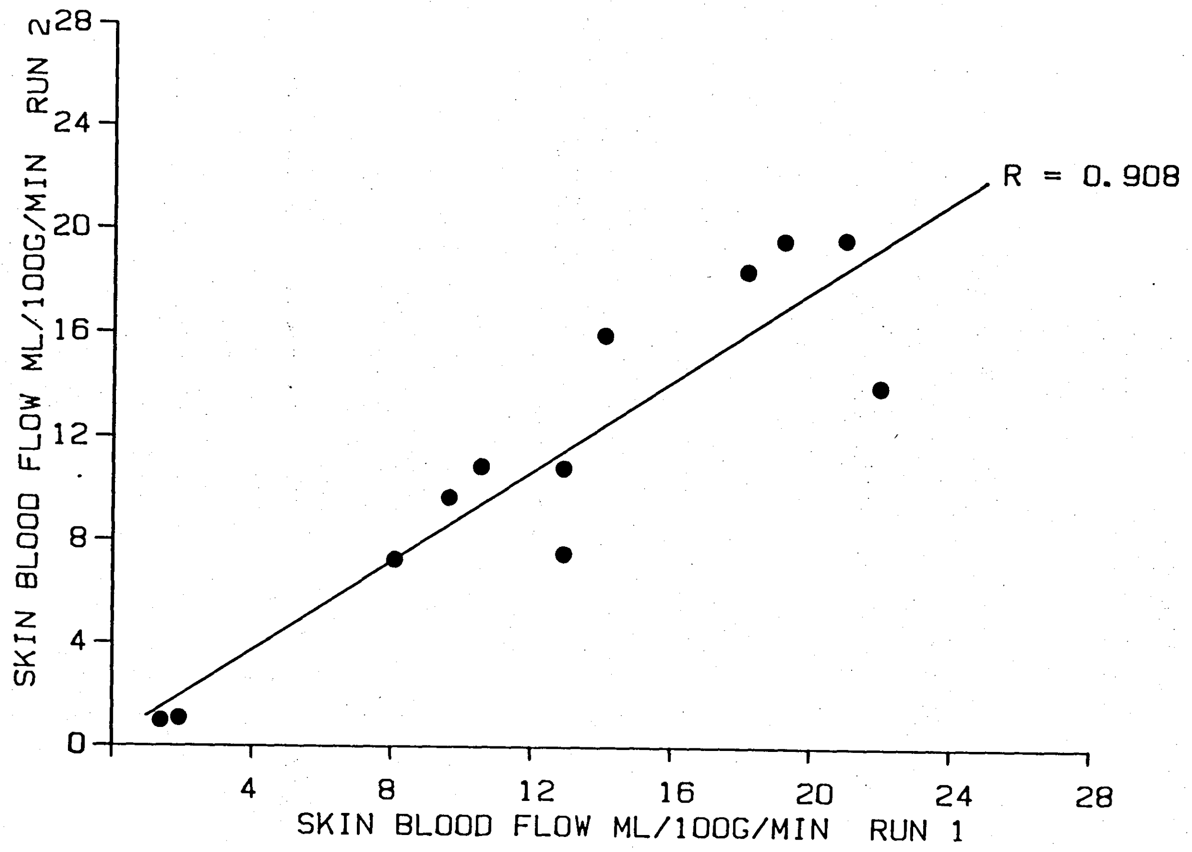

Figure 5.1.

Reproducibility of skin blood flow in patients with variable degrees of peripheral vascular disease. Clearance measurements from the dorsum of the foot (run 1) and repeated at the same site after a period of 24 hours (run 2). Correlation coefficient for runs 1 and 2 r = 0.908.

(iii) The Effect of Perfusion Pressure on Isotope Clearance.

To establish that the clearance of the isotope 125-I-IAP is dependent entirely on blood flow, a simple experiment was conducted whereby arterial pressure was occluded during clearance of the isotope.

Methods

The experiment was carried out in three individuals. Brachial systolic blood pressure was measured using a standard sphygmomanometer and the ankle systolic pressure was obtained using a sphygmomanometer and Doppler ultrasound. During the clearance phase of an intracutaneous deposit of 125-I-IAP from the dorsum of the foot, a sphygmomanometer and a pneumatic cuff around the lower third of the calf was inflated to above brachial systolic pressure. In all three individuals clearance was immediately arrested. The cuff was deflated in increments of 10mmHg to the point when clearance recommenced.

Results

Figure 5.2 illustrates the effect of inflow occlusion on clearance. It can be seen that between points A, where the cuff is inflated to systolic pressure, and point B, the pressure at which flow recommences, clearance and

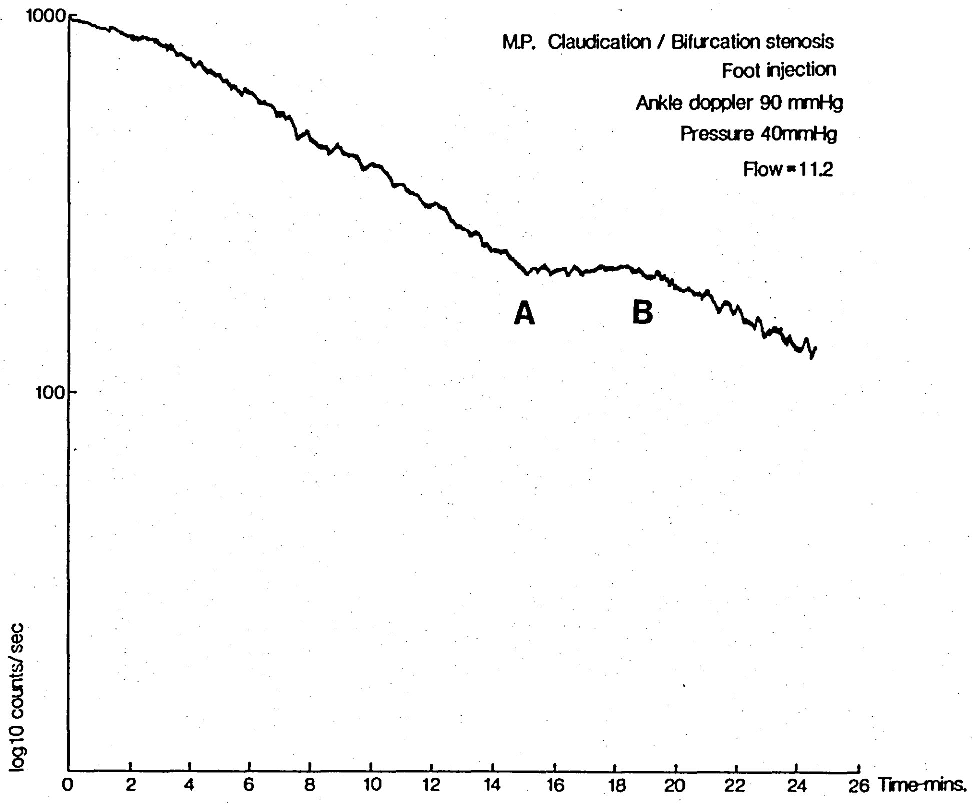

Figure 5.2.

The effect of arterial occlusion on isotope clearance. At point A cuff inflated to above arterial pressure and deflated gradually until point B where clearance recommences.

skin blood flow is arrested. Similar results were obtained in the other two individuals (Table 5.2).

Discussion

Although flow is detected in the anterior and posterior tibial arteries using the Doppler probe at a pressure of 90mmHg in the case illustrated, skin blood flow does not recommence until the pressure in the cuff is reduced to 40mmHg. This suggests that the Doppler ankle pressure so obtained is not representative of skin blood pressure in the foot. As will be discussed in a later chapter occlusive disease distal to the point at which the Doppler pressure is recorded will not be detected by this method.

PATIENT	BRACHIAL SYSTOLIC PRESSURE (mmHg)	DOPPLER ANKLE PRESSURE (mmHg)	PRESSURE A (mmHg)	PRESSURE B (mmHg)	SBF ml/100g/min
1	180	90	180	40	11.2
2	160	60	160	50	9.6
3	148	50	150	44	8.8

Table 5.2

Effect of perfusion pressure on isotope clearance and skin blood flow on the dorsum of the foot. Pressure A is equal to the systolic blood pressure and is the pressure to which the cuff placed around the leg is inflated to arrest clearance of the isotope. The cuff is gradually deflated until pressure B is reached, the cuff pressure at which clearance recommences. The skin blood flow between pressures A and B is zero. SBF is the overall skin blood flow calculated from the unarrested clearance of the isotope.

(iv) The effect of environmental temperature on skin blood flow

Methods

The influence of environmental temperature on skin blood flow was studied in four individuals by measuring the skin blood flow in the foot on three occasions at 48 hour intervals. Although the four individuals had peripheral vascular disease, the asymptomatic limb was used for this study. The initial measurements were carried out at an environmental temperature of 22° C, and subsequent assessments carried out at 28° C and 32° C. Otherwise skin blood flow was measured following the standard protocol laid out in the previous chapter.

Results

The results of this experiment are shown in table 5.3. Increasing the environmental temperature from 22° C to 28° C resulted in a significant increase in mean skin blood flow ($p = 0.034$; Wilcoxon signed rank). However a further increase in the environmental temperature to 32° C had no significant effect on mean skin blood flow ($p = 0.232$; Wilcoxon signed rank) (figure 5.3).

Patient	Skin Blood Flow		
	22°C	28°C	32°C
1	13	17	16
2	9	15	17
3	16	20	19
4	8	14	16

$p = 0.034$ $\qquad$ $p = 0.232$

NS

Table 5.3

The effect of increasing environmental temperature on skin blood flow in 4 individuals. The p values refer to the difference in mean skin blood flow at each environmental temperature.

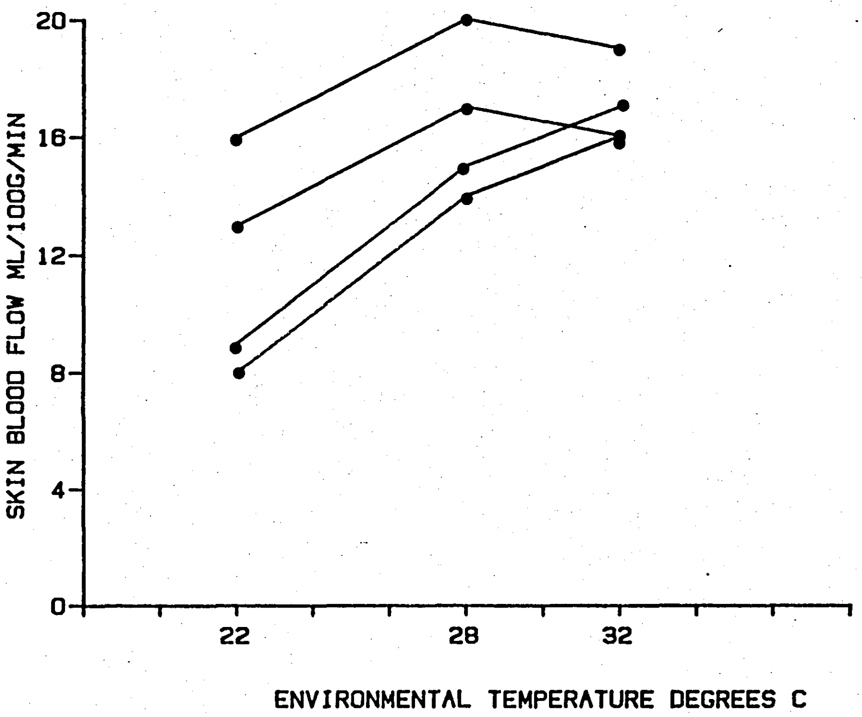

Figure 5.3.

The effect of increasing environmental temperature on skin blood flow in asymptomatic limbs in four patients.

Discussion

This experiment confirms that skin blood flow is enhanced by increasing environmental temperature but when a maximal skin blood flow is achieved a higher environmental temperature causes no further change in mean skin blood flow.

(v) Background radiation and recirculation

One of the major advantages of the local clearance technique for measuring tissue blood flow is the fact that because a small amount of radio-isotope is introduced directly into the tissue under study, the local concentration of the isotope is high while after absoption the total body dose is extremely low. There should therefore be negligible background radioactivity due to recirculation.

Methods

The amount of background radioactivity was assessed in three individuals during the clearance of the local tissue deposit. The amount of radioactivity was expressed as counts per second measured using the scintillation detector placed over the opposite limb, the trunk, the gonads, and over the thyroid gland, at the start of clearance (t = 0), at 15 minutes (t =15), and after complete clearance of the isotope (t = e)

Results

The results of this experiment are shown in table 5.4. There was no measureable radioactivity in any of the sites during, or at the completion of clearance of the isotope.

TIME	PATIENT	RADIOACTIVITY (counts per second)				
		LOCAL	CONTRA LIMB	TRUNK	GONADS	THYROID
t0	1	1021	0	0	0	0
	2	998	2	0	1	0
	3	786	0	2	2	1
t15	1	410	0	1	0	0
	2	774	2	1	0	0
	3	250	2	0	1	0
te	1	110	2	0	2	1
	2	140	3	2	0	0
	3	86	1	1	0	0

Table 5.4

Background radioactivity and recirculation

Discussion

This experiment confirms that the radiation dose to the patient is small by virtue of rapid removal of a relatively high local concentration of the tracer. The critical organ for I-125 is the thyroid gland but oral potassium iodide effectively blocks I-125 uptake by the gland.

PART III : CLINICAL APPLICATION OF SKIN BLOOD FLOW MEASUREMENT

CHAPTER 6

The Correlation between skin blood flow and symptomatic presentation, pulse pattern, Doppler ankle blood pressure, skin temperature, and angiography.

Introduction

In patients presenting with ischaemic symptoms in the limbs, attention is primarily directed at assessing muscle and skin blood flow. Unfortunately clinical assessment is only capable of providing indirect information on skin blood flow. In routine clinical practice this information is derived mainly from the severity of the patient's symptoms, the pulse pattern and the temperature of the limb, these being supplemented by Doppler ankle pressure measurement and angiography. An overall impression of the extent and severity of atherosclerosis is thus derived based on the combination of these various parameters.

The purpose of the investigations in this chapter was to examine skin blood flow in patients with impaired arterial circulation in the legs and to relate the results obtained to other clinical and laboratory criteria in the same patients.

Patients and Methods

Thirty limbs were studied in 25 patients with varying degrees of peripheral vascular disease. Symptomatic limbs were selected in 25 patients presenting with claudication (9), rest pain (8), and digital gangrene (8). In five patients, the asymptomatic contralateral limb was also studied. The patients, 14 males and 11 females, were aged 49-78 years. There were nine diabetic and 16 non-diabetic patients. Of the 30 limbs studied, 19 (16 symptomatic and 3 non-symptomatic) were from non-diabetic patients, and 11 (9 symptomatic and 3 non-symptomatic) were from diabetics.

A full detailed clinical history was obtained from all patients with regard to the presenting symptoms. Symptom categories were defined as: no symptoms; minimal claudication where claudication distance was greater than 400 metres; moderate claudication where the distance was 100-400 metres; severe claudication which was less than 100 metres; rest pain was defined as severe pain at rest relieved by dependency. Tissue loss was defined as ulceration or digital gangrene. The limb was examined with particular attention to distal palpable pulses. Doppler ankle pressure was assessed using a sphygmomanometer and cuff around the distal one-third of the leg. The cuff was inflated to above systolic pressure and the highest pressure at which flow was detected in the anterior and posterior tibial arteries, as the cuff was deflated, was recorded as the ankle Doppler pressure.

Arteriography was carried out in all patients with a view to reconstruction. Arteriograms were obtained using the femoral artery, by the Seldinger method in six patients, and by translumbar aortography in 19 patients. Severity and distribution of disease was assessed on the angiograms using a numerical scoring system. Scoring of the arteriogram was performed 'blind' without reference to the patients' symptoms, or any other available clinical material. The arterial supply of the limb was defined as six separate segments: aorto-iliac, femoral, profunda, superficial femoral, popliteal and tibial. The severity of disease was then scored at each individual segment (Table 6.1). The diameter of the arterial lumen was measured at each segment in millimetres; 'no disease' was defined when the arterial segment had no arteriographic evidence of narrowing. 'Minimal disease' was defined as irregularity of the arterial wall, or narrowing of the segment by less than 10% for a length of less than 2 cm. 'Single stenosis' was defined as narrowing of the lumen by more than 10% for a length of less than 2 cm in any arterial segment. In 'multiple stenosis' there were more than one single stenosis in any arterial segment, or the narrowed single stenosis extended for a length of greater than 2 cm in that segment of artery. 'Occlusion' was defined as total occlusion for any length in a single arterial segment. For tibial vessels the scoring system

Segment	No disease	Minimal Disease	Stenosis		Occluded
			single	multiple	
Aorto iliac	0	1	2	3	4
femoral	0	1	2	3	4
deep femoral	0	1	2	3	4
superficial femoral	0	1	2	3	4
popliteal	0	1	2	3	4

Table 6.1.

Angiography scoring system

was modified (Table 6.2).

Skin blood flow was obtained using I-125-iodoantipyrine clearance following the standard experimental protocol.

Skin temperature at an environmental temperature of 28°C. was measured using a Digitron 4702 digital thermometer (Yellow Springs Instrument Company).

Statistical significance between skin blood flows within different clinical categories was confirmed using the Mann-Whitney U test and the correlation between skin blood flow and other parameters was assessed by linear regression analysis.

Angiographic appearance	Score
no disease all 3 vessels open	0
single vessel stenosis 2 normal vessels	1
single vessel occlusion; 2 normal vessels 2 vessels stenosed; single normal vessel	2
2 vessels occluded; single normal vessel 3 vessels stenosed	3
3 vessels occluded	4

Table 6.2

Tibial and peroneal arteries: angiogram scoring system.

Results

(a) Symptomatic presentation

The relationship between skin blood flow in the foot and the symptomatic presentation in each individual limb is shown in Figure 6.1. There was no significant difference in mean skin blood flow in normal limbs and claudicant limbs (z value 0.133; p = 0.448). The difference between skin blood flow in normal limbs and in the limbs of patients with severe claudication just achieved statistical significance (z value 1.76; p = 0.039), although the numbers involved are small. There was a statistically significant difference between normal limbs and those with rest pain (z value 2.561; p = 0.0052), and a statistically significant difference between skin blood flow in normal limbs and those limbs with tissue loss (z value 2.04; p = 0.02).

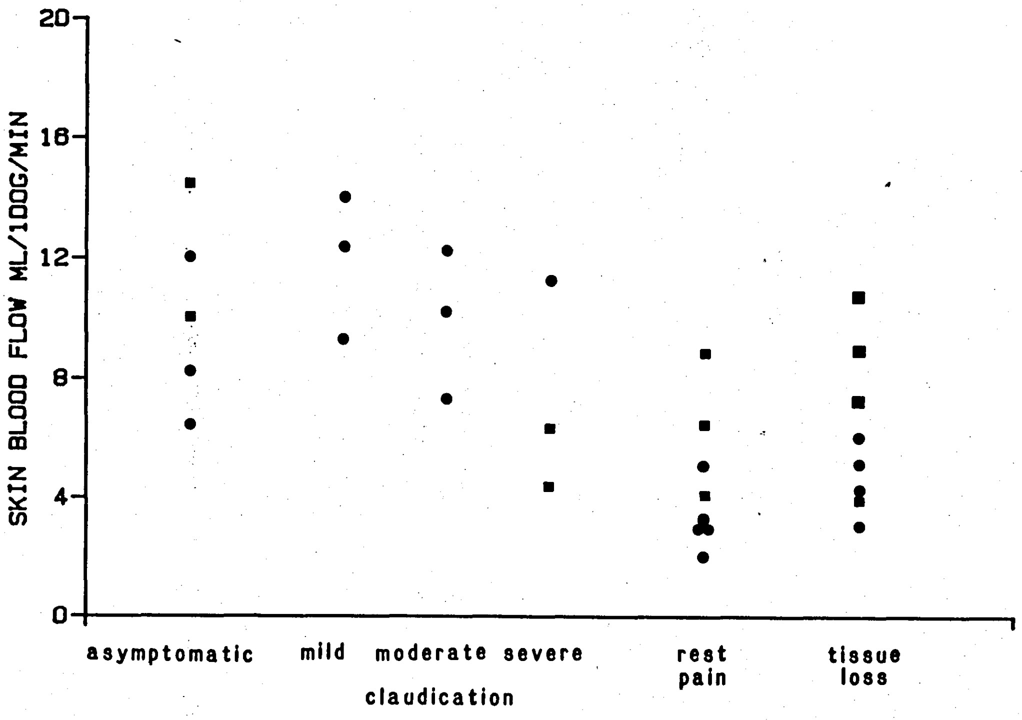

Figure 6.1.

The relationship of skin blood flow in the foot to symptomatic presentation.

■ diabetics

● non-diabetics

(b) Distal pulse

The relationship between skin blood flow and distal palpable pulse is shown in Figure 6.2. As expected, diabetic patients had predominantly distal disease. There was no significant difference in mean skin blood flow for each of the three categories of patients. Mean skin blood flow in patients where the femoral pulse was the most distal pulse, ie clinical superficial femoral occlusion was 6.1 +/- 1.17 (+/- se) ml/100g/min; mean skin blood flow where the distal pulse was the popliteal. ie in patients with infra-popliteal occlusions was 7.5 +/- 0.94 (+/- se) ml/100g/min; for patients with all pulses palpable the mean skin blood flow was 8.6 +/- 1.16 (+/- se) ml/100g/min. There was no statistical significant difference in skin blood flow in patients with palpable femoral or popliteal pulses (z value = 0.990; p = 0.161), in patients with femoral or tibial pulses (z value = 1.238; p = 0.107), or in patients with popliteal andd those with tibial pulses (z value = 0.525; p = 0.298).

(c) Doppler pressure

The relationship between Doppler ankle pressure and skin blood flow in the 30 limbs is shown in Figure 6.3. There was no correlation between skin blood flow and Doppler ankle pressure (r = 0.32). However when diabetics were excluded, the correlation in non-diabetic patients

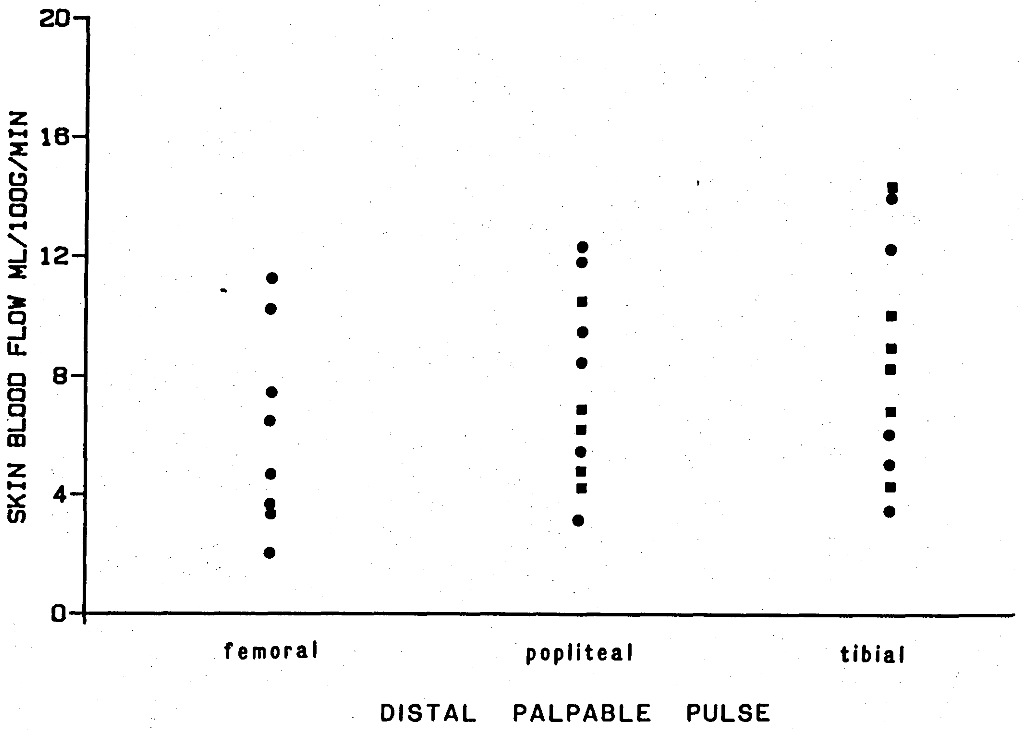

Figure 6.2.

The relationship of skin blood flow in the foot to the distal palpable pulse.

■ diabetics

● non-diabetics

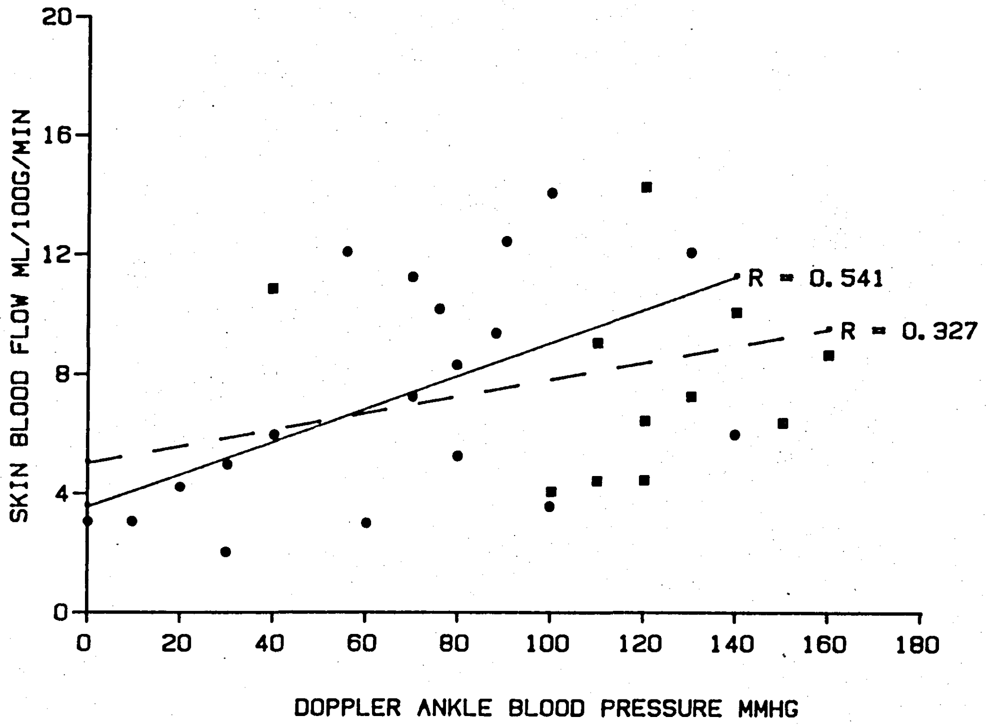

Figure 6.3.

The relationship of skin blood flow to Doppler pressure obtained in the anterior and posterior tibial arteries.

■ diabetics; ● non diabetics.

Linear regression for both diabetics and non diabetics

$y = 0.026x + 5.162$; correlation coefficient $r = 0.327$

Linear regression for non diabetics alone $y = 0.53x + 3.711$; correlation coefficient $r = 0.541$.

(r = 0.54) although this improvement did not reach statistical significance.

Skin temperature

The relationship between skin temperature on the dorsum of the foot and skin blood flow at the same site is shown in Figure 6.4. There was poor correlation between skin temperature and skin blood flow (r = 0.6).

Angiography

The relationship between angiogram score and skin blood flow is shown in Figure 6.5. There was poor correlation between the angiogram and skin blood flow (r = 0.54).

In addition, there was poor correlation between the angiogram score and Doppler (r = 0.163), the angiogram score and skin temperature (r = 0.519) and the skin temperature and Doppler pressure (r = 0.369).

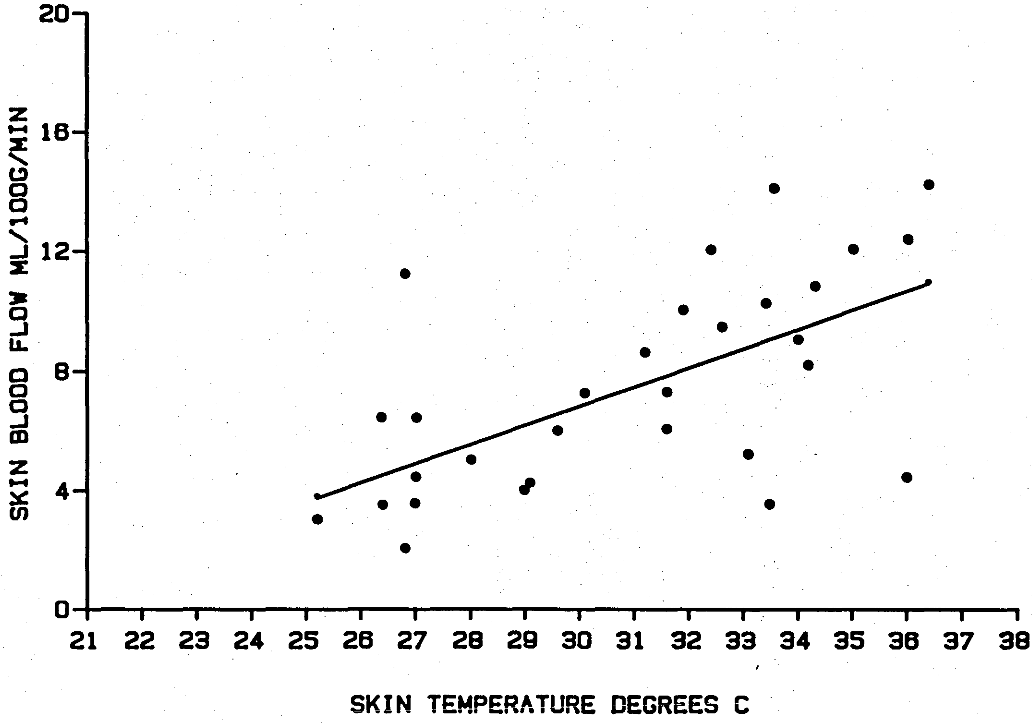

Figure 6.4.

The relationship of skin blood flow on the dorsum of the foot to surface skin temperature on the foot.

Linear regression $y = 0.639x - 12.34$;

correlation coefficient $r = 0.617$.

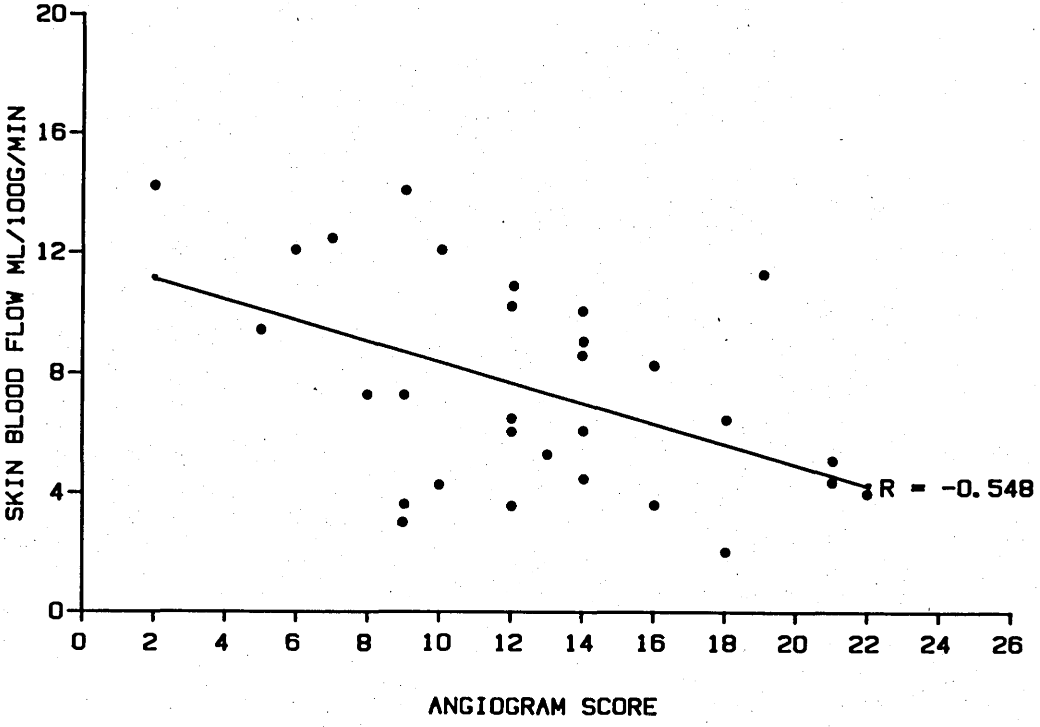

Figure 6.5.

The relationship between skin blood flow on the dorsum of the foot and the angiogram score.

Linear regression $y = -0.387x + 12.45$;

correlation coefficient $r = -0.548$

Discussion

These studies highlight some of the difficulties encountered in assessing the patient with severe peripheral vascular disease. particularly if one utilises a single test taken in isolation. Comparison of the patients own symptoms to skin blood flow in the foot revealed a significant reduction in skin blood flow in patients with severe ischaemia resulting in tissue loss but no difference in patients with claudication. Such an observation is not unexpected as claudicants may have normal muscle and skin blood flow at rest and those patients with digital gangrene and rest pain in the foot have reduced skin flow. The poor correlation between skin blood flow and distal palpable pulse, and similarly, between skin blood flow and angiogram score reflects the difficulty in assessing the functional flow in a dynamic situation from what is essentially an anatomical study. Furthermore, although the subjective interpretation of angiograms is reduced by the use of a scoring system, the scoring system is still open to a degree of observer interpretation. It is also universally accepted that angiography tends to under-estimate the degree of disease present. Furthermore, in both examination of the pulses and angiography attention is focused mainly on major vessel flow and takes no account of collateral supply which may be of great importance in the ischaemic limb. There is no doubt that angiography does not correlate either with Doppler ankle blood pressure for the same reasons. In addition, the patient with predominantly distal disease only will be assessed as having minimal disease on angiography, while the Doppler ankle pressure may be significantly reduced. Doppler ankle pressure did not correlate with skin blood flow, although the correlation improved when non-diabetic patients were studied. Once again Doppler pressure reflects pressure, and only indirectly flow within the main vessels at the level of the ankle joint, and takes no account of occlusive disease distal to this. Furthermore, where there is mural calcification within the vessel walls, failure to compress the vessel using the pneumatic cuff may give the false impression of a higher pressure within the vessel. Pre- and post-exercise ankle Doppler pressure is certainly a more relevant measure, in that it reflects the ability of the circulation to adapt to increased demands. However, as a significant number of the subjects studied had severe ischaemia with tissue loss or rest pain, exercise testing was not appropriate.

Skin temperature in the foot is highly variable and is dependent not only on main arterial flow but also on the degree of A-V shunting which may occur within the skin. Although the temperature examinations were carried out in the temperature controlled room at 28°C immediately prior to skin blood flow estimations to achieve maximal vasodilatation, arteriovenous shunting, due for example to automonic dysfunction in diabetics is impossible to quantify within the context of these experiments. The ability of isotope clearance to measure only nutritional flow, exclusively of shunting, is obviously a major advantage.

In summary these studies show that the measurement of skin blood flow by isotope clearance correlates with the severity of symptoms. None of the other parameters studied correlated well with skin blood flow mainly because they are either an anatomical assessment only, or because they provide static information in comparison to the dynamic information provided by isotope clearance.

CHAPTER 7

The effect of vascular reconstruction on skin blood flow.

Introduction

When reconstructive surgery is performed on patients with peripheral vascular disease, the primary aim of the procedure is to increase the blood supply to the extremity in question either by endarterectomy or bypass grafting. In many cases where the disease is advanced, the patient may develop ischaemic or ulcerated lesions on the foot. Pain may be a prominent feature with or without any actual tissue destruction. When surgery is performed under these circumstances the post-operative assessment is usually based on clinical observations such as the colour and warmth of the limb, the return of the pulses, and the capillary flush, as well as the subjective comments of the patient.

In chapter 5 it was demonstrated that under stable conditions skin blood flow measured by 125-I-IAP clearance remained unchanged, confirming reproducibility of the method. If the condition under which the repeat clearance is measured is altered by increasing the input via increased main vessel flow following reconstruction, then it should follow that the skin blood flow should increase also. Since the aim of surgery is to increase the amount of blood reaching the affected areas, an attempt was made to measure changes in skin blood flow in the foot following vascular reconstruction. An observed increase in the skin blood flow would add further evidence that 125-I-IAP clearance is a function of blood flow.

Methods.

Eleven limbs were studied in 10 patients before and after bypass grafting. All patients presented with severe disease with rest pain or tissue loss in all 10 patients, and severe claudication in the contralateral limb in one patient. Six patients were diabetic (60%). The clinical details, and the details concerning the type of vascular reconstruction performed is shown in table 7.1. The nature and distribution of the disease was predominantly occlusion of the aorto-iliac segment with severe superficial femoral disease in 3 patients ; aorto-femoral grafts were carried out in these patients. Femoro-popliteal grafts were performed in 4 patients because of femoro-popliteal occlusion ; in addition these patients had diffuse tibial disease with numerous infrapopliteal occlusions. Three patients had femoro-anterior tibial grafts because of popliteal and tibial occlusions.

PATIENT	SYMPTOM	DIABETES	OPERATION
CS	REST PAIN	YES	FEMORO POPLITEAL BYPASS
WM	GANGRENOUS TOE (R) CLAUDICATION (L)	NO	AORTO-BIFEMORAL GRAFT
RP	GANGRENOUS TOE	YES	FEMORO-ANTERIOR TIBIAL BYPAS
JS	GANGRENOUS TOE	YES	FEMORO-ANTERIOR TIBIAL BYPAS
MO'R	GANGRENOUS TOE	NO	AORTO-BIFEMORAL GRAFT
DMcC	GANGRENOUS TOE	YES	FEMORO-PERONEAL STEM BYPASS
LS	REST PAIN	YES	AORTO-BIFEMORAL GRAFT
GA	REST PAIN	NO	FEMORO-POPLITEAL BYPASS
NP	REST PAIN	YES	FEMORO-POPLITEAL BYPASS
JD	REST PAIN	NO	FEMORO-POPLITEAL BYPASS

Table 7.1

Clinical details and nature of procedures performed in 10 patients undergoing arterial reconstruction.

Skin blood flow was measured according to the protocol described in chapter 5. Pre-operative skin blood flow assessment was carried out on the day before surgery. Post-operative flows were carried out on the fifth post-operative day. All clearance measurements were obtained from the dorsum of the foot. In addition to skin blood flow, the result of surgery was assessed clinically by the appearance of the foot, and patency of the graft was assessed by the presence of distal palpable pulsations, or Doppler ultrasound. Differences in pre- and post-operative flows were assessed statistically by a paired t-test.

Results.

All the patients had functioning grafts when assessed on the fifth post-operative day. Mean pre-operative flows were 4.2 +/- 1.24 (mean +/- sd) ml/100g/min. Post-operative flows were significantly greater ($p<0.001$) with a mean post-operative skin blood flow of 15.1 +/- 3.5 ml/100g/min on the fifth post-operative day (Figure 7.1).

A typical pre- and post-operative clearance curve is shown on Figure 7.2.

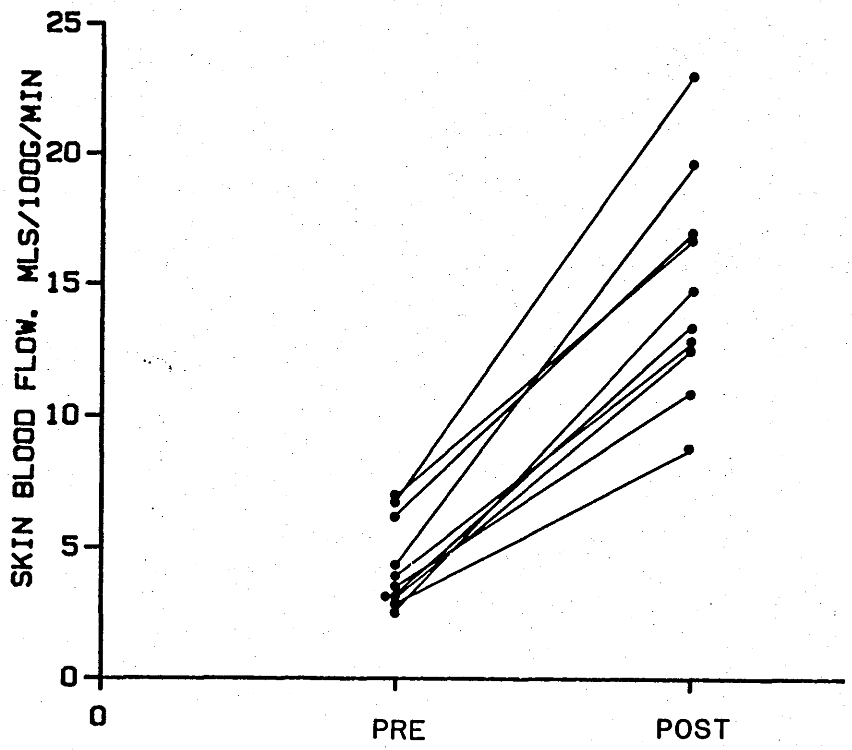

Figure 7.1.

Skin blood flow on the dorsum of the foot in 11 limbs before and after arterial reconstructive surgery.

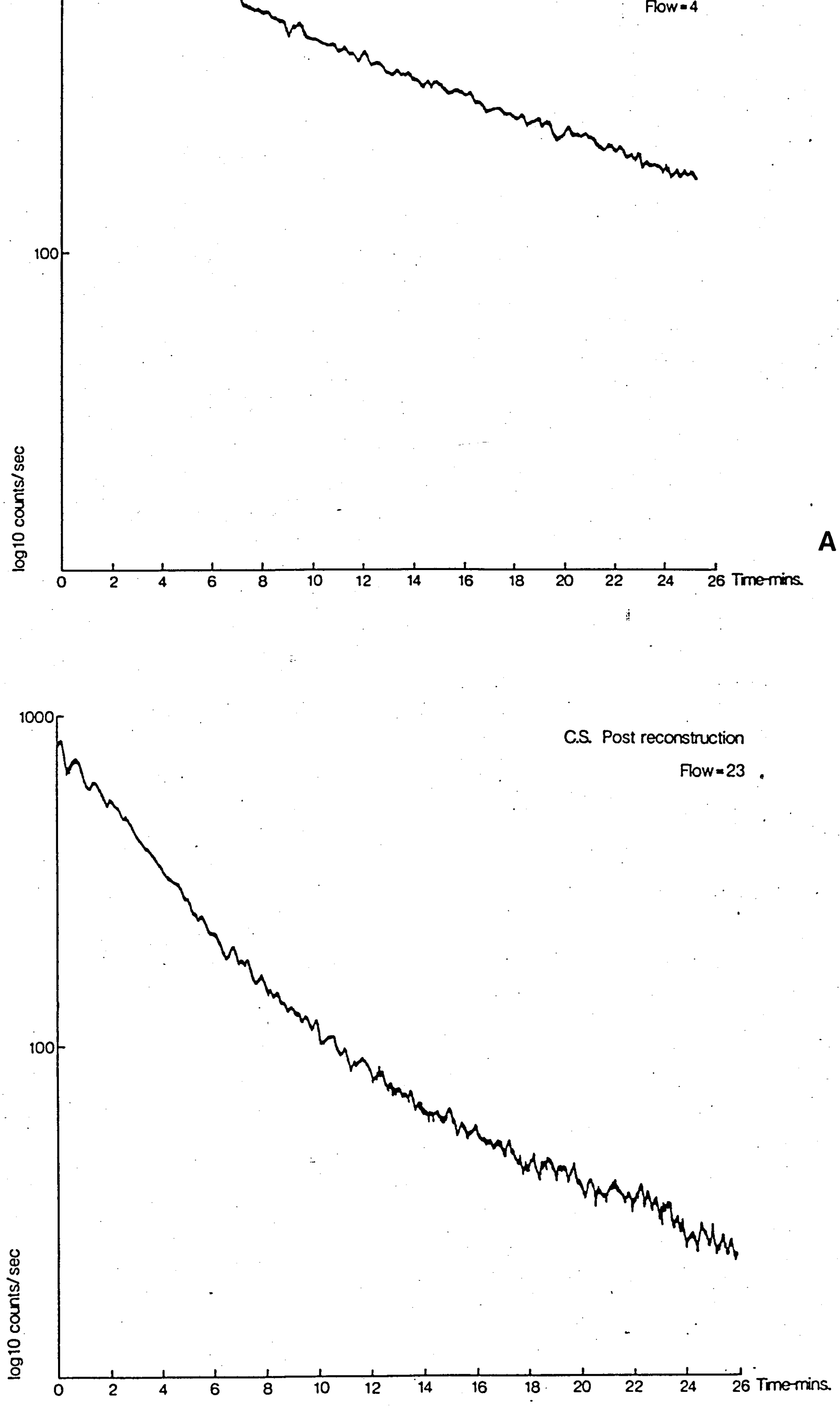

Figure 7.2.

Pre-operative (A) and post-operative (B) 125-I-iodoantipyrine clearance curves in a patient following femoral tibial vein graft.

Discussion.

If the rate of 125-I-iodoantipyrine clearance is dependent on capillary blood flow then the presented data following successful reconstruction are consistent with the hypothesis that reconstruction of ischaemic limbs by bypass grafting increases blood flow in patent capillaries.

The patients who composed the group for this study all demonstrated manifestations of severe ischaemia. In analysis of the angiographic distribution of lesions in patients with peripheral vascular disease it has been previously reported that the occlusions seen on angiography were more severe and more numerous, and occurred at multiple levels in patients with severe ischaemia when compared to those in patients with intermittent claudication (Waibel 1966; Mozersky et al 1972; Flanigan et al 1982). This was also noted in the patients in this study, with multiple level occlusions and limited run off being the predominant pattern. This accounts for the highly significant difference in skin blood flow between this group of patients and the claudicants and normal individuals reported in the previous chapters. The correlation between the clinical picture and the skin clearance data seems to support the opinion that skin clearance reflects the circulatory conditions in those atherosclerotic patients, and may be of value for the diagnosis of incipient gangrene. There was a satisfactory correlation between the clinical response following reconstruction and the post-operative skin 125-I-iodoantipyrine clearance.

CHAPTER 8.

The Effect of Lumbar Sympathectomy on Skin Blood Flow.

Introduction.

In spite of early reports documenting the relief of ischaemic pain following lumbar sympathectomy (Shaw et al 1964), experience over the past two decades has failed to define the precise role of this procedure in the management of patients with peripheral vascular disease (Plecha et al 1980). Previous studies have reported early amputation rates in excess of 40% when lumbar sympathectomy alone has been performed for attempted limb salvage (DaValle et al 1981). The results have not been materially altered with pre-operative testing to predict individual response, for in spite of an initial hyperaemia, many investigators find that sympathectomy is followed by a rapid return to normal (Dalessanor et al 1983).

The principal indication for lumbar sympathectomy is distal occlusive arterial disease that precludes arterial reconstruction because of limited or absent run off. However, the clinical role of sympathectomy has been confused by a number of conflicting reports governing its effect on cutaneous blood flow. The assumption that sympathectomy improves skin blood flow is based on observed increases in post-operative skin temperature which could be partially due to increased precapillary arterio-venous shunt flow which, as a temperature control mechanism, is under sympathetic control.

The purpose of this experiment was to use 125-I-iodoantipyrine clearance from the skin on the dorsum of the foot to assess cutaneous blood flow before and after lumbar sympathectomy in patients with severe peripheral vascular disease.

Methods.

The patients included in this study had cutaneous blood flow on the dorsal aspect of the foot measured using the standard protocol described in Chapter 4. Ten patients were studied. In 2 patients sympathectomy was performed because of prohibitive operative risk which contra-indicated formal aorto-femoral reconstruction. In the remaining 8 patients,reconstruction was not feasible due to the anatomic distribution of atherosclerosis with advanced or disseminated infra-popliteal occlusions. There was a threat to viability in the limbs of seven patients with severe claudication present in three limbs. Five of the 10 patients were diabetic.

Skin blood flow measurements were carried out on the pre-operative day and on the fifth post-operative day. In an attempt to standardise the effect of environmental

environmental conditions, factors such as time of day, relationship to meals, and other variables which may influence skin blood flow were maintained constant as far as possible. In addition to measuring the skin blood flow, pre-operative ankle Doppler pressure, and pre- and post - operative skin temperature in the foot was also measured using a Digitron electronic thermometer (Yellow Springs Instrument Co.).

Lumbar Sympathectomy was performed under general anaesthetic using an extra-peritoneal approach, with a transverse abdominal incision extending anteriorly to the lateral border of the rectus abdominus muscle. The sympathetic chain and its ganglia were identified lying anterior to the lumbar vertebrae. The third and fouth lumbar ganglia of the sympathetic chain were excised and the upper and lower ends of the remaining sympathetic chain destroyed using diathermy.

Differences in skin blood flow were assessed for statisical significance using a paired t-test.

Results.

Pre-operative Doppler ankle blood pressure in these patients is shown in figure 8.1. All the patients had absolute Doppler pressure measurements of below 40mmHg, confirming the severity of the ischaemia in this group.

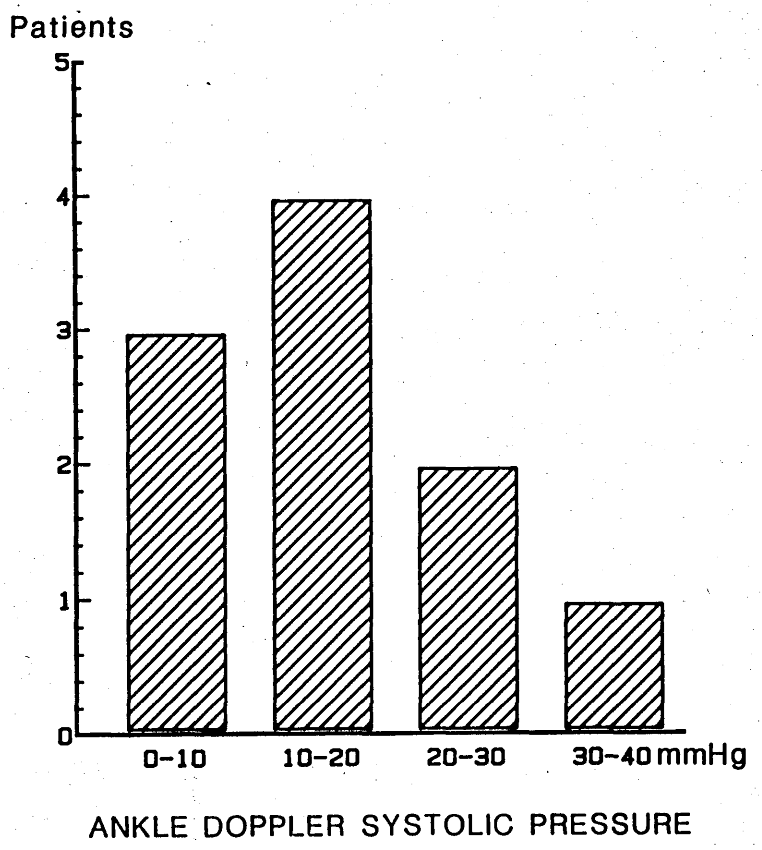

Figure 8.1.

Pre-operative Doppler ankle blood pressure in 10 patients undergoing lumbar sympathectomy.

Pre-operative skin blood flow was 7.6 +/- 2.5 (mean +/- sd) ml/100g/min. Post-operative skin blood flow was 8.1 +/- 2.8 (mean +/- sd) ml/100g/min. This did not represent a significant difference in skin blood flow between pre- and post-operative values, and was observed irrespective of whether the procedure was performed for claudication or viability threat, or in diabetics or non-diabetics. (fig 8.2)

Skin temperature increased from a mean of 28.4^{o}C to a mean of 31.2^{o}C following surgery ($p<0.01$).

The clinical outcome following sympathectomy is shown in table 8.1. Two of the three patients with tissue loss had below knee amputation performed within six months following sympathectomy. The third patient had a digital amputation which healed (SBF = 9.7 ml/100g/min). Three patients with claudication had no improvement in walking distance but noted a subjective temperature difference in the foot of the sympathectomised limb. Only the four patients who exhibited ischaemic rest pain as the predominant symptom noted an improvement in their symptoms, but this improvement was not continued with return of progressive symptoms at a period of 5 and 7 months after sympathectomy in 2 of these patients.

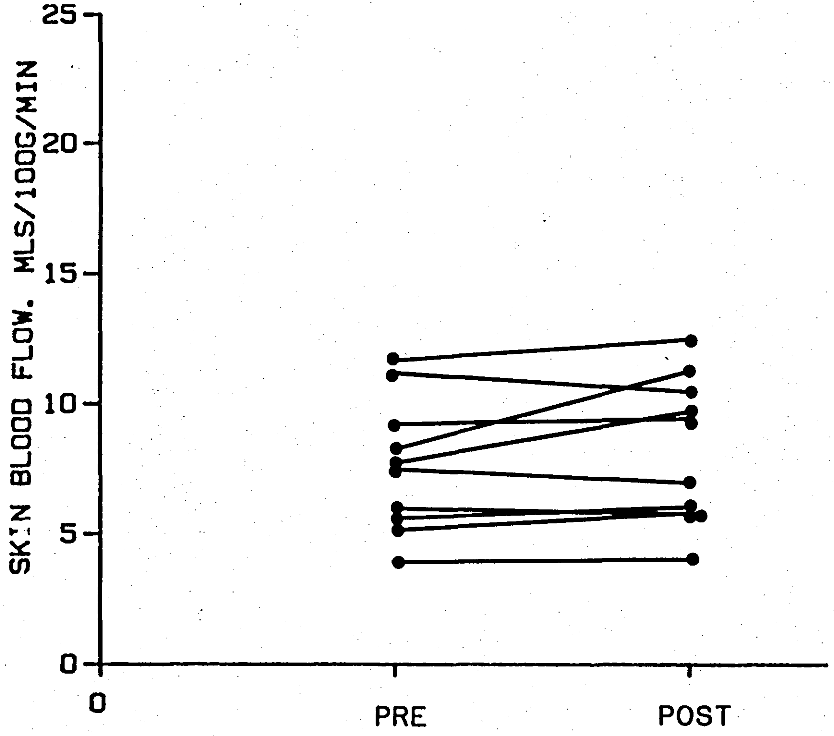

Figure 8.2.

Pre-operative and post-operative skin blood flow in patients undergoing lumbar sympathectomy.

Preoperative presentation	n	improved	amputation/level
Rest pain	4	4	-
Tissue loss	3	-	2/BK 1/Toe
Claudication	3	-	-

Table 8.1

Clinical outcome in 10 patients following lumbar sympathectomy.

Discussion.

There is little doubt that sympathectomy abolishes thermoregulatory, postural, and emotional vasoconstriction in the skin and digits of the lower extremity (De Takas and Fowler 1962). However, there is less certainty governing its effect on nutritional blood flow in the skin, and prospective clinical trials have failed to substantiate the ability of lumbar sympathectomy to heal ischaemic ulcers or alleviate ischaemic rest pain (Shumaker 1979). In a retrospective study, Kim et al (1976) reported an amputation rate in excess of 50% following sympathectomy in patients with a threat to limb viability. The variability of end stage occlusive disease, and the improvement in ischaemic ulcers after local wound care and the appropriate systemic antibiotics alone, make controlled studies difficult. Similarly progression of occlusive disease may affect the distal circulation in a manner quite independent of treatment.

The data presented in this chapter has clearly shown that there is no significant improvement in skin blood flow following sympathectomy, in contrast to the increase noted after arterial reconstruction in the previous chapter. There was however, a significant increase in skin temperature following sympathectomy.

There is general agreement concerning the effect of sympathectomy on muscle blood flow. Fyfe and Quin (1975), in a controlled clinical trial of sympathectomy in intermittent claudication, were unable to report any significant clinical benefit in terms of relief of claudication. Hoffman and Jepson (1968) using Xenon-133 clearance to assess muscle blood flow were unable to demonstrate increased muscle blood flow after sympathectomy. Perry and Morton (1978) studied muscle oxygen tension following sympathectomy, and they concluded that there was no increase in oxygen delivery to the muscle mediated by sympathectomy.

The same however is not true regarding the effect of sympathectomy on skin blood flow. Hermann et al (1970) demonstrated increased radioactive sodium clearance from the skin following sympathectomy. Morrice and his colleages (1975), in a study using xenon 133 clearance to measure skin blood flow, demonstrated a mean increase of 71% in skin blood flow in claudicants after sympathectomy. Similarly, Moore and Hall (1973) reported increased Xenon clearance after sympathectomy. However, Uhrenholdt et al (1971), using Xenon clearance, noted that the capillary blood flow decreased by 26% in patients with chronic gangrene of several toes, while increases of 30% were noted in patients with intermittent claudication. The interpretation of these findings was that all patients had increased arterio-venous shunt flow with unchanged capillary flow in those with severe ischaemia, consequent to low inflow perfusion pressure, offering an explanation for the variable response to sympathectomy depending on disease status. The interpretation of the present data, where the inflow pressure was judged by the ankle Doppler pressure, would tend to support this conclusion.

In addition to isotope clearance, other techniques have been applied to measure skin capillary blood flow after sympathectomy. Delaney and Scorpino (1973) used labelled microspheres in a canine model, and were unable to demonstrate increased skin blood flow after sympathectomy. Cronenwett (1977), using similar techniques with radioactive microspheres, reported no improvement in cutaneous blood flow, despite significant increases in total limb blood flow which were subsequently interpreted by the same authors (Cronenwett 1983) as being due to increased arterio-venous shunt flow. If the overall increase in flow is due to increased arterio-venous shunt flow it cannot be interpreted as being of clinical benefit as shunt flow is non-nutritional.

In the present study, patients with ischaemic rest pain responded to sympathectomy independent of a change in skin blood flow. This clinical response may simply be associated with the relief of cold feet and the disappearance of the burning pain which constitutes the one subjective result of sympathectomy which is consistenly appreciated by the patient. Although the majority of authors (de Takas 1975) do not believe that afferent sensory fibres exist in the sympathetic nervous system serving the extremities, Freeman et al (1950) showed in animal experiments over 30 years ago, that afferent fibres enter the central nervous system via peripheral sympathetic nerves and the sympathetic ganglia. The relief of ischaemic pain in the feet after sympathectomy may be due to a mechanism identical to that occurring in causalgia. Sensory nerve endings damaged by ischaemia may be 'cross stimulated' by intact sensory efferent fibres, or expressed differently, an artificial synapse occurs at the level of nerve injury, which permits efferent sympathetic stimuli to evoke the burning pain. This concept may explain the relief of ischaemic rest pain by adequate sympathetic denervation.

PART IV : THE USE OF ISOTOPE CLEARANCE AND SKIN BLOOD FLOW TO DETERMINE AMPUTATION LEVEL.

CHAPTER 9

Failure of Doppler Ankle Pressure to Predict Amputation Healing in the Forefoot.

Introduction.

In Chapter 2 the use of Doppler ultrasound for the selection of amputation level was discussed. Doppler ultrasound pressure at the ankle is an easily performed examination, causes no discomfort, and may be performed at the bedside. For these reasons Doppler ultrasound pressure has gained wide acceptance as a measure of the severity of peripheral vascular disease. However, when applied to the selection of the appropriate level of amputation, Doppler ultrasound has failed to define a precise value which corresponds to tissue viability and discriminates accurately between healing and non-healing. The principal role of Doppler in this context has been to select patients with localised digital ischaemic lesions suitable for conservative digital and forefoot amputation. Carter (1973) reported that foot and toe ulceration would not heal if the ankle pressure was less than 55mmHg but other investigators have failed to confirm this critical pressure (Verta et al 1976).

The aim of the work presented in this chapter was to assess critically the relationship of Doppler ankle pressure and healing in a group of patients requiring digital and forefoot amputations.

Methods.

Fifty patients with peripheral vascular disease requiring digital and forefoot amputations were included in the study. All the patients had predominant ischaemic changes confined to the forefoot, with non-healing ischaemic ulceration in 22 patients, impending or established gangrene in one or more toes in 26 patients, and non-healing of a previous digital amputation in 2 patients. There were 29 males and 21 females whose mean age was 61 (range 46 - 72). Forty amputations were performed at the mid transmetatarsal level, including 19 formal transmetatarsal amputations of the forefoot, and 21 transmetatarsal amputations of one to three toes. The remaining 10 patients had amputations performed distal to the transmetatarsal level. Thirty-four (68%) of the patients were diabetic. There was evidence of pre-operative infection, judged either by the presence of a flare extending onto the dorsum of the foot, or by positive swab culture in ulcerated areas in 18 patients (36%).

Twelve patients had previous vascular surgery; three patients had previous aorto-femoral reconstruction; nine had prior femoral distal bypass, five to the popliteal artery and four to vessels distal to the popliteal.

Grafts were functioning at the time of amputation in eleven patients.

Doppler ankle blood pressure measurement.

Pre-operative Doppler ankle blood pressure (DABP) using the method described by Yoa et al (1969), was performed in all patients using a sphygmomanometer and a pneumatic cuff applied around the lower one third of the calf. The pressure at which a Doppler signal was detected in the anterior and posterior tibial arteries as the cuff was deflated was recorded as the DABP. It was then possible to separate the patients into three groups on the basis of the pre-operative DABP :

Group 1. DABP $<$ 40 mmHg
Group 2. DABP $=$ 40 - 60 mmHg
Group 3. DABP $>$ 60 mmHg

Selection of Ampuation Level

Clinical evaluation consisted of determining the presence or absence of pedal pulses, the apparent level of ischaemia, and the extent of gangrene, ulceration, or infection. Selection of patients suitable for forefoot amputation was made solely according to clinical criteria. Patients with localised gangrene or ulceration in the forefoot distal to the transmetatarsal level were considered suitable for inclusion in the study. The presence of dependent rubor, or infection proximal to the site of amputation were considered contra-indications to transmetatarsal amputation. Infection, or the presence of a flare onto the dorsum of the foot was not considered a contra-indication, provided these appearances were localised distal to the proposed level of amputation. Drainage of abscesses and control of infection with the use of the appropriate systemic antibiotic, and debridement of necrotic tissue, were important aspects of treatment prior to definitive amputation. The surgery was carried out by vascular surgeons with particular attention to haemostasis and the avoidance of trauma to the skin edges. Skin closure was with loosely approximated polypropylene sutures (32 patients), or when it was felt that suturing should be avoided, with adhesive strips (6 patients). In 12 patients, because of the presence of infection, the skin wound was left open and delayed closure performed.

Primary healing was defined as a clean dry wound by the 14th post-operative day. Delayed healing was defined as a wound which required continued dressings, perhaps with revision but without the need for progression to a higher level, with healing by granulation eventually possible at the original level. Failure of healing or non-healing was defined as the necessity to revise the amputation to a higher level, because of progressive ischaemia or uncontrollable sepsis, or when it became necessary to attempt further reconstruction to heal an ischaemic wound.

Doppler ankle blood pressure data are expressed as mean +/- standard error for each group, as well as for healed, non-healed, diabetic, and non-diabetic categories. Healing rate is expressed as the percentage of amputations performed. Apparent differences were assessed for statistical significance using Student's t test, chi squared, or Mann Whitney tests where appropriate. For comparison of more than two groups of data, one way analysis of variance was performed to confirm differences between groups.

Results.

Thirty six of the fifty amputations (72%) healed successfully. Healing was possible in 73% of diabetics compared to 69% of non-diabetic patients. This did not represent a significant difference ($p>0.05$) between the healing rate in diabetic and non-diabetic patients.

Mean DABP in patients with healed and non -healed amputations, and in diabetics and non-diabetics is shown in Table 9.1. These differences were not statistically significant, and one way analysis of the variance between each of the categories in figure 9.1 revealed no significant difference.

PATIENT GROUP	MEAN DABP (+/- se, mmHg)		
	Pre op	Healed	Non-healed
All amputations	-	89 +/- 8	91 +/- 12
Diabetics	89 +/- 9	91 +/- 7	83 +/- 10
Non-Diabetics	92 +/- 15	86 +/- 9	106 +/- 20

Table 9.1.

Doppler ankle blood pressure (DABP) before amputation in diabetic and non-diabetic patients; healed and non-healed groups.

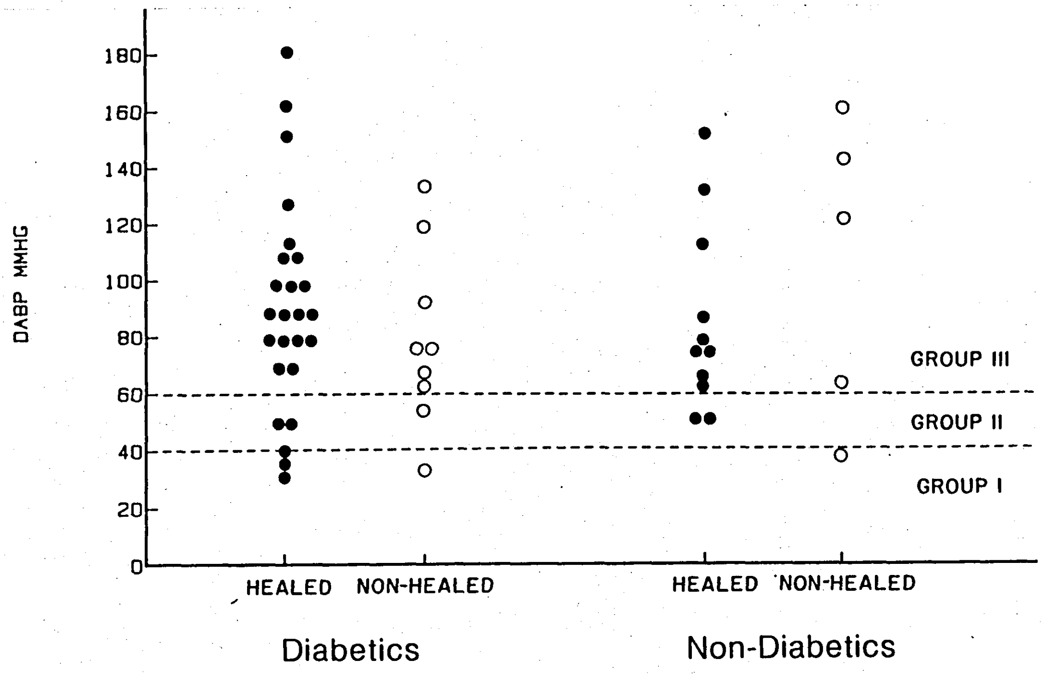

Figure 9.1.

Outcome following forefoot amputation in diabetic and non-diabetic patients relative to pre-operative Doppler ankle blood pressure.

Three of five amputations (60%) healed in group 1 (DABP <40mmHg), four of five (80%) healed in group 2 (DABP = 40-60mmHg), and twenty nine of forty amputations (72%) healed in group 3 (DABP > 60mmHg) (Figure 9.1). Eleven of the fourteen non-healed amputations had DABP in excess of 60mmHg.

In eight of the non-healed amputations, sepsis appeared to be a significant factor causing healing failure. Of thirty six successful amputations, four demonstrated delayed healing, primarily due to infection. Of these twelve patients in whom infection was considered to be a factor causing delay or failure of amputation healing, there had been evidence of infection pre-operatively in 9 patients.

Twelve of the fourteen failed amputations required revision to the below knee level, while in two diabetic patients reconstruction was attempted following amputation, because of non-healing due to ischaemia. Both of these patients had femoro-anterior tibial grafts with successful limb salvage in one of the patients; the other patient subsequently required a below knee amputation because of early graft failure. Of the thirty six patients with amputations which healed, six patients subsequently died after a mean period of 22 months following amputation; two of these patients required below knee amputations at 12 and 14 months following the initial forefoot amputation. Of the 30 patients surviving following successful primary amputation, 4 patients had evidence of progressive ischaemia and have required below knee amputation at 14, 24, 28, and 30 months respectively. Twenty-six patients have amputations which have remained healed and are fully ambulatory.

Discussion.

Transmetatarsal and partial foot amputations provide an excellent functional result in those patients with ischaemia sufficiently localised to allow primary healing. However, because of the nature of the underlying disease, some instances of wound failure and incomplete wound healing will occur. A major objective of non-invasive testing has been to identify those patients with sufficient foot perfusion compatible with healing at this level. If it were possible to fulfil this objective, then the number of wound failures could be reduced, and it might allow one to consider a conservative amputation in circumstances which, on clinical grounds alone, would be thought unfavourable. Although the clinical judgement of an experienced surgeon remains important, acknowledged difficulties in subjective clinical assessment results in failure of up to 40% of forefoot amputations. (Nicholas et al 1982; Porter et al 1981; Malone et al 1979). The overall healing rate of 72% based solely on clinical criteria achieved in this study compares favourably with that reported by others (Young 1977), and demonstrates that by focusing attention on a problem in a prospective study, that results are improved (cf. primary healing rate for distal amputations in Chapter 3).

The use of ankle Doppler pressure has been most widely employed as a simple haemodynamic index, although there has been no consensus on the minimal perfusion pressure associated with healing. Verta et al (1976) reported that in the absence of invasive infection, perfusion pressure was the single most important factor related to the outcome following amputation. They concluded that attempts at salvage of the foot by transmetatarsal amputation were futile if the Doppler pressure at the ankle was less than 35mmHg. Carter (1973) suggested that the minimum pressure required for healing was 55mmHg. Baker and Barnes (1977) reported that the minimum pressure for healing of forefoot amputation in their experience was 60mmHg. These discrepancies suggest that ankle systolic pressure does not provide a reliable end point which can be used with certainty to determine the risk of healing failure. At pressures of less than 60mmHg the patient is often experiencing ischaemic rest pain as a result of low perfusion, and it is likely that many of the patients who fall into this category are preselectd on clinical grounds for a higher amputation. However, there remains a small number who would be considered suitable for local amputation at such low pressures. Data from the present series suggest that the acceptance of a minimal perfusion pressure is a poor guide to the subsequent healing of forefoot amputations. Although the numbers are small, amputations healed in three of the five patients with pressures of less than 40mmHg, while it was noted that a pressure in excess of 60mmHg gave no assurance of successful healing. This was found not only in diabetics but also in non-diabetic patients, and the relationship between pressure and healing was not influenced by the presence or absence of pre-operative infection. The ankle systolic pressure provides only an indirect index of the skin perfusion, and takes no account of the patency of the pedal arch. Thus, the presence of distal small vessel occlusion may compromise the healing of a minor amputation despite a satisfactory pressure at the ankle. Doppler pressure values are further limited by non compressible vessels due to mural calcification which is particularly common in diabetics (Gibbons et al 1979), and result in a false impression of the true pressure.

In conclusion therefore, ankle Doppler pressure does not provide a reliable index of healing of forefoot amputations in both diabetic and non-diabetic patients. Transmetatarsal amputation should not be denied to a patient solely on the basis of a low ankle pressure.

CHAPTER 10

The Use of Skin Blood Flow to Determine Amputation Level.

Introduction

In previous chapters the need for a reliable method for measuring skin blood flow in a number of clinical situations has been established. This is particularly so in the selection of the appropriate level of amputation in patients with end stage ischaemia. A method which could accurately predict the appropriate level of amputation by minimising healing failures would shorten the recovery time for this group of patients and so reduce the time spent in hospital. Furthermore, as successful rehabilitation depends on conserving limb length, the quality of life that these patients may expect can be improved by increasing their independency by performing the most distal amputation possible.

Although the status of the arterial circulation is a major determinant of amputation wound healing, attempts at assessing the arterial circulation indirectly by assessing the skin colour,temperature, the pulse pattern, and the arteriographic patterns of disease, have not been reliable in predicting subsequent successful primary healing (DeCossart et al 1983). Nor has operative wound edge bleeding been shown to be of value when compared to wound healing (Kihn et al 1972). Primary healing rates following amputation with level selection based solely on clinical criteria have ranged from 55% to 85% with bias towards more proximal amputations at the above knee level in those achieving high rates of primary healing (Barnes et al 1976, Castroneova et al 1980, Porter et al 1981).

In recent years the plethora of laboratory investigations which clinicians have used to supplement clinical judgement when assessing amputation level is testimony to the fact that these techniques have failed to provide a reliable, simple test which provides a specific end point which can determine pre-operatively the chances of successful healing at a given level. Furthermore, attention using these techniques has been directed mainly at obtaining below knee amputation, while only few reports have addressed the problem of obtaining healing following amputation in the foot in those situations where ischaemia is localised to the toes or forefoot. If it were possible to define an absolute value above which healing could be predicted with certainty, then one could confidently perform primary amputation with high expectation of successful healing in these situations, and thus avoid the need for invasive investigation, reserving angiography for those patients identified as falling below the necessary value required for healing.

It has been established that the clearance technique is relatively simple to perform, and provides an immediate and reproducible indicator of local perfusion which is flow dependent (Chapters 4,5). The aim of the present chapter is to apply the technique pre-operatively at the site of the proposed amputation, and to relate the subsequent amputation healing to the pre-operative skin blood flow, to determine whether it is possible to identify a critical minimum skin blood flow compatible with healing.

Methods.

Eighty patients were studied. All had end stage non reconstructible vascular disease requiring amputation, or localised ischaemia in the forefoot where it was felt justified to attempt local amputation.

Measurement of skin blood flow was carried out on the day prior to surgery. The protocol described in the previous chapters for the measurement of skin blood flow using 125-I-iodoantipyrine clearance was followed throughout. Skin blood flow was measured at the site of the proposed amputation, which was selected for each patient by an independent clinician without access to the skin blood flow measurements. The level of amputation was assessed purely on clinical grounds, based on the appearance of the limb, the extent of ischaemia, the warmth and the pulse pattern. In addition, Doppler ankle pressure measurements were performed in those patients requiring foot amputations, but were not available to the surgeon, and were therefore not used for determining amputation level.

There were 49 men and 31 women of mean age 65 (range 45 - 78). Forty-two patients were diabetic.

Of the 80 patients 50 had partial foot or digital amputations, 21 had below knee amputations, and 9 had above knee amputation. Amputation healing was defined as primary, delayed or failed using the criteria defined in the previous chapter (Chapter 9).

The results are expressed as mean +/- standard error for individual healing categories and the significance of the results were defined statistically using the Mann-Whitney U test where appropriate.

Results

Primary healing rates were similar for above knee (66.6%), below knee (66.6%), and partial foot (64.0%) amputations. No significant differences in outcome could be attributed to differences in the patients' sex, or the presence of diabetes. There was a statistically significant increase ($p<0.05$) in the incidence of infection and necrosis at the amputation site, and the need for subsequent revision in younger (<60 years) than in older patients (>60 years). Pre-operative infection was associated with a 36% incidence of post-operative stump infection, compared to a 7% incidence in those patients without pre-operative infection, but because of relatively small numbers, this difference was not statistically significant.

Amputation healing and skin blood flow is summarised in table 10.1. Of the 80 patients studied, primary healing occurred in 52 patients (65%) with mean skin blood flow at the amputation site for this group of 12.1 +/- 0.6 (se) ml/100g/min. One or more wound complications occurred in 28 patients, with delayed healing in 9 (11.3%) and failure of healing in 19 (23.7%). Mean skin blood flow at the site of amputation in patients with failed healing was 5.8 +/- 1.0 (se) ml/100g/min. There was a statistically significant difference between primary healing and non-healing groups (z value = 5.364; $p<0.0003$), and between primary healing and delayed healing

Skin blood flow (mean +/- se) ml/100g/min.

	Primary healing	Delayed healing	Failed healing
Foot n	13.6 +/- 0.7 32	4.3 +/- 1.1 3	6.4 +/- 1.2 15
Below knee n	9.3 +/- 0.7 14	5.2 +/- 0.9 3	3.5 +/- 0.8 4
Above knee n	10.6 +/- 1.0 6	6.2 +/- 0.7 3	-
All n	12.1 +/- 0.6 52	5.3 +/- 0.5 9	5.8 +/- 1.0 19

Table 10.1.

Skin blood flow data relative to wound healing in 80 patients undergoing lower limb amputation.

groups (z value = 4.372; p <0.0003). There was no statistical difference between delayed healing and non-healing groups however (z value = 0.147; p = 0.4443). (figure 10.1)

Digital and partial foot amputations.

In 50 patients the ischaemic changes were sufficiently localised to allow digital or partial foot amputation. Of these patients, 32 had primary amputation healing, with failure in 15. Pre-operative foot skin blood flow in healed digital and forefoot amputations was 13.6 +/- 0.7 (SE) ml/100g/min which was statistically different (z value = 4.701; p < 0.0003) from non-healing amputations, where the skin blood flow was 6.4 +/- 1.2 (SE) ml/100g/min (figure 10.2)

Below knee amputations

At the below knee level primary healing was achieved in 14 patients whose pre-operative skin blood flow was 9.3 +/- 0.7 ml/100g/min (mean +/- SE). In 4 patients the amputation wound did not heal at the below knee level. Pre-operative skin blood flow in this group was 3.5 +/- 0.8 ml/100g/min (mean +/- SE) (figure 10.3). These differences were statistically significant (z value = 2.700; p = 0.0035).

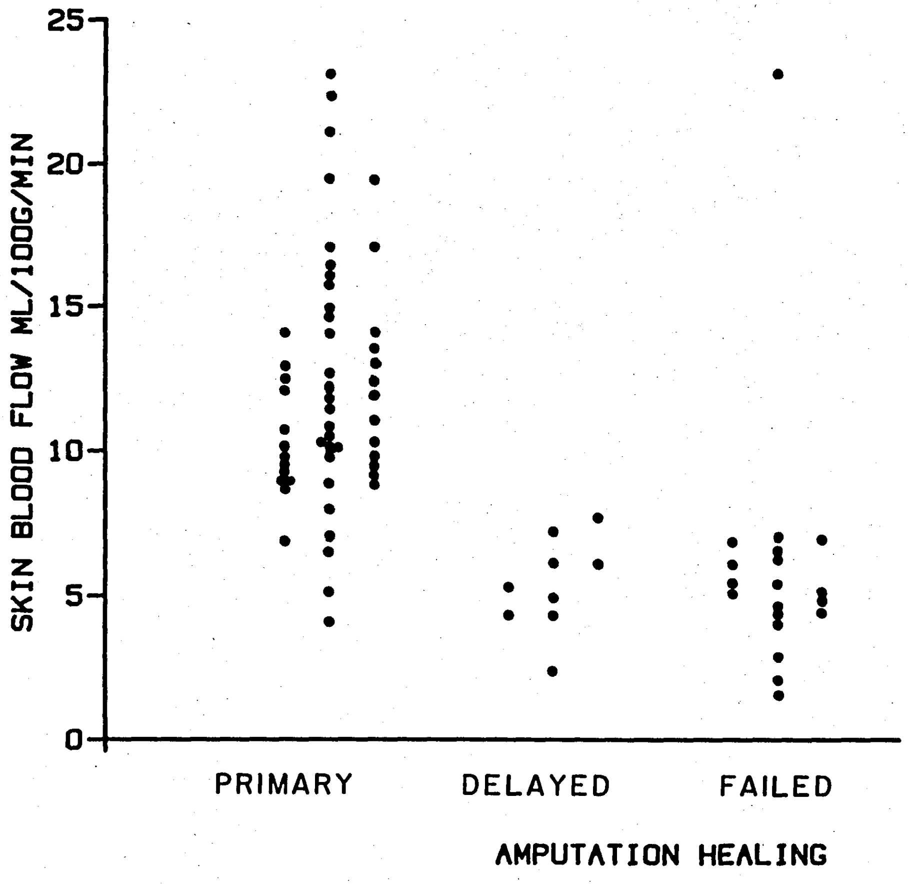

Figure 10.1.

Outcome following amputation at all levels relative to skin blood flow.

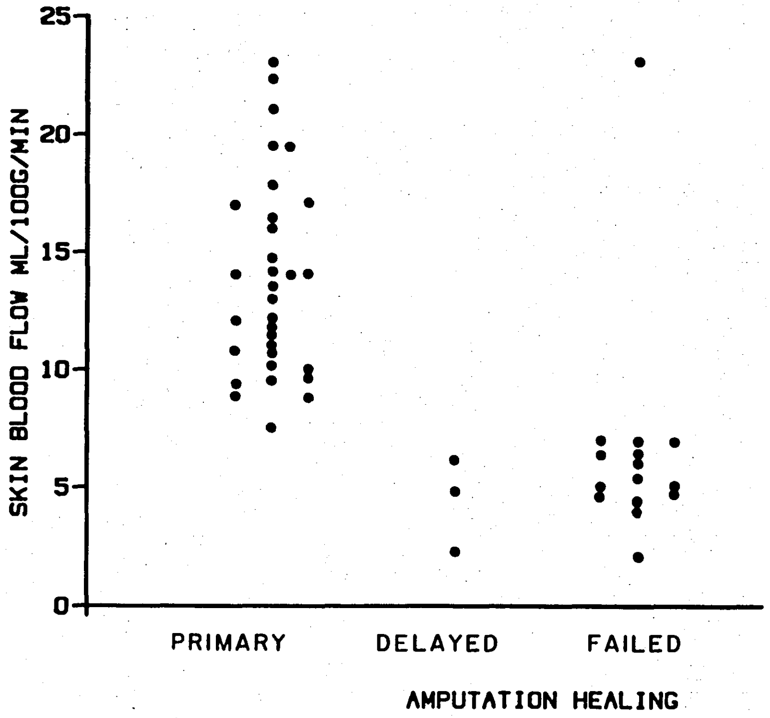

Figure 10.2.

Outcome following forefoot and digital amputations relative to skin blood flow.

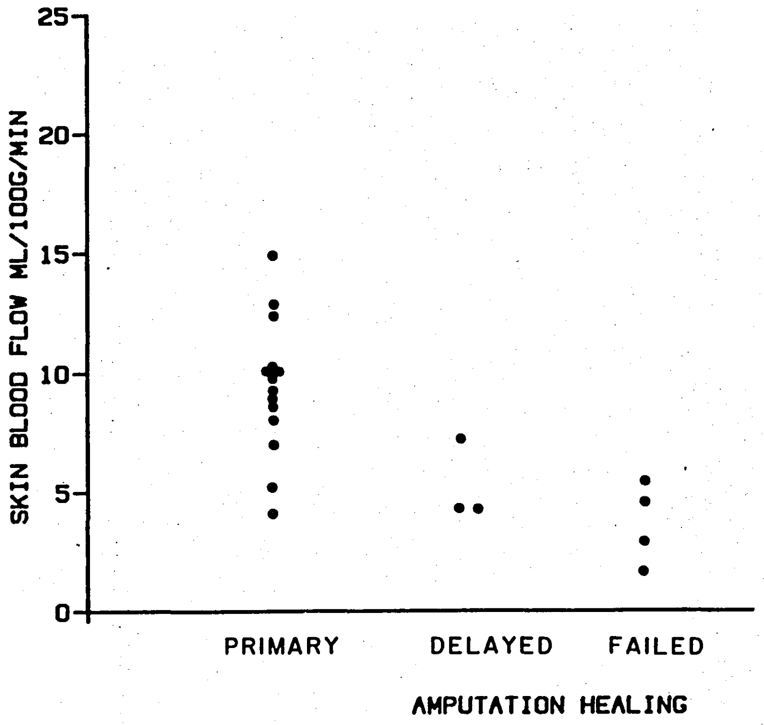

Figure 10.3

Outcome of below knee amputations relative to skin blood flow.

Above knee amputations

There were no healing failures at the above knee level. Mean skin blood flow for healed amputations was 10.6 +/- 1.0 ml/100g/min (mean +/- SE).

Discussion.

Selection of the amputation level in these patients was assessed pre-operatively using clinical judgement and demonstrates that clinical criteria are capable of predicting primary healing accurately in only 65% of cases. Since the success of amputation healing is influenced primarily by skin healing it seems reasonable that a method that can provide quantitative information on skin blood flow would identify patients with adequate nutritional blood flow for healing at a given amputation level.

A major disadvantage of all previous methods for assessing amputation wound healing potential is the inability of any one method to provide a critical end point above or below which healing can be confidently predicted. However Moore and his colleagues (1973, 1974, 1979, 1981), reported a satisfactory relationship between healing and skin blood flow using 133-Xenon clearance. In his experience all amputations with pre-operative skin blood flow in excess of 2.6ml/100g/min at the amputation site healed satisfactorily while a skin blood flow of less than 2 ml/100g/min was associated with universal failure. Holloway and Burgess (1978), using a similar technique, were unable to reproduce the results reported by Moore, and concluded that the technique was incapable of providing a critical threshold level for healing. General acceptance of the 133-Xenon method has not been universal owing mainly to the difficulty in the interpretation of the clearance data and poor reproducibility.

Another factor worth consideration is that these previous studies have been mainly concerned with amputation healing at the below knee level and have not addressed the problem of amputation healing in the foot.

In the present study skin blood flow measurements performed pre-operatively revealed a significant difference for non-healing and healing amputations. However, when considering pre-operative skin blood flow at all categories of amputation it was not possible to determine a minimum blood flow that was compatible with healing. Although at all levels of amputation there were no wound failures where the pre-operative skin blood flow was greater than 7 ml/100g/min, there were a number of patients whose amputations healed satisfactorily in the presence of a pre-operative skin blood flow which was as low as 4 ml/100g/min. However, when the healing at each amputation category was assessed independently, it was apparent that in the foot, a critical minimum value emerged for skin blood flow above which amputation healing could be confidently predicted. If one disregards the single flow of 23 ml/100g/min in the non-healing group, this minimum value appears to be a flow of 7 ml/100g/min. At the below knee level it was not possible to define a critical minimum value to identify healing and non-healing groups, although there was a significant difference in skin blood flow between these categories.

The reason for this apparent difference in the skin blood flow necessary for successful amputation healing at different levels requires explanation. In the foot there were only three patients who by definition ultimately demonstrated delayed healing. Of the 15 failed foot amputations 12 proceeded to below knee amputation after prolonged and unsuccessful attempts to achieve delayed healing. This factor tended to separate patients with foot amputations into two, rather than three categories of healing, which was not apparent for below knee amputations. This factor may have been responsible for eliminating the rather grey area of overlap between healing and non- healing for partial foot amputations with respect skin blood flow.

Another factor requiring examination is the incidence of infection, and its influence on healing rates. Despite relative ischaemia, amputations at the below knee level are less liable to become infected, compared to amputations in the foot, which are often performed in the presence of an open ulcer. Despite the use of prophylactic antibiotics, pre-operative infection was associated with an incidence of post-operative wound infection of 36%, compared to an incidence of only 7% in those patients without evidence of pre-operative infection, illustrating the influence of pre-operative wound infection on subsequent wound sepsis. An additional factor is that in the presence of ischaemia, wound infection is more likely. In these patients, a combination of infection and ischaemia are often present in non-healing wounds, and it is often difficult to establish which is the primary cause of wound failure. It is possible that when the skin blood flow is less than 7ml/100g/min in the foot, infection supervening is of greater significance than ischaemia per se as the cause of amputation failure. Furthermore, as the healing process depends on the blood supply after, rather than before amputation, factors affecting the blood supply in any amputation wound post-operatively namely trauma, wound tension, and oedema, may be of greater importance in amputations in the foot than at other sites.

CHAPTER 11

General Summary and Discussion

Occlusive peripheral vascular disease resulting in ischaemic rest pain, ulceration, or gangrene of the lower extremity presents a formidable challenge for surgeons. The majority of patients with critically ischaemic limbs have vascular anatomy suitable for vascular reconstruction provided they are an acceptable surgical risk (Veith et al 1981). The progression of atherosclerosis often results in multiple prolonged hospital admissions, and despite optimal surgical care, the outcome is often poor (Mackay et al 1986).

Although amputation of a limb is perhaps the oldest surgical procedure, it has only been in the latter half of this century that surgeons have attempted conservative distal amputations in patients with peripheral vascular disease.

Considering the prevalence of peripheral vascular disease, it is surprising that there is anything further to add regarding amputation level selection, surgical technique, or rehabilitation. It is a fact however, that practice has not kept pace with existing technology, and the purpose of this work was to address the problem of level selection in order to achieve optimal healing and so improve rehabilitation.

Traditionally surgeons have taken a rather negative approach to patients requiring amputation. They tend to perseverate, resorting to amputation after weeks of pain and debilitation. Even then, the amputation is performed with apology and a sense of failure, and until recent years, amputees were often neglected to self rehabilitation without adequate support.

When timed properly, and with consideration to physical restoration, amputation is not destructive; it can be regarded as a form of reconstruction that may be elected whenever the outlook is such that a well fitted prosthesis will provide a better result for the patient than can be obtained in a reasonable length of time with further attempts at limb salvage.

The single factor that has influenced the lot of the amputee most since 1950 is the use of plastic materials, making possible a prosthesis socket that fits the stump intimately throughout its entire length. Such total contact fit distributes pressure, and allows the use of the entire length of the stump as a weight bearing area, so that the viability of the skin is the only critical factor determining the length of the stump.

Diabetics comprise a major subcategory of patients with peripheral vascular disease. The distribution of their disease is often distal, affecting the small vessels of the leg and foot, resulting in tissue loss in the foot with the attendant risk of developing serious ascending infection. In addition, the diabetic neuropathy which is often present, increases the susceptibily to infection. The diabetic patient is subject to callous formation and beneath these callouses defects occur in the skin that allow the development of a nidus of infection that can invade the foot and cause widespread sepsis that the patient does not notice until it has become well established and has involved the soft tissues and bones of the foot. For these reasons, and because the vascular lesion is often inoperable due to absent run-off, major amputation are unfortunately common in diabetic patients. Eighty per cent of major amputations are performed on patients with diabetes (Gibbons et al 1979). It should be possible to reduce this number of major amputation by early radical surgical debridement in selected patients, by achieving healing of chronic foot lesions, by prevention or localisation of the spread of infection from the foot by conservative minor amputations, or by improving the blood supply. Unfortunately these measures are expensive in terms of time and resources, and a method which would allow the surgeon to identify patients suitable for such simple local measures directed at limb salvage, without the need for invasive testing with a view to reconstruction, would be of immense value. If one can quantify the severity of ischaemia in the foot, preliminary vascular surgery aimed at improving blood flow may allow conservative amputation with successful healing.

The current experience at the Glasgow Royal Infirmary emphasises that amputation wound healing is a significant problem in patients with peripheral vascular disease. This review confirmed that the patients are elderly, many with concurrent medical disease, in particular diabetes mellitus. With the selection of amputation level based on clinical criteria alone, primary healing rates were poor. The hospital stay was prolonged due to a combination of poor primary healing, which required re-amputation or vascular reconstruction, and delay in mobilisation due to proximal amputation in elderly patients.

A recent North American study by Mackey et al (1986) examined the economic costs of vascular reconstruction for limb salvage and amputation. These investigators found, not surprisingly, that successful revascularisation resulted in lower costs than primary amputation. The accrual cost of failed reconstruction was twice that of successful revascularisation. Primary amputation is far from an expeditious solution to the problem of limb threatening ischaemia. The non-healing of amputations and the need for late revisions, or contralateral amputation, are always risks that can result in multiple prolonged hospital admissions, just as graft failures are continuing risks in patients who undergo vascular reconstruction. The cost containment efforts for hospitalisation for amputation should focus on shortening the acute hospital stay with more efficient placement of disabled patients into less costly chronic care facilities, and the early use of out-patient rehabilitation facilities.

The selection of a patient for the provision of a lower extremity prothesis following a major lower limb amputation must be made with considerable care, for the investment in terms of effort and money is potentially very great. Above knee amputations cause the greatest problems in this respect with only 30% of all patients ever walking again. For below knee amputations this figure is nearer 70% (Warren and Kihn 1969; Burgess et al 1971; Kihn, Warren and Beebe 1972; Couch 1977). Limb length appears therefore to be a major factor in subsequent rehabilitation, although there are other factors such as debility, dementia, stroke, and stump pain. Although these and less tangible factors will compromise the rehabilitation prospects, conservation of limb length and reduction of healing failures are clearly of importance.

For some time the importance of accurate pre-operative assessment of amputation level has been recognised, in particular the role of such assessment in reducing costs and shortening convalescence. During the last decade the development of various non-invasive tests has made the vascular laboratory an integral part of the diagnostic service of many hospitals. A major objective of non-invasive technology has been to assess tissue blood flow, in particular skin blood flow, in order to predict the most distal amputation that will heal primarily. Unfortunately previous methods have failed to provide an absolute 'gold standard' measurement of skin blood flow due to the complex anatomy of the skin and subcutaneous tissues, which does not allow the quantity to be measured directly. Previous methods all directed at measuring skin blood flow all suffer from a number of disadvantages. Many of the techniques are not applicable to the study of blood flow in the clinical context either because of invasiveness or complexity.

Particular problems arise when attempting to measure this variable at extremely low values. Many techniques suffer from problems inherent in any instrumentation system, namely decreasing sensitivity when the signal level approaches the level of instrument 'noise' in the system. Thus at low flow states, variation due to electronic interference which is not present at a normal or slightly reduced flow rate will be experienced. Plethysmographic techniques only allow estimation of cutaneous blood flow in a semiquantitative fashion as subtraction procedures must be applied to correct for blood flow in subcutaneous tissue, muscle, and bone.

Heat clearance is an essentially qualitative method which may be difficult to interpret because of the complex heat exchanges between cutaneous and subcutaneous layers.

Clearance methods based on the use of radio-active tracers have been used extensively to measure blood flow. Although subcutaneous injections of 24-Na and 133-Xe have been used clinically, these techniques cannot yield values for the cutaneous layer (Barron and Veal 1951; Kovamees 1964). Many isotopes have been proven to be of little value; for example the clearance of 24-Na injected intracutaneously is proportional to the endothelial surface available for absorption and not to the blood flow (Braithewaighte 1951).

Intra-arterial injections of isotope, for example 58-Kr, for the study of cutaneous blood flow are beset with serious difficulties; the isotope may not reach the cutaneous layer immediately due to 85-Kr exchange between blood and tissue before the blood reaches the cutaneous layer (Sejrsen 1967). Furthermore diffusion of the isotope within the cutaneous layer changes the counting efficiency, and therefore intra-arterial isotopes can only be considered a semiquantitative method for the measurement of skin blood flow.

The local radio-isotope clearance technique suffers from a number of disadvantages but these can be minimised with careful attention to methodolgy (McCollum et al 1985). Although 133-Xe is widely used as the principal isotope for skin blood flow measurement there have been particular difficulties with its use, notably with regard to its affinity for adipose tissue and its biphasic clearance. 125-I-iodoantipyrine has been used in the past by Lindbjerg (1967), Zetterquist (1968), Munck et al (1967), and more recently by McCollum et al (1985) who, while emphasising the advantages of antipyrine, all recognised the difficulties in producing a stable solution without the presence of significant amounts of free iodides due to radiolysis. Recently Forrester et al (1980) described a technique for the preparation and stabilisation of a solution of 125-I-IAP in which the percentage of free iodide is less than 2% and which can be stored for up to two months.

There are certain critical comments on the local clearance method which should be addressed, as the introduction of an indicator into a volume of tissue by local injection may lead to a distortion of those phenomena which one wishes to study.

Three artefacts which may arise in relation to the injection should be mentioned. First, the injected indicator may reach other tissues than that to be studied. This is especially a problem when attempting to study flow in deep tissue but should not, with attention to technique, cause concern when applied to skin blood flow. Second, if too large a volume is injected, the partition coefficient and/or the diffusion conditions may be changed, causing an initial reduction of clearance relative to those seen with an infinitely small injected volume. This is undoubtedly the phenomenon experienced causing the occasional initial plateau in the clearance curves. Third, the injection may alter the membrane permeability, or the local flow of blood or lymph, usually by increasing flow.

The various tissue components of the injected volume, cells, interstitial connective tissue, and so forth are assumed to be labelled in proportion to the isotope distribution at diffusion equilibrium in that same tissue. On this basis it can be shown that local spreading of the indicator in a homogeneous tissue does not affect the results (Perl 1962). The detector system used in these studies is insensitive to the local spreading of the depot. Since the isotope diffuses from a stationary phase (tissue) towards the moving phase (blood and lymph), the concentration in the latter must always be smaller than the equilibrium value. This means, according to the definition of clearance, that the clearance is always slightly less than the physiological parameter one attempts to measure. The ideal situation where clearance is exactly equal to the blood flow may be very closely approximated, but never fully reached.

In general the volume labelled must contain some 'sub-volumes' from which the isotope is lost less readily than from others. Although this effect is minimised by the use of 125-I-IAP, the clearance and the clearance constant may be generally accepted to decrease with time even under steady conditions, that is, the clearance curve may not be truly mono-exponential, as was occasionally observed. However, as the average probability of escape eventually reaches a constant value, the tail part of the curve will always be a single exponential function even though the clearance value for this part of the curve may not necessarily have a clear cut physiological meaning. It follows from these considerations that if the labelling is uniform initially, it may not generally remain uniform throughout the clearance period. Thus if one can avoid or minimise injection artefacts, then it is the initial maximal clearance values which come closest to the true value for blood flow

If under steady state conditions the clearance remains essentially unchanged at the initial maximal value over a longer period of time (for example until less than 10% of the initial activity remains), then it is a corollary of the above considerations that uniform labelling is maintained. In such circumstances the local clearance method may be used to study variations in flow. Also one may then disregard the very first part of the curve where artefacts are most likely to distort it.

The isotope clearance technique used for measuring blood flow in the experimental studies has been extensively validated but prior to applying the method using I-125-iodoantipyrine further methodological studies were undertaken. It was confirmed that the clearance of the isotope is monoexponential, flow dependent and reproducible.

Clinical studies using the isotope showed poor correlation with other clinical parameters, angiography, and Doppler systolic ankle pressure, which is understandable as the local clearance technique is measuring blood flow at the tissue level. Further studies demonstrated increased clearance following successful vascular reconstruction, but the effect of lumbar sympathectomy was negligible.

The major question that this work attempted to address was whether the technique was of value in determining tissue viability as an indicator of the appropriate level of amputation, by providing a minimal skin blood flow which was compatible with amputation wound healing.

Before attempting to answer this question one must consider some aspects of wound healing which are relevant to amputation wound healing, in particular in patients with peripheral vascular disease.

Whether an amputation wound heals satisfactorily or fails is dependent on a number of factors. Although the skin blood flow and tissue viability are obvious determinants for healing, other factors such as the presence of infection, amputation technique, and haematoma formation may also adversely affect the outcome of an amputation. One could therefore argue that no single pre-operative method will ever regularly predict the success or failure of an amputation, as the healing process depends upon a number of variables, as well as the blood supply after the amputation, rather than the blood supply before it. If this dogmatic statement is correct, it is pertinent to consider the factors affecting blood flow in an amputation stump during and after the operation. Intra-operative factors include tissue trauma, dissection, excessive tissue and suture tension, which may all act together or independently to produce tissue necrosis predisposing to deep infection, or skin necrosis resulting in breakdown. Post-operative factors to be considered include oedema, with resultant increased tissue tension, trauma, further intravascular thrombosis which may have a considerable effect on the blood flow to the tissues at the tip of the stump, and infection. However, while not underestimating the role that these factors may play in wound healing, a method which will supplement the clinical acumen of the clinician, and in doing so, improve the overall healing rates will be a valuable contribution. No method can be 100% reliable as there will always be an area of marginal blood flow where these other factors will assume relative greater importance. With careful attention to detail and operative technique the effects of these factors which are eminantly avoidable can be reduced. However, it is precisely in this grey area of marginal blood flow that the selection based on clinical parameters is weakest, for the presence of healthy appearing skin is no guarantee that there will be adequate blood flow for wound healing because the blood supply required to heal an incision is greater than that required to maintain viability of intact skin.

These studies have shown that it is possible to correlate pre-operative blood flow with amputation wound healing in patients with peripheral vascular disease. When considering the overall healing rates at all levels, however, it is apparent that although there was a significant difference in the skin blood flow between healing and non-healing categories, there was considerable overlap of the values in areas of marginal blood flow, as the technique failed to provide a critical minimal flow necessary for healing. This appeared to be primarily due to the effect of healing rates for below knee amputations, for when digital and forefoot amputations were studied as a separate category, the separation between healing and non-healing amputations in terms of pre-operative skin blood flow was more pronounced. The data suggest that a critical flow of 7ml/100g/min was necessary to ensure healing. The reasons that the technique is capable of producing a discriminant value for distal amputations and not for proximal amputations requires explanation.

The role of infection as a primary cause of wound failure assumes greater importance in the foot. As infection and ischaemia coexist, particularly in the diabetic patient, it can be argued that a greater blood flow is required to counterbalance the potential effects of infection. At flow values of less than 7ml/100g/min infection supervenes, primarily because of relative ischaemia. At the below knee level, infection, while an ever present risk, is not such an important factor primarily responsible for wound failure. It appears that successful amputation healing is possible at lower rates of skin blood flow at the below knee level than would be possible in the foot.

The clinical role of the isotope clearance method is therefore for determining viability in patients with severe distal ischaemia. Where the skin blood flow is less than 7ml/100g/min, it is unlikely that ischaemic ulcers will heal spontaneously, and amputations are at risk of non-healing. In this situation, the surgeon should proceed directly to angiography to assess the possibility for vascular reconstruction. If this is anatomically possible, surgery should be performed; if not possible, sympathectomy or below knee amputation are the options, as prolonged attempts at conservative treatment are likely to be unsuccessful. Where the flow is greater than 7ml/100g/min satisfactory tissue viability is probable. In this situation digital gangrene can be confidently treated by local digital or trans-metatarsal amputation with guarantee of satisfactory healing; local ulceration is also likely to heal spontaneously with conservative measures only,provided infection is controlled by antibiotics and by promoting adequate drainage. A typical clinical algorithm using skin blood flow assessment is suggested in Figure 11.1. If used in this way therefore skin blood flow assessment will prevent unnecessary delay by identifying patients who require definitive surgery or amputation at a more proximal level, and may also prevent unnecessary angiography and perhaps reconstruction in patients with lesions which can be treated satisfactorily by local or conservative measures alone.

At the below knee level the technique provides a useful method to supplement clinical assessment of amputation level and may allow the surgeon to consider amputation at the below knee level in situations where on clinical grounds above knee amputation is indicated.

There are a number of theoretical objections to the method which must be addressed. These include the possible backflow of the isotope through the injection tract resulting in diminished clearance due to isotope 'trapping' within the needle tract and therefore not available to the capillary circulation for clearance. However the monoexponential nature of the clearance curve suggests that the uptake is from a single compartment and that backflow if any is negligible. A further possible objection is the reactive hyperaemia which is said to result from injection trauma. Reactive hyperaemia would

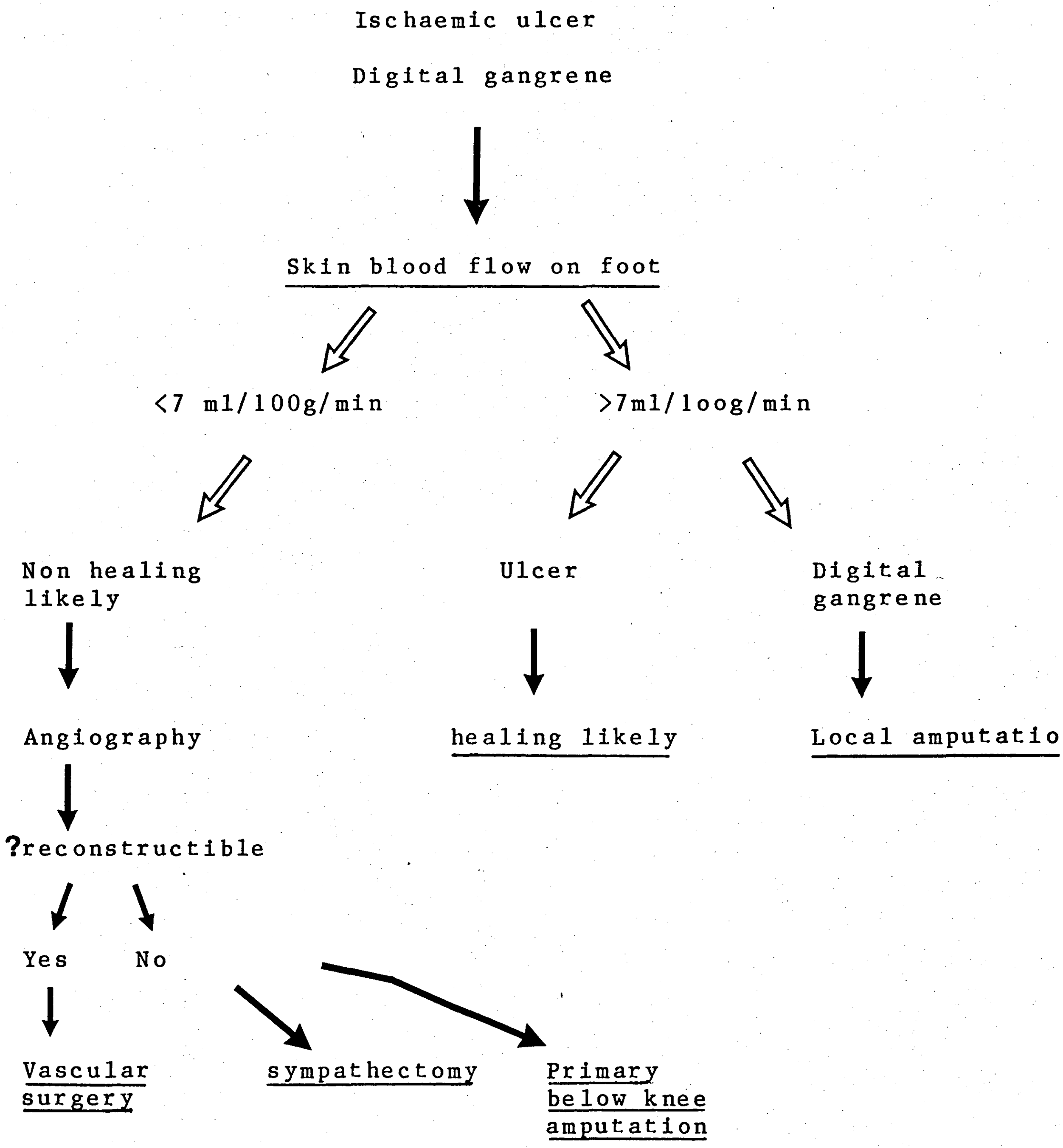

Figure 11.1

Suggested clinical algorithm for the management of severe distal ischaemia based on skin blood flow also be expected to cause deviation from the monoexponential slope which would be apparent in the first 10 minutes of the washout curve; such a deviation was not observed. In any case, as the object of the exercise is to measure the maximum blood flow attainable, reactive hyperaemia may not necessarily be a disadvantage, as one could argue that the point of obtaining a parameter in the context of this study is not to obtain an absolute value of baseline flow, but a measurement which reflects maximal flow (ie the reserve capacity), and is therefore representative of wound healing potential. Reactive hyperaemia which occurs as part of the healing process has been alluded to earlier, and the ability to quantify the potential of the reserves of the skin blood flow to adapt to increased demands may be an advantage. Previous attempts directed at avoiding reactive hyperaemia have included the use of the epicutaneous application method whereby the isotope is deposited in a 1ml reservoir formed by drapping an adhesive polythene sheet over the skin. The problems that then arise due to diffusion of the isotope from the skin, and the fixation of the isotope to subcutaneous tissue, as well as to the dermis, results in multicompartmental clearance, requiring mathematical curve stripping techniques to eliminate the slow component of subcutaneous washout from the clearance, have already been discussed in a previous chapter.

There are however, more specific disadvantages of the method. Pain at the needle tip during injection of the isotope was often noted, but was by no means universal and was difficult to quantify. The pain appeared particularly severe when injecting into ischaemic skin, but lasted only for the duration of the injection which was merely seconds. It has been suggested that the epicutaneous application of the isotope overcomes this particular problem.

Because the technique is a dynamic measurement, each assessment involves some 30 minutes, not including the preliminary time spent by the patient equilibrating in the elevated environmental temperature. In comparison to other techniques, for example transcutaneous p02 and Doppler both of which are virtually instantaneous, this is relatively long. Throughout the period when clearance is being monitored, the subject must remain immobile. Although this is achieved by cushioned supports on the limb, the patients often find it uncomfortable, particularly when there may be a painful lesion on the limb, or in the presence of rest pain when dependency of the limb may be necessary to relieve pain.

A further disadvantage of this technique is that it requires specialised equipment, although the cost of such equipment can be more than offset by the savings in cost accrued from the more rational treatment of patients with end stage peripheral ischaemia, and by the reduction of amputation wound failure. The equipment used in these studies with the exception of the temperature controlled room is readily available in any hospital physics laboratory at minimal cost.

For the future there are a number of possible options which will undoubtedly make the technique more attractive. The use of alternative isotopes for example, technetium, will allow the use of the gamma camera in preference to the collimated probe and ratemeter, making possible the simultaneous examination of several sites and rapid data processing.

The advent of improved physiological recording equipment capable of recoring over extended periods of time for example, the Novo Memolog system (Novo Diagnostics Systems, Denmark) which is a 2 channel portable recording device with 192kbit memory, capable of accepting a wide range of sensors including CdTe gamma emission detector and miniaturisedcollimated sodium iodide detector. Such an instrument makes it possible to perform bedside measurement, and ambulatory monitoring over prolonged periods. Isotope clearance measurements can then be performed as simply as transcutaneous pO2 and laser Doppler measurements, and from multiple sites simultaneously allowing the surgeon to construct a 'flow map'. Variation in regional blood supply in the skin can thus be detected, allowing the surgeon to plan the amputation flaps tailored to the blood supply.

It is these and similar techniques aimed at defining levels and patterns of tissue viability in the limbs of patients with severe peripheral vascular disease which have, and will continue to influence a positive approach to the patient facing lower limb amputation.

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