An Evaluation Of The Use Of Transcutaneous Oxygen Pressure Measurement In The Non-Invasive Vascular Laboratory – With Special Reference To Selection of Amputation Level

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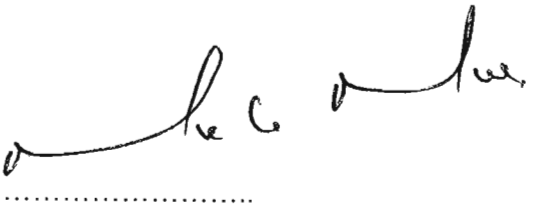
Declaration

This study represents original work by the author and has not been submitted in any form to another University. Where use has been made of the work of others it has been duly acknowledged.

The work was carried out in the Non-invasive Laboratories of the Durban Metropolitan Vascular Surgery Department, at Addington Hospital, King Edward VIII Hospital and the Nelson R Mandela School of Medicine of the University of Natal, under the supervision of Professor JV Robbs.



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MAURICE MARS

2001

Dedication

This work is dedicated to the memory of my father,

Dr Paul Ernst Mars,

a caring practitioner of the art of medicine.

Acknowledgements

Professor John Robbs for his patience, advice, guidance and friendship over the many years of the study.

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Abstract

Transcutaneous oxygen pressure measurement ($TcpO_2$) using a miniaturised Clarke electrode and a heating thermistor was developed independently by Huch *et al* and Eberhardt *et al* in 1972. After its initial use to non invasively monitor arterial partial pressure (PaO_2) in neonates it was proposed as a useful test of skin blood flow and possibly amputation wound healing level selection in patients with peripheral vascular disease. Unfortunately a wide range of predictive values emerged with some authors reporting amputations healing when the $TcpO_2$ value was 0 mmHg. The investigation, while still considered useful, has not gained widespread support.

This study investigates the use of $TcpO_2$, establishes a value for the use of the $TcpO_2$ Index to predict amputation wound healing potential and examines the hypothesis that the use of the $TcpO_2$ Index to select amputation level can reduce patient morbidity and mortality.

The literature is reviewed and a series of studies evaluating $TcpO_2$ use, undertaken in the Durban Metropolitan Vascular Service Non-Invasive Laboratories, are presented. $TcpO_2$ measurements were performed in a standardised manner with the subject supine breathing room air. Measurements were taken at fixed sites, on the mid dorsum of the foot (Foot), 10 cm distal to the tibial tuberosity and 2 cm lateral to the anterior tibial margin (BKA), 10 cm proximal to the patella in the midline (AKA) and on the chest in the mid-clavicular line. A $TcpO_2$ Index, the limb to chest ratio was defined.

$TcpO_2$ data derived from control subjects asymptomatic of peripheral vascular disease were shown to be similar to age matched pooled data derived from the literature. In patients with peripheral vascular disease, absolute $TcpO_2$ and the $TcpO_2$ Index were shown to fall from proximal to distal sites and again were no different to pooled data derived from the literature. Based on presenting symptoms, the fall in $TcpO_2$ and the $TcpO_2$ Index was significant from proximal to distal sites. The reduction in absolute $TcpO_2$ and the $TcpO_2$ was also related to the most distal pulse present. $TcpO_2$ values were found to be no different in patients with peripheral vascular disease with or without diabetes.

When comparing $TcpO_2$ and the $TcpO_2$ Index with Doppler pressure measurements at the Popliteal artery and at the foot, and the Doppler ankle brachial index (ABI), Doppler derived data were significantly higher in diabetic patients than in non-diabetic patients. No differences were noted in $TcpO_2$ data. $TcpO_2$ was compared with the ^{133}Xe radio-isotope skin washout

test. The best correlation was ($r = 0.46$) was obtained with a logarithmic curve $y = 10.862\text{Ln}(x) + 38.751$.

$TcpO_2$ was compared with antibiotic concentrations (Cefoxitin) in muscle obtained from the site of amputation and the Cefoxitin Index, the ratio of muscle antibiotic concentration to plasma concentration, as an indication of the relationship of skin $TcpO_2$ to muscle blood flow. A significant correlation was shown between the Cefoxitin Index and $TcpO_2$ ($r = 0.67$, $p = 0.035$) and the $TcpO_2$ Index ($r = 0.64$, $p = 0.045$), suggesting that skin oxygen delivery may reflect muscle antibiotic delivery and hence blood flow.

$TcpO_2$ and the $TcpO_2$ Indcx were compared with heated and unheated laser Doppler fluxmetry (LDF) in 35 patients undergoing amputation wound healing assessment. Significant correlations were shown between heated LDF, heated LDF Index and the $TcpO_2$ Index ($r = 0.63$ and $r = 0.69$, $p < 0.0001$). $TcpO_2$ Index values of 0.5 and 0.55 showed an accuracy of 96.2 % in predicting amputation outcome while LDF values of 3, 4 and 5 arbitrary units gave an accuracy of 88.5 %. Using receiver operator curves, a $TcpO_2$ Index of 0.55 was shown to be the best test.

Over the years 1987 and 1988, $TcpO_2$ data were gathered on 193 patients undergoing lower limb amputation for peripheral vascular disease. Information on the outcome of the amputation was available for 152 amputations. Circumstances which might result in a reduced pre-operative $TcpO_2$ reading were identified and criteria were set for the use of $TcpO_2$ to predict amputation wound healing potential. 122 amputations which met the defined entry criteria were available for evaluation. A $TcpO_2$ Index of 0.50 gave a definitive predictive value below which no amputation healed. Similarly no amputation with an absolute $TcpO_2$ of less than 27 mmHg healed. Receiver operator characteristic curves showed the $TcpO_2$ Index to be a better test than absolute $TcpO_2$. A $TcpO_2$ Index of 0.55 was shown to have the best sensitivity of 96.7 %, with a specificity of 79.8 % and an accuracy of 90.2 %.

When introduced to clinical practice, correct use of the $TcpO_2$ Index of 0.55 resulted in a reduction in amputation revision rate from 40.3 % in 1987, to 8.2 % in 1990. Initially some surgeons felt that the $TcpO_2$ Index predicted amputation wound failure at distal sites at which healing could be expected on clinical criteria, and chose amputate at sites with a $TcpO_2$ Index value less than 0.55. These amputations failed to heal. As surgeons gained confidence in the test, they chose to follow the $TcpO_2$ data more often and the percentage of amputations performed at sites predicted by the $TcpO_2$ Index to fail, fell from 35.5 % in 1987 to 6.6 % in 1990.

Over a 15 year period at King Edward VIII Hospital, the amputation revision rate has fallen from an average of 32.7 % in the first five years when $TcpO_2$ data were not available to the surgeon, to 21.4 % and 22.9 % in the two subsequent 5 year periods when $TcpO_2$ data were available. The mortality rates were unchanged. The decline in revision rates was less than expected and relates to the fact that approximately only 42 % of patients requiring amputation undergo the test. This is because it is time consuming and available only during weekday office hours.

These studies have confirmed the usefulness of $TcpO_2$ measurement in the non-invasive vascular laboratory. The index is shown to be superior to absolute $TcpO_2$ as a predictive test of amputation wound healing. The introduction of several criteria to define when $TcpO_2$ use is appropriate has refined the investigation and made it clinically useful in our setting. A $TcpO_2$ Index of 0.55 in the appropriate patient is a useful test to predict amputation wound healing and its use has resulted in reduced patient morbidity and mortality, confirming the hypothesis tested.

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Abbreviations

ΔPO_2 (el)	partial pressure of oxygen consumed by the electrode
ΔPO_2 (temp)	difference in partial pressure of oxygen due to heating effect
ΔPO_2	difference in partial pressure of oxygen
ABI	ankle brachial index
AKA	above knee amputation
ANOVA	analysis of variance
au	arbitrary units
B	blood flow
BKA	below knee amputation
λ	blood - skin coefficient
C_0	tissue concentration of the indicator at time 0
CaO_2	concentration of oxygen in the blood at the arterial end of a capillary
Ci	Curie
CVI	chronic venous incompetence
CO	cardiac output
cO_2	concentration of oxygen
C_t	tissue concentration of the indicator at time t
CvO_2	concentration of oxygen in the blood at the venous end of a capillary
DO_2	total oxygen delivery
E	effectiveness of local blood supply
F	perfusion coefficient
FIO_2	inspired oxygen concentration
Font	Fontaine
G	gangrene
GHb	glycosylated haemoglobin
Hb	haemoglobin
HBA1c	haemoglobin A
HPLC	high performance liquid chromatography
IC	intermittent claudication
ICD	international classification of diseases
ICU	intensive care unit
IL	ischaemic lesion
K	washout rate coefficient

LDF	laser Doppler fluxmetry
MAxL	mid axillary line
MC	mid clavicular line
MIC	minimum inhibitory concentration
n	number (sample size)
O_2	oxygen
ORI	oxygen recovery index
ORT	oxygen recovery time
PAOD	peripheral arterial occlusive disease
PaO_2	arterial partial pressure of oxygen
PO_2	partial pressure of oxygen
PVD	peripheral vascular disease
PvO_2	venous partial pressure of oxygen
r	correlation coefficient
ROC	receiver operator characteristic
RP	rest pain
RPI	regional perfusion index
SC	sub clavicular
SD	standard deviation
$T_{½}$	half-time of the indicator clearance
$TcpO_2$	transcutaneous oxygen partial pressure measurement
$TcpCO_2$	transcutaneous carbon dioxide partial pressure measurement
TMA	transmetatarsal amputation
U	ulcer
VO_2	oxygen consumption
Xe	Xenon

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Chapter 1

Introduction and Statement of the Problem

Amputation

"One of the meanest and yet one of the greatest operations in surgery,
mean when resorted to where better may be done,
great as the only step to give comfort and prolong life"

(Ferguson, W., 1865)

Limb amputation is one of the oldest forms of surgery. For most of man's history, trauma and warfare have been the major reason for limb ablation and in previous era a surgeon's skill was often measured by the speed with which an amputation could be performed. Following the Industrial Revolution, changing lifestyles and disease patterns have led to peripheral vascular disease and diabetes mellitus superseding warfare and trauma as the major reason for limb amputation.

Despite rapid and profound advances in vascular surgery over the past 60 years, many patients still face amputation. A better understanding of the metabolic demands of prosthetic use, advances in prosthetic design and a desire to improve rehabilitation has changed the approach to amputation surgery. The quick fix of a proximal amputation that is almost certain to heal, has been replaced by a desire to leave the patient with a stump that offers the best biomechanical advantage, in the belief that this will allow better rehabilitation and an improved quality of life. This equates to preserving as many functional joints as possible, or amputating as distally as will heal.

The downside of this approach is increased morbidity and mortality, and compromised rehabilitation for those unfortunate patients in whom the initial distal amputation fails and a more proximal revision is required. What is needed is a test that rapidly and reproducibly predicts whether an amputation will heal or fail at a given site.

The advances in vascular surgery have been paralleled by technological advances in the investigative techniques used to evaluate limb perfusion in peripheral vascular disease. Despite this, there is as yet no one investigation of amputation wound healing potential that has gained universal acceptance. This is not really surprising as wound healing is dependent

on many factors both local and systemic, and it is most unlikely that any test will achieve the goal of being 100 % accurate.

Transcutaneous oxygen pressure measurement ($TcpO_2$) was initially used as a non-invasive measure of arterial oxygen partial pressure in neonates. It has subsequently been used in different branches of medicine to assess changes in skin oxygenation and by implication skin blood perfusion. $TcpO_2$ measurement is widely held to be one of the better tests of skin perfusion.

Its use in predicting amputation wound healing was investigated in several centres during the 1980's. The search was for "one number", a value above which an amputation would heal and below which it would fail. This approach takes no cognisance of the numerous variables that affect $TcpO_2$ values, not least of which are cardiac output, local oedema and the site of probe placement. Many of the reports were of relatively small sample size and predictive levels proposed were based on even smaller numbers of failed amputations within these series.

These reports fell broadly into three groups, those which reported amputations healing with a $TcpO_2$ value of zero, albeit in a very small number of patients, and those which proposed useful predictive values. The predictive values were either relatively low, below 20 mmHg or high 20 – 40 mmHg. Grey areas emerged in which the test appeared less reliable. The basic $TcpO_2$ test was then augmented by the use of stress tests, inhalation of oxygen, and postural changes in attempts to improve the accuracy of the investigation. A normalised $TcpO_2$ value, being the limb to chest ratio was proposed as another method of improving the test by reducing variables associated with systemic oxygen delivery. Conflicting reports emerged on the use of this index in amputation level selection.

After the initial enthusiasm in the use of $TcpO_2$ to predict wound healing, interest waned. There has to date been no long-term study on the establishment of a predictive value, its validation, and the effect of its subsequent implementation on amputation revision rates.

This study examines the hypothesis that the use of a transcutaneous oxygen pressure index to assist in the selection of amputation levels in patients with peripheral vascular can reduce patient morbidity and mortality.

Chapter 2

Transcutaneous Oxygen Pressure Measurement

This chapter reviews the literature and will trace the development of transcutaneous oxygen pressure measurement, describe the blood supply of skin and discuss the theoretical model of factors influencing oxygen delivery to the skin surface. Evidence of clinical support for the model will be presented. The concept of the $TcpO_2$ Index will be introduced, and the use of absolute $TcpO_2$ and the $TcpO_2$ Index in clinical practice will be reviewed.

2.1 Historical perspective

In 1851 Gerlach reported his observations on the exchange of oxygen and carbon dioxide between skin and ambient air. This he termed cutaneous respiration, analogous to gas exchange in the lungs. He noted that "the experiments gave proof that, indeed, the skin respires or rather that the blood on its way through the dense capillary network in the most superficial layer of the skin respires" and "that the cutaneous respiration depended on the quantity of blood streaming through the most superficial skin capillaries and on its flow velocity… Therefore, everything that increases the amount of blood within the skin raises cutaneous respiration." as quoted by Lubbers, D.W. (1981) from (Nashashibi, M. *et al.*, 1992).

"Cutaneous respiration", or rather the passage of gas through the skin was confirmed by Baumberger, J.P and Goodfriend, R.B. in 1951 and Rooth, G. *et al.* in 1957. This was done by immersing a finger in a phosphate buffer heated to 45 °C and measuring the partial pressure of oxygen (PO_2) in the buffer. Irrespective of the initial PO_2 of the buffer, they found the PO_2 in the buffer approached the arterial partial pressure of oxygen (PaO_2) during finger immersion.

In 1972, Huch, A *et al.* and Eberhardt, P. *et al.* both reported the use of a miniaturised Clark polarographic electrode on the skin to measure what they considered to be arterial oxygen concentration (Clark, L. C., Jr., 1981). This lead to the use of $TcpO_2$ in clinical practice.

2.2 Structure and blood supply of skin

The skin is the external envelope surrounding the healing mass of bone, muscle, and soft tissue following amputation. It is also the tissue sampled when attempting to predict amputation wound healing using $TcpO_2$. The factors that will influence both healing and wound healing prediction are the thickness of the skin, and its blood supply.

The blood supply of skin is complex and shows regional variation (Ryan, T. J., 1991). It has been described as ranging from the oily rain forests of the axilla to the tundra of the leg. The blood supply serves two functions, the delivery of nutrients to the dermis, epidermis and adnexae, and temperature regulation. Variations in skin blood supply may be due to differences in the number of dermal papillary capillary loops per square millimetre, and differences in the arterial supply of the plexuses feeding the capillary loops. These may be due to variation in the level at which arteries perforate muscle, and whether or not the perforating arteries subsequently run subfascially or extrafascially and finally where arterial branches are given off to skin. The presence and abundance of anastomoses in fascial and subdermal plexuses will also influence skin blood flow. The anatomy and structure of the blood supply and blood vessels is not constant and changes with ageing, disease- such as diabetes, and trauma (Pasyk, K. A. *et al.*, 1989).

The description of the blood supply of the skin has changed little since the work of Spaltehof in 1893. It is usually described as being derived from large arteries in the subcutaneous layer which send branches superficially to form a horizontally oriented network (*rete cutaneum*) at the junctional zone between the dermis and hypodermis. From this plexus, branches supply the sweat glands, the deeper portions of the hair follicles, and the dermis. In the dermis they form a further network between the papillary and reticular layers (the *rete subpapillare*). This plexus supplies capillaries to the sebaceous glands, the intermediate portion of the hair follicle and capillary loops which run up into the papillary pegs (Figures 2.1 and 2.2) (Spaltehof, W., 1893; Leeson, T. S and Leeson, C. R., 1970).

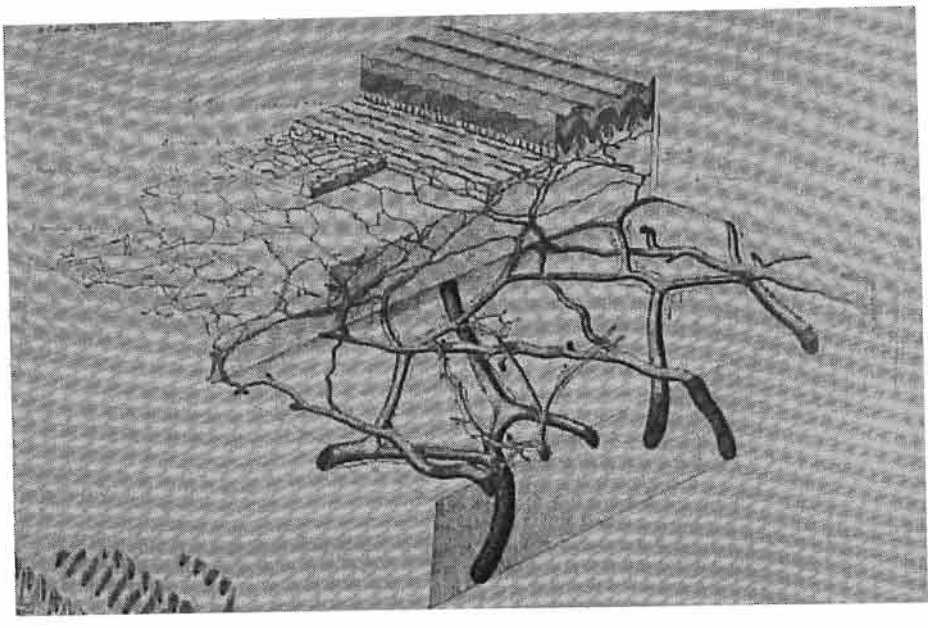


Figure 2.1. Spaltehof's original description of skin blood flow from (Spaltehof, W., 1893).

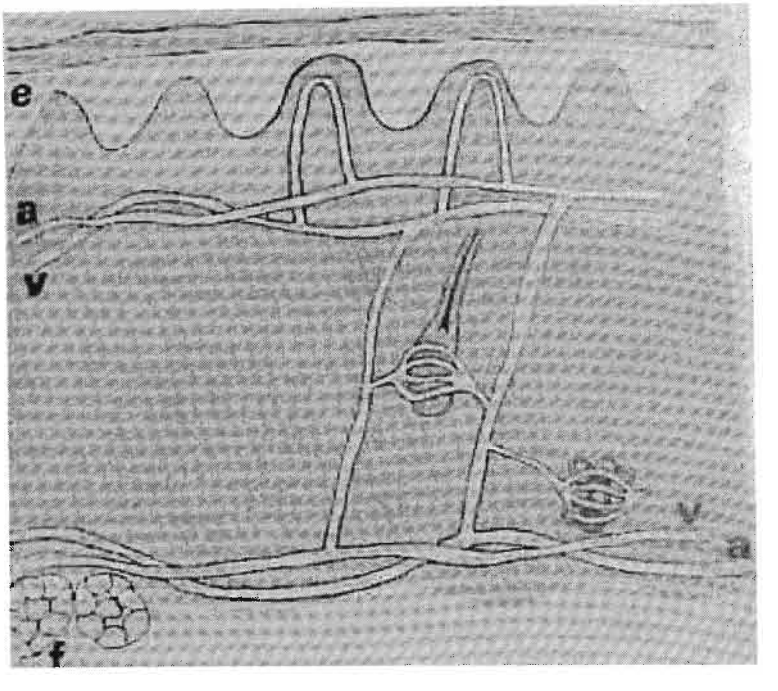


Figure 2.2. Schematic representation of the blood supply of skin. e = epidermis, a = artery in upper horizontal plexus, v = vein in upper horizontal plexus, a and v = artery and vein in the extrafascial, deep horizontal plexus.

There is usually only one capillary loop per papilla. Being hairpin shaped, the diameter of the lumen at the bend is compromised and has been reported as being 3.5 to 6 μm in diameter. This is a site at which red blood cells and larger white blood cells can readily become plugged

(Braverman, I. M and Yen, A., 1977; Higgins, J. C. and Eady, R. A. J., 1981). One capillary loop supplies 0.04 – 0.27 mm^2 of skin surface (Spaltehof, W., 1893) and the average distance between capillary loops is 50 – 100 μm (Carrier, E. B., 1922). While there are normally about 60 – 70 capillary loops per mm^2 this number is reduced in the legs, and this is thought to be the result of gravitational stasis (Ryan, T. J., 1991). The skin of the thigh is reported to have 29 capillary loops per mm^2 and the count drops still further in pre-tibial skin (Pasyk, K. A. *et al.*, 1989).

Complex arteriovenous anastomotic channels exist in the skin, which can alter the nutritive blood flow. Grant and Bland, counted 93 – 501 anastomoses per mm^2 (Grant, R. T. and Bland, E. F, 1931). Brakkee and Vendrik conducted a radio-isotope study and suggested that 60% of skin blood volume passes through such anastomotic shunts (Brakkee, A. J. and Vendrik, A. J., 1970). The role of these shunts is important in temperature control and as part of the natural rerouting response to cold induced increase in haematocrit in the papillary capillary loops.

This classical approach to the blood supply of the skin does not take into account the source of the "large arteries in the superficial layer". Based on observations of the difficulty of raising extrafascially based skin flaps in the leg, Haertsch (1981) conducted a series of cadaveric studies to investigate the source of the blood supply of skin. He found that branches of the major axial arteries supplied adjacent muscle groups and that branches of these nutrient vessels passed through the muscle to perforate the investing fascia. Once through the fascia, an extrafascial plexus is formed. This plexus communicates with and feeds the subdermal plexus (Haertsch, P. A., 1981a; Haertsch, P. A., 1981b) (Figure 2.3).

The vessels forming the extrafascial plexus are arranged as linear sets of perforators. A series of perforating arteries arising from the posterior tibial artery is arranged linearly along the medial border of the tibia. Laterally, three similar linear arrays of perforating arteries were noted. The first, arising from the anterior tibial artery, occurs along the anterior border of the tibia and consists of vessels which have not passed through the muscle of the anterior compartment. The second series of perforators, also derived from the anterior tibial artery runs along the line of the anterior peroneal septum separating the anterior and peroneal compartments. The third set of perforators, derived from the peroneal artery is situated along the line of the posterior peroneal septum. Additional perforators come through the gastrocnemius and soleus muscles.

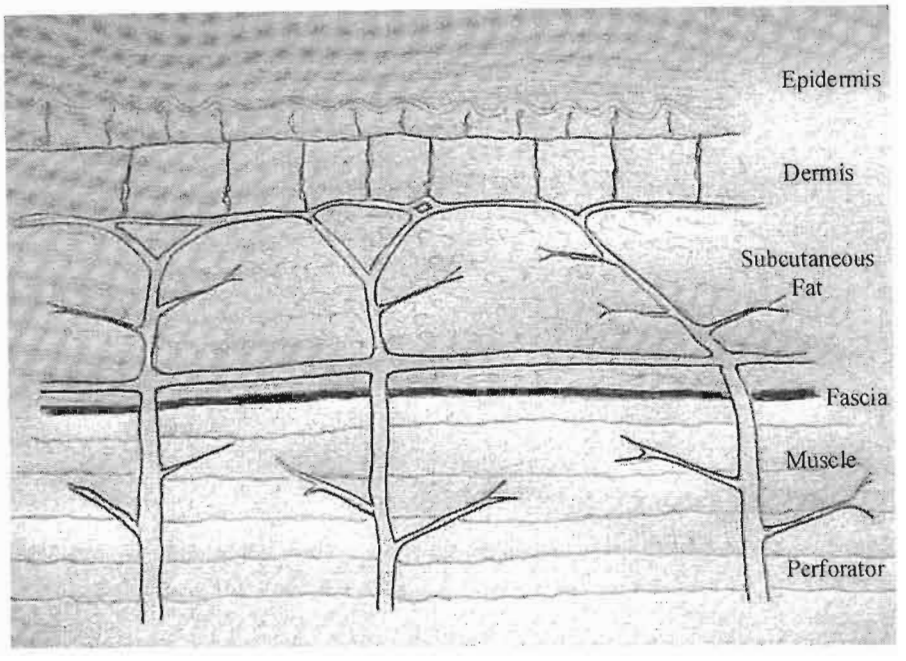


Figure 2.3. Schematic representation of the blood supply of the skin, drawn after (Haertsch, P. A., 1981a).

In addition to the perforators, the nutrient vessels running with the saphenous, sural and sural communicating nerves also gave branches that supplied cutaneous regions. The origin of the saphenous artery proximal to the knee joint may explain the inconsistent relationship of an absent popliteal pulse with below knee amputation skin wound healing (Figures 2.4 and 2.5).

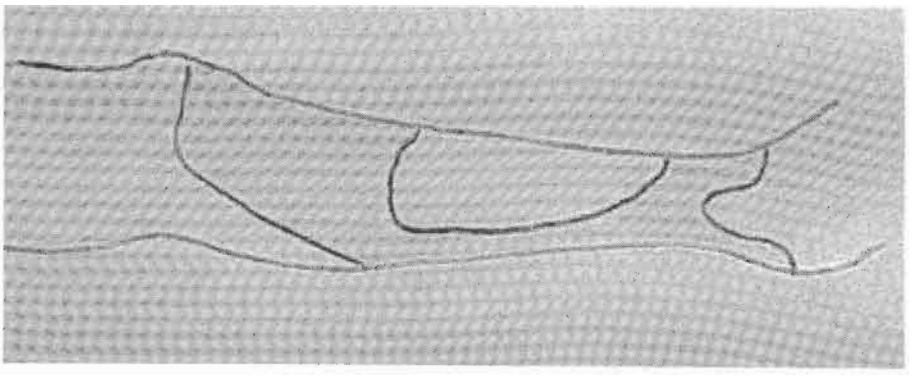


Figure 2.4. The shaded area on the lateral aspect of the leg represents the skin supplied by the peroneal artery, drawn after (Haertsch, P. A., 1981a).

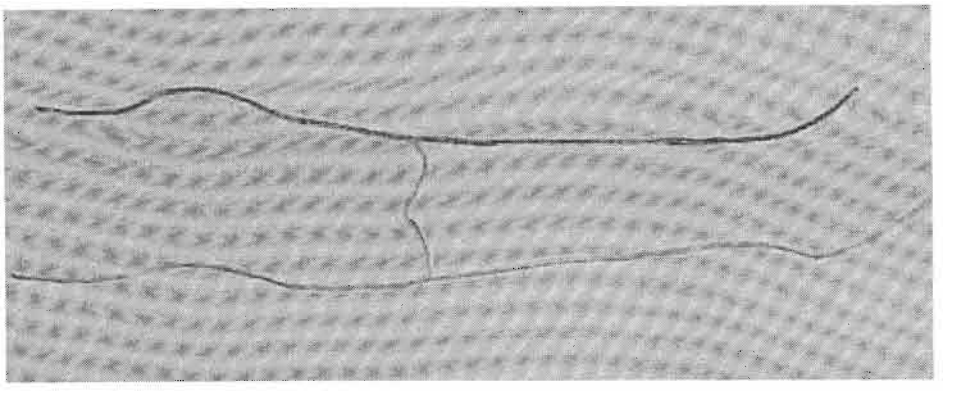


Figure 2.5. The shaded area on the medial aspect of the leg represents the skin supplied by the saphenous artery, drawn after (Haertsch, P. A., 1981a).

While helping to solve the problem of raising flaps on the leg, by changing the plane of dissection from extrafascial to subfascial, this work showed that the blood supply of the skin is substantially different to Manchot's classic description of the cutaneous blood supply derived from underlying muscle (Manchot, C., 1889) (Figure 2.6).

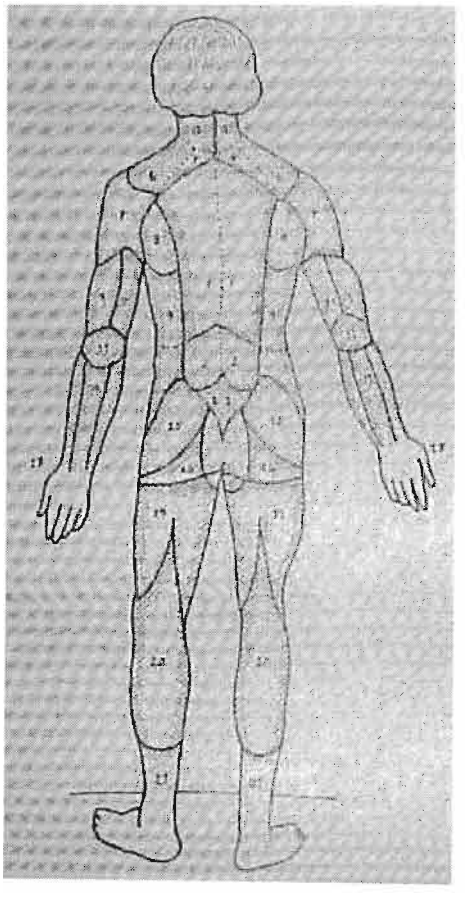


Figure 2.6. Manchot's description of the blood supply of skin based on the blood supply of the underlying muscle (Manchot, C., 1889).

2.2.1 Relationship of skin capillary density to $TcpO_2$

What is the effect of skin capillary density on $TcpO_2$? Using simultaneous capillaroscopic videomicroscopy and $TcpO_2$ measurement, Franzeck showed a relationship between $TcpO_2$ and capillary density and morphology in patients with differing degrees of chronic venous incompetence (CVI) (Franzeck, U. K. *et al.*, 1984; Franzeck, U. K. *et al.*, 1993). In 24 healthy subjects they found the mean $TcpO_2$ in the medial ankle - lower leg region to be 56.8 $\pm$ 9.9 mmHg with capillary density averaging 45 capillaries.mm^{-2}. In patients with CVI the $TcpO_2$ was reduced to 47.7 $\pm$ 14.5 mmHg and the capillary density to 40 capillaries.mm^{-2}. These changes did not reach statistical significance. Morphologically, the capillaries of patients with CVI were dilated, tortuous and were frequently surrounded by a distinct halo. In hyperpigmented, indurated, and hyperkeratotic areas, $TcpO_2$ fell significantly to 22.5 $\pm$ 7 mmHg ($p < 0.001$) and the capillary density was less than 10 capillaries.mm^{-2}. In these regions the capillaries were extremely dilated with irregularly shaped arteriolar and venular limbs. In the centre of areas of white atrophy, no capillaries were visualised and the $TcpO_2$ fell to 0 mmHg. At the borders of these areas, the capillaries were enlarged and meandering and appeared glomerular like. They concluded that the $TcpO_2$ levels appeared to depend on capillary density.

Slagsvold,C.E. *et al.*, (1991) looked at postischemic $TcpO_2$ response following release of tourniquet cuff occlusion, expressed as oxygen reappearance time (ORT) and oxygen recovery index (ORI). They too found a relationship between the severity of capillary morphological changes and in this case ORT and ORI and concluded that major changes in capillary structure observed in critically ischaemic skin may hamper O_2 diffusion and modify both ORT and ORI. Jacobs *et al.* have shown a relationship between Fontaine classification, capillary density and morphology and $TcpO_2$ (Jacobs, M. J. *et al.*, 1992).

2.3 What does $TcpO_2$ measure?

The simplest answer is, that it measures the partial pressure of oxygen that diffuses from dermal capillary loops, and that is therefore not required for cellular metabolism. In unheated skin of normal healthy people, $TcpO_2$ has been found to average 2 – 3 mmHg with a range of 0 – 7 mmHg (Evans, N. T. S and Naylor, P. F. D., 1967a; Evans, N. T. S and Naylor, P. F. D., 1967b).

Keller describes a model of oxygen consumption in the skin in which skin is divided into three layers. Layer one is the zone around the ascending limb of the dermal capillary loop, in which oxygen diffuses from the capillary to supply adjacent cells. Layer two consists of the metabolically active cells superficial to the curve of the capillary loop that will demand oxygen. Layer three is made up of the non-metabolically active cells on the surface of the skin. $TcpO_2$ measures the unused oxygen that reaches the surface of the skin (Keller, H. P. *et al.*, 1978).

$TcpO_2$ can then be described by the following formula. (It should be remembered that diffusion of a gas in solution, in this case oxygen, is driven not by the concentration gradient, but by the partial pressure gradient.)

$$TcpO_2 = PaO_2 - \Delta PO_2(1) - \Delta PO_2(2) - \Delta PO_2(3) \qquad 1.$$

Where PaO_2 = arterial partial pressure of oxygen

ΔPO_2 = fall in oxygen tension in (1) layer 1, (2) layer 2, (3) layer 3.

From this it can be seen that $TcpO_2$ reflects the balance between oxygen delivered to the tissue, and oxygen consumed by the tissue. Both supply and demand will be affected by central and local factors. Central factors include cardiac output, blood pressure, oxygenation of blood and haemoglobin concentration. Local factors are local blood flow, local oxygen consumption (which may change in ischaemic skin) and local changes in diffusion conditions, such as oedema. In normal skin, with normal circulation, the local flow can increase under conditions of hyperaemia such that the oxygen offered to the tissue exceeds the demand.

Standardisation of blood flow conditions can be achieved by heating the skin and inducing maximum vasodilatation. With maximal hyperaemia the greatest volume of oxygen is available to the respiring cells in the skin. Under these conditions the effectiveness of local blood supply (E) can be measured as the percentage fraction of arterial PO_2.

$$E = \frac{TcpO_2}{PaO_2} \cdot 100 \qquad 2.$$

E is normally ~ 100 %. Under this condition of maximal hyperaemia, the $TcpO_2$ is almost equal to PaO_2. If the effectiveness of local blood supply (E) becomes smaller, then $TcpO_2$ becomes flow dependent.

Three other factors that have to be borne in mind are, the effect of heat on the oxygen haemoglobin dissociation curve, consumption of oxygen by the polarographic probe and the effect of heat on the metabolic rate of respiring cells in the skin. With heating of the skin to 43 °C, the temperature of capillary blood rises to about 41 °C. Every degree Celsius rise in blood temperature causes an approximate 5 % increase in oxygen release from haemoglobin (Clark, L. C. *et al.*, 1953). So the 4 °C increase will result in approximately 20 % more oxygen being made available. This changes equation 1 to

$$TcpO_2 = PaO_2 + \Delta PO_2(temp) - \Delta PO_2(1) - \Delta PO_2(2) - \Delta PO_2(3) \qquad 3.$$

Where $\Delta PO_2(temp)$ = partial pressure of oxygen due to heating effect

The probe electrode consumes oxygen thereby setting up a diffusion gradient to the probe. Under heating conditions the equation must then be modified to

$$TcpO_2 = PaO_2 + \Delta PO_2(temp) - \Delta PO_2(1) - \Delta PO_2(2) - \Delta PO_2(3) - \Delta PO_2(el) \qquad 4.$$

Where $\Delta PO_2(el)$ = partial pressure of oxygen consumed by the probe.

An assumption is made that the $\Delta PO_2(temp) \sim \Delta PO_2(el)$ and that the two cancel each other out. This appears to be valid for neonates with thin skin, and under these circumstances $TcpO_2$ can be used to non-invasively monitor PaO_2. This does not necessarily hold true for adults.

In summary, if blood flow is adequate $TcpO_2$ follows changes in arterial PO_2. If blood flow is compromised, and arterial PO_2 maintained, $TcpO_2$ follows changes in blood flow. It is this that makes $TcpO_2$ useful in the evaluation of patients with peripheral vascular disease. It is however important to bear in mind that some patients with peripheral vascular disease may have other pathology that compromises oxygenation and cardiac output. The use of the $TcpO_2$ index, the ratio of limb to chest $TcpO_2$, overcomes this problem in part.

The description given above is a simplification of the work of Lubbers, "Theoretical basis of transcutaneous blood gas measurements" (Lubbers, D. W., 1981). Some of the points will be expanded using Lubbers' arguments. In order to understand the physiology of oxygen delivery to and transport through skin and its subsequent measurement on the surface of skin, it is necessary to describe in more detail,

a) tissue oxygenation, oxygen consumption and blood supply of skin,

b) oxygen exchange through the epidermis,

c) the capillary loop model of epidermal O_2 supply

d) the effect of heating on the O_2 dissociation curve of haemoglobin and re-describe the O_2 dissociation curve to reflect arterio-venous differences in PO_2,

e) the effect of temperature on the PO_2 in the capillary dome

2.3.1 Tissue oxygenation, oxygen consumption and blood supply of skin

Under steady state conditions and normoxia, the supply of oxygen almost exactly meets the demand for oxygen. Oxygen consumption (VO_2) is the product of blood flow and oxygen extraction from the blood.

$$VO_2 = B \cdot (CaO_2 - CvO_2) \qquad 5.$$

Where B = blood flow

CaO_2 = concentration of oxygen in the blood at the arterial end of the capillary

CvO_2 = concentration of oxygen in the blood at the venous end of the capillary

It is important to distinguish between the concentration of oxygen and the partial pressure. The concentration is a function of the volume of oxygen bound to haemoglobin and in solution in plasma. Fully saturated haemoglobin binds 1.34 ml of oxygen per gram of haemoglobin. At a haemoglobin concentration in blood of 15 $g.dl^{-1}$, and at full saturation, 1 dl of blood contains 20.1 ml of oxygen bound to haemoglobin.

Oxygen consumption for unheated skin in a resting individual at room temperature is given as 3 $ml.kg^{-1}.min^{-1}$. As blood flow is described in terms of flow per 100 g of tissue per minute, oxygen consumption of skin is more conveniently expressed as 0.3 $ml.100\ g^{-1}.min^{-1}$.

If oxygen consumption is kept constant, equation 5 can be rewritten as

$$B \propto \frac{1}{(CaO_2 - CvO_2)} \qquad 6.$$

Therefore, when delivering a fixed volume of oxygen to the skin, if the blood flow is low the resultant oxygen extraction is high, with the CvO_2 after passage through the capillary being low and *vice versa*. The relationship is known as the "circulatory hyperbola" (figure 2.7).

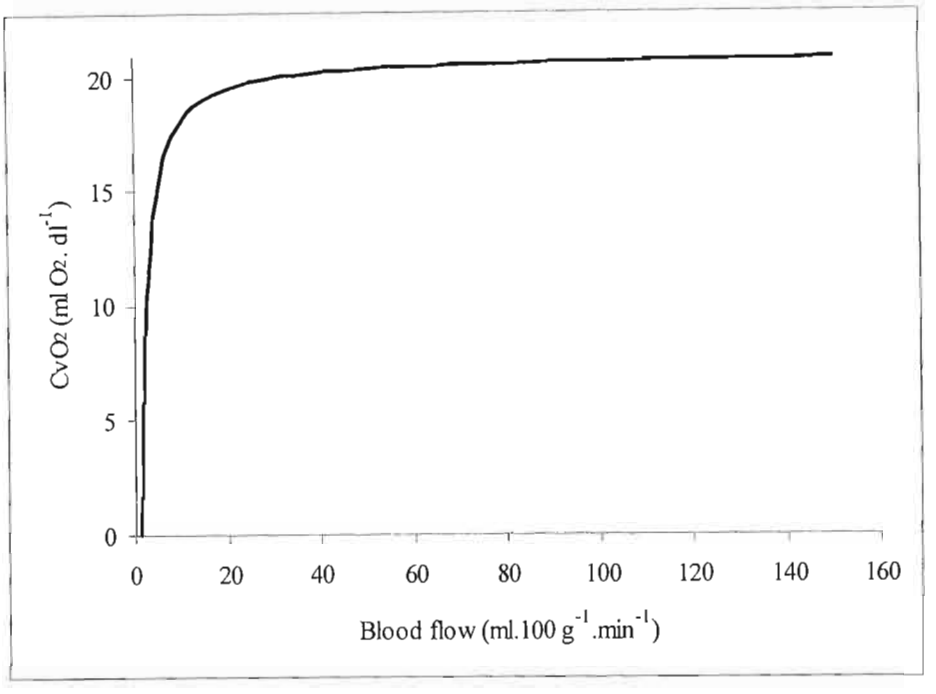


Figure 2.7. Blood flow is calculated from equation 5 with oxygen consumption assumed to be constant at 0.3 ml.100 g^{-1}.min^{-1} and arterial oxygen concentration = 21 ml.dl^{-1}.

As can be seen in figure 2.7, the CvO_2 relationship to blood flow is hyperbolic. There are three different regions in the curve. In the initial part of the curve, from blood flows of 0 - 5 ml.100 g^{-1}.min^{-1}, CvO_2 changes substantially with small changes in blood flow. These large changes in CvO_2 are an indication of increased oxygen extraction at low flow, in order to deliver a fixed volume of oxygen to the skin. The middle part of the curve is from blood flows of 5 – 90 ml.100 g^{-1}.min^{-1}, where CvO_2 changes with blood flow. In the third part, from 90 ml.100 g^{-1}.min^{-1}, CvO_2 is almost independent of flow. At high blood flow, very little oxygen is extracted from blood to meet the cellular demands and the venous oxygen concentration is accordingly high.

2.3.2 Effect of temperature

Blood flow is affected by temperature. At temperatures of 20 – 24 °C blood flow is ~ 0.5 – 1 ml.100 g^{-1}.min^{-1}. Under thermal neutral conditions the blood flow of the skin of the forearms, legs and trunk is 4 – 5 ml.100 g^{-1}.min^{-1} (Fagrell, B., 1995). This falls in the first zone of figure 2.7, in which blood flow is low and O_2 extraction is low. Above 29 °C blood flow increases more rapidly and maximum flow occurs at 45 °C, with maximum blood flow of the skin

reported at 100 ml.100 g^{-1}.min^{-1} and 160 ml.100 g^{-1}.min^{-1} (Edholm, O. G. *et al.*, 1956; Greenfield, A. D. M., 1963).

2.3.3 Oxygen exchange through the epidermis

Oxygen transport through the epidermis is by diffusion. The driving force of diffusion for a gas in solution is not the concentration difference, but rather the difference in partial pressure of the gas. Diffusion occurs across two compartments, the cellular region in which oxygen is consumed, and the acellular or dead portion made up of the *stratum corneum* and part of the *stratum granulosum*. The oxygen flux or rate of diffusion is different in these two compartments.

In the viable portion, the rate of diffusion will be affected by VO_2 and the thickness of the layer. In the non-viable region the rate of diffusion will be dependent on the partial pressure gradient and the resistance to diffusion, which will be a function of the diffusion distance and the O_2 conductivity of the *stratum corneum*.

2.4 The capillary loop model of epidermal O_2 supply

The loop structure of the dermal capillary provides an unusual situation in which the standard concepts of O_2 supply to tissue using the Krogh model of parallel straight capillaries do not necessarily hold true. In the Krogh model there is a constant decline in oxygen concentration from the arterial to venous end of the capillary. In the loop however, it is proposed that oxygen leaves the capillary in the ascending limb of the loop and the O_2 concentration falls. In the descending loop oxygen is taken up from the interstitial fluid and the oxygen concentration actually rises as the blood passes along the descending limb, thus creating an oxygen diffusion shunt. The descending limb "consumes" oxygen adding an additional demand for oxygen from the ascending limb. This causes the oxygen concentration in the ascending limb to fall rapidly, with the O_2 concentration in the "dome" of the capillary loop being the lowest. The effect of O_2 shunt diffusion on oxygen concentration in the capillary loop is shown in figure 2.8.

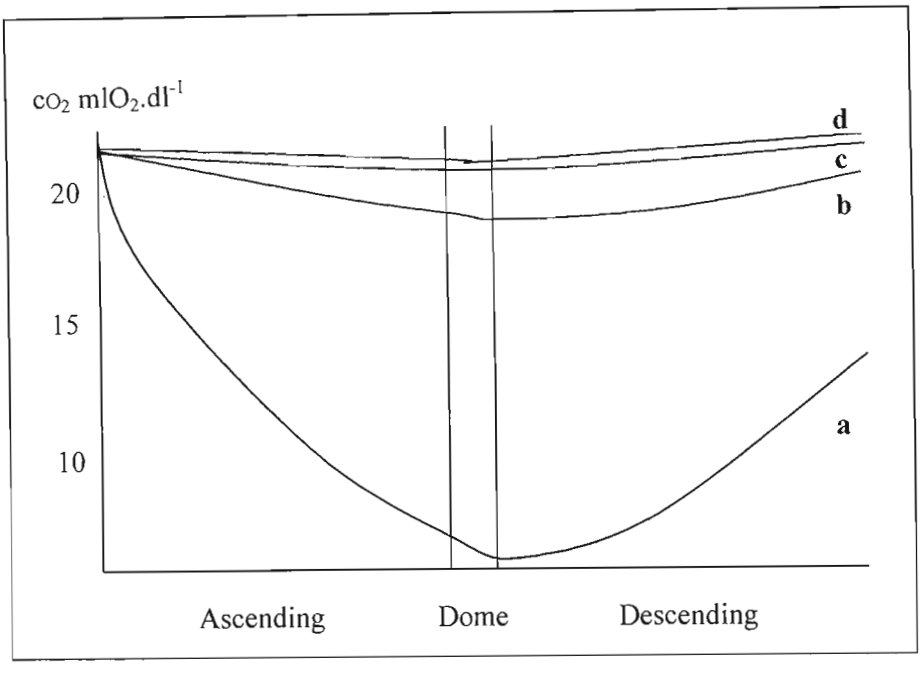


Figure 2.8. The effect of O_2 shunt diffusion on the oxygen concentration (cO_2 in $mlO_2.dl^{-1}$) in the dome and venous ends of the capillary loop. Curve **a** is calculated for a blood flow of 1.0 ml.100 $g^{-1}.min^{-1}$, curve **b** = 10 ml.100 $g^{-1}.min^{-1}$, **c** = 40 ml.100 $g^{-1}.min^{-1}$ and **d** = 100 ml.100 $g^{-1}.min^{-1}$. Drawn after (Lubbers, D. W., 1981).

From figure 2.8 it can be seen that at low flow rates the oxygen concentration in the dome is very low. In the Krogh model of straight capillaries the concentration at the dome, the middle of the capillary, would be half the value between the arterial and the venular ends. In the capillary loop model, the O_2 concentration in the dome would only approximate a value half that between the arterial and venular ends, at very high blood flow rates. The low O_2 concentration in the dome at normal and low blood flow probably explains why $TcpO_2$ is very low, 2 - 3 mmHg, when measured in unheated skin (Evans, N. T. S and Naylor, P. F. D., 1967a; Evans, N. T. S and Naylor, P. F. D., 1967b). At very high flow rates, the CaO_2 - CvO_2 difference is very small and the blood at the venular end of the capillary can be considered to be "arterialised". This, then, is the rationale for heating the skin under the $TcpO_2$ electrode.

2.4.1 The effect of heating on the O_2 dissociation curve of haemoglobin and re-description of the O_2 dissociation curve to reflect capillary arterio-venous differences in PO_2

The oxygen haemoglobin dissociation curve, is well known and is usually presented in the format of figure 2.9, with the y axis representing the percentage saturation of haemoglobin when exposed to different partial pressures of oxygen. The sigmoidal shape is due to the non-linear binding of oxygen to haemoglobin, resulting from changes in the arrangement of the haem moieties in haemoglobin as oxygen is bound. An increase in blood temperature is associated with a shift of the curve to the right.

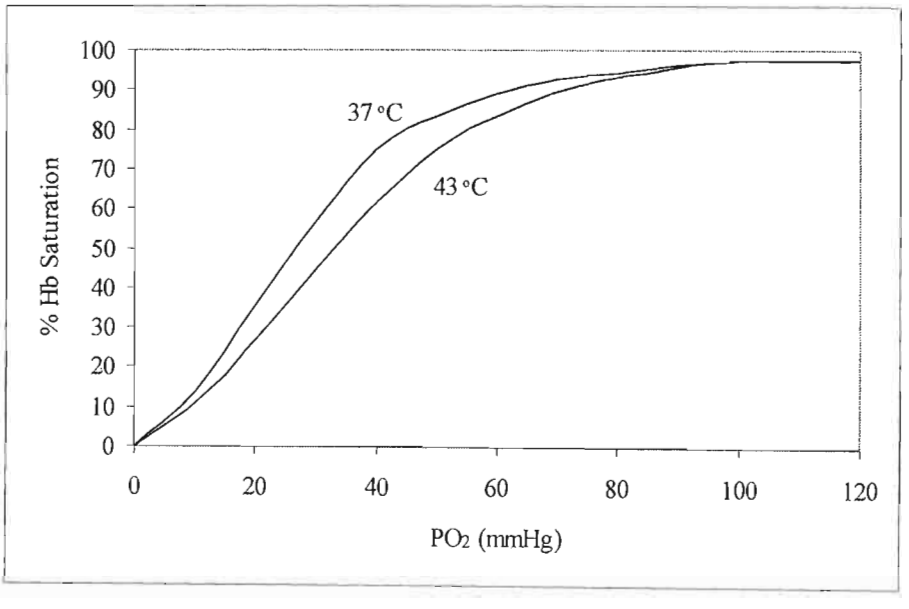


Figure 2.9. The oxygen haemoglobin dissociation curves of human blood at 37 °C and at 43 °C, showing the relationship between PO_2 and haemoglobin saturation.

The curve can also be presented in terms of the oxygen concentration in blood (figure 2.10).

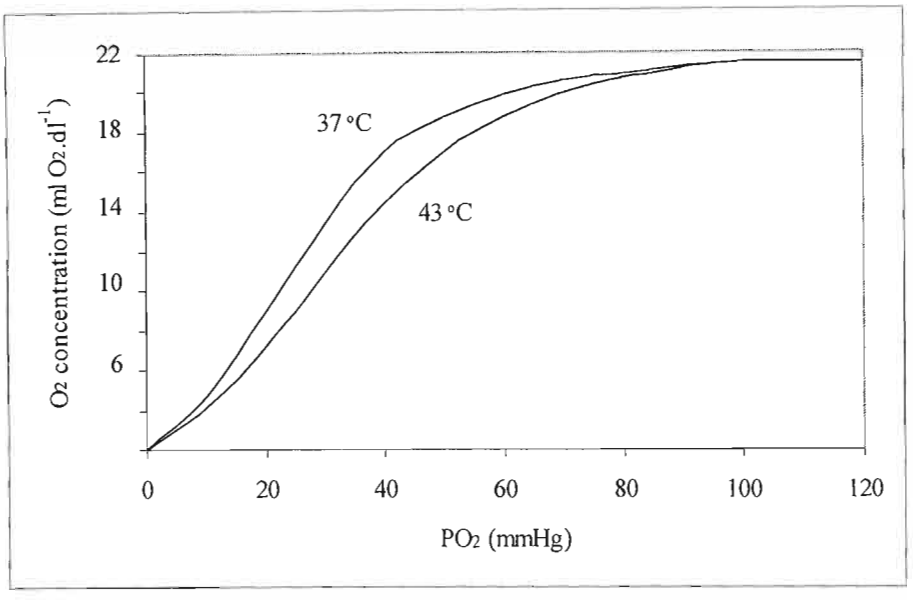


Figure 2.10. The oxygen haemoglobin dissociation curves of human blood at 37 °C and at 43 °C, showing the relationship between PO_2 and oxygen concentration in the blood.

What is the effect of the shift of the curve to the right at 45 °C? At the higher temperature, any given partial pressure of oxygen in blood will be associated with a lower concentration of haemoglobin bound oxygen *ie* more oxygen will have been released from haemoglobin.

As diffusion of oxygen in solution through the epidermis is dependent on the partial pressure of oxygen, and not its concentration, we need to describe the oxygen partial pressure gradient from the capillary to the skin surface. To do this, the changes in blood oxygen concentration depicted in the oxygen haemoglobin dissociation curve must be described in terms of changes in blood PO_2. This can be done by calculating the oxygen concentration difference CaO_2 - CvO_2, and then using this to extrapolate PO_2's from the oxygen haemoglobin dissociation curve. If skin oxygen consumption is taken as 0.3 ml O_2.100 g^{-1}.min^{-1}, blood flow as 100 ml.100 g^{-1}.min^{-1}, and using equation 5

$$VO_2 = B \cdot (CaO_2 - CvO_2) \qquad 5.$$

$$(CaO_2 - CvO_2) = \frac{0.3 \text{ ml } O_2.100 \text{ g}^{-1}.\text{min}^{-1}}{100 \text{ ml}.100 \text{ g}^{-1}.\text{min}^{-1}}$$

$(CaO_2 - CvO_2) = 0.3$ ml $O_2.dl^{-1}$

The skin blood flow of 100 ml.100 $g^{-1}.min^{-1}$ is chosen to represent the blood flow that would be associated with heating to maximal flow.

Knowing the oxygen concentration difference, the PO_2's at the arterial and venous ends of the capillary can be read off the dissociation curve. If for example the oxygen concentration at the arterial end is x ml $O_2.dl^{-1}$, the associated partial pressure of oxygen in blood would be y mmHg. To derive the PO_2 at the venous end, the PO_2 at an oxygen concentration of (x – 0.3 ml O_2.dl) is then read. The oxygen partial pressure difference between the arteriolar and venous ends of the capillary (PaO_2 - PvO_2) at any given PO_2 on the dissociation curve can then be calculated. The difference (PaO_2 - PvO_2) can then be plotted against PO_2 to give a modified dissociation curve (figure 2.11).

From figure 2.11 it can be seen that a blood PO_2 of 100 mmHg at 37 °C requires a PaO_2 - PvO_2 difference of 15 mmHg, whereas at 45 °C a difference of only 6 mmHg is needed.

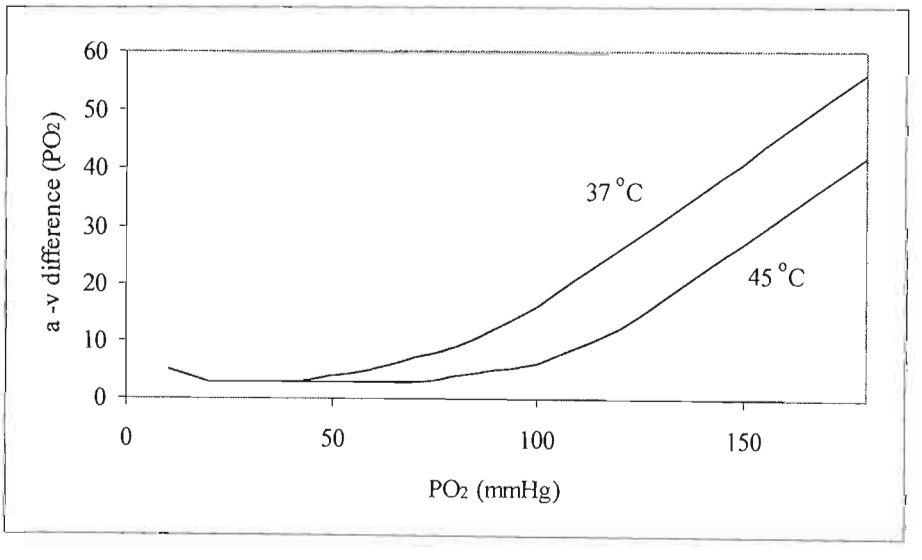


Figure 2.11. Capillary arterio-venous PO_2 difference plotted against blood PO_2. Curves have been generated based on a tissue VO_2 of 0.3 ml O_2.100 $g^{-1}.min^{-1}$ and blood flow of 100 ml.100 $g^{-1}.min^{-1}$, for temperatures of 37 °C and 45 °C.

2.4.2 The effect of temperature on the PO_2 in the capillary dome

Heating skin to 45 °C results in an almost linear temperature gradient through the skin. As the dermal capillary loops are usually perpendicular to the skin surface, blood will be warmed as it passes up the arterial arm of the capillary loop, and the effect of the shift in the oxygen haemoglobin dissociation curve will come into play. This will increase the blood PO_2 in the ascending limb, relative to its partial pressure in unheated skin, thereby increasing the oxygen partial pressure gradient driving diffusion of oxygen from the capillary to the skin surface. Indeed the temperature induced increase in PO_2 up the ascending limb is almost sufficient to maintain a constant PO_2 in the ascending limb. The increase in temperature will also increase skin oxygen consumption and alter the diffusion properties of O_2 in the epidermis.

2.5 Summary

To summarise the $TcpO_2$ measurement in the normal and dysvascular patient, the problem can be considered to one of oxygen supply and demand (Table 2.1).

Table 2.1. Summary of physiological compensation in heated and unheated skin of people with normal blood flow and patients with mild and severe peripheral arterial occlusive disease (PAOD), and the effect on $TcpO_2$.

	Normal	**Mild to moderate PAOD**	**Severe PAOD**
Blood flow	Normal	↓ Mild to moderate	↓ Severe
Unheated skin	Supply ≥ Demand	Supply ≥ Demand	Supply < Demand
Compensation	None	↑ O_2 extraction from Hb ie ↑ (CaO_2 - CvO_2), meets demand	↑ O_2 extraction from Hb ie ↑ (CaO_2 - CvO_2), fails to meet demand
$TcpO_2$ reading	2 –3 mmHg	Reduced, 0 mmHg	Reduced, 0 mmHg
Heated skin	↑ blood flow	↑ blood flow	↑ blood flow
Compensation	Supply > Demand	Supply > Demand, but because O_2 extraction already ↑, O_2 reserve is reduced	Supply < Demand, and ↑ O_2 supplied is consumed by cells. Insufficient O_2 reserve
$TcpO_2$ reading	Normal, 60 – 80 mmHg	Reduced 0 <60 mmHg	0 mmHg

2.6 Clinical support of the theoretical model

2.6.1 The role of the skin

Both skin thickness and capillary density will influence $TcpO_2$. Takiwaki, H. *et al.*, (1991) have shown that stripping the *stratum corneum* results in increased $TcpO_2$ values and Franzeck, U. K. *et al.*, (1984) and Slagsvold, C. E. *et al.*, (1991) have shown the relationship of capillary density and capillary morphology to $TcpO_2$.

2.6.2 The effect of altering blood flow

The theoretical relationship between oxygen delivery and blood flow proposed by Lubbers was confirmed in an elegant study by Tremper. Using an anaesthetised dog model they monitored arterial PO_2 (PaO_2), mean venous PO_2 (PvO_2), cardiac output (CO) and O_2 delivery during changes in inspired oxygen concentration (FIO_2) and standardised hypovolaemic shock. They confirmed that $TcpO_2$ followed PaO_2 during variations in FIO_2 when the cardiac output was in the normal range. In the active haemorrhage stage, PaO_2 remained constant while $TcpO_2$, PvO_2 and cardiac output decreased simultaneously. The $TcpO_2$ dropped from values approaching PaO_2 to PvO_2 and fell to below PvO_2 when $TcpO_2$ was less than 20 mmHg. They concluded that $TcpO_2$ is an accurate non-invasive method for monitoring peripheral oxygen delivery and is a valuable tool for the study of disturbed circulation in various shocked states. In low flow hypovolaemic shock $TcpO_2$ follows O_2 delivery (the product of blood oxygen content and flow) and not PaO_2, with the hypovolaemic study demonstrating that $TcpO_2$ is a sensitive indicator of peripheral perfusion (Tremper, K. K. *et al.*, 1979).

These observations were confirmed in a porcine model by Rowe, M. I. and Weinberg, G., (1979) and subsequently in a clinical setting by Tremper, K. K. *et al.*, (1980) and Tremper, K. K. and Shoemaker, W. C., (1981) who reported observations of patients in an intensive care unit who underwent continuous $TcpO_2$ monitoring and frequent haemodynamic monitoring during cardiac decompensation, arrest, and cardiopulmonary resuscitation. The weighted mean correlation coefficients between $TcpO_2$ and O_2 delivery as well as between $TcpO_2$ and cardiac output were 0.94 and 0.96, respectively. During cardiac decompensation, the cardiac output, $TcpO_2$, and mixed venous oxygen tension fell, with the $TcpO_2$ falling below the PvO_2 when the $TcpO_2$ was less than 25 mmHg. A $TcpO_2$ greater than 40 mmHg

corresponded to normal cardiac index, O_2 delivery, VO_2, PvO_2, and arterial pH, while a $TcpO_2$ of less than 25 mmHg corresponded to large reductions of these variables.

This enabled Shoemaker, W. C. and Vidyasagar, D., (1981) to propose the following framework for interpreting $TcpO_2$ values, beginning with the premise that $TcpO_2$ values are dependent on both PaO_2 and flow:

a) when flow is adequate, $TcpO_2$ follows PaO_2
b) when flow is compromised but PaO_2 is adequate, $TcpO_2$ tracks flow
c) throughout both of these circumstances and when both saturation and flow are compromised, $TcpO_2$ follows oxygen delivery.

Eickhoff investigated the effect of heating on autoregulation of skin blood flow by studying $TcpO_2$ in both unheated and heated skin in elevated and dependent legs. Additional changes in venous pressure were induced by blood pressure cuff inflation. Using a heating probe set at 43 °C and inferring skin blood flow from the energy required to maintain the probe temperature, they confirmed that heating abolished autoregulation and normal vasoconstrictor responses, and showed $TcpO_2$ to positively correlate to mean arterial pressure, perfusion pressure and venous pressure. They proposed that $TcpO_2$ is a function of the blood flow under the probe and that it is a parameter determined by many variables of which arterial pressure is of particular clinical importance (Eickhoff, J. H. *et al.*, 1980; Eickhoff, J. H. and Jacobsen, E., 1980).

Following up on Keller's report of the use of $TcpO_2$ to monitor skin flaps in an animal model (Keller, H. P. *et al.*, 1978) Achauer confirmed that that $TcpO_2$ followed FIO_2 in skin flaps in a rabbit model. Again the potential use of $TcpO_2$ in prediction of flap survival was proposed (Achauer, B. M. *et al.*, 1979).

2.7 $TcpO_2$ and peripheral vascular disease

In patients with peripheral vascular disease (PVD) it is the metabolic status of the tissues that determines when the haemodynamic impairment becomes clinically and symptomatically significant. $TcpO_2$ gives an indication of the relationship between a haemodynamically critical stenosis and a metabolically critical stenosis.

Initial use of $TcpO_2$ was as a non-invasive measure of arterial PO_2. After promising results in neonates, attempts were made to confirm its validity in adults. As has been described in the studies in shock models, $TcpO_2$ is dependent not only on PaO_2 but also blood flow. In 1978

Tonnesen reported on $TcpO_2$ measurements made in patients with imminent foot gangrene. Using a tilt table to alter hydrostatic pressure and hence perfusion pressures, he found that oxygen tension reached zero at a toe systolic blood pressure of 5 - 10 mmHg (tilt toe up) and reached arterial oxygen tension at about 50 to 70 mmHg (tilt toe down). In legs with severe arterial obstruction and ischaemic rest pain, oxygen tension rose from zero only when systolic toe blood pressure reached 20 - 50 mmHg. Using 90m Tc-pretechnetate and histamine isotope washout, significant isotope clearance was seen at low $TcpO_2$ pressures. This he attributed to a "gas leak" from the arterioles into the surrounding tissue counter current gas shunting (Tonnesen, K. H., 1978).

$TcpO_2$ was then investigated in many situations of altered blood flow. Initially these involved comparison of values in normal control subjects with patients with PVD (Matsen, F. A. 3d *et al.*, 1980; White, R. A. *et al.*, 1982). The use of $TcpO_2$ to distinguish between Fontaine grades and thus the severity of PVD was investigated (Clyne, C. A. et al, 1982; Becker, F., 1985). Its use in amputation surgery and wound healing prediction soon followed. This included prediction of ulcer healing and flap survival (Keller, H. P. *et al.*, 1978; Rhodes, G. R. and Cogan, F., 1985). As it became apparent that absolute $TcpO_2$ could not always readily determine healing outcome, additional tests and manoeuvres were introduced to augment the use of absolute $TcpO_2$. These include postural change, either elevation or dependency (Franzeck, U. K. *et al.*, 1982; Matsen, F. A. 3d *et al.*, 1984), hyperaemic response to ischaemia (Kram, H. B. *et al.*, 1984; Kram, H. B. *et al.*, 1985), exercise (Ohgi, S. *et al.*, 1981; Hauser, C. J. and Shoemaker, W. C., 1983), inhalation of various concentrations of oxygen (Harward, T. R. *et al.*, 1985; Rhodes, G. R. and Cogan, F., 1985) and use of a reference point as in the $TcpO_2$ Index (Kram, H. B. and Shoemaker, W. C., 1983; Mustapha, N. M. *et al.*, 1983). The influence of diabetes mellitus on $TcpO_2$ predictive values was investigated (Hauser, C. J. *et al.*, 1984; Wyss, C. R. *et al.*, 1984; Wyss, C. R. *et al.*, 1987).

$TcpO_2$ was compared with numerous other tests and investigations, including pulse status, angiographic scores (Becker, F., 1985; Byrne, P. *et al.*, 1984), segmental systolic pressures (Cina, C. *et al.*, 1984), Doppler pressure indices (Cina, C. *et al.*, 1984; Matsen, F. A. 3d *et al.*, 1980), toe systolic pressures, plethysmography (Becker, F., 1985), pulse volume recordings (Hauser, C. J., 1987), ^{133}Xe, thermography and skin temperature (Vincent, J. L. *et al.*, 1988; Wagner, W. H. *et al.*, 1988), flourescein angiography (Wagner, W. H. *et al.*, 1988) and laser Doppler (Caspary, L. *et al.*, 1987; Matsen, F. A. 3d *et al.*, 1984).

Having gained acceptance as a reputable test, it was soon used to evaluate skin oxygenation, and by implication the status of skin blood flow, albeit with some difficulty to replicate in

terms of prediction of amputation wound healing. It became a standard means of evaluating the efficacy of drugs on peripheral circulation (Peabody, J. L., 1979; Sunder-Plassmann, L. *et al.*, 1981). Apart from measuring change after drug treatment it was used to measure change in blood flow during and after revascularisation surgery to predict successful outcome of surgery and to monitor for subsequent occlusion (Gannon, M. X. *et al.*, 1986; Kram, H. B. *et al.*, 1984; Kram, H. B. and Shoemaker, W. C., 1983). This evolved into its use as an indication for the need for treatment and prediction of outcome and more recently it has been incorporated in and used to direct decisions in treatment algorithms (Batay-Csorba, P. A. *et al.*, 1987; Bunt, T. J. and Holloway, G. A., 1996).

In other branches of medicine it was widely used in neonatal monitoring as a non-invasive measure of arterial PO_2, or at least as an indication of change in arterial PO_2 (Friis Hansen, B., 1977; le Souef, P. N. *et al.*, 1978). It was also extensively investigated as a means of foetal monitoring in obstetric practice (Fall, O. *et al.*, 1979; Weber, T. and Secher, N. J., 1980). Prior to the advent and implementation of pulse oxymetry it was used to monitor PO_2 during anaesthesia (Eberhard, P. and Mindt, W., 1981; Odoom, J. A. *et al.*, 1986) and in the ICU setting (Al-Diaidy, W. *et al.*, 1977; Tremper, K. K. and Shoemaker, W. C., 1981).

The use of $TcpO_2$ has been suggested in the diagnosis of arterial trauma (Kram, H. B. *et al.*, 1984; Kram, H. B. and Shoemaker, W. C., 1984), investigation of chronic venous insufficiency (Neumann, H. A. *et al.*, 1984; Quigley, F. G. and Faris, I. B., 1989), Buerger's disease (Insall, R. L. *et al.*, 1989), and Raynaud's phenomenon (Wollersheim, H. and Thien, T., 1988). It is routinely used in monitoring and evaluation of hyperbaric oxygen therapy (Mathieu, D. *et al.*, 1990; van der Kleij, A. J. *et al.*, 1997). More recently it has been used in evaluating the effects on skin blood flow of spinal cord stimulation, in patients with PVD not suitable for reconstructive surgery (Kumar, K. *et al.*, 1997; Sciacca, V. *et al.*, 1986).

2.8 $TcpO_2$ Index

In 1983, Hauser, C. J. and Shoemaker, W. C., 1983 proposed the use of a $TcpO_2$ regional perfusion index (RPI), the limb to chest ratio, to "... develop $TcpO_2$ measurements into a practical method for assessing peripheral vascular disease...". Their rationale was based on observations that $TcpO_2$ is a function of total oxygen delivery (DO_2), where DO_2 is the product of the cardiac index (cardiac output per square meter body surface area) and arterial oxygen content (Tremper, K. K. *et al.*, 1979). They assumed that the wide variability noted when $TcpO_2$ was used to assess PVD might be due to variations in systemic DO_2. The limb to

chest index would be independent of DO_2 and should reflect local limb oxygen supply and demand relationships.

They studied the effect of postural change and exercise on both absolute $TcpO_2$ and the index in young and older asymptomatic subjects, and older subjects with intermittent claudication. They reported the following observations: "... the test is easy to perform, reproducible, non-invasive, highly specific and directly reflective of the underlying vascular pathophysiology." and "Use of the RPI obviates the effects of cardiopulmonary function upon local $TcpO_2$, resulting in an accurate and usable index of local limb perfusion."

2.8.1 Use of the $TcpO_2$ Index in monitoring revascularisation

Kram followed up Hauser's work in 1983 with a report on the use of both absolute $TcpO_2$ and the Index in monitoring successful revascularisation of a patient with an acute arterial occlusion (Kram, H. B. and Shoemaker, W. C., 1983). Gannon, M. X. *et al.*, (1986) investigated the use of the index before during and after reconstructive surgery. The index was not found to be any better than absolute $TcpO_2$ in the assessment of the severity of disease but they did find the index useful in monitoring the efficacy of arterial reconstruction during and after surgery. They proposed that an immediate rise in the index on reperfusion obviated the need for completion angiography.

Osmundson, P. J. *et al.*, (1988) reported the foot index to differentiate between severe and mild ischaemia, and that revascularisation led to an increase in the index. Moosa, H. H. *et al.*, (1988) also showed that absolute $TcpO_2$ and the $TcPO_2$ index are equally effective in monitoring peripheral arterial insufficiency before and after surgery. The use of the index and absolute $TcpO_2$ to assess the need for urgent revascularisation and post operative prediction of successful outcome was proposed by Lalke *et al.* An index of 0.46 or less and an absolute $TcpO_2$ of 22 mmHg or less was associated with a need for urgent revascularisation. Postoperatively an Index of 0.53 or an absolute value of 22 mmHg indicated that the revascularisation was likely to fail (Lalka, S. G. *et al.*, 1988).

2.8.2 The relationship of the $TcpO_2$ Index to PVD and diabetes

In 1984 Hauser *et al.* reported the use of the index in determining the severity of limb hypoxia in the feet of Diabetics. They again pointed out both the stability of the index, to within $1 - 2\ \%.h^{-1}$ despite momentary changes in cardiorespiratory status, and the observation that

the index removes changes in absolute $TcpO_2$ associated with age. In patients with comparable vascular disease status, they found the index values in diabetic patients to be the same as those in non diabetic patients (Hauser, C. J. *et al.*, 1984). They also compared the diagnostic value of the index against Doppler ankle-brachial pressure ratios, pulse volume recordings and toe pulse reappearance time in 64 limbs of patients with diabetes. These limbs were clinically classified into groups based on claudication, rest pain, and the presence of gangrene. The $TcpO_2$ index had a significantly higher diagnostic accuracy than the other tests and the degree of hypoxia observed correlated with clinical symptoms (Hauser, C. J. *et al.*, 1984a; Hauser, C. J. *et al.*, 1984b).

Kram, H. B. *et al.*, (1984) showed the index at the foot to be significantly lower in patients with PVD and in patients who had undergone unsuccessful revascularisation, than in controls. Arnold, T. *et al.*, (1993) found the index to discriminate between the severity of vascular disease in diabetics and to indicate the efficacy of revascularisation.

Insall, R. L. *et al.*, (1989) used the index to evaluate the worth of Buerger's test in claudicants with arteriosclerosis obliterans admitted for vascular surgery. Doppler and transcutaneous oxygen pressures and indices were significantly lower in Buerger test positive legs.

2.8.3 The $TcpO_2$ Index and venous ulcers

Stacey, M. C. *et al.*, (1987) used the index, based on an upper arm reference point, to investigate the lower limb skin perfusion in patients with venous ulcers. They showed the unaffected contralateral leg to have significantly higher values than the affected limb, and significantly reduced index values when compared to age and sex matched controls. They followed this up with a study in which the $TcpO_2$ index was assessed as an indicator of risk of re-ulceration in 68 limbs with healed venous ulcers. The indices of limbs that re-ulcerated were not significantly lower than those of limbs that remained healed at 1 year. A high index was not shown to be beneficial in preventing ulcer recurrence (Stacey, M. C. *et al.*, 1990).

2.8.4 $TcpO_2$ Index and venous incompetence.

Scott used $TcpO_2$, laser Doppler flowmetry and video capillary microscopy, to investigate changes in leg skin, in supine and dependent positions, in normal controls and patients with superficial venous incompetence and deep venous incompetence. There was a decrease in the $TcpO_2$ index in all three groups on dependency, which they attributed to the veno-arteriolar

reflex (Scott, H. J. *et al.*, 1990). This is in contrast to Hauser's initial paper on the use of the index where the Index was higher in the erect position than when supine in both controls and patients with PVD (Hauser, C. J. and Shoemaker, W. C., 1983).

2.9 Summary

Absolute $TcpO_2$ and the $TcpO_2$ Index have been examined in various clinical settings in patients with peripheral vascular disease. The majority of reports show both absolute $TcpO_2$ and the $TcpO_2$ Index to be of use in demonstrating alteration of blood flow, in PVD or improved blood flow following revascularisation. The $TcpO_2$ Index theoretically removes the influence of variables associated with oxygen delivery.

Chapter 3

$TcpO_2$ Measurement – Methodology

3.1 Apparatus

Four commercially available $TcpO_2$ monitors were used at different times during the study - two Hellige Servomed transcutaneous oxygen monitors and two Hewlett Packard oxygen monitors (figure 3.1).

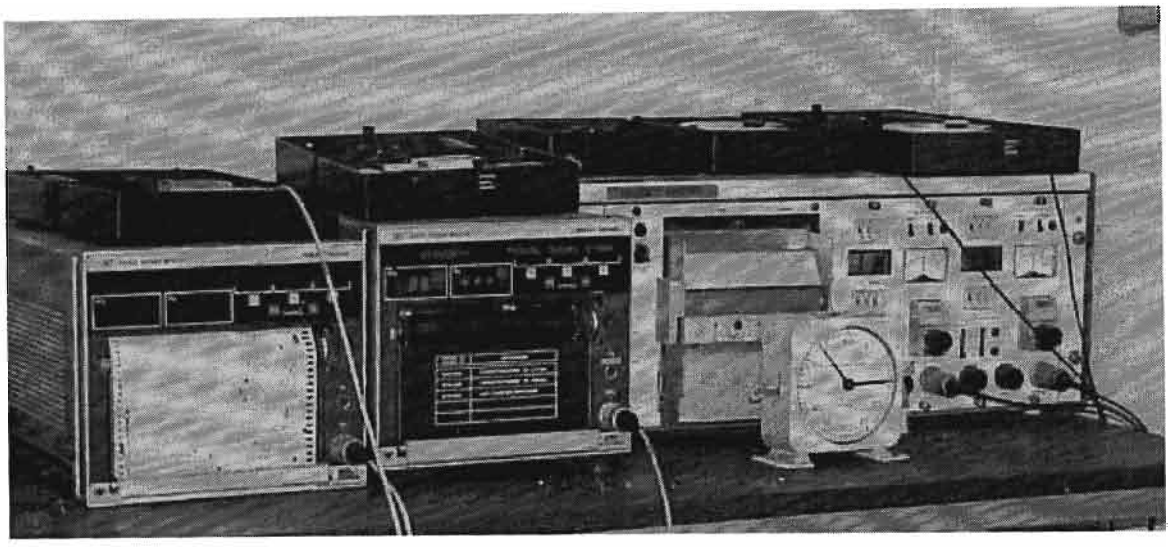


Figure 3.1. Hewlett Packard and Hellige Servomed transcutaneous oxygen monitors used for the studies.

3.2 Machine calibration

The machines were set up and calibrated according to the manufacturers instructions. After an initial warm up period of 15 minutes the calibration procedure was started. The first step was calibration to room air. Changes in barometric pressure are automatically taken into account by the monitor. This was followed by zero calibration, which involves placing a drop of zeroing fluid on the membrane of the probe, over the glass ring of the electrode. After zeroing, the solution was wiped off the membrane and the machine automatically recalibrated against room air. Recalibration was performed for each patient tested to minimise the chances of machine drift during the course of a day.

The membranes and electrolyte solution in the miniaturised Clark electrodes were replaced every 2 weeks, or sooner if problems were experienced during the zeroing procedure. The membranes, retaining rings and electrolyte solution used were obtained from the manufacturer's agents.

3.3 Patient positioning and acclimatisation

Patients lay supine on the examination couch, with two pillows provided, for 20 minutes while the machine stabilised. The non-invasive laboratory is air-conditioned and the temperature is usually maintained at 20 – 22 °C, although this was not always the case. The limb being assessed was left exposed. Patients were asked to keep as still as possible during measurements. This was not always possible, bearing in mind that testing procedure took between 45 minutes and an hour on average and some patients had rest pain.

Patients with orthostatic dyspnoea needed to be positioned in a less recumbent position. All measurements were made without the patients being on supplemental oxygen.

3.4 Probe attachment

The sites to be measured were first cleaned with an alcohol solution and shaved if necessary. The probe was attached to the skin using a double-sided adhesive ring over a drop of distilled water. On occasion it was noted that the contact solution leaked out through wrinkles in the adhesive ring and the probe was re-sited. Rarely the probe worked loose from the adhesive ring, usually as the result of patient movement. When this happened the TpO_2 readings rose rapidly to approximate atmospheric PO_2 of ~ 156 mmHg. The probe was then re-sited.

Care was taken to position the patients in such a way so as not to apply any pressure on the probe, as this would result in diminished skin blood flow. The cable of the probe was loosely attached to the skin using adhesive tape so as to reduce the likelihood of the probe being pulled off the skin.

3.5 Probe siting

Depending on the study being performed, $TcpO_2$ measurements were made at several of the following sites (Figure 3.2).

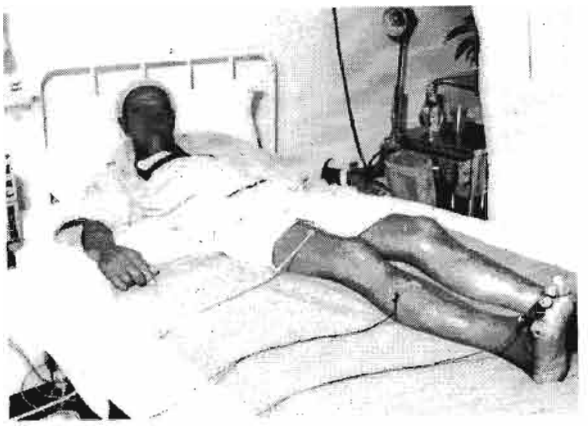


Figure 3.2. Patient with a gangrenous fourth toe. $TcpO_2$ electrodes positioned on the dorsum of the foot, the below knee and above knee sites.

3.5.1 Chest

The chest reference probe was placed on the left anterior chest wall, 5 cm below the clavicle in the mid-clavicular line.

3.5.2 Above knee site

Above knee (AKA) measurements were routinely made 10 cm proximal to the patella in the anterior midline. If the $TcpO_2$ value obtained indicated that healing would not occur at that level, the probe was moved 10 cm proximally and the test repeated. If the repeated measurement also revealed inadequate oxygen it was repeated a further 10 cm proximally.

3.5.3 Below knee site

Below knee (BKA) measurements were made at the proposed anterior skin flap margin. This was standardised at 10 cm below the tibial tuberosity and 2 cm lateral to the tibial margin, over the anterior compartment of the leg. The site was used for $TcpO_2$ measurement in patients who had already undergone Guillotine amputation.

3.6.4 Foot

For measurements made on the foot, the probe was routinely placed on the mid-dorsum of the foot. If ulceration or gangrene of the foot precluded use of this site, the probe was placed on the margin of the ulcer or gangrenous area on the dorsum of the foot as near to the mid-dorsum site as possible.

3.7 Probe temperature

All measurements were made with the heating thermistor set at 45 °C based on the arguments presented in chapter 2. The manufacturers warn of the possibility of this temperature causing burns. While this has been reported in long term neonatal monitoring, in our experience of measuring adults with thicker skin, no patient developed a burn as a result of $TcpO_2$ measurement. A local area of hyperaemia was noted in fair skinned patients after removal of the probe, and this resolved within 30 minutes on average.

3.8 Stabilisation time

The manufacturers state that stabilisation occurs within 15 minutes and recommend that $TcpO_2$ readings can be taken 15 minutes after starting the test. Early observation using the oximeters lead us to believe that stabilisation may not have occurred after 15 minutes in all patients. A pilot study was conducted in which $TcpO_2$ was measured in the routine manner at the different levels and values were recorded 5, 10, 15 and 20 minutes after starting the test. The subject population consisted of "normal" controls and patients with peripheral vascular disease, tables 3.1, 3.2 and 3.3.

Table 3.1. Mean $TcpO_2$ values (mmHg) and 1 SD, obtained 5, 10, 15 and 20 minutes after starting the test.

	Foot	BKA	AKA	Chest
n =	62	107	79	55
5 min	31.6 ± 18.4	38.6 ± 22.0	43.2 ± 20.8	53.5 ± 12.6
10 min	38.9 ± 20.9	47.2 ± 20.1	52.4 ± 19.2	59.5 ± 11.8
15 min	44.3 ± 20.9	52.3 ± 18.3	56.4 ± 18.0	60.9 ± 11.9
20 min	45.6 ± 20.2	54.2 ± 17.4	56.9 ± 17.9	61.5 ± 12.1

Table 3.2. The mean differences in $TcpO_2$ measurements (mmHg) and 1 SD, of sequential readings taken 5 minutes apart.

	Foot	BKA	AKA	Chest
n =	62	107	79	55
5 – 10 min	7.3 ± 10.6	8.6 ± 8.8	9.2 ± 7.7	6.0 ± 5.9
10 – 15 min	5.4 ± 7.4	5.1 ± 6.7	4.0 ± 4.7	1.4 ± 3.2
15 – 20 min	1.3 ± 3.9	1.9 ± 3.9	0.5 ± 2.4	0.6 ± 2.9

Table 3.3. The median increase, maximal increase and the percentage of subjects in whom the increase in $TcpO_2$ was 5 mmHg or more, at the various sites, for readings taken at 15 and 20 minutes.

	Foot	BKA	AKA	Chest
n =	62	107	79	55
Median	1	2	0	0
Max change	17	18	11	10
% ≥ 5 mmHg	14.5	15.9	0.6	9.1

The changes in $TcpO_2$ between 5 minute time intervals were analysed by repeated measures ANOVA and post hoc testing using the Tukey-Kramer test to determine if there was a difference between mean values at 15 minutes and 20 minutes, table 3.4.

Table 3.4. Results of analysis of the changes in $TcpO_2$ values at 5 minute intervals by repeated measures ANOVA and post hoc testing.

	Foot	BKA	AKA	Chest
ANOVA	< 0.0001	< 0.0001	< 0.0001	< 0.001
5 – 10 min	< 0.001	< 0.001	< 0.001	< 0.001
10 – 15 min	< 0.001	< 0.001	< 0.001	> 0.05
15 – 20 min	> 0.05	> 0.05	> 0.05	> 0.05

It was noted that there was no significant difference in the $TcpO_2$ recorded after 15 minutes and after 20 minutes at any of the sites and that stabilisation appears to occur sooner at the Chest. In light of the finding that in up to 16 % of subjects, an increase in $TcpO_2$ of 5 mmHg or more occurred between the 15 and 20 minutes measurements, it was decided to extend the stabilisation time from 15 to 20 minutes. It should also be noted that stabilisation appears to occur sooner on the chest site than at a peripheral site. The effect of this on the $TcpO_2$ Index is that an Index reading made after 10 or 15 minutes would be lower than a measurement recorded after 20 minutes.

3.9 $TcpO_2$ patient data sheet

Patient information was recorded on a standardised patient data sheet (Appendix A). Information was entered on admission to hospital and the hospital notes were reviewed on discharge. In some studies, $TcpO_2$ measurements were not always taken at all four sites for one limb and simultaneous measurement of chest and limb $TcpO_2$ was not always feasible.

Chapter 4

$TcpO_2$ in Control Subjects

4.1 Introduction

In this chapter, the literature on $TcpO_2$ and the $TcpO_2$ Index measurement in control subjects will be reviewed and summarised. Clinical data on control subjects collected in our studies will be presented and compared with the relevant data from the literature.

4.2 Literature review

Measurement of $TcpO_2$ in controls is subject to the same variability of machine, probe temperature, probe placement and stabilisation time to be discussed in chapter 10. Furthermore an assumption is made that the subjects do indeed have normal oxygen delivery. It became apparent from early studies that "normal" $TcpO_2$ tends to vary with age and in some instances gender (Ohgi, S. *et al.*, 1981; Yip, W. C. *et al.*, 1983). In older control subjects $TcpO_2$ values tended to decrease as measurements were made more distally. In these older subjects several factors have to be considered. Skin thickness decreases with age and should theoretically be associated with higher $TcpO_2$ values. However capillary density in the limbs also decreases with age, reducing $TcpO_2$ values (Takiwaki, H. *et al.*, 1991; Slagsvold, C. E. *et al.*, 1991). With increasing age it is possible that some of the control subjects may have mild impairment of pulmonary or cardiac function, which would reduce oxygen delivery and reduce $TcpO_2$.

4.2.1 Absolute $TcpO_2$

The following 20 papers that present data on Control subjects were analysed (Table 4.1).

Table 4.1. Previous studies presenting absolute $TcpO_2$ data on control subjects, clinically free of peripheral vascular disease. Numbers in parentheses indicate the number of limbs studied if different to the number of patients (n) in the study.

Author	n =	Age (y)	Chest (mmHg)	AKA (mmHg)	BKA (mmHg)	Foot (mmHg)
Matsen	13	22 - 35	84.1 ± 14.7	73.5 ± 13.8	75.9 ± 11.8	62.4 ± 13.1
Ohgi	30	23 -34	73 ± 11		70. ± 9	
Clyne	10	51 - 80		64.2 ± 6.0	63.4 ± 4.7	59.4 ± 3.7
Dowd	73	50 - 85				70 ± 9
Franzeck	24	19 - 75	64.2 ± 10.8		56.8 ± 9.9 (35)	
Dowd	91	12 - 94	69 ± 11		69 ± 9	
	25				70 ± 9	67 ± 11
Fairs	5				81.8 ± 3.8	
Mustapha	6	17 - 25	80.9 ± 9.2		92.3 ± 8	
	6	54 - 64	67.9 ± 14.4		78.7 ± 7.6	
Hauser	6	25 – 35	78.8 ± 7.6 (12)	73.8 ± 11.1(12)	70.0 ± 12.1(12)	69.8 ± 5.2 (12)
	6	55 - 65	63.5 ± 9.4 (12)	64.3 ± 6.6 (12)	56.4 ± 9.7 (12)	58.9 ± 3.5 (12)
Bongard	50					54.5 ± 7
Benscoter	21	17 - 72	67.3 ± 9.4	64.3 ± 8	60.5 ± 7	54.4 ± 9.7
Cina	22	22 – 35	82 ± 6		74 ± 6	75 ± 5
	10	45 - 77	66 ± 3		64 ± 4	63 ± 4
Byrne	36	25 - 79		65.8 ± 7.8	63.3 ± 7.8	60.1 ± 6.8
Kram	22	20 - 70	54.5 ± 9.2		53.1 ± 14.9	47.2 ± 11.6
McCollum	17	63 ± 12		64 ± 10 (11)	59 ± 10 (17)	5 7 ± 10 (11)
Oh	36					60.1 ± 7.1
Gannon	10	31				72.8 ± 7.5
Becker						67 ± 7
Allen	21	21 -81				60.1 ± 9.8
Luciani	52	20 - 65				45.1± 14.1

Note: the data has in some instances been converted from kiloPascals (kPa) and where standard errors of the mean were presented, these have been converted to standard deviations. In some papers the data were extracted from figures, when not given in tabular form or in the text.

(Matsen, F. A. 3d *et al.*, 1980; Ohgi, S. *et al.*, 1981; Franzeck, U. K. *et al.*, 1982; Dowd, G. S. *et al.*, 1982; Clyne, C. A. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Dowd, G. S. *et al.*, 1983; Hauser, C. J. and Shoemaker, W. C., 1983; Bongard, O. and Krahenbuhl, B., 1984; Cina, C. *et al.*, 1984; Kram, H. B. *et al.*, 1984; Byrne, P. *et al.*, 1984; Benscoter, J. L. *et al.*, 1984;

Becker, F., 1985; McCollum, P. T. *et al.*, 1986; Gannon, M. X. *et al.*, 1986; Allen, P. I. and Goldman, M., 1987; Fairs, S. L. *et al.*, 1987; Oh, P. I. *et al.*, 1987; Lusiani, L. *et al.*, 1988)

In only 4 studies shown in table 4.1, was $TcpO_2$ measured at all sites, including the chest. Most studies focussed on the foot. The averages of the pooled data are shown in table 4.2. As there are major differences in sample sizes in the various studies, it is not appropriate to merely average the results of the studies. To overcome this problem the weighted mean was calculated. Every mean given in the table 4.1 was multiplied by the number of limbs studied. The products obtained were summed and divided by the sum of the number of limbs studied. This was done for each amputation level and gives the correct mean for any given level. As the individual $TcpO_2$ values of every subject in each study were not available, it was not possible to calculate the standard deviation.

Table 4.2. Summary of the absolute $TcpO_2$ data in table 4.1. The average of the $TcpO_2$ means (mmHg) presented in table 4.1 is shown as the uncorrected mean. The mean calculated from the sample size is presented as the corrected mean. The data represents all age groups.

		Chest	**AKA**	**BKA**	**Foot**
All	Studies	12	7	17	17
	n =	257	109	350	430
Uncorrected	mean	70.9 ± 9.0	67.1 ± 4.5	68.1 ± 10.3	61.0 ± 8.1
Corrected	mean	69.8	66.4	66.6	60.0

Analysis of variance (ANOVA) shows a statistical difference between the means at the four sites measured ($p = 0.0263$). Post hoc testing using Tukey-Kramer multiple comparisons test revealed a significant difference between the means at the Chest and the Foot ($p < 0.05$).

The studies reported looked at different age ranges and this may account for the statistical difference noted. The influence of age was examined by comparing studies in which the age groups were adequately defined (table 4.3).

Table 4.3. Summary of studies in which the patient populations were either younger or older than 35 years. Uncorrected and corrected mean $TcpO_2$ is expressed in mmHg.

		Chest	AKA	BKA	Foot
Younger than 35 y	Studies	4	1	4	2
	n =	71	13	71	35
Uncorrected	mean	80 ± 4.9	73.5	78.1 ± 9.8	68.7 ± 8.9
Corrected	mean	78.5	73.5	74.2	70.3
Older than 35 y	Studies	8	6	13	15
	n =	186	96	279	395
Uncorrected	mean	66.4 ± 6.7	66.1 ± 3.8	65.1 ± 8.6	60.0 ± 7.9
Corrected	mean	66.4	65.4	64.6	59.0
<35y v >35y	p =	0.0052		0.0214	0.1663

ANOVA of the values in the over 35 y group showed no significant intra-group differences ($p = 0.142$). Similarly no significant intra-group differences were shown in the under 35 y group ($p = 0.304$). Comparison of the individual measurement sites showed significant differences between the two age groups at the Chest ($p = 0.0052$) and BKA sites ($p = 0.0214$). Comparison at the AKA site was not possible because of insufficient data. These results would suggest that the statistical difference noted between the chest and the foot level in the ANOVA of the combined data reflected a difference in the normal ranges for different ages (Figure 4.1).

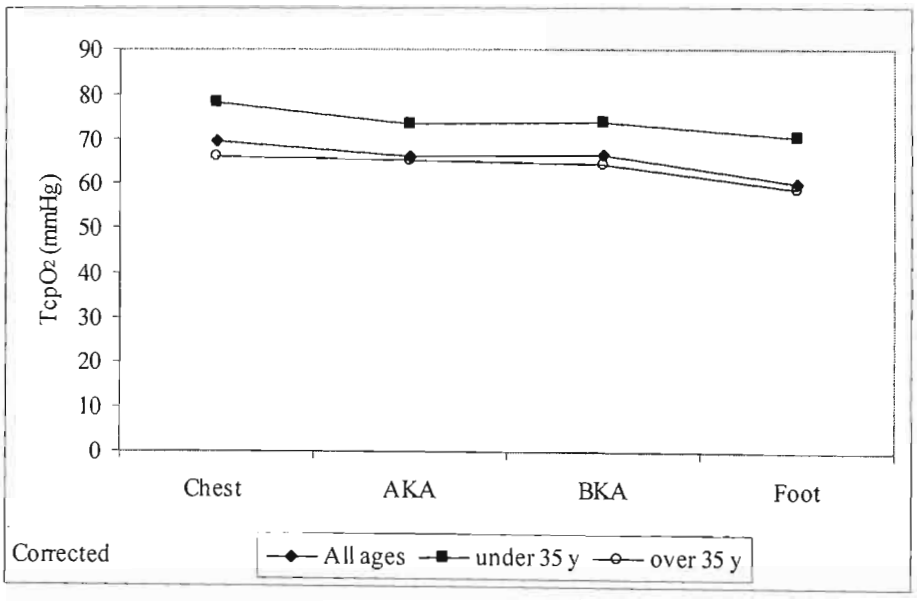


Figure 4.1. Mean absolute $TcpO_2$ from control patients of different ages.

4.2.2 $TcpO_2$ Index

The data from four papers presenting control data for the $TcpO_2$ index are shown in table 4.4. The corrected means are shown in table 4.5 and the comparison of age groups in table 4.6.

Table 4.4. Studies presenting control data for the $TcpO_2$ index. Numbers in parentheses indicate the number of limbs studied if different to the number of patients (n) in the study.

Author	n =	Age (y)	Chest (mmHg)	AKA (mmHg)	BKA (mmHg)	Foot (mmHg)
Mustapha	6	17 - 25	80.9 ± 9.2		1.16 ± 0.1	
	6	54 - 64	67.9 ± 14.4		1.20 ± 0.4	
Hauser	6	25 – 35	78.8 ± 7.6 (12)	0.93 ± 0.11 (12)	0.89 ± 0.13 (12)	0.89 ± 0.09 (12)
	6	55 - 65	63.5 ± 9.4 (12)	1.02 ± 0.1 (12)	0.90 ± 0.15 (12)	0.93 ± 0.06 (12)
Kram	22	20 - 70	54.5 ± 9.2		53.1 ± 14.9 0.97 ± 0.20	47.2 ± 11.6 0.88 ± 0.22
Gannon	10	31				0.99 ± 0.22

(Mustapha, N. M. *et al.*, 1983; Hauser, C. J. and Shoemaker, W. C., 1983; Kram, H. B. *et al.*, 1984; Gannon, M. X. *et al.*, 1986).

Table 4.5. Summary of the $TcpO_2$ index data in table 4.4. The average of the $TcpO_2$ index means presented in table 4.1 is shown as the uncorrected mean (mmHg). The mean calculated from the sample size (n =) is presented as the corrected mean. The data represents all age groups.

		Chest	AKA	BKA	Foot
All	Studies	5	2	5	3
	n =	46	12	46	34
Uncorrected	mean	69.1 ± 10.95	0.98 ± 0.06	1.02 ± 0.15	0.90 ± 0.03
Corrected		64.0	0.98	1.01	0.89

ANOVA revealed no differences between indices at the different levels ($p = 0.382$). The limited number of studies available does not allow for meaningful investigation of the difference in age groups (table 4.6 and figure 4.2). It should be noted that the absolute $TcpO_2$ recorded on the chest is again higher in the younger subjects, 79.9 mmHg, than in the older subjects, 58.5 mmHg.

Table 4.6. Summary of studies in which the patient populations were either younger or older than 35 years. The average of the $TcpO_2$ index means presented in table 4.1 is shown as the uncorrected mean (mmHg). The mean calculated from the sample size (n =) is presented as the corrected mean.

		Chest	AKA	BKA	Foot
Older than 35 y	Studies	3	1	3	2
	n =	34	6	34	28
Uncorrected	mean	62.0 ± 6.8	1.02	1.02 ± 0.2	0.91 ± 0
Corrected		58.45	1.02	1.00	0.89
Younger than 35 y	Studies	2	1	2	1
	n =	12	6	12	6
Uncorrected	mean	79.85 ± 1.5	0.93	1.03 ± 0.2	0.89
Corrected		79.85	0.93	1.03	0.89

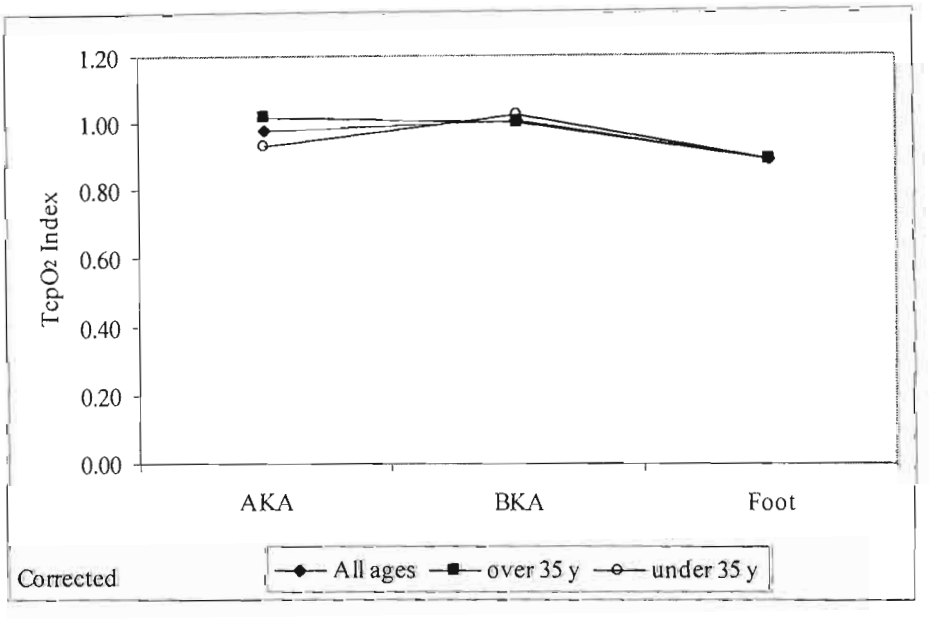


Figure 4.2. Pooled $TcpO_2$ Index values at the different amputation levels, for the combined data and studies reporting subjects under and over 35 years of age.

In the absence of sufficient data to compare age groups it is interesting to look at the data available from the absolute $TcpO_2$ control studies and extrapolate $TcpO_2$ Index data from them. The $TcpO_2$ indices calculated from the corrected means in tables 4.2 and 4.3 are shown with the data from the $TcpO_2$ Index control studies in table 4.7.

Table 4.7. $TcpO_2$ Index values calculated from the pooled mean values obtained in control studies reporting absolute $TcpO_2$ values, and the $TcpO_2$ Index values from control studies.

	AKA	BKA	Foot
Absolute $TcpO_2$			
All subjects	0.95	0.95	0.86
Over 35 y	0.98	0.97	0.89
Under 35 y	0.94	0.95	0.90
$TcpO_2$ Index			
All subjects	0.98	1.01	0.89
Over 35 y	1.02	1.00	0.89
Under 35 y	0.93	1.03	0.89

It can be seen that the use of the index appears to reduce the difference between absolute $TcpO_2$ values noted in the two age groups. In both old and young control subjects there is a drop in both $TcpO_2$ and $TcpO_2$ index at the foot. At the BKA site the trend is for the value to rise in the young group and fall in the older group.

4.3 Study to Determine $TcpO_2$ Control Values in Our Laboratory

4.3.1 Method

30 subjects were studied. All were asymptomatic of peripheral vascular disease. $TcpO_2$ measurements were made in the standard way at the routine amputation sites. In some subjects, readings were obtained from sites on both legs. The median age of the controls was 73 y (range 34 – 93 y).

4.3.2 Results and Discussion

The results of absolute $TcpO_2$ measurements made at the different levels is shown in table 4.8.

Table 4.8. Absolute $TcpO_2$ values of control subjects expressed in (mmHg).

	Chest	AKA	BKA	Foot
n =	26	36	37	34
Mean	60 ± 12.7	62.8 ± 13.9	60.5 ± 12.4	54.5 ± 12.7
Max	79	88	90	81
Median	62	61	60	54
Min	36	38	39	28

ANOVA of the absolute $TcpO_2$ data shows no difference between sites measured ($p = 0.058$). This however borders on significance, with the greatest difference being between the AKA and Foot levels.

A comparison of the absolute $TcpO_2$ data from this study with the literature controls is shown in (figure 4.3.). The control values in our study are lower than the average from the literature, but importantly the literature data falls within one deviation of the means in our study.

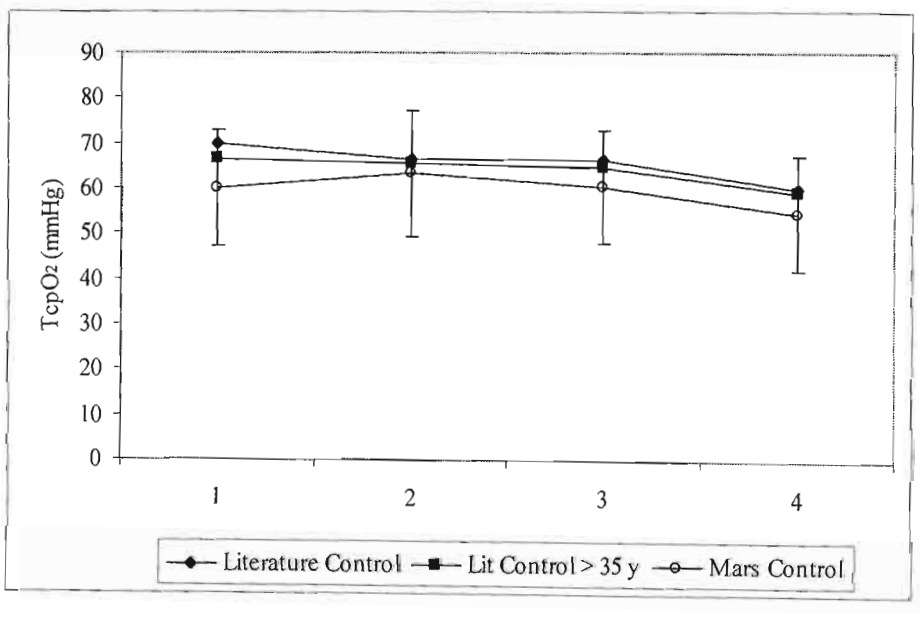


Figure 4.3. The mean absolute $TcpO_2$ (mmHg) and 1 SD of control subjects from local study, the pooled mean of control studies reported in the literature and the pooled mean values of studies reporting control subjects older than 35 years.

The data for $TcpO_2$ Index from the control patients studied are shown in table 4.9.

Table 4.9. The $TcpO_2$ Index of control subjects.

	AKA	**BKA**	**Foot**
n =	34	34	32
Mean	1.05 ± 0.17	1.05 ± 0.23	0.92 ± 0.25
Max	1.67	1.78	1.61
Median	1.02	1.05	0.9
Min	0.7	0.68	0.57

ANOVA shows a significant intra-group difference ($p = 0.025$) with post hoc testing using the Tukey-Kramer test showing the difference to be between the Foot and the other two sites ($p < 0.05$). The comparison with the literature control is shown in figure 4.4.

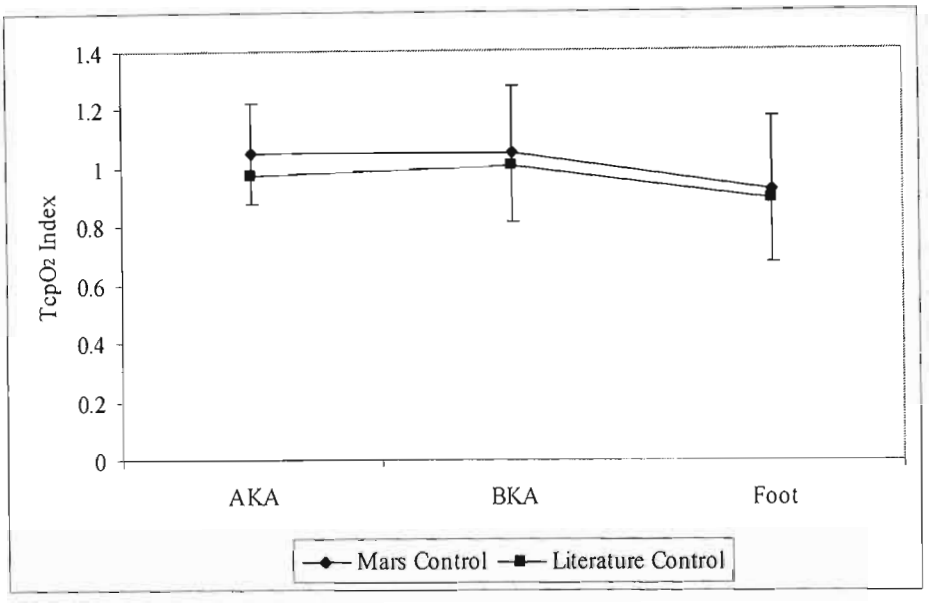


Figure 4.4. $TcpO_2$ Index control values shown as mean and 1 SD and the mean Index values of controls derived from the literature.

4.3.3 Summary

The literature reports a trend for $TcpO_2$ values to fall from proximal to distal in people asymptomatic of peripheral vascular disease, and for $TcpO_2$ values to be lower in older people. Data pooled from the 20 studies reporting control $TcpO_2$ values shows there to be a significant fall in $TcpO_2$ between the chest and the foot. Control subjects under the age of 35 y had significantly higher $TcpO_2$ values at the chest and BKA sites than older subjects. The $TcpO_2$ index reduces variation due to age. The data from the local control subjects is similar to the age matched data from the literature.

Chapter 5

$TcpO_2$ in Patients with Peripheral Vascular Disease

5.1 Introduction

In this chapter, the literature on $TcpO_2$ and the $TcpO_2$ Index measurement in patients with peripheral vascular disease will be reviewed and summarised as will the literature on $TcpO_2$ and diabetes mellitus. Clinical data on patients with PVD collected in our studies will be presented and compared with the relevant data from the literature. The relationship of $TcpO_2$ and the $TcpO_2$ Index to patients' major presenting symptom and pulse status will be investigated.

5.2 Literature review

5.2.1 Absolute $TcpO_2$

The earliest report of $TcpO_2$ in patients with peripheral vascular disease was that of Matsen in 1980. In all, 23 studies have been reported on patients with PVD. The absolute $TcpO_2$ with respect to severity of the disease, based on the major presenting symptom, has been reported in 17 studies. Different criteria have been used to group patients. These include Fontaine classification and various groupings of patients with intermittent claudication, rest pain, ischaemic ulcers, ischaemic skin lesions without ulceration and gangrene. The precise definitions of each of these presentations were not given in the papers, and no differentiation between focal gangrene and more widespread gangrene appears to have been made. Data in subsequent tables are pooled based on the presentation as described in the papers referred to.

The twenty-three studies reviewing absolute $TcpO_2$ values of patients with peripheral vascular disease are summarised in table 5.1.

Table 5.1. Absolute $TcpO_2$ values reported in 23 major studies reporting $TcpO_2$ of patients with peripheral vascular disease. Abbreviations Font = Fontaine, I.C. = Intermittent claudication, U = Ulcer, I.L.= Ischaemic lesion, R.P.= Rest Pain, G. = Gangrene, D = Diabetic. Numbers in parentheses indicate the number of limbs studied if different to the number of patients entered in study and shown under (n =).

Author	Symptoms	n =	Chest (mmHg)	AKA (mmHg)	BKA (mmHg)	Foot (mmHg)
Matsen		9	47.7 ± 13	47.1 ± 13.3	34.4 ± 9.9	16.4 ± 21.8
Ohgi	Font 1 Font 2 R.P + G	59 in total			63 56 36	
Clyne	I.C. R.P.	10 9		66.7 ± 9.1 54.8 ± 16.2	63.5 ± 8.6 50.2 ± 16.2	50.5 ± 10.3 35.9 ± 16.0
Dowd	I.C. I.L. G.	15 14 33				52 ± 12 33 ± 9 10
Franzeck		69	52.6 ± 13.1		31.7 ± 18.1(93)	
Mustapha		32	61.9 ± 13.1		43.7 ± 15.3	
Hauser	I.C.	13	61.0 ± 28.8	57.3 ± 32.1	48.7 ± 33.5	45.6 ± 44.7
Hauser	(D) I.C. R.P. G.	10 9 13				40 ± 4 18 ± 4 16 ± 4
Bongard	I.C. R.P. + G.					40.8 ± 8 16.1 ± 15
Benscoter	I.C. + R.P. U. G.	24 11 17	64.3 ± 7.7 62.1 ± 10.5 64.1 ± 10.3	53.1 ± 14.6 55.3 ± 8.9 55.8 ± 12.2	46.1 ± 17.0 44.9 ± 11.8 33.3 ± 19.2	32.4 ± 22.5 36.3 ± 15.7 10.1 ± 13.3
Cina	I.C.	31			54 ± 5	45 ± 6
	R.P.	26			41 ± 7	17 ± 6
	Impending G.	12			30 ± 9	8 ± 2
Ratliff	R.P.+U.+G.	62		52.5 ± 15	37.2 ± 16.7	
Byrne	I.C. I.C. R.P	68 17 32		53.9 ± 7.0 65.5 ± 7.1 49.9 ± 13.7	8.2 ± 9.9 59.1 ± 4.9 29.1 ± 19.7	36.8 ± 12.1 55.7 ± 4.3 3.68 ± 3.7
Kram	I.C. + R.P.	19	50.2 ± 1.1		38.8 ± 16.6	31.5 ± 17.4
Rhodes	U. + G.	12	65 ± 14		38 ± 16	14 ± 8
McCollum	R.P. + G.	46		54 ± 12	35 ± 21	18 ± 21 (38)
Oh	R.P.+U.+G.	31 69				4.2 ± 5.3 5.4 ± 5.0
Gannon	I.C. R.P.	16 16				34.5 ± 16 8.3 ± 11
Becker	Font 1 Font 2 Font 2 Font 3 Font 4	334 495 93 6				54.5 ± 12.5 47.7 ± 17 46.0 ± 19 11 ± 9.2 2.6 ± 1.1
Allen		12				23.1 ± 20.3
Wyss	(foot amps)	31		49.2	40.8	31.2
	(BKA)	116		45.6	31.2	15.6
	(AKA)	43		36	16.8	10.8
Lalke	I.C. (D) IC R.P.+U.+G. (D)RP+U+G	31 4 32 22				19.5 ± 11.7 20.8 ± 10.8 8.6 ± 9.2 11.6 ± 10.2

(Matsen, F. A. 3d *et al.*, 1980; Ohgi, S. *et al.*, 1981; Franzeck, U. K. *et al.*, 1982; Dowd, G. S. *et al.*, 1982; Clyne, C. A. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Dowd, G. S. *et al.*, 1983; Hauser, C. J. and Shoemaker, W. C., 1983; Bongard, O. and Krahenbuhl, B., 1984; Cina, C. *et*

al., 1984; Ratliff, D. A. *et al.*, 1984; Kram, H. B. *et al.*, 1984; Byrne, P. *et al.*, 1984; Benscoter, J. L. *et al.*, 1984; Hauser, C. J. *et al.*, 1984; Rhodes, G. R., 1985; Becker, F., 1985; McCollum, P. T. *et al.*, 1986; Gannon, M. X. *et al.*, 1986; Allen, P. I. and Goldman, M., 1987; Oh, P. I. *et al.*, 1987; Lalka, S. G. *et al.*, 1988; Wyss, C. R. *et al.*, 1988).

The data were pooled using the same method as for the control data. The pooled data for peripheral vascular disease of different severity is shown in table 5.2.

Table 5.2. Summary of the absolute $TcpO_2$ data in table 5.1. The average of the $TcpO_2$ means (mmHg) presented in table 5.1 is shown as the uncorrected mean. The mean calculated from the sample size is presented as the corrected mean. The data represents patients of all age groups with PVD of different severity.

		Chest	**AKA**	**BKA**	**Foot**
All	Studies	9	15	26	41
	n =	206	508	765	1298
Uncorrected	Mean	58.8 ± 6.7	53.1 ± 7.5	42.0 ± 11.5	25.3 ± 35.1
Corrected	Mean	57.7	50.5	37.6	33.5

The data in table 5.2 show that in patients with PVD, the absolute $TcpO_2$ falls from proximal to distal reflecting the fall in oxygen delivery. It has been suggested that $TcpO_2$ measurement can be used to distinguish between the different Fontaine grades (Becker, F., 1985). The data from table 5.1 categorised according to predominant presentation is shown in table 5.3.

Table 5.3. Summary of the absolute $TcpO_2$ (mmHg) data in table 5.1. The mean calculated from the sample size is presented as the mean. The data have been categorised according to the severity of the presentation as described in the papers.

		Chest	**AKA**	**BKA**	**Foot**
Intermittent Claudication	Studies	1	4	7	14
	n =	13	108	139	1044
	Mean	61.0	57.3	52.0	47.3
Rest pain	Studies	2	3	5	8
	n =	43	65	110	228
	Mean	58.1	51.8	39.0	15.7
Gangrene	Studies	1	1	2	5
	n =	17	17	29	81
	Mean	64.1	55.8	31.9	10.1
Rest Pain, Ulcer, Gangrene	Studies	2	3	6	12
	n =	29	125	149	285
	Mean	64.5	53.5	35.6	9.5

The fall in absolute $TcpO_2$ at the different levels in patients with PVD is shown in figure 5.1.

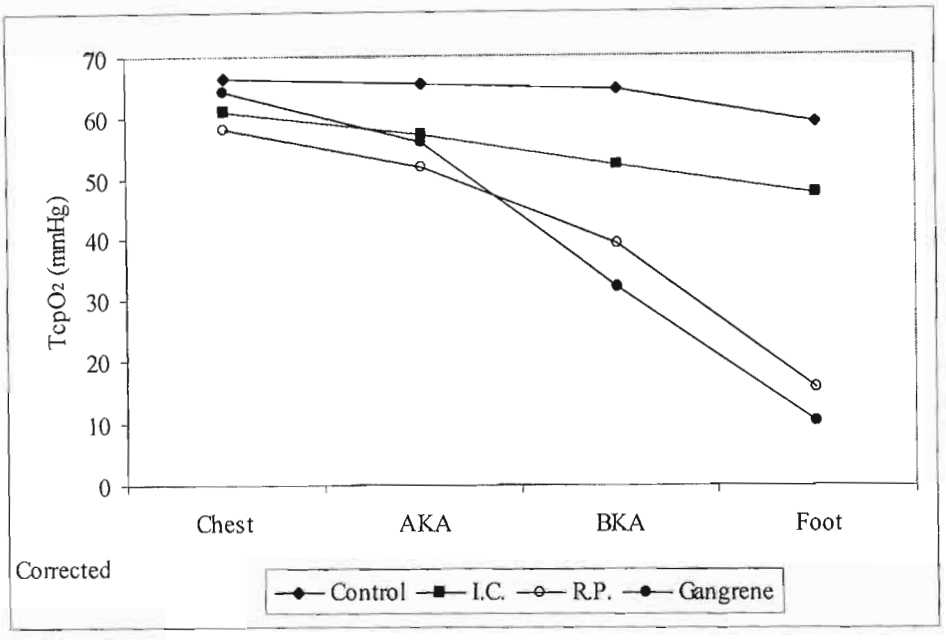


Figure 5.1. The mean absolute $TcpO_2$ (mmHg) of control subjects and patients with intermittent claudication (I.C.), rest pain (R.P.) and gangrene derived from the literature.

The fall in absolute $TcpO_2$ from the AKA level to the Foot level was tested by ANOVA to investigate possible intra-group changes for each presentation at the different levels, and the results are presented in table 5.4. Inter-group differences at the various levels are shown in table 5.5.

Table 5.4. Results of ANOVA comparing the mean $TcpO_2$ values obtained at the AKA, BKA and Foot sites for each of the three presentations, based on the pooled data derived from the literature. Post hoc testing was performed using the Tukey-Kramer test.

	ANOVA p	**AKA vs BKA** p	**AKA vs Foot** p	**BKA vs Foot** p
Intermittent Claudication	0.0016	> 0.05	< 0.01	< 0.05
Rest Pain	0.0005	> 0.05	< 0.001	< 0.01
Gangrene	< 0.0001	< 0.001	< 0.001	<0.001

Table 5.5. Results of ANOVA comparing the difference in mean $TcpO_2$ values obtained for the different clinical presentations at each of the different amputation levels, based on the pooled data from the literature. Post hoc testing was performed using the Tukey-Kramer test.

	AKA	BKA	Foot
ANOVA	= 0.084	< 0.0001	< 0.0001
I.C. vs R.P	> 0.05	< 0.01	< 0.001
I.C. vs G.	> 0.05	< 0.001	< 0.001
R.P. vs G.	> 0.05	> 0.05	> 0.05

The results of tables 5.4 and 5.5 indicate that the fall in absolute $TcpO_2$ mirrors both the severity of the disease and that $TcpO_2$ is able to discriminate between intermittent claudication and more severe disease presentation.

5.2.2 $TcpO_2$ Index

The data from eight studies reporting the evaluation of the $TcpO_2$ index in PVD are presented in table 5.6.

Table 5.6. $TcpO_2$ Index values from 8 studies reporting $TcpO_2$ Index of patients with peripheral vascular disease. Abbreviations, I.C. = Intermittent claudication, U = Ulcer, R.P. = Rest Pain, G.= Gangrene D, = Diabetic. Numbers in parentheses indicate the number of limbs studied if different to the number of patients entered in a study and shown under (n =).

Author	Symptoms	n =	Chest (mmHg)	AKA	BKA	Foot
Mustapha		32	61.9 ± 13.1		0.73 ± 0.3	
Hauser	I.C.	13	61 ± 28.8	0.95 ± 0.11	0.82 ± 0.17	0.78 ± 0.20
Hauser	(D) I.C. R.P. G.	10 9 13				0.62 + 0.05 0.34 ± 0.06 0.26 ± 0.06
Hauser	I.C. R.P. G.	14 8 7		0.96 0.93 0.85	0.79 0.63 0.62	0.69 0.41 0.17
Kram	I.C.+ R.P.	19	50.2 ± 11.1		0.74 ± 0.24	0.60 ± 0.29
Cina	I.C. R.P. G.	24 18 9				0.70 0.29 0.08
Gannon	I.C. R.P.					0.59 ± 0.28 0.15 ± 0.20
Lalke	I.C. (D) I.C. RP+U+G DRP+U+G					0.41 ± 0.22 (11) 0.42 ± 0.59 (3) 0.17 ± 0.17 (15) 0.19 ± 0.19 (11)

(Mustapha, N. M. *et al.*, 1983; Hauser, C. J. and Shoemaker, W. C., 1983; Cina, C. *et al.*, 1984; Kram, H. B. *et al.*, 1984; Hauser, C. J. *et al.*, 1984; Hauser, C. J. *et al.*, 1984; Gannon, M. X. *et al.*, 1986; Lalka, S. G. *et al.*, 1988).

The data were pooled using the same method as for the control data. The pooled means for the $TcpO_2$ Index of patients with peripheral vascular disease of different severity are shown in table 5.7.

Table 5.7. Summary of the $TcpO_2$ index data in table 5.6. The average of the $TcpO_2$ index means calculated from table 5.6 is shown as the uncorrected mean. The mean calculated from the sample size is presented as the corrected mean. The data represents all age groups and PVD of different severity.

		AKA	**BKA**	**Foot**
All	Studies	4	5	17
	n =	48	61	208
Uncorrected	Mean	0.92 ± 0.05	0.72 ± 0.09	0.40 ± 0.22
Corrected	Mean	0.93	0.74	0.43

The data in table 5.7 shows that in patients with PVD, the $TcpO_2$ Index falls from proximal to distal reflecting the fall in oxygen delivery as was demonstrated with absolute $TcpO_2$. The data from table 5.6 categorised according to predominant presentation is shown in table 5.8.

Table 5.8. Summary of the $TcpO_2$ index data in table 5.6. The mean calculated from the sample size is presented as the mean. The data has been categorised according to the severity of the presentation. The small sample size and the nature of the reports necessitated combining data on rest pain, ulcers and gangrene with gangrene.

		AKA	**BKA**	**Foot**
Intermittent Claudication	Studies	2	2	7
	n =	27	27	91
	Mean	0.96	0.80	0.64
Rest Pain, Ulcer, Gangrene	Studies	2	3	9
	n =	21	15	106
	Mean	0.90	0.63	0.23

The comparison of the $TcpO_2$ Index with the control data generated from the literature is shown in figure 5.2.

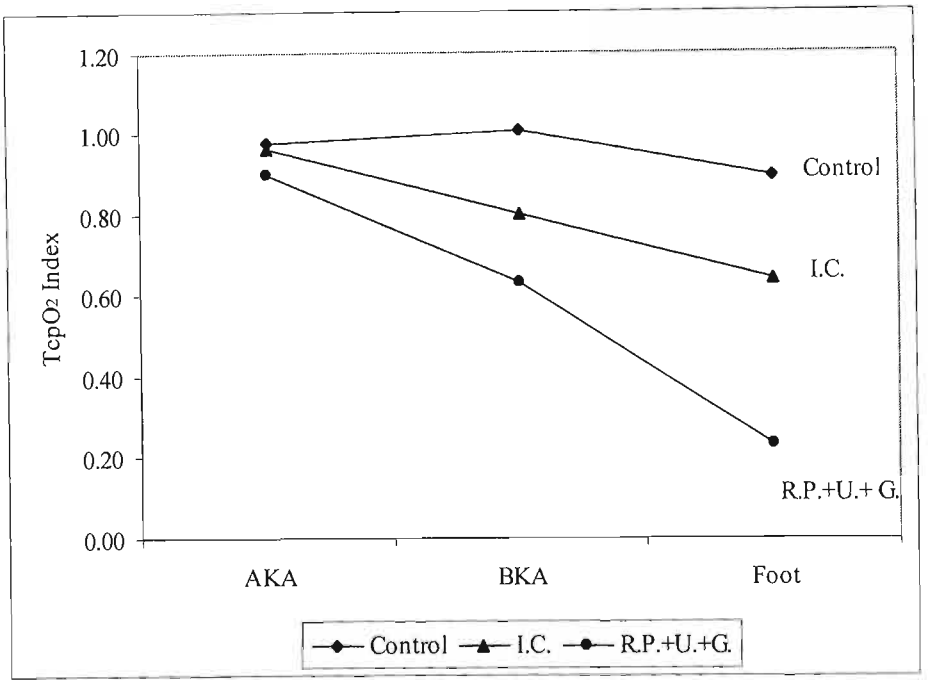


Figure 5.2. The $TcpO_2$ Index of control subjects and patients with intermittent claudication (I.C.), and rest pain and gangrene (G.) and ulceration (U.), derived from the literature.

In the absence of the raw data from the studies reported in the literature the averaged data available for statistical analysis is too small at the AKA and BKA levels to allow confident interpretation. There were insufficient data to perform tests for normality of distribution and the assumption was made that the data was not normally distributed. Non-parametric Kruskal-Wallis analysis of variance was performed to investigate intra-group differences. For intermittent claudication, the Kruskal-Wallis test showed there to be a significant difference ($p = 0.0076$). Post hoc testing using Dunn's multiple comparisons test showed there to be a significant difference between AKA and Foot levels ($p < 0.05$). Similarly the Kruskal-Wallis test showed a significant difference between levels in the rest pain and gangrene results ($p = 0.0183$). Post hoc testing showed the difference to again be between the AKA and Foot levels ($p < 0.05$).

5.3 Diabetes Mellitus and $TcpO_2$

The management of peripheral circulatory sequelae of diabetes mellitus remains a challenging problem. Issues pertinent to the interpretation of $TcpO_2$ in diabetic patients are, changes in the microcirculation, to which may be added macrocirculatory dysfunction, rheological changes, the effect of glycemic control, and the possible influence of associated peripheral neuropathy.

Questions that have been frequently asked of studies using $TcpO_2$ in wound healing prediction are, whether there is any difference between patients with PVD and diabetics, with or without PVD, and whether peripheral neuropathy affects $TcpO_2$?

The literature is reviewed and grouped into studies using $TcpO_2$ to investigate the effect of diabetes on the microcirculation and rheological changes, and the effects of glycemic control, diabetes and PVD, and neuropathy on $TcpO_2$.

The relationship of $TcpO_2$ to other Doppler pressure measurement in diabetic patients and the issue of medial sclerosis is discussed in chapter 6.

5.3.1 Diabetes and the microcirculation

In 1981, Ewald reported the use of $TcpO_2$ as a possible test for early detection of diabetic microvascular disorders. Using a forearm hyperaemia model, with $TcpO_2$ probe temperatures of 35 °C and 37 °C they demonstrated a significant reduction in hyperaemic $TcpO_2$ values in diabetic children, when compared to normal children (Ewald, U. *et al.*, 1981). This was followed by Railton, R. *et al.*, (1983) who measured $TcpO_2$ at the foot and arm in 16, Type 1 (insulin-dependent) diabetic patients who had no evidence of vascular or neurological disease on simple clinical examination and in 30 non-diabetic subjects. Diabetics had significantly lower $TcpO_2$ at the foot and the hyperaemic response in the arm was also significantly lower. This was interpreted as reflecting abnormal capillary blood flow in diabetic patients and they concluded that $TcpO_2$ might prove useful in the early assessment of peripheral vascular problems in diabetes.

Weindorf, N. *et al.*, (1987) expanded on the work of Ewald and confirmed that the $TcpO_2$ hyperaemic test with the probe at 37 °C can recognise and quantify diabetic microangiopathy. In addition $TcpO_2$ measurements made with a probe temperature of 45 °C showed reduced $TcpO_2$ values in these patients.

Kobbah, A. M. *et al.*, (1988) used the hyperaemic tests to evaluate young diabetics at diagnosis, before administration of insulin and 1, 6, 12 and 24 months after diagnosis. They found vascular reactivity to be significantly lower in diabetic children at diagnosis than in controls. After the first month of treatment reactivity had returned to normal. However 2 years later, the reactivity was again significantly lower in diabetic children than in the control group. They proposed that the mechanism underlying the initial, reversible impairment of vascular reactivity on admission is different from that of the late reduction, which might be a very early manifestation of the later structural diabetic microangiopathy.

Ubbink, D. T. *et al.*, (1993) used capillary microscopy, $TcpO_2$ and laser Doppler fluxmetry to examine the effects of diabetes on claudication and critically ischaemic limbs with or without measurable Doppler ankle pressures. They found that in critically ischaemic patients, the microcirculation was no more compromised than in non-diabetics and concluded that when vascular disease becomes severe, the influence of diabetes on the microcirculation is outweighed by the effects of atherosclerosis.

al-Arafaj, A. *et al.*, (1994) used $TcpO_2$ to evaluate the possible use of a new, radiolabelled, *in vivo* marker of tissue hypoxia, iodoazomycinarabinoside ([^{123}I]IAZA) to determine the severity of disease in patients with diabetic ulcers. The test uses standard gamma camera imaging methods. $TcpO_2$ was found to correlate inversely with [^{123}I]IAZA, with diffusely increased uptake in limbs with reduced $TcpO_2$ levels and focal increased uptake in ulcers and in areas of atrophic skin change.

Schwingshandl, J. *et al.*, (1996) investigated the hyperaemic response in the forearm in adolescents with type I diabetes and non-diabetic adolescents. Hyperaemic $TcpO_2$ increases were significantly lower in the diabetic group than in the control group. Girls were found to have significantly higher baseline $TcpO_2$ values than boys and abnormal values for oximetry were associated only with some autonomic nerve function abnormalities. Lower values in diabetic subjects are weakly associated with diabetes duration and metabolic control, independent of gender.

Mayrowitz and Larsen investigated the influence of the macrocirculation and microcirculation on $TcpO_2$ values in diabetic and non-diabetic subjects. Macrocirculatory parameters, cardiac output, leg blood flow and Doppler systolic pressures were not different between groups. $TcpO_2$ as expected, was significantly reduced in the diabetic group, and they concluded that the findings suggest a link between the diabetic $TcpO_2$ deficit and the microcirculatory

submaximal vasodilatory response, with little if any role of macrocirculatory factors (Mayrovitz, H. N. and Larsen, P. B., 1994; Mayrovitz, H. N. and Larsen, P. B., 1996).

5.3.2 Rheology

Le Devehat measured the micro-rheological parameters of plasma viscosity, albumin, fibrinogen, red cell aggregation times, disaggregation threshold and red cell aggregate structure index in control subjects and in diabetic patients, with or without angiopathy, whose glycemic control was considered to be either good or poor. $TcpO_2$ was significantly reduced in diabetics, and rheological disturbances, which were related to plasma viscosity and several parameters of aggregation-disaggregation phenomenon, were present (Le Devehat, C. and Khodabandehlou, T., 1990; Le Devehat, C. *et al.*, 1994).

Young, M. J. *et al.*, (1996) investigated rheological and microvascular parameters in control subjects, diabetics with neuropathy and diabetics without neuropathy. $TcpO_2$ was significantly higher in control subjects than in neuropathic diabetic patients. In diabetics without neuropathy, $TcpO_2$ was not significantly different to the other two groups. Erythrocyte aggregation, fibrinogen and plasma and corrected whole-blood viscosity were all significantly different in neuropathic diabetic patients compared with control subjects, as were assessments of microvascular flow. These results suggest that haemorheological changes are associated with disturbances of microvascular flow and diabetic peripheral neuropathy in the absence of other diabetic complications.

Khodabandehlou, T. *et al.*, (1998) studied the effect of a hyperglycaemic spike of short duration on the haemorheology of the microcirculation of insulin dependent diabetics and a non-diabetic control group. Hyperglycaemia induced significant decreases in erythrocyte aggregation, blood and plasma viscosity, platelet count and in fibrinogen and albumin levels in the diabetic patients with no change in non-diabetic controls. These changes which would be expected to improve $TcpO_2$ were associated with a significant decrease in $TcpO_2$.

5.3.3 Glycemic Control

Ewald, U. and Tuvemo, T., (1985) showed the reduction in post ischaemic hyperaemic response in Type 1 diabetic children to correlate to both short-term and long-term diabetic control. Urinary glucose excretion during the night preceding the test showed the highest correlation to the peak of the postocclusive reactive hyperaemia. There was only a weak

correlation with triglycerides and glycosylated haemoglobins and no significant correlation with fasting plasma glucose.

Jorgensen, R. G. *et al.*, (1988) measured the $TcpO_2$ hyperaemic response in young type 1 diabetics without overt angiopathy and in controls. If the glycosylated haemoglobin (GHb) was 9.5 % or less the hyperaemic response was not statistically different from normal control subjects. If the GHb was greater than or equal to 12.5 % the postischemic blood flow response did not occur.

Iino, K. *et al.*, (1997) investigated the relationship of $TcpO_2$ to glycemic control and diabetic complications in patients with non-insulin dependent diabetes mellitus. Patients were divided into 3 groups based on HbA1c levels. HbA1c < 7.0 % indicated good control, 7 – 8.9 % fair control, and >9 % poor control. $TcpO_2$ of the good and fair control groups was not significantly different to non-diabetic control subjects. The poor control group had significantly reduced $TcpO_2$ compared to the non-diabetic controls and the good control group. They also showed that if the glycemic control of patients in the poor control group was improved, $TcpO_2$ values increased. Patients in the poor control group who did not improve their glycemic control showed no change in $TcpO_2$. These findings suggest that tissue oxygenation in diabetic patients is related to glycemic control.

5.3.4 Peripheral Vascular Disease

Franzeck, U. K. *et al.*, (1982) reported on $TcpO_2$ values in 69 patients, 33 of whom were diabetic. The $TcpO_2$ of diabetics was not different to that of non-diabetics. Cina found $TcpO_2$ to discriminate between all degrees of ischaemia in both diabetic and non-diabetic patients with PVD (Cina, C. *et al.*, 1984). Hauser showed the $TcpO_2$ Index to have a higher diagnostic accuracy of disease severity than Doppler ankle brachial ratios and pulse volume recordings (Hauser, C. J. *et al.*, 1984). Additionally significant hypoxia predicted large-vessel angiographic lesions.

Modesti evaluated $TcpO_2$, strain gauge plethysmography and Doppler in the assessment of peripheral vascular disease in diabetics who were asymptomatic of PVD. In asymptomatic diabetics, $TcpO_2$ and plethysmography were able to detect a subgroup of patients with significantly reduced perfusion (Modesti, P. A. *et al.*, 1987).

Wyss investigated the relationship of $TcpO_2$ and ankle Doppler pressures in diabetic and non-diabetic patients before and after by-bass surgery or angioplasty. In non-diabetic patients a

$TcpO_2$ of more than 20 mmHg or an ankle pressure of more than 75 mmHg after the procedure, was associated with resolution of clinical symptoms within 60 days. Pressures below this necessitated amputation. In diabetic patients the results were not as clear-cut. Post operative pressures below 20 mmHg were associated with unfavourable outcomes, while pressures above 20 mmHg were frequently associated with a poor outcome in terms of resolution of rest pain and slow ulcer healing (Wys, C.R. *et al.*, 1987).

Rooke retrospectively studied 256 limbs of patients with PVD to assess the effects of age, sex, smoking, and diabetes on lower limb $TcpO_2$. When limbs with similar occlusive disease severity were compared, $TcpO_2$ remained consistently lower in diabetic than in non-diabetic patients (Rook, T.W. and Osmundson, P.J., 1990).

Arnold, T. *et al.*, (1993) measured the $TcpO_2$ Index in patients, before and after revascularisation procedures. Measurements were made in the supine position and after leg elevation. The index was effective in assessing the clinical severity of ischaemia preoperatively and increased perfusion postoperatively, regardless of degree of ischaemia or diabetes. The fall in $TcpO_2$ Index with limb elevation was greater after surgery, an effect probably due to the improved vascular reserve. The decrease in $TcpO_2$ Index with elevation was significantly greater in diabetics than in non-diabetics and may indicate loss of vasoconstrictor reflexes.

5.3.5 Wound Healing

Karanfilian, R. G. *et al.*, (1986) reported the outcome of 20 amputations and 39 debridements in diabetic and non-diabetic patients. At a predictive value of 10 mmHg, the accuracy of the test for non-diabetics was 100 % and for diabetics 91 %.

Malone compared $TcpO_2$, the $TcpO_2$ Index, $TcpCO_2$, the $TcpCO_2$ Index, ankle brachial pressures and ^{133}Xe skin washout. No statistically significant differences were noted between values obtained in diabetic and non-diabetic patients for amputations that healed or failed, except in the case of ^{133}Xe. In amputations that healed, the mean ^{133}Xe was significantly higher in diabetics than in non-diabetics. In this series, an absolute $TcpO_2$ of 20 mmHg was felt to be a better indicator of amputation outcome than the $TcpO_2$ index. No amputation with a $TcpO_2$ Index of less than 0.44 healed. They concluded that diabetes did not have an effect on the success of amputation healing or on the $TcpO_2$ test results (Malone, J. M. *et al.*, 1987).

Wyss, C. R. *et al.*, (1988) reported $TcpO_2$ to have a similar predictive value of amputation wound failure in diabetic and non-diabetic patients.

Quigley, F. G. and Faris, I. B., (1991) used $TcpO_2$ to predict ulceration of the foot. They found 30 mmHg to be the best predictive value, and of equal worth in diabetic and non-diabetic feet. Pecoraro, R. E. *et al.*, (1991) investigated the use of $TcpO_2$ in the predicting healing of diabetic ulcers. Using standardised local wound care in all patients, the initial ulcer healing rate was significantly related to $TcpO_2$. There was a 39 times increased risk of failure if the average $TcpO_2$ around the ulcer was less than 20 mmHg.

Pinzur used $TcpO_2$ to monitor the efficacy of decompression of infected diabetic feet, prior to definitive amputation. He showed that $TcpO_2$ increased after emergency drainage of infected feet and $TcpO_2$ was used to assist in amputation level detection (Pinzur, M. S. *et al.*, 1993).

Padberg. reported the use of $TcpO_2$ to estimate the probability of wounds healing in ischaemic limbs. Using stepwise multiple regression $TcpO_2$ was shown to be superior to ankle systolic pressures and ankle systolic indices. $TcpO_2$ achieved an accuracy of 83 %, which was not affected by diabetes (Padberg, F. T. *et al.*, 1996).

5.3.6 Neuropathy

Gaylarde measured $TcpO_2$ in the legs and feet of diabetics with and without peripheral neuropathy and in controls. At a probe temperature of 37 °C, $TcpO_2$ in the legs and feet of diabetic patients with peripheral neuropathy was significantly higher than in control subjects and diabetic patients without neuropathy. The expected fall in $TcpO_2$ from proximal to distal site was absent in diabetics with neuropathy. At a probe temperature of 44 °C $TcpO_2$, was significantly lower in neuropathic and non-neuropathic diabetic patients, than in control subjects. It is suggested that this represents loss of vasoconstrictor tone and loss of the ability to dilate with heating in diabetic patients and may contribute to the pathogenesis of ulcers and gangrene in the diabetic (Gaylarde, P. M. *et al.*, 1988).

Young established a relationship between peroneal nerve conduction and $TcpO_2$ in diabetics, with higher $TcpO_2$ values associated with faster conduction velocities (Young, M. J. *et al.*, 1992). In a subsequent study they investigated the effect of limb revascularisation on peroneal nerve conduction in non-insulin dependent diabetics. They showed that revascularisation lead to significant increases in both $TcpO_2$ and peroneal motor nerve conduction velocity. In the

unoperated contralateral limb no change in peroneal nerve conduction velocity was seen (Young, M. J. *et al.*, 1995).

A similar study of insulin dependent diabetics by Veves, showed increased $TcpO_2$ in the revascularised limb, but no significant change in peroneal nerve conduction. They concluded that reversal of hypoxia does not result in any significant improvement of the nerve function measurements (Veves, A. *et al.*, 1996). In a subsequent study from the same group, Akbari investigated whether revascularisation and reversal of hypoxia slows the progression of neuropathy. Neuropathy and hypoxia were assessed the day before the operation and during the follow-up visit. Again they found that in the revascularised limb, peroneal nerve conduction velocity remained unchanged during the follow-up period but noted significant deterioration in the leg not operated on. $TcpO_2$ values increased significantly in the revascularised limb and remained unchanged in the unoperated limb. They concluded that successful revascularisation and reversal of hypoxia halts the progression of diabetic neuropathy (Akbari, C. M. *et al.*, 1997). This further supports the role of hypoxia in the pathogenesis of nerve destruction in diabetes.

Uccioli. noted again that diabetic patients have lower $TcpO_2$ values than non-diabetic patients with peripheral vascular disease of comparable severity and investigated the role of autonomic neuropathy on foot $TcpO_2$ in non insulin dependent diabetic patients without peripheral vascular disease. They found that diabetic patients had lower $TcpO_2$ values than age and sex matched controls and that there was no difference in $TcpO_2$ values at the foot between non-insulin dependent diabetic patients with and without autonomic neuropathy. They concluded that autonomic neuropathy is unlikely to contribute to the development of foot lesions during induction of foot skin ischaemia (Uccioli, L. *et al.*, 1994).

Boyko, in a study of 657 diabetic subjects found that the mean $TcpO_2$ at any of 4 sites was not influenced by presence of autonomic neuropathy, either at 37 °C or at 44 °C. They concluded that autonomic neuropathy is not an important determinant of $TcpO_2$ in the feet of diabetic subjects (Boyko, E. J. *et al.*, 1996).

5.3.7 Summary

The literature shows that the $TcpO_2$ hyperaemic test can demonstrate the presence of microcirculatory disturbances in diabetics. In juvenile onset diabetes, the initial pre-treatment reduction in $TcpO_2$ is reversible in the short term following initiation of treatment and that subsequent microcirculatory disturbances may be due to a different mechanism. The

microcirculatory changes are associated with rheological changes, including increased viscosity, which in itself may affect $TcpO_2$ measurements.

A relationship of $TcpO_2$ to glycemic control has been shown, with poorly controlled diabetics having lower $TcpO_2$'s than well controlled diabetics. Improving control improves $TcpO_2$ and a hyperglycemic spike results in a fall in $TcpO_2$. The relationship may be dependent on the duration of the disease as $TcpO_2$ in juvenile diabetics under control worsens after initial recovery.

In patients grouped according to severity of clinical ischaemia, diabetic patients have lower $TcpO_2$ values than non-diabetics. It is suggested that with worsening ischaemia, macrocirculatory pathology appears to supersede microcirculatory disturbance.

$TcpO_2$ appears to be of equal worth in predicting amputation and wound outcome in both diabetics and non-diabetics, and $TcpO_2$ does not appear to be influenced by the presence of diabetes in these patients.

In diabetic neuropathy, the $TcpO_2$ may be elevated at low probe temperatures, but at temperatures of 44 and 45 °C there does not appear to be any difference between diabetics with or without peripheral neuropathy. The role of revascularisation and the effect of reversal of hypoxia on large nerve function is not as yet clear.

For the use of $TcpO_2$ in prediction of amputation wound healing, theoretically there does not appear to be any need to propose different predictive values for diabetics and non-diabetics. The basic principle of optimising diabetic control during the peri-operative period should be closely adhered to. The outcome of an amputation in a diabetic may be influenced by other factors associated with diabetes which influence wound healing and higher rate of failures at sites predicted to heal could be expected.

5.4 Prospective Study of the Relationship of Absolute $TcpO_2$ and the $TcpO_2$ Index to Symptoms

5.4.1 Method

Four hundred patients were entered in a prospective study. $TcpO_2$ summaries were compiled at the time of examination and updated on review of the patient records after discharge. Routine $TcpO_2$ measurements were made and 393 sets of patient data were suitable for review.

For the purpose of this study patients were classified according to the degree of severity of their presenting condition. These were graded as intermittent claudication, pre-gangrenous including rest pain and ischaemic skin changes, ischaemic ulceration, and gangrene including digits and forefoot, implying a progression of ischaemia. Obviously many patients had more than one of these presentations. Clinical classification, based on the potential for limb salvage, was according to the most severe presentation. In our series a large number of the patients were undergoing assessment for amputation, with the result that there is a preponderance of patients with gangrene, and very few presenting with only claudication.

5.4.2 Results and discussion

5.4.2.1 Absolute $TcpO_2$ data

The data are presented in table 5.9 and figure 5.3.

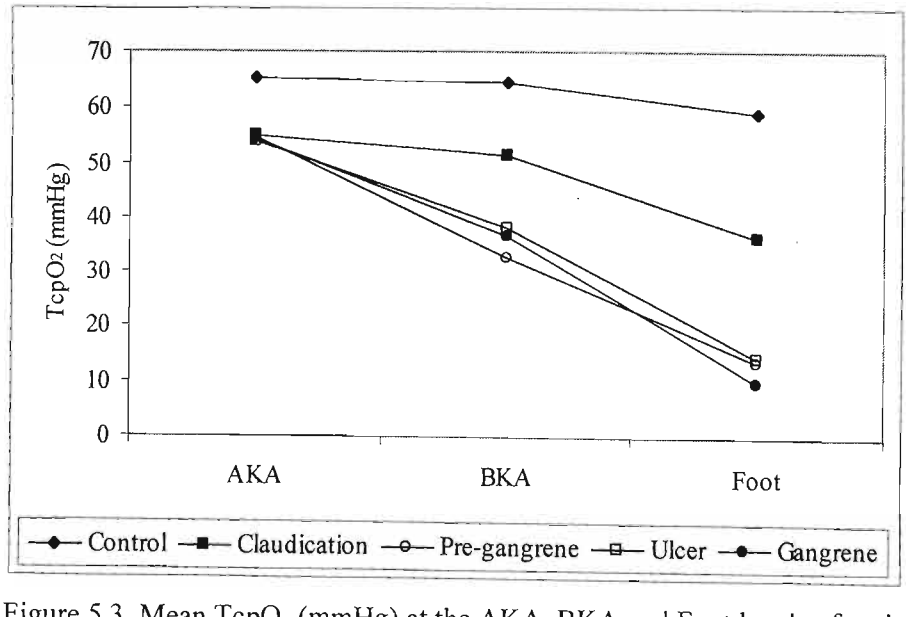


Figure 5.3. Mean $TcpO_2$ (mmHg) at the AKA, BKA and Foot levels of patients with PVD, based on the presentation.

As can be seen in figure 5.3 there is a consistent reduction in $TcpO_2$ value at the BK level with respect to the AK level. At the BK level the decrease occurring in claudicants is less than in the other patient groups. At the level of the Foot a trend appears to develop based on the severity of presentation. Claudicants have better $TcpO_2$ values than patients with ischaemic ulcers, who in turn have higher $TcpO_2$ values than patients with pre-gangrenous symptoms or gangrene.

Table 5.9. The absolute $TcpO_2$ (mmHg) of patients presenting with PVD of different severity.

Presentation		Chest	AKA	BKA	Foot
Claudication	n =	26	26	27	26
	Average	54.2 ± 13.1	54.9 ± 15.3	51.2 ± 16.0	36.2 ± 27.1
	Range	28 - 80	20 - 88	14 - 83	0 - 81
	Median	51	55.5	49	44.5
Pre-gangrene	n =	90	91	93	85
	Average	58.0 ± 12.5	54.7 ± 15.1	32.6 ± 22.2	13.6 ± 19.1
	Range	19 - 87	16 - 83	0 - 74	0 - 64
	Median	59	56	36	0
Ulcer	n =	65	61	65	59
	Average	56.7 ± 14.5	53.8 ± 16.2	38.2 ± 21.8	14.2 ± 18.5
	Range	28 - 87	3 - 87	0 - 76	0 - 63
	Median	58	57	41	0
Gangrene	n =	212	206	205	207
	Average	59.0 ± 13.4	54.4 ± 14.6	36.8 ± 20.2	9.9 ± 15.3
	Range	15 - 90	7 - 91	0 - 85	0 - 62
	Median	59	55	39	0

When analysing the data it became apparent that the data for the foot were seldom Gaussian in distribution. This could in part be expected, as in patients with for example gangrene, there were many with a $TcpO_2$ value of 0 mmHg. As there cannot be any values below 0 mmHg the distribution will be skewed. What is the effect of this maldistribution? This can be seen by comparing the mean with the median (figure 5.4).

While the mean and median values are similar at the AKA and BKA for all presentations, at the Foot level this only holds for claudicants. For all other presentations the median $TcpO_2$ value at the Foot is on average ~10 mmHg lower than the mean.

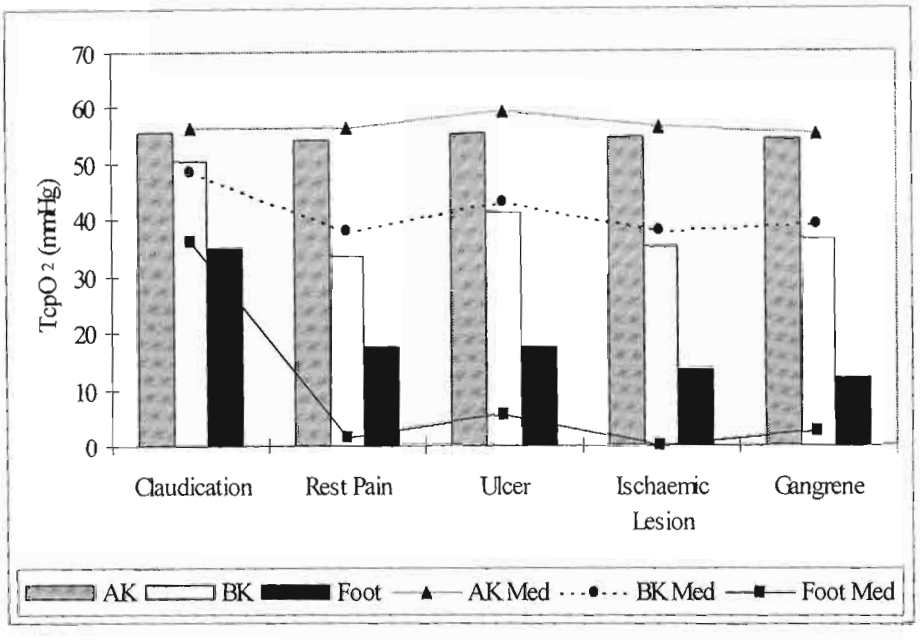


Figure 5.4. The mean $TcpO_2$ (mmHg) for the various presentations at the AK, BK and Foot levels plotted as bar histograms. Superimposed, as line graphs are the median values for the presentations at the different levels.

The differences in mean $TcpO_2$ were analysed for inter and intra-group differences at each level and for the 4 different presentations. The results of the ANOVA's are shown in table 5.10 and table 5.11. The data were checked for differences in standard deviation using Bartlett's test and for Gaussian distribution by the Kolmogorov-Smirnov method. As several data sets had significant differences in SD's or were non Gaussian in distribution, non-parametric analyses were performed using the Kruskal-Wallis test ($p < 0.0001$) with *post hoc* testing using Dunn's multiple comparisons test.

Table 5.10. Results of Dunn's multiple comparisons test following intra-group ANOVA of the mean $TcpO_2$ data for each level and each presentation.

	Gangrene	**Ulcer**	**Pre-gangrene**	**Claudication**
Foot vs BK	< 0.001	< 0.001	< 0.001	> 0.05
Foot vs AK	< 0.001	< 0.001	< 0.001	< 0.01
BK vs AK	< 0.001	< 0.01	< 0.001	> 0.05

Within each presentation there were significant falls in absolute $TcpO_2$ from proximal to distal levels, except in the Claudication group in which the difference was only significant between the most proximal and distal levels.

Table 5.11. Results of Dunn's multiple comparisons test following inter-group ANOVA of differences in mean $TcpO_2$ (mmHg) at the three levels. The shaded cells highlight the statistically significant differences.

		AKA	BKA	Foot
		p	p	p
Claudication vs	Pre-gangrene	> 0.05	< 0.001	< 0.001
	Ulcer	> 0.05	< 0.05	< 0.01
	Gangrene	> 0.05	< 0.01	< 0.001
Pre-gangrene vs	Ulcer	> 0.05	> 0.05	> 0.05
	Gangrene	> 0.05	> 0.05	> 0.05
Ulcer vs	Gangrene	> 0.05	> 0.05	> 0.05

Inter-group differences were only noted between Claudication and all other presentations at the Foot and BKA levels.

In summary, the absolute $TcpO_2$ data of this study show that for any given form of presentation except Claudication, the absolute $TcpO_2$ drops significantly from amputation level to amputation level. Between groups however $TcpO_2$ will only distinguish between Claudication and all other groups at the BKA and Foot levels.

5.4.2.1.1 Comparison of absolute $TcpO_2$ study data with literature data

How do these data compare with the previous literature? The results for intra-group variation are quite similar, table 5.12. The data for patients presenting with rest pain were extracted from the pre-gangrene data for more valid comparison with the available literature data.

Table 5.12. A comparison of the pooled data from the literature, (table 5.3) and the data from this study (table 5.9). The differences are highlighted in the shaded cells.

	Gangrene		Rest Pain		Claudication	
	Study	Literature	Study	Literature	Study	Literature
Foot vs BK	< 0.001	< 0.001	< 0.01	< 0.01	> 0.05	< 0.05
Foot vs AK	< 0.001	< 0.001	< 0.001	< 0.001	< 0.01	< 0.01
BK vs AK	< 0.001	< 0.001	< 0.001	>0.05	> 0.05	> 0.05

The differences noted between the BK and Foot levels in the Claudication group, may well be result of different sample size. In the literature, data on a total of 1044 feet are presented whereas in our study the Claudication group was the smallest with data on only 26 feet. In the Rest Pain group the difference between AKA and BKA sites was not significant in the pooled

literature data. The clinical reason for this difference is not obvious. Based on the observation that our patients tend to present late in the disease process, it could be argued that even those with rest pain present later than First World patients.

5.4.2.1.2 Review of absolute $TcpO_2$ data based on diabetic status

The data presented in table 5.9 are presented based on the diabetic status of the patients in tables 5.13 and 5.14.

Table 5.13. A comparison of the mean and median $TcpO_2$ expressed in (mmHg) of diabetic and non-diabetic patients based on their presentation.

		Chest	AKA	BKA	Foot
Pregangrene					
Non-diabetic	n =	74	75	77	69
	Average	59.6 ± 11.5	57.2 ± 14.6	34.3 ± 22.1	13.2 ± 18.6
	Range	35 - 85	16 - 83	0 - 74	0 - 64
	Median	61.5	58	38	0
Diabetic	n =	16	16	16	16
	Average	59.6 ± 11.5	43.0 ± 12.2	24.6 ± 21.7	15.3 ± 21.6
	Range	19 - 87	16 - 42	0 - 68	0 - 63
	Median	57.5	42	19.5	0
Ulcer					
Non-diabetic	n =	50	47	50	45
	Average	57.2 ± 14.2	52.6 ± 16.8	37.1 ± 22.2	11.8 ± 14.2
	Range	29 - 87	3 - 87	0 - 76	0 - 47
	Median	58	54	39.5	0
Diabetic	n =	15	14	15	14
	Average	55.0 ± 16.0	58.1 ± 13.5	42.0 ± 20.9	21.9 ± 24.3
	Range	28 - 75	29 - 81	0 - 63	0 - 63
	Median	52	57.5	11.5	11.5
Gangrene					
Non-diabetic	n =	163	157	155	157
	Average	59.5 ± 12.9	54.0 ± 14.5	36.5 ± 20.1	9.1 ± 14.7
	Range	16 - 90	7 - 85	0 - 85	0 - 54
	Median	60	55	38	0
Diabetic	n =	49	49	50	50
	Average	57.3 ± 15.1	55.7 ± 15.0	55.7 ± 15.0	12.1 ± 16.9
	Range	15 - 88	20 - 91	0 - 77	0 - 2
	Median	55	57	42.5	2

Table 5.14. A comparison of the mean and median $TcpO_2$ expressed in (mmHg) of diabetic and non-diabetic patients presenting with claudication.

		Chest	AKA	BKA	Foot
Non-diabetic	n =	25	25	26	25
	Average	54.3 ± 13.2	55.1 ± 15.6	51.3 ± 16.3	37.0 ± 27.4
	Range	28 - 80	20 - 88	14 - 83	0 - 81
	Median	51	56	49.5	47
Diabetic	n =	1	1	1	1
	Average	50	49	48	17

With only one diabetic presenting with claudication as the major presenting symptom, statistical analysis was not possible.

The data of all the diabetic patients and non-diabetics were analysed for changes in mean absolute $TcpO_2$ between measurement levels, based on the presentation, table 5.15.

Table 5.15. Results of Dunn's multiple comparisons test following intra-group ANOVA of the mean $TcpO_2$ data for each level and each presentation in diabetic patients and non-diabetic (Non Diab) patients.

	Gangrene		Ulcer		Pre-gangrene	
	Diabetic	Non Diab	Diabetic	Non Diab	Diabetic	Non Diab
Foot vs BK	< 0.001	< 0.001	> 0.05	< 0.001	> 0.05	< 0.001
Foot vs AK	< 0.001	< 0.001	< 0.01	< 0.001	< 0.05	< 0.001
BK vs AK	< 0.001	< 0.001	> 0.05	< 0.05	> 0.05	< 0.001

Differences in mean $TcpO_2$ values between measurement sites in diabetic patients were less significant than in non-diabetic patients. In the group of diabetic patients presenting with ulcers the fall in $TcpO_2$ distally down the leg was not significant between levels. This may be the result of a mix of diabetic and ischaemic ulcers. To determine if there was a difference between $TcpO_2$ values in diabetic and non-diabetic patients, the difference in mean $TcpO_2$ values at each level was compared for each presentation, table 5.16.

Table 5.16. Results of Dunn's multiple comparisons test following intra-group ANOVA's of the mean $TcpO_2$ data for each level and each presentation comparing diabetic and non-diabetic patients.

	Gangrene	Ulcer	Pre-gangrene
Foot	> 0.05	> 0.05	> 0.05
BKA	> 0.05	> 0.05	> 0.05
AKA	> 0.05	> 0.05	> 0.05

No significant differences were found between diabetics and non-diabetics.

5.4.2.2 $TcpO_2$ Index data

The $TcpO_2$ Index data is summarised in table 5.17 and the change in $TcpO_2$ Index at the different levels in the four patient groups is shown in figure 5.5.

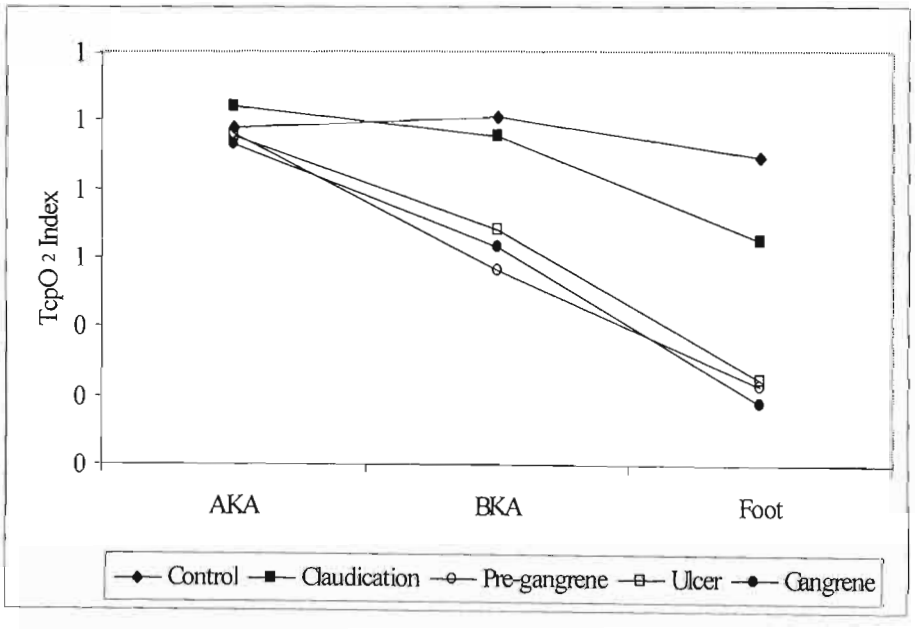


Figure 5.5. Mean $TcpO_2$ Index at the AKA, BKA and Foot levels based on presentation.

Table 5.17. The $TcpO_2$ Index at the AKA, BKA and Foot sites, of patients presenting with PVD of different severity.

Presentation		AKA	BKA	Foot
Claudication	n =	26	26	25
	Average	1.04 ± 0.25	0.95 ± 0.23	0.65 ± 0.50
	Range	0.33 - 1.48	0.41 - 1.58	0 - 1.35
	Median	1.05	0.97	0.75
Pre-gangrene	n =	86	88	80
	Average	0.96 ± 0.25	0.56 ± 0.39	0.23 ± 0.34
	Range	0.29 - 1.57	0 - 1.32	0 - 1.24
	Median	0.96	0.63	0
Ulcer	n =	60	63	58
	Average	0.95 ± 0.24	0.68 ± 0.41	0.25 ± 0.33
	Range	0.06 - 1.76	0 - 1.97	0 - 1.15
	Median	0.96	0.75	0
Gangrene	n =	208	205	205
	Average	0.93 ± 0.25	0.63 ± 0.34	0.18 ± 0.27
	Max	1.79	1.82	1.20
	Min	0.13	0.00	0.00
	Median	0.94	0.69	0

Again, the median $TcpO_2$ index the Foot level for all groups except Claudication was lower . The difference ranged from 0.18 to 0.25 (Figure 5.6).

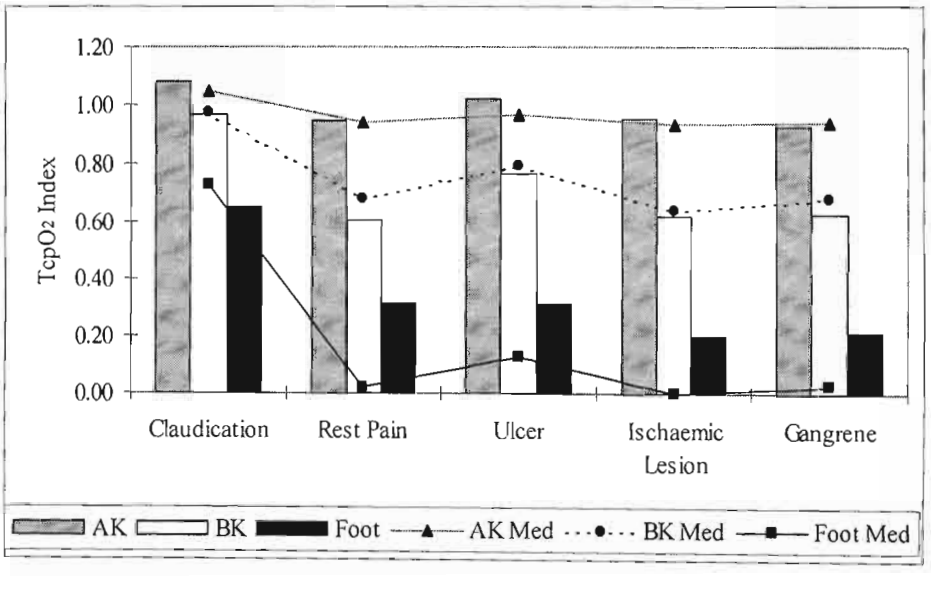


Figure 5.6. The mean $TcpO_2$ Index for the various presentations at the AKA, BKA and Foot levels plotted as bar histograms. Superimposed as line graphs are the median (Med) values for the presentations at each level.

Inter and intra-group differences were analysed by non-parametric ANOVA using the Kruskal-Wallis test with *post hoc* testing using Dunn's multiple comparisons test (table 5.18 and 5.19).

Table 5.18. Results of Dunn's multiple comparisons test following ANOVA of the mean $TcpO_2$ Index data for each level and each presentation.

	Gangrene	**Ulcer**	**Pre-gangrene**	**Claudication**
Foot vs BK	< 0.001	< 0.001	< 0.001	> 0.05
Foot vs AK	< 0.001	< 0.001	< 0.001	< 0.001
BK vs AK	< 0.001	< 0.01	< 0.001	> 0.05

Table 5.19. Results of Dunn's multiple comparisons test following ANOVA of inter-group differences in mean $TcpO_2$ (mmHg) at the three levels. The shaded cells highlight the statistically significant differences.

		AKA	**BKA**	**Foot**
Claudication vs	Pre-gangrene	> 0.05	< 0.001	< 0.001
	Ulcer	> 0.05	< 0.01	< 0.01
	Gangrene	> 0.05	< 0.001	< 0.001
Pre-gangrene vs	Ulcer	> 0.05	> 0.05	> 0.05
	Gangrene	> 0.05	> 0.05	> 0.05
Ulcer vs	Gangrene	> 0.05	> 0.05	> 0.05

How does this compare to the literature?

5.4.2.2.1 Comparison of $TcpO_2$ Index data with literature data

As the reported studies provided insufficient data to compare all 5 patient groups the study results are shown plotted against the pooled data derived from the literature (figures 5.7).

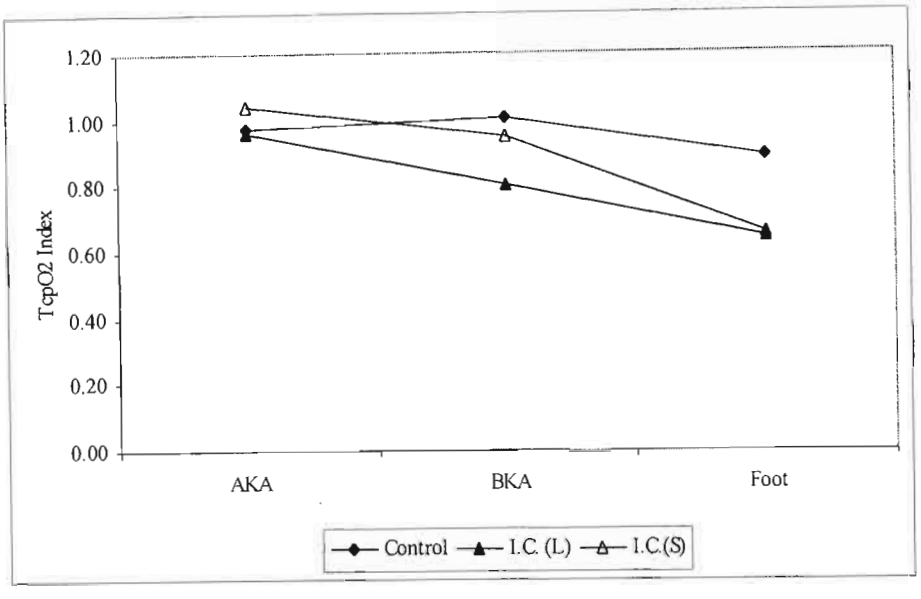


Figure 5.7. Mean $TcpO_2$ Index values of pooled data of controls, and patients with intermittent claudication derived from the literature (L) and study patients with intermittent claudication (S).

The pooled data from the literature are derived from relatively small samples, 27 patients each at the AKA and BKA levels and 91 patients at the Foot. The study data are derived from 25 AKA measurements, 25 BKA and only 26 Foot measurements. The patient populations are not well described and are homogenous only in the fact that intermittent claudication is the presenting symptom. The severity of claudication is unknown in the pooled data, while in the study patients, walking distances varied from less than 50 m to more than 500 m.

Accepting this limitation the data can be assessed in terms of the reduction in $TcpO_2$ Index from level to level. In patients with intermittent claudication as their presenting symptom, it would be expected that the Foot $TcpO_2$ values would be more representative of the disease severity than either the AKA or BKA values. The fall from the AKA level to BKA level is 0.16 in the pooled data and 0.09 in the study and the fall from BKA to Foot is 0.24 and 0.30 respectively. While the fall from BKA to Foot in the study patients is greater than in the pooled data, the effect of this is that the mean value of the Foot Index of both groups is almost the same, 0.64 and 0.65.

Limited data and the method of reporting in the literature necessitated pooling Index data for patients with rest pain and gangrene. The study data for patients whose major presentation

was either gangrene or rest pain were combined and are plotted with the literature data in figure 5.8.

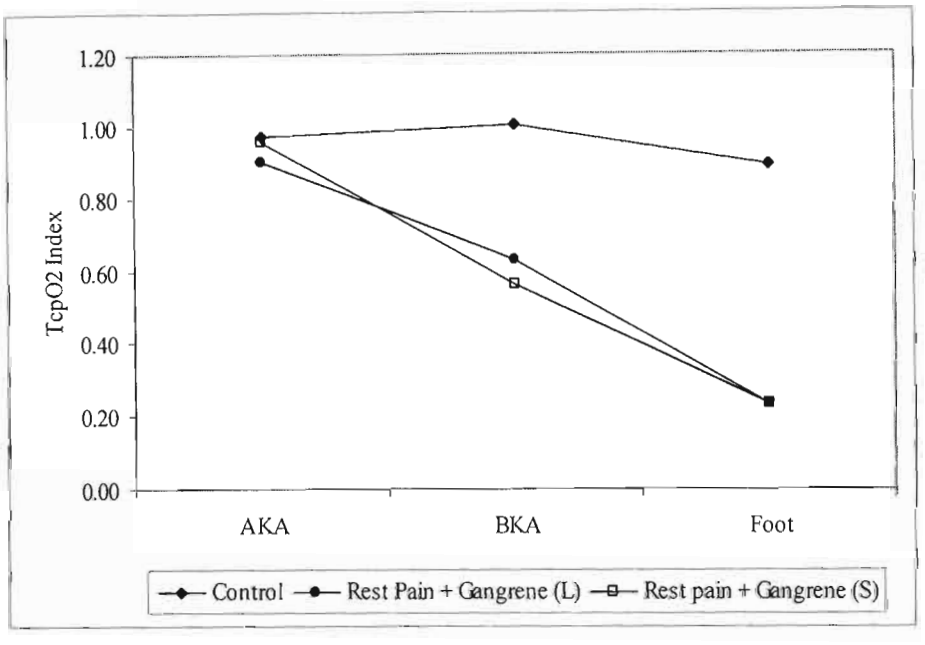


Figure 5.8. Mean $TcpO_2$ Index values of pooled data of controls, and patients with rest pain and gangrene derived from the literature (L) and the study patients (S).

The results shown in figures 5.7 and 5.8 would suggest that the $TcpO_2$ Index data derived from our patient population are no different to that in other studies.

5.4.2.2.2 Review of the $TcpO_2$ Index data based on diabetic status

The data presented in table 5.17 are presented based on the diabetic status of the patients in tables 5.20, 5.21.

Table 5.20. A comparison of the $TcpO_2$ Index of diabetic and non-diabetic patients presenting with claudication.

		AKA	BKA	Foot
Non-diabetic	n =	25	26	25
	Average	1.04 ± 0.26	0.95 ± 0.24	0.66 ± 0.50
	Range	0.33 – 1.48	0.41 – 1.58	0 – 1.35
	Median	1.05	0.97	0.76
Diabetic	n =	1	1	1
	Average	49	48	17

With only one diabetic presenting with claudication as the major presenting symptom, statistical analysis was not possible.

Table 5.21. A comparison of the $TcpO_2$ of diabetic and non-diabetic patients presenting with pregangrene, ulcers or gangrene.

		AKA	BKA	Foot
Pregangrene				
Non-diabetic	n =	70	72	64
	Average	0.99 ± 0.25	0.57 ± 0.37	0.22 ± 0.33
	Range	0.29 – 1.57	0 – 1.32	0 – 1.24
	Median	0.995	0.645	0
Diabetic	n =	16	16	16
	Average	0.81 ± 0.20	0.47 ± 0.44	0.27 ± 0.37
	Range	0.53 – 1.29	0 – 1.23	0 – 1.13
	Median	0.76	0.25	0
Ulcer				
Non-diabetic	n =	46	48	44
	Average	0.92 ± 0.26	0.65 ± 0.42	0.21 ± 0.31
	Range	0.06 – 1.76	0 – 1.97	0 – 1.15
	Median	0.95	0.66	0
Diabetic	n =	14	15	14
	Average	1.03 ± 0.17	0.78 ± 0.37	0.38 ± 0.37
	Range	0.75 – 1.3	0 – 1.25	0 – 0.92
	Median	1	0.87	0.31
Gangrene				
Non-diabetic	n =	157	155	157
	Average	0.91 ± 0.26	0.63 ± 0.35	0.16 ± 0.26
	Range	0.13 – 1.79	0 – 1.82	0 – 1.2
	Median	0.93	0.66	0
Diabetic	n =	48	49	49
	Average	1.00 ± 0.23	0.64 ± 0.33	0.23 ± 0.31
	Range	0.51 – 1.62	0 – 1.18	0 – 1.05
	Median	0.98	0.75	0.05

The data of all the diabetic patients and non-diabetics were analysed for changes in mean $TcpO_2$ Index between measurement levels, based on the presentation, table 5.22.

Table 5.22. Results of Dunn's multiple comparisons test following intra-group ANOVA of the mean $TcpO_2$ Index data for each level and each presentation in diabetic patients and non-diabetic (Non Diab) patients.

	Gangrene		Ulcer		Pre-gangrene	
	Diabetic	Non Diab	Diabetic	Non Diab	Diabetic	Non Diab
Foot vs BK	< 0.01	< 0.001	> 0.05	< 0.001	> 0.05	< 0.001
Foot vs AK	< 0.001	< 0.001	< 0.001	< 0.001	< 0.01	< 0.001
BK vs AK	< 0.001	< 0.001	> 0.05	< 0.05	> 0.05	< 0.001

The results were similar to the absolute $TcpO_2$ results. The difference in mean $TcpO_2$ Index values between measurement sites in diabetic patients was less significant than in non-diabetic patients. In the group of diabetic patients presenting with ulcers, the fall in $TcpO_2$ distally down the leg was not significant between levels. As stated before, this may be the result of a mix of diabetic and ischaemic ulcers. To determine if there was a difference between $TcpO_2$ values in diabetic and non-diabetic patients, the difference in mean $TcpO_2$ values at each level was compared for each presentation, table 5.23.

Table 5.23. Results of Dunn's multiple comparisons test following intra-group ANOVA's of the mean $TcpO_2$ Index data for each level and each presentation comparing diabetic and non-diabetic patients.

	Gangrene	Ulcer	Pre-gangrene
Foot	> 0.05	> 0.05	> 0.05
BKA	> 0.05	> 0.05	> 0.05
AKA	> 0.05	> 0.05	> 0.05

No significant differences were found between diabetics and non-diabetics.

5.5 Prospective Study on the Relationship of $TcpO_2$ and Pulse Status

5.5.1 Method

400 patients with PVD were entered in the prospective study. $TcpO_2$ summaries were compiled at the time of examination and updated on review of the patient records after discharge. The $TcpO_2$ measurements were made in the routine way.

The pulse status of 367 limbs on which $TcpO_2$ measurements were recorded, form the study group. Patients were categorised according to the most distal palpable pulse in the affected limb. Pulses were recorded as either present or absent, with no attempt made to grade pulse pressure or volume. If one arterial pulse was felt at the foot, the patient was classified as having a foot pulse.

5.5.2 Results

5.5.2.1 Absolute $TcpO_2$

The mean absolute $TcpO_2$ in the leg based on the most distal palpable pulse is shown in table 5.24 and figure 5.9.

Table 5.24. Mean absolute $TcpO_2$ (mmHg) at the different amputations levels, of patients grouped according to their most distal palpable pulse (Lowest Pulse).

Lowest Pulse	Chest	AKA	BKA	Foot
Foot	56.9 ± 15.5	58.2 ± 15.8	52.4 ± 18.6	41.7 ± 23.4
Popliteal artery	60.2 ± 11.2	60.1 ± 12.4	49.4 ± 17.2	22.0 ± 22.0
Femoral artery	58.5 ± 12.4	56.9 ± 13.4	38.4 ± 21.2	15.7 ± 20.5
No Limb Pulse	57.3 ± 13.1	47.5 ± 18.1	28.4 ± 23.1	10.0 ± 16.2

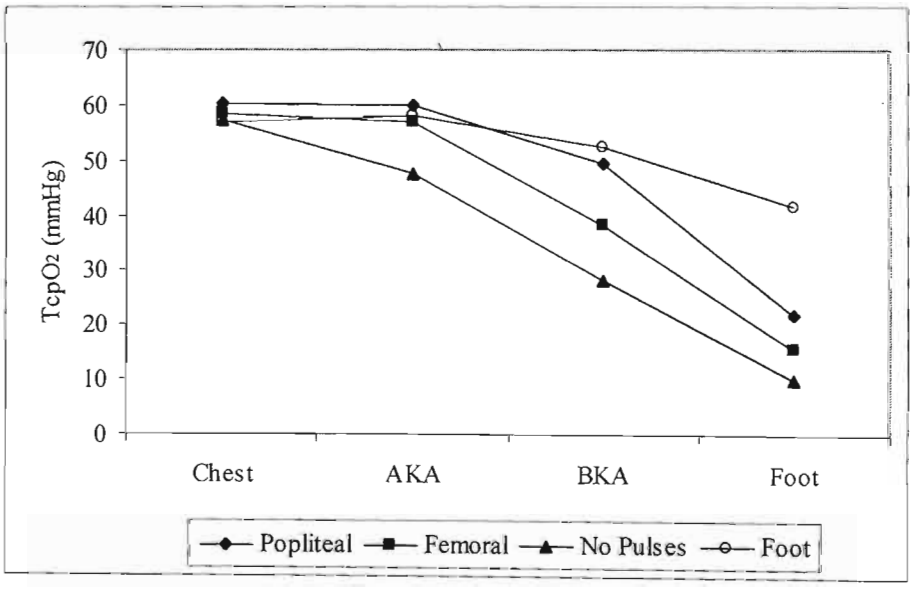


Figure 5.9. Mean $TcpO_2$ at the four measurement sites, of patients grouped according to their lowest palpable pulse.

With patients grouped according to their most distal palpable pulse, repeated measures analysis of variance was performed to determine possible intra-group differences in $TcpO_2$ values obtained at the different measurement sites (table 5.25) and ANOVA was performed to determine inter-group differences (table 5.26).

Table 5.25. Results of repeated measures ANOVA comparing $TcpO_2$ measurements at the different measurement sites of patients grouped according to their most distal palpable pulse.

	Most distal palpable pulse			
	Foot	**Popliteal**	**Femoral**	**No Pulse**
n =	71	62	179	55
	p	p	p	p
Chest vs AKA	> 0.05	> 0.05	> 0.05	< 0.01
BKA	> 0.05	< 0.001	< 0.001	< 0.001
Foot	< 0.001	< 0.001	< 0.001	< 0.001
AKA vs BKA	> 0.05	< 0.001	< 0.001	< 0.001
Foot	< 0.001	< 0.001	< 0.001	< 0.001
BKA vs Foot	< 0.001	< 0.001	< 0.001	< 0.001

Table 5.26. Results of inter-group ANOVA comparing the effect of the most distal pulse on $TcpO_2$ values at the different measurement sites.

Most Distal Pulse	**Chest**	**AKA**	**BKA**	**Foot**
	p	p	p	p
Foot vs Popliteal	> 0.05	> 0.05	> 0.05	< 0.001
Femoral	> 0.05	> 0.05	< 0.001	< 0.001
No Pulses	> 0.05	< 0.001	< 0.001	< 0.001
Popliteal vs Femoral	> 0.05	> 0.05	< 0.01	> 0.05
No Pulses	> 0.05	< 0.001	< 0.001	< 0.01
Femoral vs No Pulses	> 0.05	< 0.001	< 0.001	> 0.05

These data show that in clinically symptomatic patients $TcpO_2$ is significantly decreased at measurement sites distal to the lowest palpable pulse. In addition there is a significant gradient in $TcpO_2$ distal to the lowest pulse. In those patients with a palpable pedal pulse, $TcpO_2$ values at the foot were significantly lower than at the BKA site. The percentage fall in $TcpO_2$ from the AKA site to the Foot ranged from 28 % in patients with a pedal pulse to 79 % in patients with absent limb pulses. The fall in $TcpO_2$ at the BKA site was greater in patients with no popliteal pulses than in patients in whom the popliteal pulse was the lowest pulse present. This suggests that the magnitude of the fall in $TcpO_2$ is dependent on the level of the occlusion.

5.5.2.2 $TcpO_2$ Index

Similar observations were noted for the $TcpO_2$ index, table 5.27 and figure 5.10.

Table 5.27. Mean $TcpO_2$ Index at the different amputation levels, of patients grouped according to their most distal palpable pulse (Lowest Pulse).

Lowest Pulse	AKA	BKA	Foot
Foot	1.06 ± 0.29	0.95 ± 0.37	0.74 ± 0.40
Popliteal	1.01 ± 0.18	0.83 ± 0.31	0.37 ± 0.36
Femoral	1.00 ± 0.25	0.67 ± 0.39	0.27 ± 0.36
No Limb Pulse	0.84 ± 0.28	0.51 ± 0.39	0.39 ± 0.29

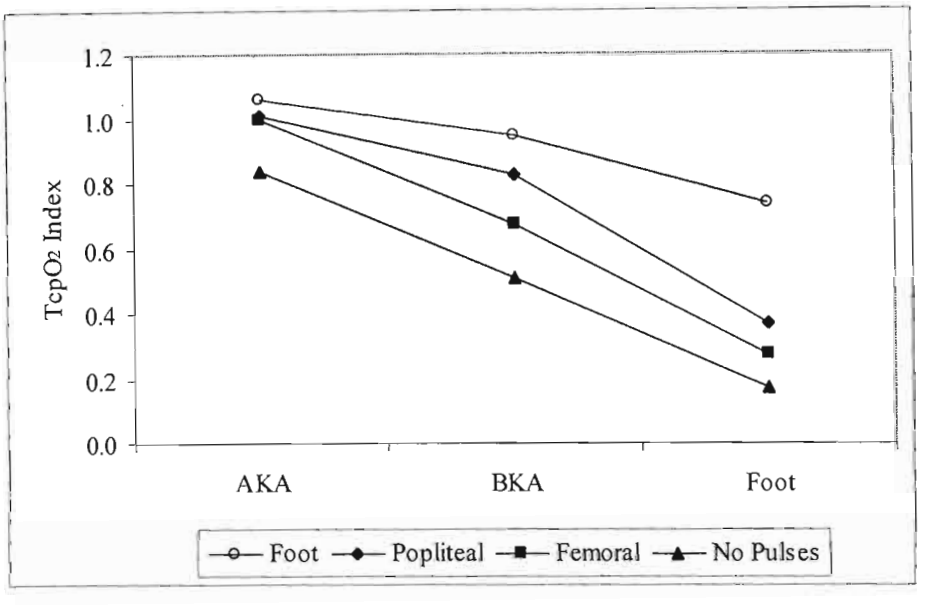


Figure 5.10. Mean $TcpO_2$ Index at the three measurement sites, of patients grouped according to their lowest palpable pulse.

With patients grouped according to their most distal palpable pulse, repeated measures analysis of variance was performed to determine possible intra-group differences in $TcpO_2$ Index values obtained at the different measurement sites (table 5.28) and ANOVA was performed to determine inter-group differences (table 5.29).

Table 5.28. Results of repeated measures ANOVA comparing $TcpO_2$ Index measurements at the different measurement sites in patients grouped according to their most distal palpable pulse.

	Foot	**Popliteal**	**Femoral**	**No Pulse**
n =	71	62	179	55
	p	p	p	p
AKA vs BKA	> 0.05	< 0.001	< 0.001	< 0.001
Foot	< 0.001	< 0.001	< 0.001	< 0.001
BKA vs Foot	< 0.001	< 0.001	< 0.001	< 0.001

Table 5.29. Results of inter-group ANOVA comparing the effect of the most distal pulse on $TcpO_2$ Index values at the different measurement sites.

		AKA	**BKA**	**Foot**
		p	p	p
Foot vs	Popliteal	> 0.05	> 0.05	< 0.001
	Femoral	> 0.05	< 0.001	< 0.001
	No Pulses	< 0.001	< 0.001	< 0.001
Popliteal vs	Femoral	> 0.05	< 0.05	> 0.05
	No Pulses	< 0.01	< 0.001	< 0.05
Femoral vs	No Pulses	< 0.001	> 0.05	> 0.05

The $TcpO_2$ Index data mirrors the results obtained with absolute $TcpO_2$.

5.5.3 Summary

Changes in absolute $TcpO_2$ and the $TcpO_2$ Index measured at the standard amputation sites are a reflection of pulse status. $TcpO_2$ values fall distal to the lowest palpable pulse and a $TcpO_2$ gradient is established below the level of occlusion. The magnitude of the fall is dependent on the level of the occlusion. $TcpO_2$ values are shown to reflect the adequacy of arterial inflow and hence oxygen delivery.

Chapter 6

Comparison of $TcpO_2$ with Doppler Arterial Pressure Studies in Patients with Peripheral Vascular Disease

6.1 Introduction

In this chapter the literature relating to comparisons of Doppler pressure studies with $TcpO_2$ in patients with PVD will be reviewed. Data from a prospective study will be presented comparing $TcpO_2$ with Doppler arterial pressures in patients with PVD requiring amputation. Possible differences between diabetic and non-diabetic patients will be investigated.

6.2 Doppler pressure studies and $TcpO_2$

The use of systolic Doppler pressures to predict amputation healing has been widely reported. The test, measuring ankle, calf and thigh systolic pressure is easily reproducible and repeatable although there is some inter observer variability. It is simple, relatively inexpensive and noninvasive. A proximal stenosis results in a fall in pressure and it is this fall in pressure which has been utilised in trying to predict amputation wound healing. The test can be refined by normalising the lower limb pressure by relating it to Brachial systolic pressure, making the assumption that there is no stenosis in the vascular tree proximal to the site of brachial artery pressure measurement.

While some papers have suggested the use of Doppler systolic pressures or the Doppler pressure Index to predict amputation, there are two limitations that have led people to stop using Doppler pressure derived values for amputation level selection. These are, that the pressures may be high in patients with incompressible vessels, as in diabetic medial sclerosis, and that the test is poor in predicting which amputations will fail *ie* it has poor specificity. The problem is usually summarised as follows: a high Doppler pressure does not ensure the likelihood of successful healing and a low Doppler ankle pressure does not rule out the possibility of primary healing.

It has been suggested that the problem associated with high pressures in Diabetic patients with medial sclerosis can be overcome by elevating the foot and recording the elevation

height at which the Doppler signal disappears; the vertical height is then multiplied by 0.735 to give the pressure in mmHg. This method is seldom reported in the literature.

When used for the prediction of amputation wound healing, the greatest of the ankle pressures or indices has been taken to represent the ankle pressure or index.

In addition to Doppler ankle and thigh pressures, photoplethysmographic measurement of toe pressures have been used to augment the information derived from ankle pressure studies.

6.2.1 Literature review of Doppler pressure studies reported with $TcpO_2$ studies

When Burgess compared absolute $TcpO_2$ with Doppler pressure "ischaemic ratio's" in their patient population of 39 BKA's, two thirds of whom were diabetic, they reported that healing only occurred when the "below-the-knee" ratio was 0.34 or more (Burgess, E. M. *et al.*, 1982). They were however unable to elicit pulses below the knee in 10 of their patients. Seven of the amputations performed on these 10 patients healed. Effectively their threshold for healing based on Doppler pressure indices was 0. It is not clear from the paper as to which arterial pressure was used to compute the ratio as pressures were measured below the knee and at the ankle.

No correlation between predictability of $TcpO_2$ measurements and Doppler indices could be demonstrated in 14 healed amputations in Benscoter's series (Benscoter, J. L. *et al.*, 1984). Katsamouris could also find no correlation between amputation outcome and Doppler segmental pulse pressure or pulse volume in 17 of their patients. They noted that segmental pressures were unobtainable in 3 patients because of incompressible vessels and undetectable in 4 patients, and all 7 had successful amputation healing. Five of 12 patients who healed amputations had pulse volume recording amplitudes that were less than the average for three patients whose amputations failed (Katsamouris, A. *et al.*, 1984). No direct comparison of $TcpO_2$ and Doppler pressures or pulse volume was made.

Similarly Ratliff, D. A. *et al.*, (1984) could find no relationship between ankle systolic pressure and amputation healing in 34 BKA's. Of interest is that 16 of 29 healed BKA's had unrecordable ankle systolic pressures.

Karanfilian *et al.* combined their data from 20 amputations with that of 37 ischaemic ulcerations or gangrenous changes of the foot and compared $TcpO_2$ with unheated laser Doppler, Doppler ankle pressures and the ankle brachial index (ABI). The definition of amputation wound healing allowed for a local revision or debridement to have failed, before the amputation was deemed to have failed. A best fit technique was used to analyse the data and determine the level at which each test would yield the greatest accuracy for wound healing. The criteria reached by this method were a $TcpO_2$ greater than 10 mmHg, a laser Doppler skin blood flow of more than 40 mV, a laser Doppler pulsewave amplitude greater than 4 mV (with both criteria having to be met) and an ankle systolic pressure greater than 30 mmHg. The sensitivity or true positive test for predicting healing was best for $TcpO_2$ (100 %) with laser Doppler and Doppler ankle pressures being 79 % and 75 % respectively. The specificity, or true negative, was highest for laser Doppler at 96 %, with $TcpO_2$ being 88 % ankle Doppler pressures a very poor predictor of failure at 26 %. The overall accuracy of $TcpO_2$ was 95 %, laser Doppler 87% and Doppler ankle pressures 52 % (Karanfilian, R. G. *et al.*, 1986). It should be noted that the laser Doppler measurements were performed using an unheated probe.

Rhodes reported on 5 amputations performed 10 – 20 days after distal tibial revascularisation. Amputation level selection was based on a clinical judgement and a $TcpO_2$ of 25 mmHg or more and all healed. Ankle brachial indices were 0.75 or more in all patients prior to amputation (Rhodes, G. R. and King, T. A., 1986).

Campbell, W. B. and Morris, P. J., (1987) used ankle Doppler pressures and below knee $TcpO_2$'s to assist in the evaluation of their study on the comparison of healing and rehabilitation in patients undergoing Gritti-Stokes or BKA. Of 24 limbs amputated, it was not possible to measure ankle pressures in 7, and no Doppler signal was detectable in 8 limbs. They report pressures of 70 mmHg or less in 8 patients and a pressure of 84 mmHg in 1 limb. A Pearson's correlation performed on the ankle pressure and $TcpO_2$ data of 19 patients extracted from the paper, gives in an r value of 0.2. Only 1 of the amputations for which paired data are provided, failed to heal, with an ankle pressure of 0 mmHg and a BKA $TcpO_2$ of 3.5 kPa (26 mmHg).

Hauser compared the ABI with a $TcpO_2$ index derived either from the chest or the forearm. In a group of 66 amputations, the $TcpO_2$ index of the 21 failed amputations was significantly lower than those that healed. The difference in ABI between the two groups was not significant. He concluded that the Doppler ABI data were of little value and problems were encountered with pain on cuff inflation, and high readings in diabetics were so frequent as to

render the test "...nearly useless". In addition, neither pulse volume recordings nor digital plethysmography was practical for patients with tissue loss (Hauser, C. J., 1987).

Malone compared $TcpO_2$ data obtained from 51 amputations with ABI in 46 amputations, intra-dermal ^{133}Xe in 41 amputations, and Doppler derived popliteal artery pressure in 34 limbs. $TcpO_2$ and the $TcpO_2$ index were shown to statistically differentiate between failed and healed amputations at all three amputation levels, AKA, BKA and transmetatarsal (TMA). None of the other investigations were statistically reliable discriminators between successful and failed outcome. The mean ABI of failed amputations 0.78 ± 0.4 ($n = 11$) was actually higher than that of healed amputations 0.74 ± 0.4 ($n = 35$). While the Popliteal artery pressures were on average lower in amputations that failed, this did not reach significance at any of the amputation levels (Malone, J. M. *et al.*, 1987).

Amputation level selection based on segmental pressures of 70 mmHg or more was found to have a poorer sensitivity and specificity for diabetics 82 % and 0 % and non-diabetics 42 % and 100 % than selection based on $TcpO_2$. A $TcpO_2$ of more than 10 mmHg or an increase of $TcpO_2$ of 10 mmHg or more following oxygen inhalation had a sensitivity 100 % and specificity 88 %. Similar results were found for an ABI set at 0.45 or more for diabetics and 0.35 or more for non-diabetics (Oishi, C. S. *et al.*, 1988).

Wagner found Doppler derived femoral blood pressures to be significantly different between healed ($n = 30$) and failed AKA's ($n = 2$). Pressures at other levels and ABI's were not different. For BKA's there was no difference in pressures at any level in the limb or ABI, between 52 healed and 8 failed amputations. Using the common predictive level of 70 mmHg, 12 BKA's healed with pressures less than 70 mmHg and 5 failed with pressures above this level. Similarly setting the predictive value at an ABI of 0.45 to accommodate the mixed pool of diabetic and non-diabetic patients, there were 10 amputations which healed below this level and 4 which failed above it (Wagner, W. H. *et al.*, 1988).

Wyss, C. R. *et al.*, (1988) measured the ankle blood pressure in 87 of 144 patients undergoing BKA, and noted that the number of failures increased as the pressure at the ankle decreased. This relationship was not as consistent as that observed in the 144 BKA amputations for which $TcpO_2$ data were available. Amputations performed at the foot were not associated with low ankle pressures. There did not appear to be relationship between ankle pressure and outcome. This may have been due to high ankle pressures in diabetics with medial sclerosis.

The receiver operator curves produced from Padberg's data from 80 wounds (51 amputations and 29 non healing ulcers) show $TcpO_2$ and heated laser Doppler to be superior predictors of wound outcome than ABI (Padberg, F. T. *et al.*, 1992).

ABI's were used as part of a battery of criteria that had to be met for amputation level selection in 38 amputations performed about the foot by Pinzur. These included a minimum serum albumin concentration of 3.0 $gm.dl^{-1}$, a total lymphocyte count of 1500 or more and an ABI of 0.5 or more. The failure rate was 15.8%, and it was noted that 8 patients "... exhibited pipe-stemming where their ankle brachial index was greater than 1." In 2 of these patients the $TcpO_2$ was less than 20 mmHg and both required subsequent revision (Pinzur, M. S. *et al.* 1992).

Using stepwise multiple logistic regression analysis Padberg compared the usefulness of $TcpO_2$ with arterial segmental pressures and ABI. $TcpO_2$ was found to be the best test for predicting healing or failure. It was also relatively unaffected by the presence of diabetes or chronic renal failure (Padberg, F. T. *et al.*, 1996).

6.2.2 Prospective study comparing Doppler pressure studies with $TcpO_2$ in patients with peripheral vascular disease requiring amputation

Two hundred patients undergoing pre-amputation assessment of wound healing potential were entered in a prospective study. $TcpO_2$ summaries were compiled at the time of examination and on review of the patient records after discharge.

6.2.2.1 Method

Doppler pressure studies were undertaken using standard techniques with measurements made at the thigh, popliteal artery and ankle, Dorsalis Pedis artery, Tibialis Posterior artery and the Perforating Peroneal artery. Brachial artery pressure was measured and the limb brachial index Doppler Index calculated. All pressure measurements were made in the Non-Invasive Laboratory by the vascular technicians. The $TcpO_2$ measurements were made in the routine way.

Complete data sets were available for 164 patients who underwent amputation. For amputations about the foot, ankle Doppler data were compared with Foot $TcpO_2$ data. For BKA and AKA's the Doppler data were compared with Popliteal artery pressures.

The Doppler data derived from calf pressures were handled in two ways. The Doppler pressures and indices based on the best of the three ankle pressures were compared with $TcpO_2$ and the $TcpO_2$ Index.

The relationship between $TcpO_2$ and Doppler was investigated at the amputation level, and at the other levels in all patients. The Doppler data from the ankle were compared with the Foot $TcpO_2$ for foot amputation, and the popliteal artery data were compared with the BKA $TcpO_2$ values for BKA. The Popliteal artery Doppler pressures were compared with the AKA $TcpO_2$ for AKA's.

In addition the ankle derived Doppler pressures of all patients were compared with the Foot $TcpO_2$ and the Popliteal artery Doppler data with the BKA $TcpO_2$.

The data was first checked for normal distribution using the Kolmogorov and Smirnov test. If the data was non-Gaussian in distribution, non-parametric correlation was performed using the Spearman rank test. In subsequent correlations, Pearson product moment correlation or Spearman's rank correlation was performed where appropriate. Comparison of means was by unpaired t-test (two tailed) with the data being checked for difference in standard deviation and Gaussian distribution. If the data was Gaussian in distribution but with a significant difference between standard deviations Welch's Correction was used. If the standard deviations were significantly different, the non-parametric Mann Whitney test was used.

6.2.2.2 Results and Discussion

770 complete data sets of Doppler pressures recorded at the ankle and Popliteal artery, and $TcpO_2$ recorded at the foot, BKA and AKA levels were available for evaluation. These included measurements made at sites other than the level ultimately chosen for amputation. 506 data sets were available comparing Doppler data from the ankle with Foot $TcpO_2$, and the Popliteal artery data with BKA $TcpO_2$. This excludes AKA $TcpO_2$ measurements for which no directly comparable Doppler data were gathered. The descriptive statistics of these 506 sets are shown in table 6.1 and the relationship of $TcpO_2$ and Doppler pressures and the $TcpO_2$ Index and the Doppler Index are shown in table 6.2 and figures 6.1 and 6.2.

Table 6.1. $TcpO_2$, $TcpO_2$ Index, Doppler pressure and ankle brachial Doppler Index expressed as mean and 1 SD, from 506 sets of data taken about the foot and knee, as a group and based on diabetic status. Comparison of means of diabetic and non-diabetic subjects is shown (p =), with significant differences highlighted.

	All	**Diabetic**	**Non-diabetic**	
n =	506	107	399	p =
$TcpO_2$ (mmHg)	32.0 ± 24.5	33.2 ± 25.0	31.7 ± 24.4	0.6663
$TcpO_2$ Index	0.55 ± 0.43	0.58 ± 0.41	0.55 ± 0.43	0.4396
Doppler (mmHg)	112.8 ± 61.7	132.1 ± 62.5	107.6 ± 60.5	0.0003
Doppler Index	0.73 ± 0.39	0.81 ± 0.38	0.71 ± 0.39	0.0215

The Doppler data gathered from diabetic patients were significantly higher than in non-diabetic subjects. This would be in keeping with the expectation that some of these subjects had less compressible vessels. For this difference to be valid, it must be assumed that the disease process was similar in both diabetic and non-diabetic groups. If it is accepted that $TcpO_2$ and the $TcpO_2$ Index are valid indicators of the severity of the disease process (Chapter 4) the assumption that the disease process was similar can be investigated. This can be done by comparing $TcpO_2$ and the $TcpO_2$ Index in diabetics and non-diabetics from the pooled data and from the data gathered at the foot and BKA levels (Table 6.2).

Table 6.2. $TcpO_2$, $TcpO_2$ Index, Doppler pressure and Doppler Index expressed as mean and 1 SD, from data taken about the foot and knee in diabetic and non-diabetic subjects. Comparison of means of diabetic and non-diabetic subjects is shown (p =), with significant differences highlighted.

	Diabetic	**Non-diabetic**	**p =**
Foot	n = 50	n = 189	
$TcpO_2$ (mmHg)	25.0 ± 24.7	21.5 ± 23.0	0.2584
$TcpO_2$ Index	0.43 ± 0.40	0.36 ± 0.41	0.1772
Doppler (mmHg)	106.7 ± 62.3	88.2 ± 59.5	0.0488
Doppler Index	0.65 ± 0.37	0.58 ± 0.38	0.2232
BKA	n = 57	n = 211	
$TcpO_2$ (mmHg)	40.3 ± 23.2	41.0 ± 21.7	0.7956
$TcpO_2$ Index	0.70 ± 0.32	0.72 ± 0.39	0.8391
Doppler (mmHg)	154.3 ± 54.0	124.9 ± 56.1	0.0007
Doppler Index	0.95 ± 0.32	0.83 ± 0.37	0.0342

The $TcpO_2$ data in table 6.2 would suggest that on average the disease severity was not significantly different in the diabetics and non-diabetics, although the $TcpO_2$ data at the foot are slightly higher in the diabetic group. This would support acceptance of the differences noted in table 6.1.

The correlation between $TcpO_2$ and Doppler data for the pooled data and diabetic and non-diabetic groups was examined (Table 6.3).

Table 6.3. The results of correlation between $TcpO_2$ and the $TcpO_2$ Index with Doppler systolic pressure and the Doppler Index. For each correlation the sample size (n), Spearman correlation coefficient (r) and the significance level (p) are shown.

		Doppler (mmHg)		**Doppler Index**	
All	n =	**r =**	**p**	**r =**	**p**
$TcpO_2$ (mmHg)	506	0.4693	< 0.0001	0.5079	< 0.0001
$TcpO_2$ Index		0.4745	< 0.0001	0.4942	< 0.0001
Diabetics					
$TcpO_2$ (mmHg)	107	0.4323	< 0.0001	0.5213	< 0.0001
$TcpO_2$ Index		0.4534	< 0.0001	0.5058	< 0.0001
Non-diabetics					
$TcpO_2$ (mmHg)	399	0.4798	< 0.0001	0.5066	< 0.0001
$TcpO_2$ Index		0.4807	< 0.0001	0.4936	< 0.0001

The high levels of significance reached in these correlations reflect both the relatively large sample sizes and the wide range of values being compared. The correlation should rather be assessed in terms of the correlation coefficient "r" which at best is 0.52 giving $r^2 = 0.2704$, which is not a very powerful correlation. This can be seen in figure 6.1.

The large sample size obscures some interesting data in figure 6.1. A $TcpO_2$ of 0 mmHg was recorded 111 times, with a Doppler value of 0 mmHg in 27 instances and 84 Doppler readings above 0 mmHg. Conversely the Doppler pressure was 0 mmHg in 34 instances with the $TcpO_2$ being zero 27 times. In 4 of the other 7 subjects the $TcpO_2$ was less than 10 mmHg. This difference is significant $p < 0.0001$ (Fishers exact test). Again this supports previous observations that a high Doppler pressure does not guarantee a successful amputation. A similar situation is seen when comparing $TcpO_2$ Index with Doppler Index (figure 6.2).

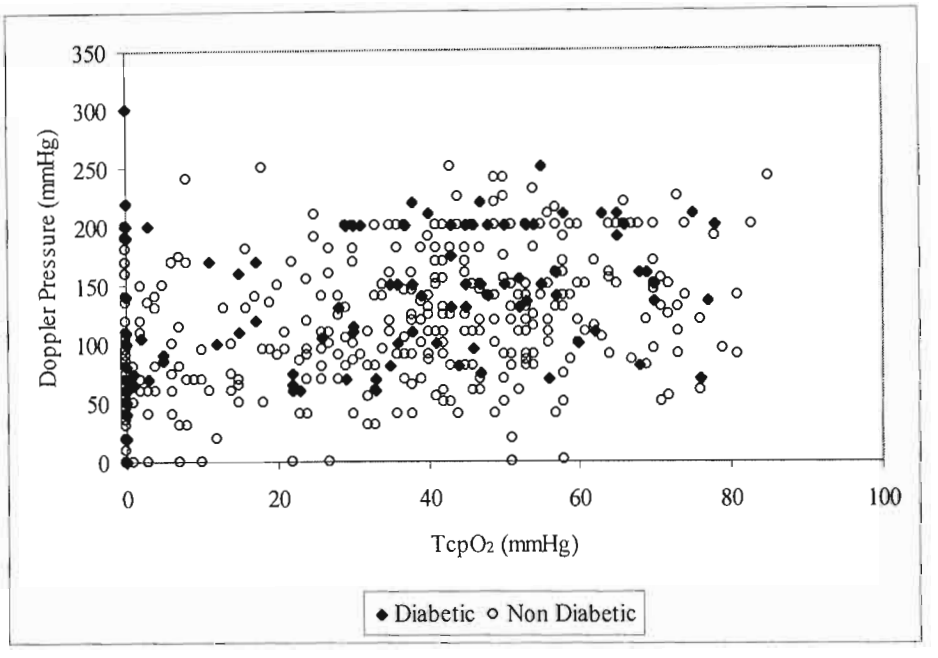


Figure 6.1. Scattergram of the relationship between Doppler pressures and absolute $TcpO_2$ values, based on foot and knee data sets in diabetic and non-diabetic patients.

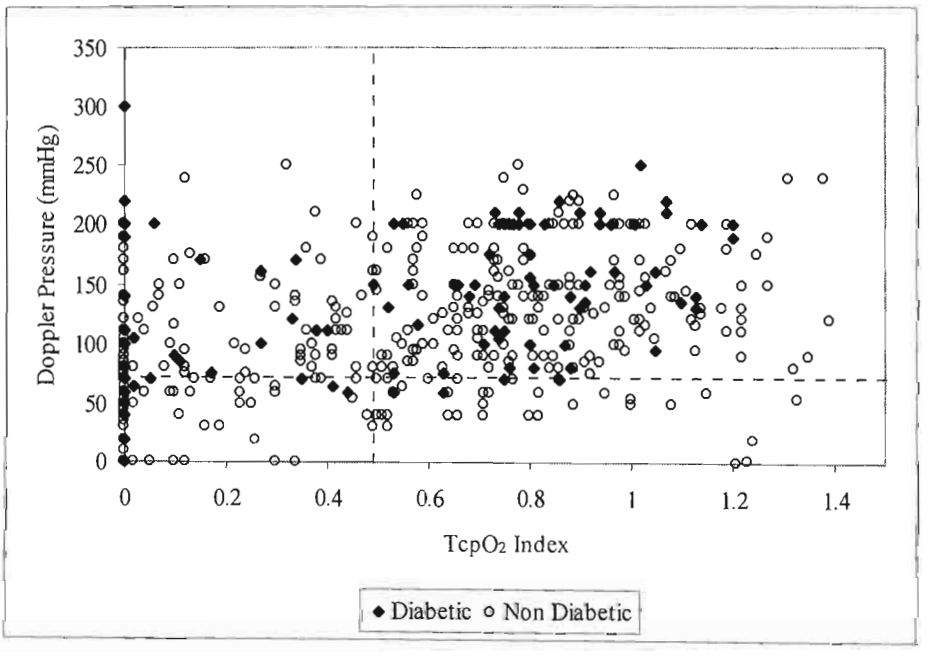


Figure 6.2. Scattergram of the relationship between Doppler pressures (mmHg) and the $TcpO_2$ Index, based on foot and knee data sets in diabetic and non-diabetic patients. A vertical line has been drawn at a $TcpO_2$ Index of 0.5 and a horizontal line at a Doppler pressure of 70 mmHg.

What does this mean in terms of amputation wound healing prediction? A Doppler pressure of 70 mmHg or more is generally held to be sufficient for an amputation to heal at both the Foot and BKA levels. The relative sensitivity and specificity of Doppler pressures can be investigated if the following assumption is made, that in our setting, only 1 % of amputations performed at a site with a $TcpO_2$ Index of less than 0.5 will heal. This is based on the sensitivity and specificity data for the $TcpO_2$ Index in amputation wound healing prediction presented in chapter 10. In figure 5.2, all points to the left of the vertical line depicting a $TcpO_2$ Index of 0.5 would be expected to fail. Similarly, all points above the horizontal line drawn at a Doppler pressure of 70 mmHg would be expected to heal (n = 120). There are 265 points in the upper right quadrant, which both the $TcpO_2$ Index and Doppler pressure would predict to heal (true positives) and in the lower left quadrant, there are 62 points where both tests predict failure (true negatives). 29 points are in the lower right quadrant which the $TcpO_2$ Index would predict to heal and Doppler, to fail. The sensitivity of a Doppler pressure of 70 mmHg would be 90.1 % and the specificity 43.4 %, with an overall accuracy of 70.6 %, assuming the $TcpO_2$ Index to be valid.

Does this hold true in the 164 patients who underwent amputation? Comparison of the $TcpO_2$ and Doppler data of the healed and failed amputations is shown in table 6.4.

Table 6.4. Comparison of the means of $TcpO_2$ and Doppler data of healed and failed amputations. Statistical analysis is by unpaired t-test with Welch's correction used for the $TcpO_2$ Index data where there was a significant difference in the standard deviations.

	Healed	**Failed**	**p**
n =	117	47	
$TcpO_2$ (mmHg)	48.5 ± 12.7	19.3 ± 15.7	< 0.0001
$TcpO_2$ Index	0.83 ± 0.24	0.33 ± 0.27	< 0.0001
Doppler Pressure (mmHg)	122.1 ± 55.2	93.9 ± 55.0	= 0.0006
Doppler Index	0.80 ± 0.34	0.60 ± 0.28	= 0.0003

The data from all 4 tests show significant differences between the amputations that healed and those that failed for all four investigations. The relationship of the $TcpO_2$ Index to Doppler systolic pressures at the amputation level is shown in figure 6.3.

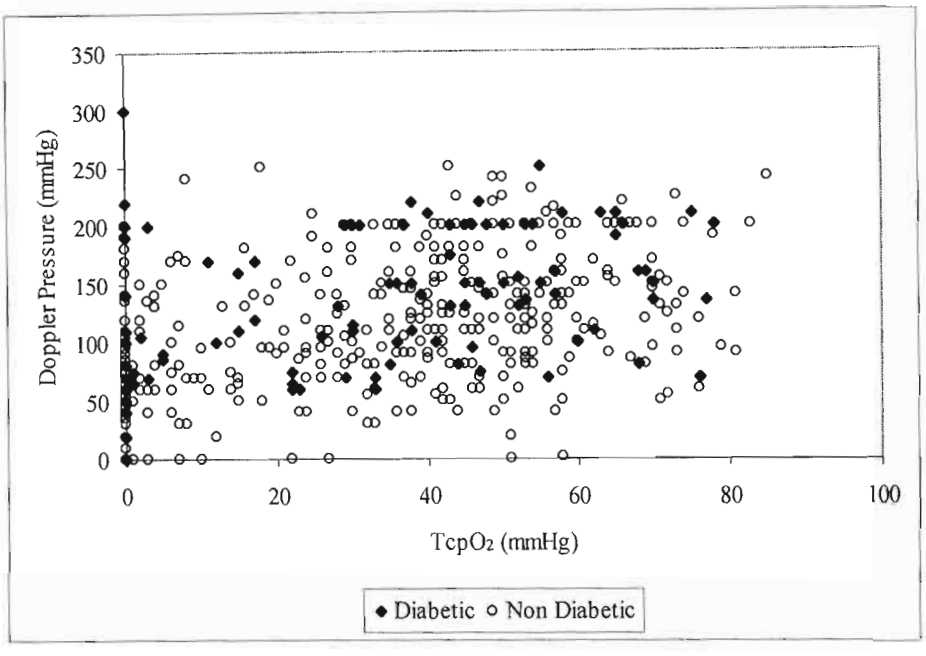


Figure 6.3. Scattergram of the relationship between $TcpO_2$ (mmHg) and Doppler pressures at the amputation level in 164 patients who underwent amputation. Spearman correlation coefficient ($r = 0.2441$, $p = 0.0016$).

In this patient cohort the sensitivity, specificity and accuracy of various Doppler pressures and $TcpO_2$ Indices is shown in tables 6.5 and 6.6.

Table 6.5. The sensitivity, specificity, and accuracy based on 164 amputations, with the Doppler pressure predictive value set at values from 0 - 130 mmHg.

Doppler Pressure (mmHg)	Sensitivity %	Specificity %	Accuracy %
0	98.3	0.0	70.1
10	98.3	0.0	70.1
20	98.3	0.0	70.1
30	98.3	0.0	70.1
40	98.3	6.4	72.0
50	95.7	14.9	72.6
60	90.6	21.3	70.7
70	85.5	40.4	72.6
80	77.8	51.1	70.1
90	70.1	51.4	65.6
100	59.0	70.2	62.2
110	54.7	74.5	60.4
120	47.9	76.6	56.1
130	41.0	76.6	51.2

Table 6.6. The sensitivity, specificity, and accuracy based on 164 amputations, with the $TcpO_2$ Index predictive value set at 0 - 1.1.

$TcpO_2$ Index	Sensitivity	Specificity	Accuracy
	%	%	%
0	100.0	21.3	77.4
0.1	100.0	31.9	80.5
0.2	100.0	40.4	82.9
0.3	100.0	42.6	83.5
0.4	100.0	55.3	87.2
0.45	100.0	57.4	87.8
0.5	100.0	70.2	91.5
0.55	97.4	78.7	92.1
0.6	87.2	87.2	87.2
0.7	70.9	91.5	76.8
0.8	47.9	93.6	61.0
0.9	33.3	100.0	52.4
1	16.2	100.0	40.2
1.1	11.1	100.0	36.6

When Doppler pressures were used to predict amputation healing, pressures of 50 and 70 mmHg provided the best accuracy of 72.6 %. A $TcpO_2$ Index of 0.55, provided the best accuracy at 92 %. The results achieved based on a predictive level set at a Doppler pressure of 70 mmHg are similar to those predicted from the pooled data from all sites. These were a sensitivity of 90.1 %, a specificity of 43.4 % and an accuracy of 70.6 %.

Is there any difference in results between amputations performed at the foot or below the knee? (Table 6.7)

Table 6.7. Comparison of the means of $TcpO_2$ and Doppler data of healed and failed amputations at the Foot and BKA levels.

	Healed	**Failed**	**p**
Foot			
n =	12	24	
$TcpO_2$ (mmHg)	43.8 ± 10.5	15.2 ± 14.7	< 0.0001
$TcpO_2$ Index	0.77 ± 0.16	0.26 ± 0.24	< 0.0001
Doppler Pressure (mmHg)	118.3 ± 55.5	83.1 ± 46.5	= 0.0527
Doppler Index	0.78 ± 0.39	0.54 ± 0.26	= 0.0773
BKA			
n =	69	23	
$TcpO_2$ (mmHg)	48.5 ± 13.9	24.1 ± 15.8	< 0.0001
$TcpO_2$ Index	0.83 ± 0.27	0.44 ± 0.41	< 0.0001
Doppler Pressure (mmHg)	139.4 ± 50.5	100.4 ± 59.3	= 0.0029
Doppler Index	0.89 ± 0.31	0.62 ± 0.27	= 0.0003

At the Foot level, the difference in absolute $TcpO_2$ and the $TcpO_2$ Index between healed and failed amputations was highly significant. The difference in the Doppler derived data bordered on statistical significance. This failure to demonstrate a statistical difference is due in part to the large variance in both healed and failed amputations caused by relatively high Doppler pressures associated with medial sclerosis. At the BKA level incompressible vessels are uncommon and the difference in $TcpO_2$ and Doppler derived data was significantly different in healed and failed amputations.

The possibility of a difference in the worth of both tests was investigated by calculating sensitivity and specificity for amputations at the Foot and BKA levels at different predictive values (tables 6.8 and 6.9).

Table 6.8. The sensitivity, specificity, and accuracy based on 36 amputations performed at the foot, with the Doppler pressure predictive value set at 50, 60 and 70 mmHg, and the $TcpO_2$ index set at 0.5, 0.55 and 0.6.

Foot	**Sensitivity**	**Specificity**	**Accuracy**
Doppler pressure	%	%	%
50 mmHg	91.7	16.7	41.7
60 mmHg	83.3	29.2	47.2
70 mmHg	75.0	50.0	58.3
$TcpO_2$ Index			
0.5	100.0	79.2	86.1
0.55	100.0	87.5	91.7
0.6	83.3	91.7	88.9

Table 6.9. The sensitivity, specificity, and accuracy based on 92 amputations performed below the knee, with the Doppler pressure predictive value set at 50, 60 and 70 mmHg, and the $TcpO_2$ index set at 0.5, 0.55 and 0.6.

BKA	**Sensitivity**	**Specificity**	**Accuracy**
Doppler pressure	%	%	%
50 mmHg	100.0	13.0	78.3
60 mmHg	94.2	13.0	73.9
70 mmHg	94.2	30.4	78.3
$TcpO_2$ Index			
0.5	100.0	60.9	90.2
0.55	98.6	69.6	91.3
0.6	87.0	82.6	85.9

Based on the data in tables 6.8 and 6.9, Doppler pressures are a better predictor of healing at the BKA level and a better predictor of failure at the Foot level. In terms of accuracy Doppler is a better predictor of outcome at the BKA level than at the foot. The best accuracy with Doppler is achieved at a pressure of 70 mmHg. The $TcpO_2$ Index provides the best accuracy at both sites.

This is confirmed by receiver operator characteristic curves (ROC) (Figure 6.4) in which the $TcpO_2$ Index curve is to the left of the Doppler pressure curve and the area under the $TcpO_2$ curve is greater than that of the Doppler curve.

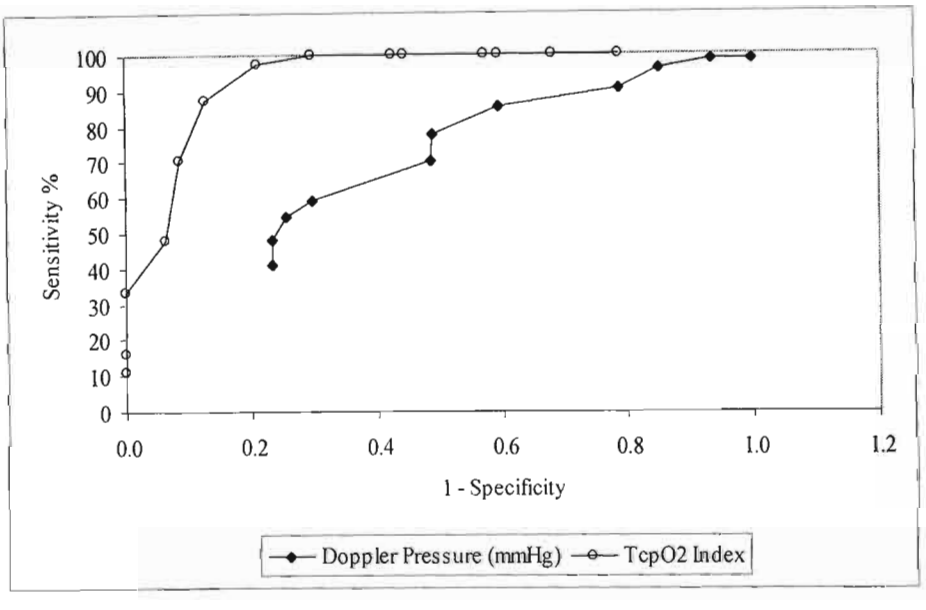


Figure 6.4. Receiver operator characteristic curves for $TcpO_2$ Index and Doppler Pressure (mmHg) based on the outcome of 164 amputations.

6.3 Summary

This study confirms previous observations that the absolute $TcpO_2$ and the $TcpO_2$ Index are similar in diabetic and non-diabetic patients with PVD of similar severity. Reviewing the outcome of 164 amputations, the mean $TcpO_2$, $TcpO_2$ Index, Doppler pressure, and Doppler ABI were all significantly lower in amputations that failed to heal. Based on receiver operator characteristic curves Doppler pressures of 50 mmHg or 70 mmHg to offered an accuracy for predicting healing of only 72 %, with a low specificity. A $TcpO_2$ Index of 5.5 gave an accuracy of 92 %.

Doppler pressure measurement is a better predictor of outcome of below knee amputations than amputations at the foot. The $TcpO_2$ Index is equally good at predicting amputation outcome at either of these sites, and is better than Doppler pressures for predicting amputation wound healing.

Chapter 7

Comparison of $TcpO_2$ with the ^{133}Xenon Radio-isotope Washout Test of Skin Blood Flow

7.1 Introduction

In this chapter the literature relating to the use of the ^{133}Xenon radio-isotope washout test of skin blood flow will be reviewed. Data from a prospective study comparing $TcpO_2$ with the ^{133}Xenon washout test will be presented.

7.2 The ^{133}Xenon radio-isotope washout test of skin blood flow

Amputation wound healing is dependent on many factors, one of which is adequacy of skin blood flow. As described in chapter 2, skin blood flow can be considered as capillary or nutritional blood flow and blood flow short circuited through arteriovenous communications. Nutrient capillary blood flow can be assessed by measurement of the rate of clearance of an intradermal injection of the radio-isotope ^{133}Xenon (^{133}Xe) (Malone, J. M. *et al.*, 1981). Bohr, H., (1967) was the first to report the use of ^{133}Xe to predict healing of an amputation. Subsequently capillary skin blood flow measurement using the ^{133}Xe skin clearance test gained popularity in the early 80's when Moore and his colleagues proposed it as the gold standard for amputation level selection (Malone, J. M. *et al.*, 1981).

The test is based on the Kety principle. The theoretical principles for the calculation of blood flow from clearance of inert gases were presented by Kety in 1949. These are (i) that the logarithm of the tracer concentration (the radio-activity count over the deposit) diminishes linearly with time, (ii) the arterial concentration and hence recirculation of the tracer is negligible, (iii) the tracer leaves the deposit only via venous drainage, (iv) the tissue is homogenously diffused and (v) the tracer reaches an instant diffusion equilibrium between blood and tissue. (Kety, S. S.,1949)

^{133}Xenon is an inert gas which is freely diffusible, lipophilic and which can only be cleared from the site of injection by transport across the capillary cell membrane (Lassen, N. A. *et al.*, 1964; Sejrsen, P,1967). It produces beta and gamma emission and has a half-life of 5.3 days (Kostuik, J. P. *et al.*, 1976). The rate of Xenon transport across the capillary membrane is

proportional to the differential concentration of ^{133}Xe on both sides of the membrane, and is thus directly related to the rate of blood flow through the capillary system. Ladefoged, J, (1966) has stated that there is an instant diffusion equilibrium for ^{133}Xe. The amount of the injected tracer deposited in a tissue principally decreases along an exponential curve, the slope of which is the clearance constant. Having reached the blood it is loosely bound to haemoglobin and is cleared from the body via the lungs. ^{133}Xe recirculation has been shown by Sejrsen, P and Tonnesen, K. H, (1967) to be very low.

The decay of Xenon from the injection site is said to consist of three phases, although this has not always been demonstrated (Palmer, B., 1972). There is an initial accelerating phase, lasting from 15 to 30 s, followed by a more rapid phase lasting 3 to 5 minutes going to a slower phase. The slope of the second rapid phase is the clearance constant. The half-time of the indicator clearance ($T_{½}$) is derived by plotting the log of the counts per minute, during the rapid phase, drawing a tangent to the rapid part of the curve and extrapolating it back to zero. The clearance is not mono-exponential because ^{133}Xe is lipophilic.

Kety demonstrated that the amount of a local indicator decreased according to a single mono-exponential described by the equation

$$Ct = C_0 \exp \frac{(-F \cdot t)}{\lambda} \qquad 6.$$

Where Ct and C_0 denote the tissue concentrations of the indicator at times t and 0
F = perfusion coefficient in ml / 100 g tissue / min

λ = blood – skin partition co-efficient in ml / g

This can be rearranged to

$$F = K \cdot \lambda \cdot 100 \qquad 7.$$

where K is the washout rate constant which can be derived from

$$K = \frac{\text{Log}_N 2}{T_{½}} \qquad 8.$$

where $T_{½}$ represents the half-time of the indicator clearance, and can be calculated from the slope of the washout curve.

Substituting equation 3 in equation 2

$$F = \frac{\text{Log}_N 2 \,.\, \lambda \,.\, 100}{T_{½}} \qquad 9.$$

$$F = \frac{0.693 \text{ x } 0.7 \text{ x } 100}{T_{½}}$$

$$F = \frac{48.51}{T_{½}}$$

The partition co-efficient is usually given as 0.7 (Moore, W. S., 1973). This is however the co-efficient for muscle, and has resulted in some debate, as the partition co-efficient for skin is not known. Indeed it is almost impossible to achieve an accurate partition co-efficient in the skin because of the lipophilic nature of ^{133}Xe. In the absence of a true partition co-efficient, the value of 0.7 is regularly used in the formula and as it is a first order constant in the equation it does not alter the relative numerical value and interpretation of the results (Moore, W. S., 1973; Holloway, G. A., Jr. and Burgess, E. M., 1978).

Similarly the specific gravity of skin, which should ideally be used in the equation, is seldom used by others. We have used it in computing skin blood flow. This results in a 5 % reduction in the value obtained.

Potential problems identified with intradermal injection of Xenon are backflow of Xenon along the injection track, causing a rapid decline in Xenon activity and resultant high clearance rate and reactive hyperaemia to the injection, again resulting in an elevated clearance rate. Using laser Doppler, Holloway, G. A. (1980) showed that insertion of a needle into the skin increased local blood flow up to sevenfold for up to 20 min. Carlin noted ^{133}Xe washout to be affected by haematocrit and Ryo reported the influence of lymphatic drainage. Spence, V. A. *et al.*, (1984) adopt a different methodology to everyone else and argue that it is reasonable to allow 10 minutes to elapse after injection before recording the washout, to allow for the "injection trauma" to subside.

Burgess, E. M. and Matsen, F. A., (1981) identify several assumptions made when using ^{133}Xenon skin clearance. These are that

i) the skin blood flow per unit volume is inversely related to the time required for the detected activity of the injected ^{133}Xenon to decrease by one half,

ii) the skin blood flow measured by this technique represents the healing potential of the skin,

iii) the ^{133}Xe used in this technique can be reproducibly injected to the same depth in the skin,

iv) the amount of skin blood flow required for healing of an amputation is reasonably constant from patient to patient

v) the trauma of injecting the ^{133}Xe does not adversely affect the validity of the measurement.

7.3 Literature Review

Bohr, H., (1967) was the first to report the use of ^{133}Xe for amputation wound prediction. A BKA with a blood flow of 0.2 ml / 100mg tissue / min failed to heal and when it was revised above the knee at a level with a blood flow of 2.0 ml / 100mg tissue / min, healing ensued.

Palmer, B., (1972) showed in a rat study that the depth of anaesthesia reduced clearance (blood flow) as did vasoconstriction. Not unexpectedly, heating increased flow. The volume of the bolus dose also influences clearance, with a large bolus of 0.08 ml clearing significantly more slowly than 0.02 and 0.04 ml.

Moore, W. S., (1973) measured ^{133}Xe derived skin blood flow in 30 patients with peripheral vascular disease undergoing 33 BKA's. Amputation was followed by immediate post-operative prosthetic fitting. The ^{133}Xe bolus was injected into "the anterior skin over the tibial plateau, 10 cm distal to the tibial tuberosity." This site was selected because BKA wound breakdown usually occurs in the anterior midline. The skin blood flows ranged from 0.55 to 4.17 ml / 100 g tissue / min. Moore later identified a consistent error in his calculations and increased all the values by a factor of 4, giving skin blood flows of 2.2 to 16.68 ml / 100 g tissue / min. Three amputations failed to heal because of ischaemia and a fourth required proximal revision because of sepsis. The corrected blood flow values for the three "ischaemic" failures were 2.2, 2.24 and 2.36 ml / 100 g tissue / min. The lowest blood flow associated with healing was 0.62 corrected to 2.48 ml / 100 g tissue / min. He could find no correlation between ^{133}Xe skin blood flow and angiographic findings or the presence or absence of peripheral pulses in his patient cohort.

Kostuik, J. P. *et al.*, (1976) used an epicutaneous technique which does not require intradermal injection. This is based on the observation by Sejrsen that normal skin acts as a one way valve allowing ^{133}Xe to diffuse into the skin, but restricts diffusion out of the skin, by virtue of a diffusion barrier beneath the *stratum corneum* (Sejrsen, P, 1968). They note that blood flow rates decline the more distal the measurement is made on the limb and that temperature and perspiration also affect blood flow. Their subjects were wrapped in blankets, to produce maximal vasodilatation prior to testing. In the description of the method used to calculate the flow rate the standard formula is given. However the values given contain a computational error in that when they multiply (100 x 0.7 x 0.693) they get a product of 48.4 and not 48.51. If they have used the error, then the blood flows reported will be slightly lower than the true blood flow. Based on the half-life times from our own study, the shortest being 3.8 min, the maximum error would be of the order of $\pm$ 0.03 ml / 100 g tissue / min calculated from the difference between 48.51 and 48.4 divided by 3.8.

In a study of 29 patients undergoing amputation, level selection was made on clinical criteria. Three amputations failed to heal, and had ^{133}Xe blood flows of 0.13, 0.56 and 2.32 ml / 100 g tissue / min. It is interesting to note that 11 of the 26 amputations that healed had ^{133}Xe values of less than 2.4 ml / 100 g tissue / min and all 11 were below Moore's absolute cutoff of 2.3 ml / 100 g tissue / min. Three amputations healed at levels below 1.0 ml / 100 g tissue / min, with the lowest flow associated with healing being 0.3 ml / 100 g tissue / min. Based on this information they chose a predictive value of 1.5 ml / 100 g tissue / min to predict wound healing. This would have given a sensitivity of 69.2 %, specificity of 66.7 % and an accuracy of 76.9 %. Of some concern is that at the predictive level 1.5 ml / 100 g tissue / min, 8 amputations would have had the potential to heal at a more distal level.

In a second part to the prospective study ^{133}Xe blood flow of 1.5 ml / 100 g tissue / min was used to prospectively determine amputation level selection in 13 patients. All 13 amputations healed. In 1 of the 13 patients, the amputation was performed at a ^{133}Xe blood flow of 1.4 ml / 100 g tissue / min. A problem with this study is that one is not sure as to the number of amputations that had the potential to heal at a more distal site (Kostuik, J. P. *et al.*, 1976).

Roon A. J. (1977) extended Moore's original report on the use of ^{133}Xe for amputation wound healing prediction. In Moore's first series of 33 amputations no amputation performed at a site with a blood flow of less than 2.7 ml / 100 g tissue / min healed. In Roon's series of 62 amputations the highest flow for an extremity that failed to heal because of ischaemia was 2.62 ml / 100 g tissue / min. Of the first 32 amputations there were 10 amputations performed

at blood flow levels of less than 2.7 ml / 100 g tissue / min, 5 of which healed. At this point a modification to the protocol was introduced, whereby multiple measurements (at least 2) were made on patients who had an initial blood flow rate less than the critical level. In the subsequent 30 amputations using this amended protocol "no extremity with a flow lesser than 2.7 healed primarily". They state that failures occurring at blood flow rates greater than 2.7 ml / 100 g tissue / min were due to causes other than ischaemia. The data of the amputations with blood flows below 2.7 ml / 100 g tissue / min that healed are not given. Based on this experience, they conclude that a trial amputation should be offered if the ^{133}Xe derived blood flow is between 2.3 and 2.7 ml / 100 g tissue / min (Roon, A. J. *et al.*, 1977).

Malone, reporting on what appears to be largely the same patient cohort as Roon and Moore, states that amputations performed at levels with ^{133}Xe blood flows 2.7 ml / 100 g tissue / min have been associated with 100 % primary healing and that it has been their policy to offer trial amputation at a conservative distal level when the blood flow has been above 2.0 ml / 100 g tissue / min (Malone, J. M. *et al.*, 1981). In this gray zone between 2.0 and 2.7 ml / 100 g tissue / min 50 % of amputations heal. These are probably the 5 of 10 amputations below 2.7 ml / 100 g tissue / min that healed in Roon's series.

Holloway, G. A., Jr. and Burgess, E. M., (1978) measured ^{133}Xe clearance at 3 sites, 1 cm medial and 1 cm lateral to the midline, 10 cm below the inferior margin of the patella, and 15 cm below the patellar margin posteriorly. In a study of 22 amputations, 19 healed primarily and three required revision. A wide range of overlap in ^{133}Xe blood flows was obtained with amputations healing at less than 0.01 ml / 100 g tissue / min and revision being required at blood flows of 0.5, 3.1 and 7.5 ml / 100 g tissue / min. They suggested that the predictive level be set at 1.0 ml / 100 g tissue / min.

In 1981, Malone proposed ^{133}Xe skin clearance as the "gold standard for amputation level selection. Reporting a new series of 137 amputations, 6 of which required revision. Wound failure occurred in two amputations performed at blood flows below 2.0 ml / 100 g tissue / min and 4 at values above 2.6 (3.3 – 11.3) ml / 100 g tissue / min giving an accuracy of 97 %. In this series the minimum blood flow for primary healing was 2.2 ml / 100 g tissue / min, slightly lower than the 2.6 ml / 100 g tissue / min previously reported. This they attributed to the change from the single point measurement using a Geiger counter and rate log meter to multiple point analysis using a gamma camera with computer enhancement (Malone, J. M. *et al.*, 1981).

McCollum investigated the skin blood flow at 3 points about a BKA site using ^{125}I - 4 iodoantipyrine. The sites were 10 cm distal to the tibial tuberosity, 3 cm medial and 3 cm lateral to the anterior tibial border and posteriorly, 15 cm distal to the tibial tuberosity in the midline. The blood flow on the medial side was found to be significantly higher than on the lateral side. The lateral measurements were also significantly lower than the posterior measurements (McCollum, P. T. *et al.*, 1985 and 1986).

Silberstein reported on 46 amputations, in which ^{133}Xe was measured using a gamma camera. Amputations performed at sites with a blood flow equal to or greater than 2.4 ml / 100 g tissue / min, healed in 38 of 39 cases. At sites with blood flows of less than 2.4 ml / 100 g tissue / min, 4 of 7 amputations healed. ^{133}Xe derived blood flow of 2.4 ml / 100 g tissue / min had a sensitivity of 90.1 %, a specificity of 75 %, a positive predictive value of 97.4 %, a negative predictive value of 42.9 % and an accuracy of 89.1 % (Silberstein, E. B. *et al.*, 1983).

Harris, J. P. *et al.*, (1986) reported on the outcome of 17 amputations, 5 of which failed. They followed the dual injection site method of Malone and used a gamma camera. No amputation with a ^{133}Xe blood flow of less than 1.0 ml / 100 g tissue / min healed. Only 1 amputation with a blood flow greater than 1.0 ml / 100 g tissue / min failed to heal.

In 1987, Malone revisited the use of ^{133}Xe, when they prospectively compared ^{133}Xe with $TcpO_2$, transcutaneous carbon dioxide pressure measurement ($TcpCO_2$), a $TcpO_2$:$TcpCO_2$ ratio, the $TcpO_2$ index, a $TcpCO_2$ index, ankle brachial pressure index, and absolute popliteal artery Doppler systolic pressure. Wound failure was defined as any wound that required major or minor revision. 52 amputations were studied, 41 of which underwent ^{133}Xe skin clearance tests. Amputation level selection was based on the ^{133}Xe blood flow and all amputations were expected to heal. Six of the 41 ^{133}Xe based amputations failed. There was no statistical difference between the mean ^{133}Xe blood flows of amputations that healed 5.1 ± 2.9 ml / 100 g tissue / min and those that failed 7.5 ± 7.1 ml / 100 g tissue / min. While this may at first appear surprising, it should be remembered that all the amputations were performed at ^{133}Xe levels above at least 2.0 ml / 100 g tissue / min and all were expected to heal.

All five amputations performed at blood flows of less than 2.6 ml / 100 g tissue / min healed. The assumption is made that there were no amputations performed at blood flows of less than 2.0 ml / 100 g tissue / min, although this is not stated. Malone concluded that the data from this study indicate that ^{133}Xe skin blood flow is not statistically reliable as a prospective test for amputation level selection because the overlap in values of patients who healed and failed

is too great (Malone, J. M. *et al.*, 1987). It could be however be argued that the 6 amputations in this group that failed (14.6 %), represent those amputations that fail for reasons other than skin ischaemia. The data from the other arms of the study unfortunately do not support this argument. The mean $TcpO_2$ of the healed amputations 32.5 $\pm$ 8.1 mmHg was significantly higher than the failed amputations 11.8 $\pm$ 5.6 mmHg ($p = 0.001$). A similar picture emerged from the $TcpO_2$ index data, with the average for those that healed being 0.80 $\pm$ 0.75 and those that failed 0.29 $\pm$ 0.14 ($p = 0.001$). It would appear from the $TcpO_2$ data that significant ischaemia was present when the ^{133}Xe values were above 2.0 ml / 100 g tissue / min.

It is interesting to note that of the 10 amputations in which the level was selected on clinical grounds alone, 5 failed.

7.3.1 Comparison of $TcpO_2$ and the ^{133}Xe radio-isotope washout test

This raises the question of correlation of ^{133}Xe and $TcpO_2$ and the $TcpO_2$ index. Bongard studied the relationship between pedal $TcpO_2$ and pedal ^{133}Xe skin blood flow in 9 normal subjects and 5 patients with rest pain with or without gangrene. A significant positive correlation was found between normal subjects, $r = 0.77$ ($p < 0.001$) but no correlation was found in the ischaemic patients (Bongard, O. and Krahenbuhl, B., 1984).

7.4 Prospective study comparing $^{133}Xenon$ skin clearance with $TcpO_2$ measurement

The aim of the Xenon studies was to examine the correlation between ^{133}Xe derived blood flows and absolute $TcpO_2$ values and later $TcpO_2$ Index in normal subjects and patients with peripheral vascular disease, accepting the fact that while ^{133}Xe washout is considered to be a test of skin blood flow, $TcpO_2$ does not directly measure skin blood flow.

The following issues were considered when planning the study. Access was only available to a single collimator and not a gamma camera, so only a single ^{133}Xe reading could be made and not dual readings. The ^{133}Xe and $TcpO_2$ measurements should ideally be made at the same site and simultaneously. Clearly this is not possible. If performed in sequence, the skin heating performed in the $TcpO_2$ test could affect the ^{133}Xe result if $TcpO_2$ was performed before the ^{133}Xe. Likewise, the injection trauma and hyperaemia may influence the $TcpO_2$ reading, and leak of residual ^{133}Xe or plasma from the injection track might interfere with the

contact solution under the $TcpO_2$ probe. As a compromise and accepting the shortcomings, it was decided to perform the $TcpO_2$ simultaneously at adjacent sites on the leg.

7.4.1 Method

7.4.1.1 ^{133}Xenon injection

^{133}Xenon gas dissolved in saline was purchased from the Atomic Energy Board in Pretoria. The multidose vial contained approximately 10 mCi in 10 ml saline. The activity of the vial was assessed prior to each session of tests and the volume drawn up adjusted accordingly to achieve a dose of 20 – 40 μCi. This equated to 0.02 to 0.04 ml. The ^{133}Xenon in saline was drawn up anaerobically from the multidose vial into a diabetic syringe with a 27 G needle. This was then injected intradermally at a site 10 cm distal to the tibial tuberosity, 1 cm lateral to the anterior tibial margin. The hypodermic needle was inserted with the opening pointing anteriorly to insure that the bolus was injected intradermally. The needle was left in situ for 15 seconds, to minimise extravasation on subsequent withdrawal.

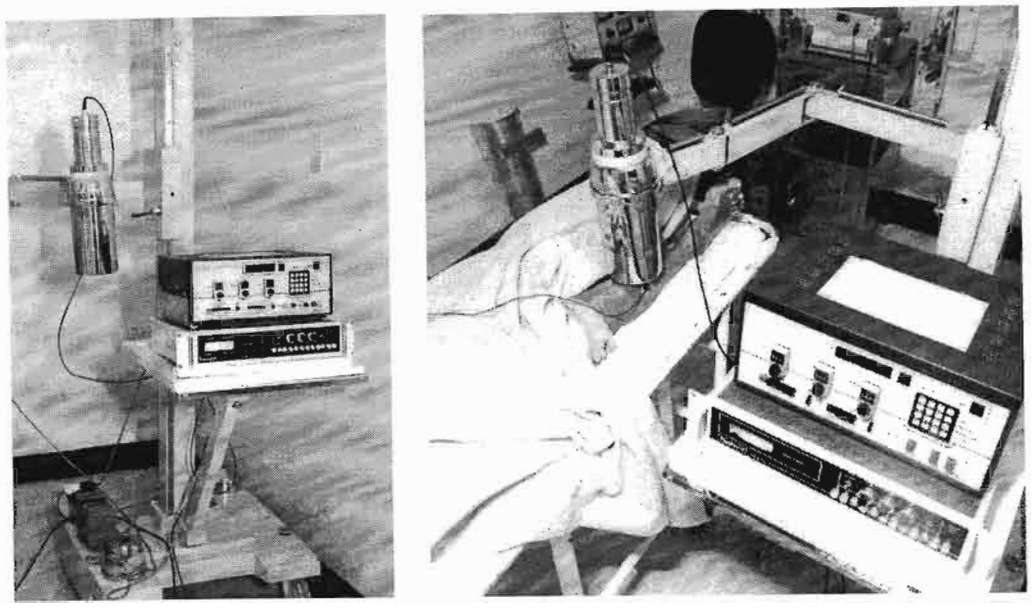
7.4.1.2 $TcpO_2$ measurement

Patients were taken to the Nuclear Medicine Department at Addington Hospital. They lay supine and were allowed 15 minutes to acclimatize to the ambient air-conditioned room temperature which was maintained between 22 and 25 °C. The $TcpO_2$ electrode was then applied using standard techniques to the below knee amputation site, 10 cm below the tibial tuberosity and 2 cm lateral to the anterior tibial margin. The probe temperature was set at 45 °C. After 10 minutes of measurement, the ^{133}Xenon was injected intradermally without disturbing the $TcpO_2$ probe. The $TcpO_2$ measurement was recorded 10 minutes later, after a total measuring time of 20 minutes. In a second study, $TcpO_2$ measurements were taken simultaneously at the BKA level and on the chest anteriorly, 5 cm below the clavicle in the mid-clavicular line, with the measurement recorded after 20 min.

7.4.1.3 ^{133}Xenon washout measurement

Gamma activity was measured using a single sodium iodide (NaI) scintillation crystal detector in a collimator with a scaler-ratemer and a chart recorder was used. The collimator was positioned 10 – 12 cm from the proposed injection site and background readings of radio-activity taken. After injection of the ^{133}Xe, the total number of counts was recorded for the

first 15 seconds of every minute for 10 minutes. The data from the first 6 minutes were used to compute $T_{½}$ using specific software (figure 7.1,a and b).



a b

Figure 7.1a. Sodium iodide (NaI) scintillation crystal detector in a collimator with a scaler-ratemer and a chart recorder. Figure 7.1b, Collimator positioned over injection site and $TcpO_2$ probe attached to skin adjacent the injection site.

7.4.1.4 Statistical methods

Data are described as means and one standard deviation, with 95 % confidence intervals given. Prior to correlation, data were checked for Gaussian distribution according to the method of Kolmogorov and Smirnov. If the data followed a Gaussian distribution Pearson's correlation was performed (parametric) and if one or more of the data sets was not Gaussian in distribution Spearman's rank correlation was performed. Runs tests were performed after linear regression to determine whether nonlinear curve fitting would be more appropriate. Where nonlinear curve fitting was indicated, logarithmic and 2^{nd} order polynomial curves were tested and compared by F test to determine the better fit.

7.4.2 Results and discussion

74 subjects underwent ^{133}Xe and $TcpO_2$ measurement at the below knee site, with the chest $TcpO_2$ measured in 48 of these subjects. The descriptive statistics of these two groups are given in table 7.1 and the correlation between ^{133}Xe washout derived blood flow and $TcpO_2$ is shown in figure 7.2.

Table 7.1. The means, standard deviations, confidence limits, maxima, minima, and medians of the ^{133}Xe and $TcpO_2$ for the 74 sets of readings made at the below knee site.

	^{133}Xe	$TcpO_2$
	ml / 100 g tissue / min	mmHg
n =	74	74
Mean	4.13 ± 3.36	50.5 ± 21.1
Lower 95% conf. limit	3.35	45.6
Upper 95% conf. limit	4.91	55.4
Minimum	0.20	0
Median (50^{th} percentile)	3.59	55
Maximum	15.94	85

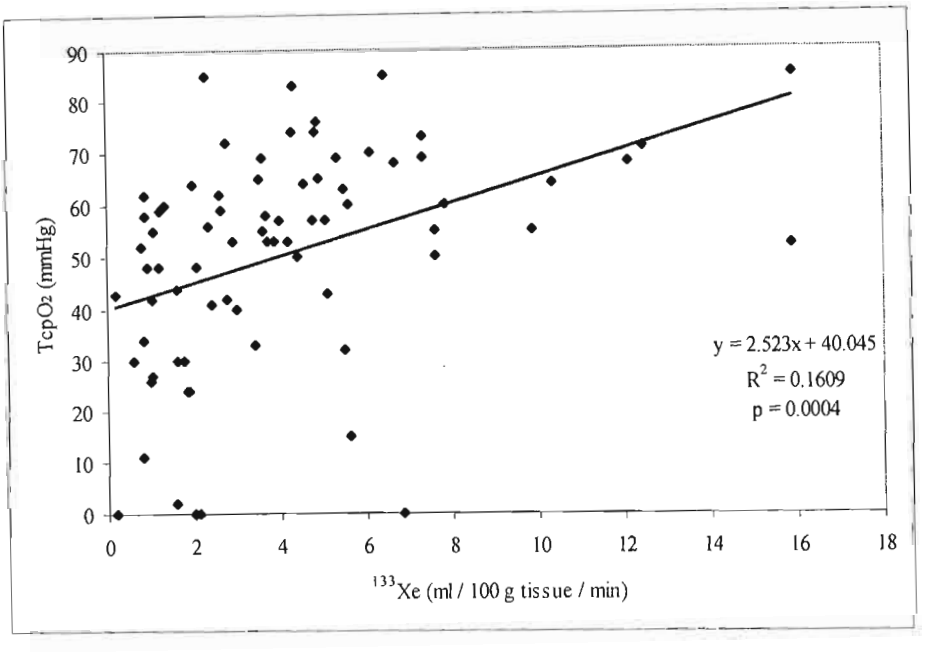


Figure 7.2. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ measurements made in 74 subjects. The regression line and equation are shown. A significant correlation is shown ($p < 0.0004$).

Although there is a statistically significant correlation between ^{133}Xe and $TcpO_2$ measurements Pearson's correlation coefficient is low ($r = 0.4$). A runs test confirmed that the relationship is linear, with 43 points above the line, 31 below, and 31 runs with $p = 0.092$. Despite this evidence of linearity, visually the data looks as if it would be better fitted with a curve. This would be in keeping with the observation that $TcpO_2$ to be more sensitive at low arteriovenous pressure gradients. If there is variability in $TcpO_2$ response at different blood flows, the data may be better fitted with a curve than a straight line (figure 7.3).

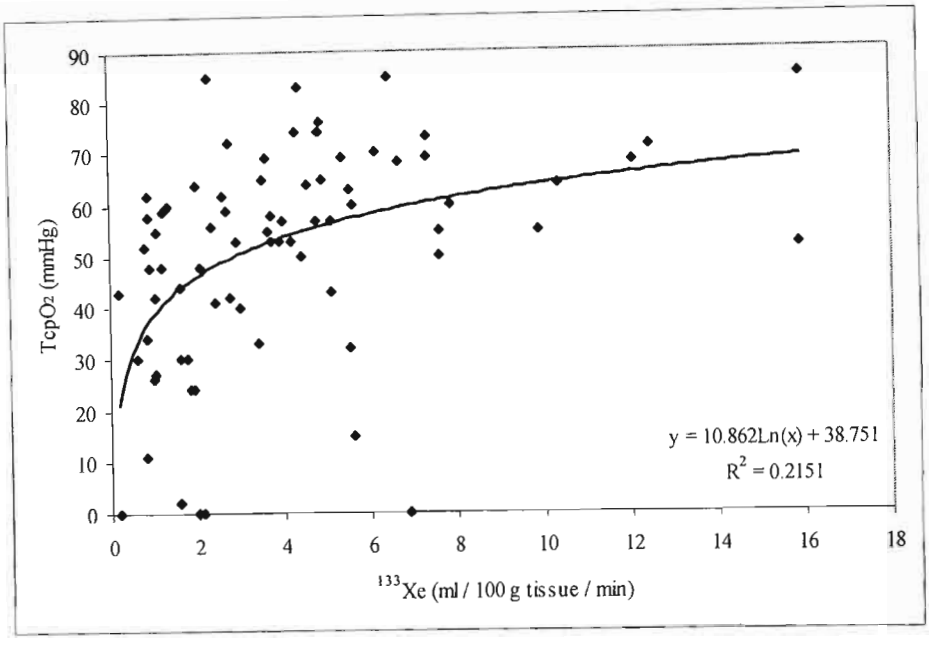


Figure 7.3. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ measurements made in 74 subjects. The logarithmic curve returns a Pearson's of correlation coefficient (r = 0.46).

In figure 7.3 the data has been fitted with the logarithmic curve y = 10.862Ln(x) + 38.72 which improves the correlation coefficient from r = 0.4 to r = 0.46.

Although the correlation coefficient is relatively low, statistical significance is reached. The clinical worth of this correlation needs to be questioned. As has been stated, Malone *et al.* (1987) selected amputations based on ^{133}Xe blood flow levels greater than 2.0 ml / 100 g tissue / min and had failure in 6 of 41 amputations. While there was no difference between mean ^{133}Xe levels in the healed in failed amputations, significant differences between the two groups were present when assessed in terms of absolute $TcpO_2$ and the $TcpO_2$ index (Malone, J. M. *et al.*, 1987). This signifies that some low $TcpO_2$ values were associated with "high" or acceptable ^{133}Xe levels and *vice versa*. The data in figure 7.1 presents a slightly different picture. There are a few low $TcpO_2$ values occurring with ^{133}Xe blood flows of more than 2.0 ml / 100 g tissue / min, but there are a surprising number of patients with $TcpO_2$ values of above 30 mmHg and ^{133}Xe values below 2.0 ml / 100 g tissue / min. Based on our experience of no amputation with an absolute $TcpO_2$ of less than 27 mmHg healing (chapter 11), this might suggest that healing could be expected in some patients with ^{133}Xe blood flows below 2.0 ml / 100 g tissue / min.

The spread of $TcpO_2$ values at low ^{133}Xe levels is compatible with the observations of Kostuik, J. P. *et al.*, (1976) and Holloway, G. A., Jr. and Burgess, E. M., (1978). Perhaps the use of the

$TcpO_2$ Index may show a better correlation, although this is unlikely given the relationship of the absolute value to the Index?

48 subjects underwent ^{133}Xe and $TcpO_2$ measurement at the below knee site, chest $TcpO_2$ measurement. The descriptive statistics of these two groups are given in table 7.2 and the correlation between ^{133}Xe washout derived blood flow and $TcpO_2$ is shown in figures 7.4, 7.5, 7.6, and 7.7.

Table 7.2. The means, standard deviations, confidence limits, maxima, minima, and medians of the ^{133}Xe and $TcpO_2$ and the $TcpO_2$ Index for the 48 sets of readings made at the below knee site for which the $TcpO_2$ Index could be calculated.

	^{133}Xe	**$TcpO_2$**	**$TcpO_2$ Index**
	ml/100g tissue/min	mmHg	
n =	48	48	48
Mean	3.71 ± 3.11	50.3 ± 22.4	0.85 ± 0.35
Lower 95% conf. limit	2.81	43.8	0.05
Upper 95% conf. limit	4.61	56.8	0.95
Minimum	0.2	0	0
Median (50th percentile)	2.87	55	0.92
Maximum	15.94	85	1.7

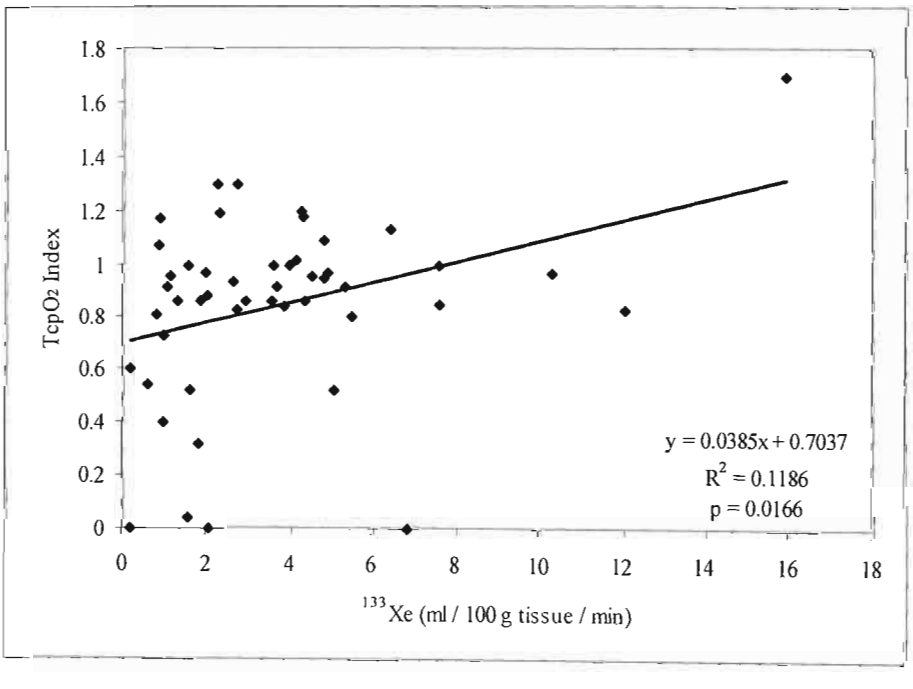


Figure 7.4. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 48 subjects. The regression line and equation are shown. A significant correlation is shown (p = 0.0166).

Again there was a significant correlation ($p = 0.0166$) with a low correlation coefficient ($r = 0.27$). The runs test showed 31 points above the line, 17 below, and 8 runs with ($p < 0.0001$), suggesting that the data follow a curve rather than a straight line (figure 7.5).

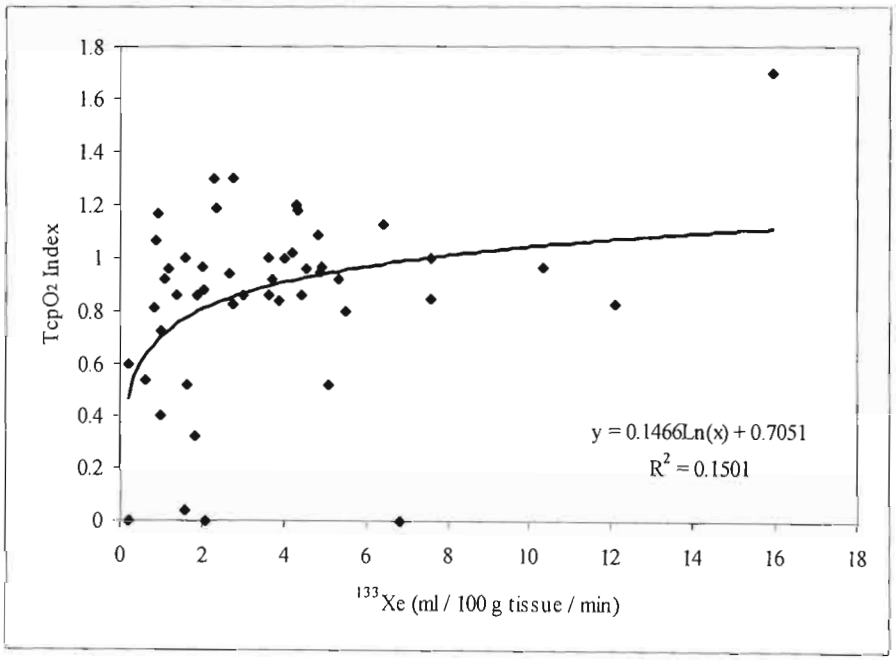


Figure 7.5. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 48 subjects. The logarithmic curve returns a correlation coefficient ($r = 0.38$).

Fitting the logarithmic curve $y = 0.1466Ln(x) + 0.7051$ improves the correlation from $r = 0.27$ to $r = 0.38$.

The correlation of the absolute $TcpO_2$ with ^{133}Xe in these 48 subjects is similar to the larger group of 74 subjects (figure 7.6).

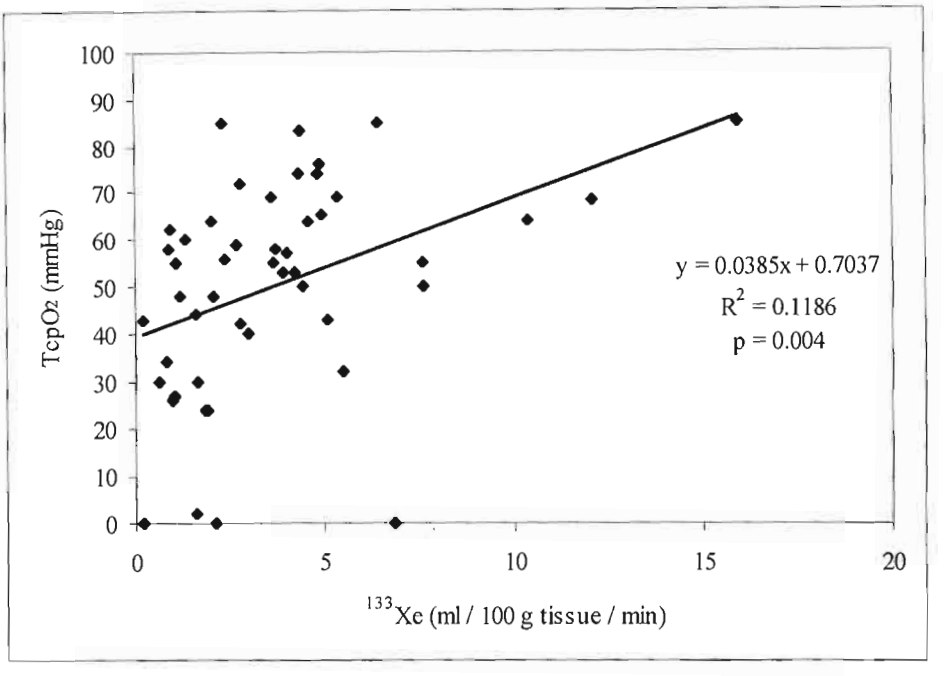


Figure 7.6. Scattergram of the ^{133}Xe blood flows and absolute $TcpO_2$ measurements made in 48 subjects. The correlation was significant ($p = 0.004$).

The runs test showed 26 points above the line, 22 below, and 15 runs $p = 0.0028$, again strongly suggesting that the data would be better fitted with a curve, figure 7.7.

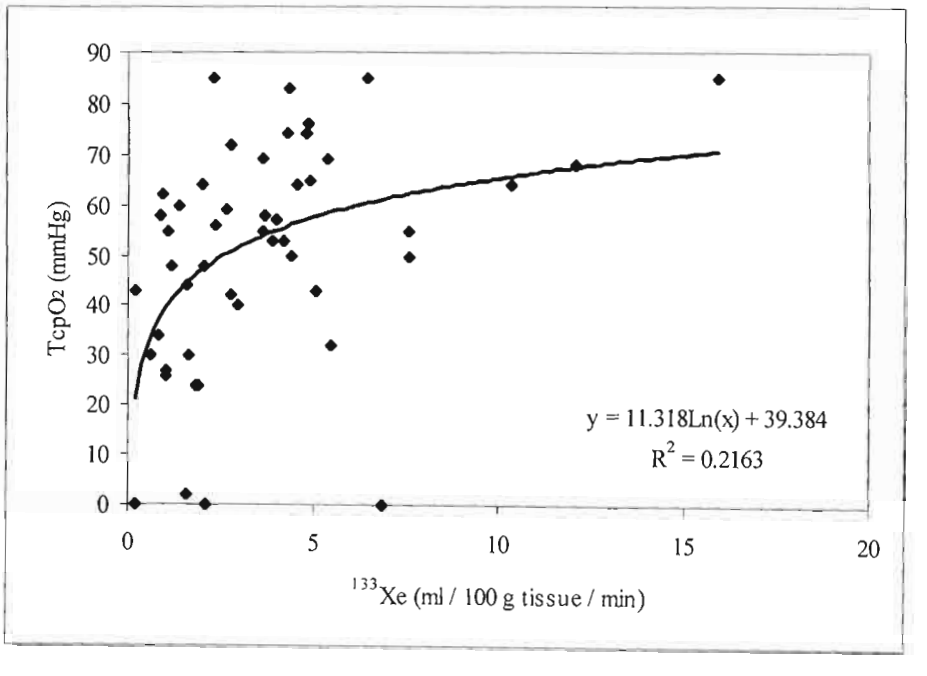


Figure 7.7. Scattergram of the ^{133}Xe blood flows and absolute $TcpO_2$ measurements made in 48 subjects. The logarithmic curve returns a correlation coefficient ($r = 0.47$).

The logarithmic curve improves the correlation coefficient from r = 0.34 to r = 0.47. Again statistically significant correlation was achieved with low correlation coefficients.

As Malone had found after selecting amputations on the basis of a ^{133}Xe blood flow of more than 2.0 ml / 100 g tissue / min, there was still a significant difference in $TcpO_2$ and $TcpO_2$ Index between healed and failed amputations. The data were re-examined in terms of this predictive level (Table 7.3 and 7.4 and figures 7.8, 7.9, 7.10, 7.11).

Table 7.3. The means, standard deviations, confidence limits, maxima, minima, and medians of the ^{133}Xe and $TcpO_2$ and the $TcpO_2$ Index for the 16 sets of readings made at the below knee site for which the $TcpO_2$ Index could be calculated where the ^{133}Xe value was below 2.0 ml / 100 g tissue / min.

	^{133}Xe	**$TcpO_2$**	**$TcpO_2$ Index**
	ml/100g tissue/min	mmHg	
n =	16	16	16
Mean	1.11 ± 0.51	35.4 ± 18.8	0.68 ± 0.35
Lower 95% conf. limit	0.83	25.4	0.48
Upper 95% conf. limit	1.39	45.5	0.86
Minimum	0.20	0	0
Median (50th percentile)	1.06	32	0.73
Maximum	1.90	62	1.17
Correlation r =		-0.037	0.101
r^2		0.0014	0.01
p =		0.892	0.709

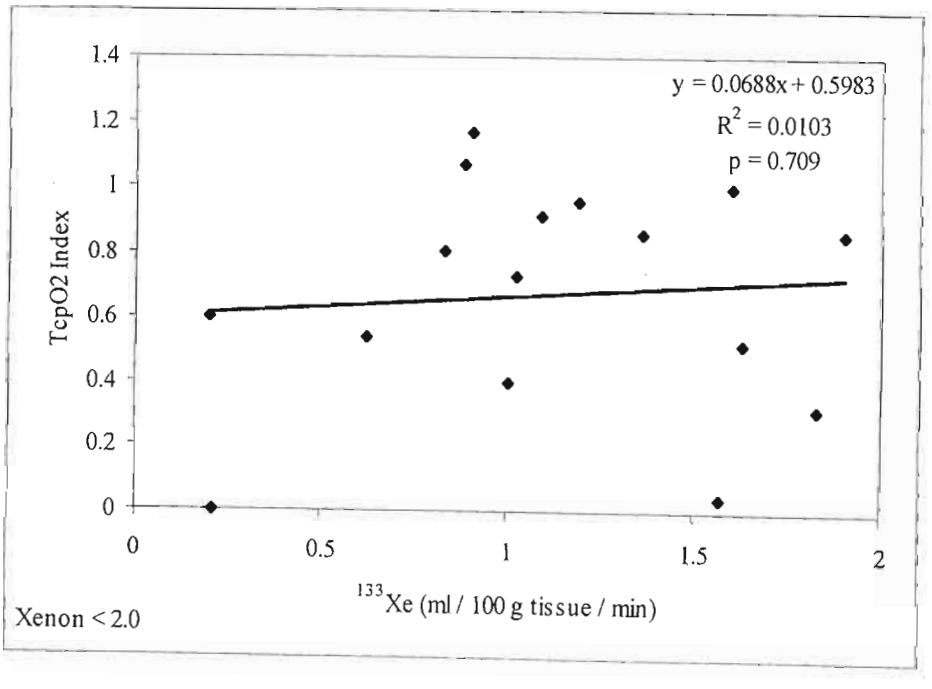


Figure 7.8. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 16 subjects with a ^{133}Xe less than 2.0 ml / 100 g tissue / min.

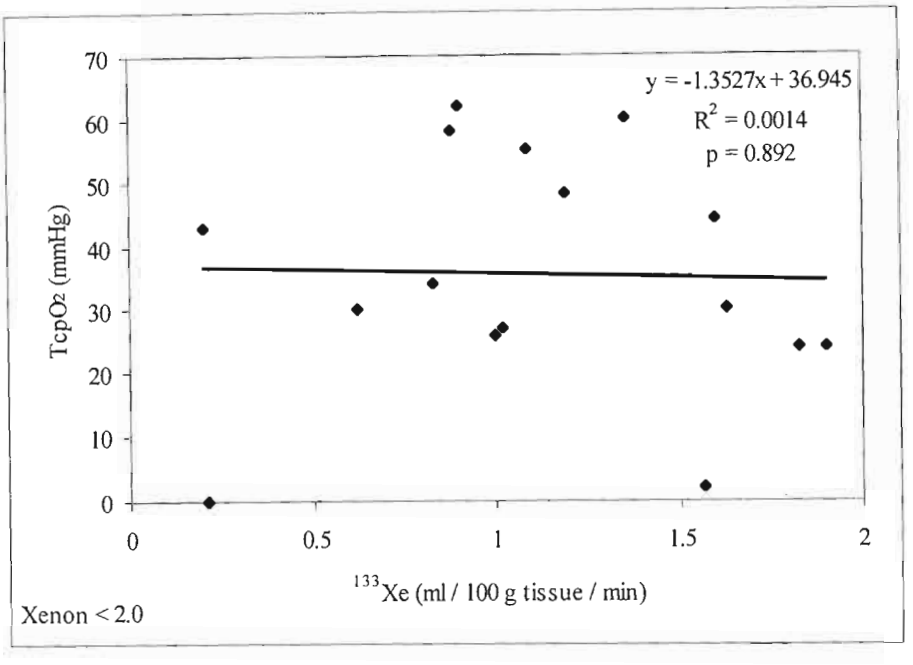


Figure 7.9. Scattergram of the ^{133}Xe blood flows and absolute$TcpO_2$ measurements made in 16 subjects with a ^{133}Xe less than 2.0 ml / 100 g tissue / min.

Based on our experience with amputation wound healing at an index set at 0.55 and an absolute $TcpO_2$ of more than 27 mmHg, the $TcpO_2$ data at 11 of the sixteen sites with a ^{133}Xe of less than 2.0 ml / 100 g tissue / min would have been compatible with healing.

Table 7.4. The means, standard deviations, confidence limits, maxima, minima, and medians of the ^{133}Xe and $TcpO_2$ and the $TcpO_2$ Index for the 32 sets of readings made at the below knee site for which the $TcpO_2$ Index could be calculated where the ^{133}Xe value was equal to or more than 2.0 ml / 100 g tissue / min.

	^{133}Xe	**$TcpO_2$**	**$TcpO_2$ Index**
	ml/100g tissue/min	mmHg	
n =	32	32	32
Mean	5.0 ± 3.05	57.8 ± 20.4	0.93 ± 0.32
Lower 95% conf. limit	3.9	50.4	0.82
Upper 95% conf. limit	6.1	65.1	1.05
Minimum	2.0	0	0
Median (50^{th} percentile)	4.33	58.5	0.96
Maximum	15.94	85	1. 7
Correlation r =		0.213	0.217
r^2		0.045	0.047
p =		0.242	0.233

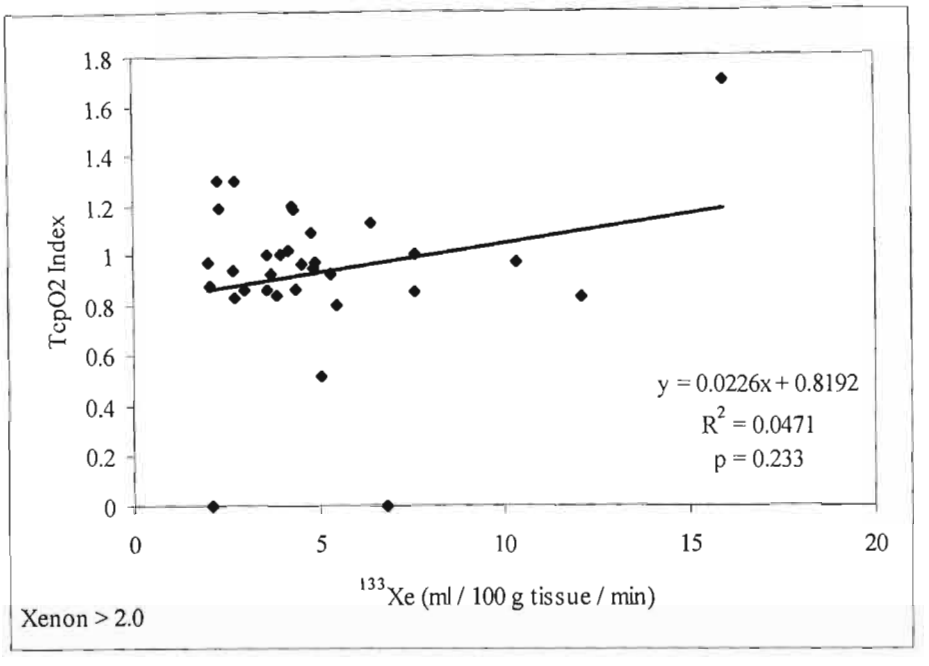


Figure 7.10. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 32 subjects with a ^{133}Xe more than 2.0 ml / 100 g tissue / min.

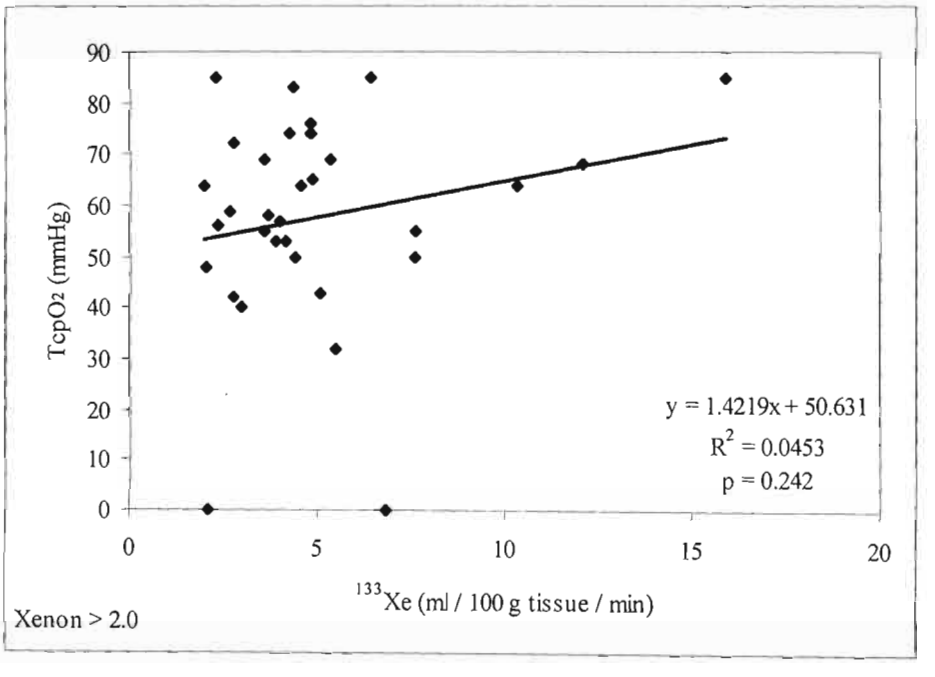


Figure 7.11. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ measurements made in 32 subjects with a ^{133}Xe more than 2.0 ml / 100 g tissue / min.

Figures 7.10 and 7.11 show that when the ^{133}Xe derived blood flow is greater than 2.0 ml / 100 g tissue / min, the $TcpO_2$ values are usually high. The correlation in both instances is not significant.

The data were then examined with respect to a $TcpO_2$ index of 0.55 (figures 7.12 and 7.13).

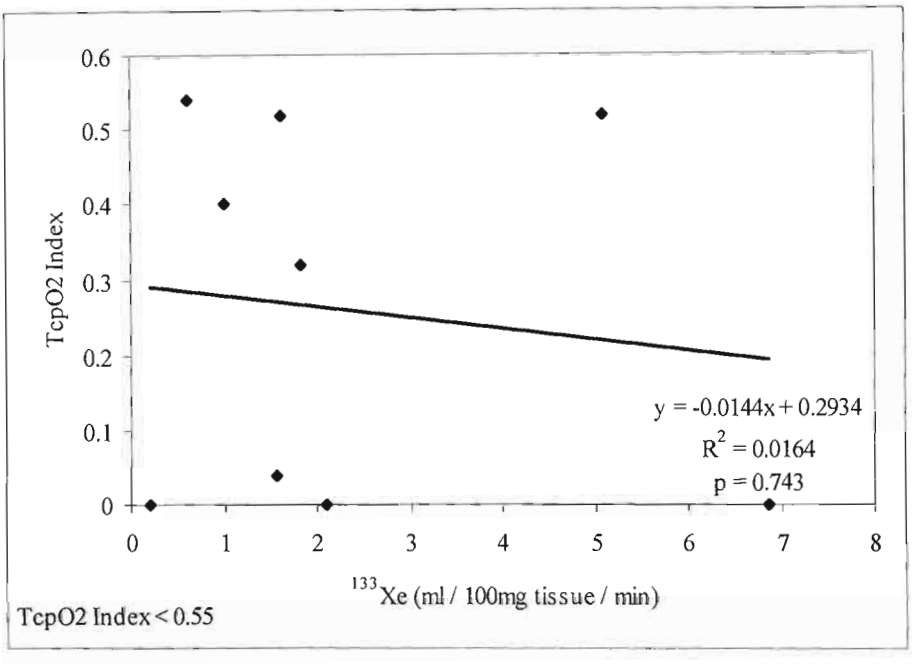


Figure 7.12. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 9 subjects with a $TcpO_2$ index of less than 0.55.

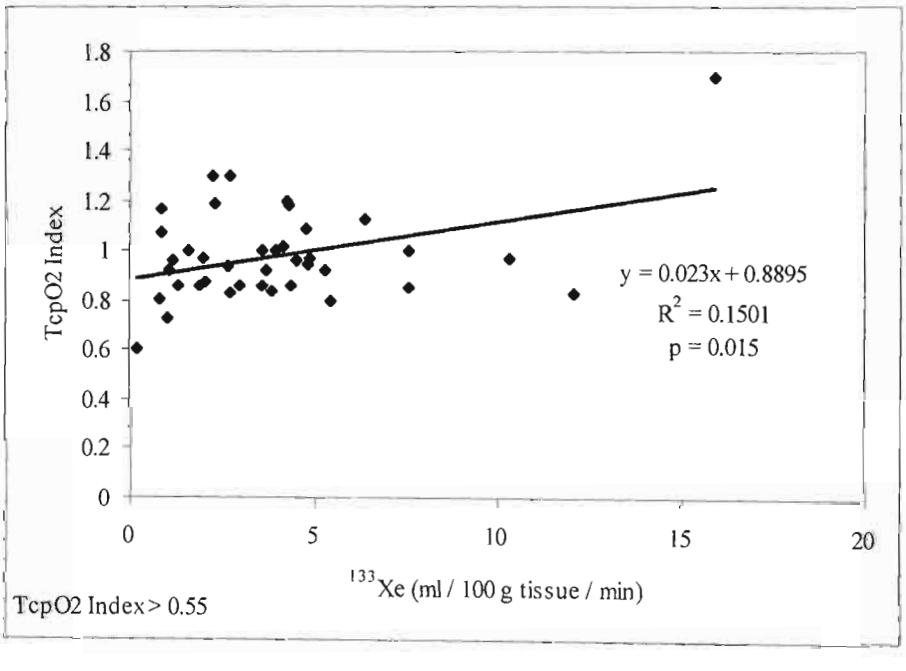


Figure 7.13 Scattergram of the ^{133}Xe blood flows and $TcpO_2$ Index measurements made in 39 subjects with a $TcpO_2$ Index of more than 0.55.

Ten patients subsequently underwent amputation with 4 of the amputations healing. Amputation level selection was based on clinical criteria. The outcome of the amputations is shown in figure 7.14.

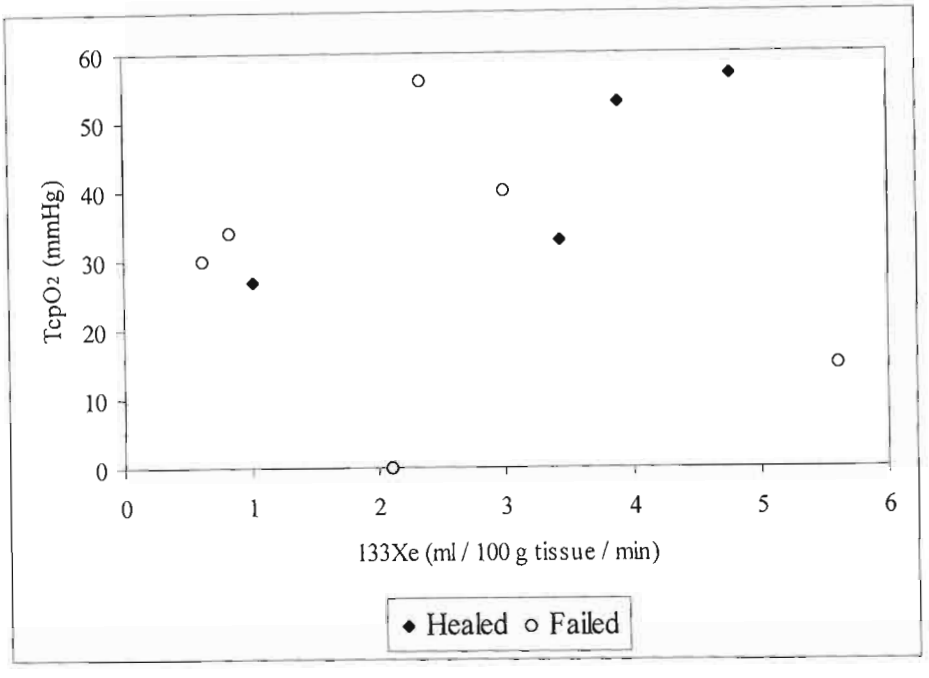


Figure 7.14. Scattergram of the ^{133}Xe blood flows and $TcpO_2$ measurements made in 10 subjects who underwent amputation.

In this small group of patients a predictive level based on a ^{133}Xe derived skin blood flow of 2.0 ml / 100 g tissue / min would have had a sensitivity of 75 %, a specificity of 33.3 % and an accuracy of 50 %.

7.4.3 Summary

The correlation between ^{133}Xe a measure of skin blood flow and $TcpO_2$, which is related to skin blood flow, was low although reaching statistical significance on occasion. The relationship between the two was better fitted by a logarithmic curve, than straight line. This is to be expected if the sensitivity of $TcpO_2$ to changes in blood flow is greater at low flow states.

7.4.4 Possible explanations for the results obtained and limitations

1. ^{133}Xe washout measures skin blood flow while $TcpO_2$ is related to skin blood flow, but is not a measure of skin blood flow.

2. Use of the equipment. Although the nuclear medicine department is well trained in the use of the equipment, intradermal ^{133}Xe evaluation of skin blood flow was new to them. As the method was consistent throughout, any systematic error should be constant and thus not affect the correlation.

3. Intradermal injection. As has been stated, problems exist regarding consistent injection at the same depth and back flow of ^{133}Xe in saline from the injection track. These are relatively uncontrollable variables as is injection trauma. All injections were given by the author, so as to minimise variation.

Chapter 8

The Relationship of $TcpO_2$ to Antibiotic Delivery to Muscle at the Site of Amputation

8.1 Introduction

This chapter presents data of a prospective study comparing absolute $TcpO_2$ and the $TcpO_2$ Index to the concentration of antibiotics in muscle sampled at the level of amputation. The muscle antibiotic concentration is taken as a function of muscle blood flow.

8.2 $TcpO_2$ and muscle blood flow

This has been published as "Do pre-operative antibiotics reach the operative field in amputation surgery for peripheral vascular disease?" (Mars, M., *et al.,* 1990), see appendix b.

Amputation wound healing is dependent on many factors, and one of the criticisms of $TcpO_2$ measurement has been that it gives information only of the blood flow and not of muscle blood flow. Until Haertsch's description of the extrafascial plexus (Haertsch, P. A., 1981a; Haertsch, P. A., 1981b), blood supply of the skin had been described as being derived from the underlying muscles (Manchot, C., 1889) and so $TcpO_2$ might have been expected to reflect muscle blood flow. Measurement of muscle blood flow can be made invasively using ^{133}Xe muscle clearance, and muscle PO_2 can be measured using specially designed polarographic needle probes. No simple validated non-invasive test of muscle blood flow is available. Near infra-red spectroscopy is a potential new test of muscle ischaemia that offers promise.

Many of the amputations that failed in our series became infected, despite our routine policy of peri-operative antibiotic prophylaxis (Huizinga, W. K. J. *et al.*, 1983). Knowing that nutrient oxygen delivery is diminished in patients with PVD, is antibiotic delivery similarly affected? Do prophylactic antibiotics reach the site of surgery in patients with PVD? Does the disease process in the vessels affect the uptake of antibiotics? Does $TcpO_2$ measurement, an indicator of nutrient delivery to skin reflect antibiotic delivery to muscle?

To answer some of these questions, a study was undertaken to compare amputation healing with antibiotic concentration in both the patient's plasma, and muscle taken from the site of amputation; and also to establish if there was any relationship between pre-operative $TcpO_2$ measurement and tissue antibiotic concentration.

8.2.1 Method

10 patients who required lower limb amputation for PVD were studied. They were not diabetic and all had serum creatinine clearance values within the normal range, 70 – 100 $ml.min^{-1}$. $TcpO_2$ was measured in the routine manner on the day before surgery. The surgeon was blinded to the $TcpO_2$ values and the amputation level was selected on clinical criteria. All amputations were performed by the same surgeon, using the same techniques of a long posterior flap and myoplasty for below knee amputations and equal anterior and posterior flaps with myodesis for above knee amputations. In all cases the deep fascia was sutured and the skin approximated with Steristrips®.

All amputations were performed under general anaesthesia. Immediately after induction, a 2 g bolus of cefoxitin sodium was administered intravenously. At the moment of dividing the limb, a 5 ml venous blood sample was taken from a peripheral arm vein and collected in a heparinised tube. The blood sample was immediately centrifuged and the plasma removed for analysis.

Cubes of muscle (2 cm^3) were taken from each of the compartments of the most proximal part of the amputated limb. Plasma and tissue samples were frozen and stored at –20 °C.

Plasma and muscle antibiotic concentrations were measured using high performance liquid chromatography (HPLC) (Robbs, J. V. *et al.*, 1989). All assays were performed in duplicate and the mean antibiotic concentration of the compartment with the lowest antibiotic concentration was taken as the muscle antibiotic concentration.

8.2.2 Results

The patient group comprised 8 men and 2 women, with an average age of 55.6 y (range 36 – 70 y). There were 5 BKA's and 5 AKA's. Four of the amputations healed, 2 at each level. All the amputations that failed to heal had become infected. Muscle antibiotic concentrations

ranged from 6 - 40 $\mu g.ml^{-1}$. The relationship of cefoxitin muscle concentration and outcome is shown in figure 8.1.

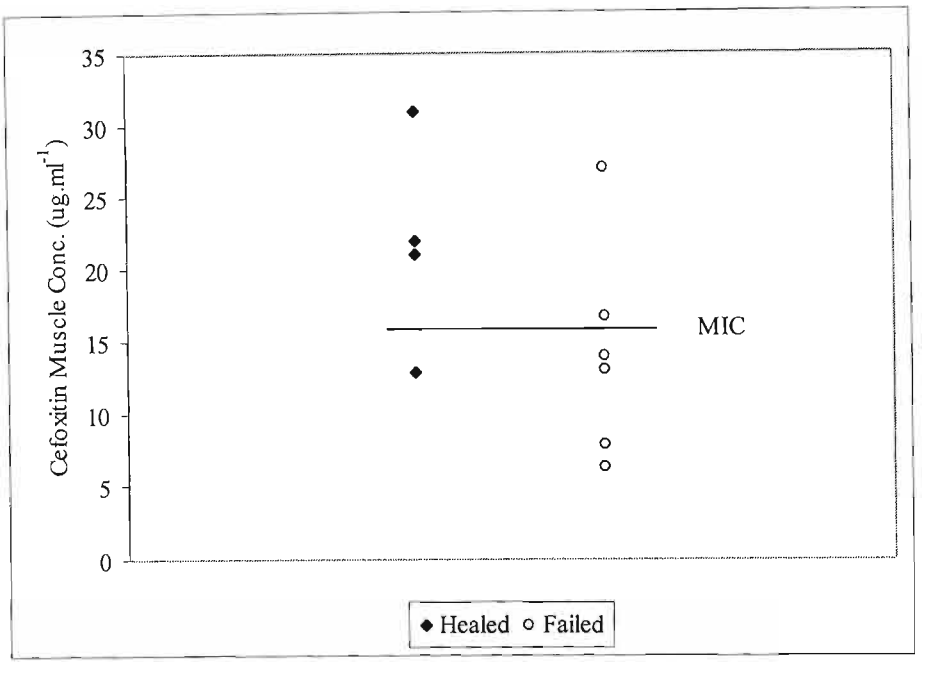


Figure 8.1. The cefoxitin concentration in muscle at the time of amputation, with respect to subsequent wound healing. (MIC = minimum inhibitory concentration for cefoxitin).

The plasma antibiotic concentrations were high, ranging from 57.2 – 134.2 $\mu g.ml^{-1}$. A trend was shown of a difference in the distribution of the antibiotic between the two groups. Amputations that healed had lower plasma antibiotic concentrations and higher muscle antibiotic concentrations than those that failed. This difference in the antibiotic distribution can be expressed as the ratio of muscle antibiotic concentration to plasma antibiotic concentration, which we have called the cefoxitin index (Table 8.1). Use of the cefoxitin index reduces the area of overlap seen with the muscle cefoxitin concentrations (figure 8.2).

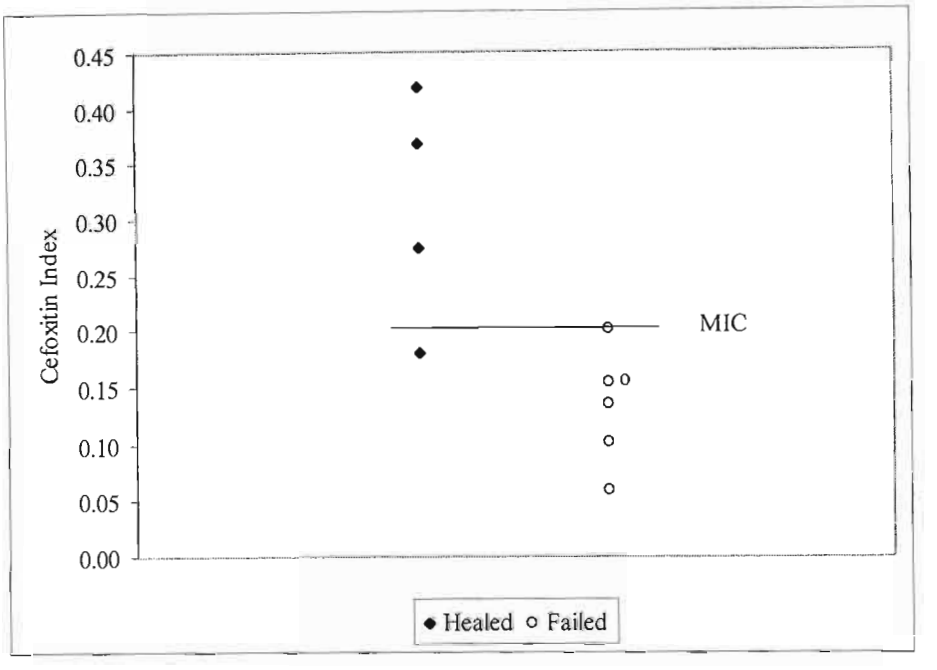


Figure 8.2. The cefoxitin index at the time of amputation, with respect to subsequent wound healing. (MIC = minimum inhibitory concentration for cefoxitin).

Table 8.1. Comparison of the mean antibiotic concentrations in plasma and muscle, taken at the moment of amputation in successful and failed operations. The antibiotic distribution is expressed as the cefoxitin index, being the ratio of muscle to plasma antibiotic concentrations.

	Healed	**Failed**	**p =**
Plasma ($\mu g.ml^{-1}$)	70.3 ± 7.5	106.1 ± 27.2	0.035
Muscle ($\mu g.ml^{-1}$)	21.7 ± 7.4	14.3 ± 7.42	0.15
Cefoxitin Index	0.31 ± 0.11	0.13 ± 0.05	0.006

The difference in $TcpO_2$ and $TcpO_2$ Index between healed and failed amputations is shown in table 8.2.

Table 8.2. Comparison of the mean $TcpO_2$ and mean $TcpO_2$ Index in successful and failed amputations. The antibiotic distribution is expressed as the cefoxitin index, being the ratio of muscle to plasma antibiotic concentrations.

	Healed	**Failed**	**p =**
$TcpO_2$ (mmHg)	56.5 ± 12.0	26.2 ± 18.7	0.022
$TcpO_2$ Index	0.95 ± 0.16	0.44 ± 0.27	0.011

Linear regression of muscle cefoxitin concentrations and $TcpO_2$ and the $TcpO_2$ Index and the cefoxitin index and $TcpO_2$ and the $TcpO_2$ Index were performed. The results are shown in table 8.3 and figures 8.3 and 8.4.

Table 8.3. Linear regression of muscle cefoxitin concentrations compared with $TcpO_2$ and the $TcpO_2$ Index and the cefoxitin index compared with $TcpO_2$ and the $TcpO_2$ Index.

	$TcpO_2$		**$TcpO_2$ Index**	
	r =	p =	r =	p =
Muscle cefoxitin concentration	0.41	0.240	0.38	0.141
Regression equation	y = 11.38 + 0.15x		y = 11.42 + 8.77x	
	$TcpO_2$		**$TcpO_2$ Index**	
	r =	p =	r =	p =
Cefoxitin Index	0.67	0.035	0.64	0.045
Regression equation	y = 0.065 + 0.0035x		y = 0.059 + 0.22x	

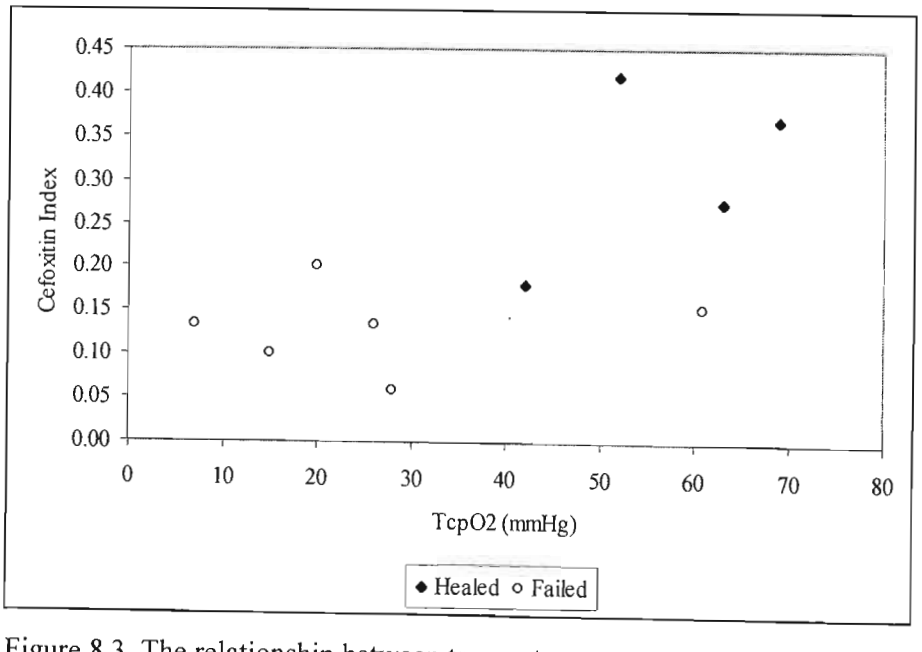


Figure 8.3. The relationship between transcutaneous oxygen pressure measurement and the distribution of cefoxitin as expressed by the cefoxitin index.

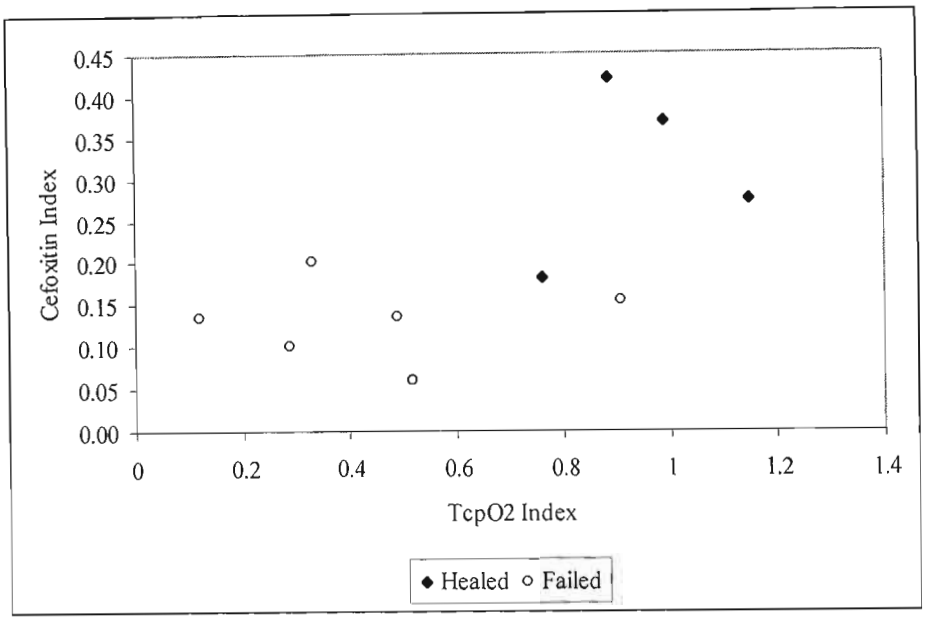


Figure 8.4. The relationship between transcutaneous oxygen index and the distribution of cefoxitin as expressed by the cefoxitin index.

8.2.3 Discussion

The minimum inhibitory concentration (MIC) of cefoxitin is given as 16 $\mu g.ml^{-1}$ for anaerobes and from 3 – 12.5 $\mu g.ml^{-1}$ for aerobes (Sutter, V. L. *et al.*, 1978; Birnbaum, J. *et al.*, 1978). The plasma cefoxitin concentrations would appear to have been adequate at the time of surgery. At the tissue level, however, in half the amputations the MIC for anaerobes had not been achieved. In 4 of these 5 patients the wounds subsequently became infected and needed revision.

There are several possible reasons for failure to achieve the MIC.

1. The average time from cefoxitin administration to plasma sampling was 28.5 min. The half-life of cefoxitin is 45 to 60 min and so a steady state of plasma to muscle antibiotic equilibrium may not yet have been reached, with antibiotic uptake still occurring at the time of surgery.

2. The dose of 2 g may have been inadequate, although this is unlikely as it is the recommended dose for patients with normal renal function.

3. In areas of ischaemia there may be loss of antibiotic receptor binding sites on the cell membrane.

4. Reduced blood flow to the area may have resulted in less antibiotic being delivered to the tissue with resultant lower cellular concentrations.

The difference in antibiotic distribution between the two groups as reflected by the cefoxitin index, suggests that the amputations that healed were associated with better delivery and or extraction of the antibiotic.

A $TcpO_2$ Index of 0.55 would correctly have predicted failure in 5 of the 6 amputations that failed and an index value of 0.5 would correctly have predicted 4 of the 6 failures. One amputation failed with a $TcpO_2$ of 61 mmHg and a $TcpO_2$ Index of 0.91 both of which would suggest more than adequate skin perfusion. The cefoxitin index in this patient was relatively low, 0.15. It is possible that in this patient muscle perfusion was inadequate, despite adequate skin perfusion.

Both absolute $TcpO_2$ and the $TcpO_2$ Index showed a significant correlation with the cefoxitin index. From the regression equation, a cefoxitin index value equal to a $TcpO_2$ index of 0.55 was extrapolated. This was a cefoxitin index of 0.18, below which healing would not be expected. Interestingly, no amputation with a cefoxitin index of less than 0.18 healed. There was one amputation performed at a cefoxitin index of 0.18 which healed. The $TcpO_2$ index at this site was 0.76.

What of the role of peri-operative antibiotics in amputation surgery in PVD? To be of use, the antibiotic concentration at the cellular level needs to be adequate. If an amputation is performed at a site with inadequate perfusion, antibiotic delivery is going to be impaired. In addition it has been shown that stump $TcpO_2$ falls during the first week after amputation. If the wound fails to heal on the basis of ischaemia, it is unlikely that the antibiotics administered peri-operatively will be of much benefit and the patient will be at risk of local infection in the ischaemic wound.

These results suggest that while $TcpO_2$ does not measure muscle blood flow, it may reflect the muscle blood flow status in some patients. The low muscle antibiotic concentrations in the presence of what appear to be adequate $TcpO_2$ values may explain some of the failures of amputations performed at sites that have a relatively high absolute $TcpO_2$ and $TcpO_2$ Index.

8.3 Limitations of this study

The small sample size limits the power of the study.

It was unfortunate that the time from antibiotic administration to taking the blood specimen at the time of limb division was less than the half-life of the antibiotic. There is a doubt that steady state equilibrium between plasma antibiotic and muscle bound antibiotic had been reached. The muscle concentrations and the cefoxitin index may have been higher had steady state been reached and may continue to rise in the distal muscle of the stump after amputation.

Chapter 9

A Comparison of $TcpO_2$ With Laser Doppler Fluxmetry in Patients With Peripheral Vascular Disease

9.1 Introduction

This chapter reviews the literature on comparisons of Laser Doppler fluxmetry and $TcpO_2$. Data from a prospective study of patients with PVD undergoing evaluation of amputation wound healing potential will be presented.

9.2 Laser Doppler fluxmetry

Laser Doppler Fluxmetry (LDF) has been proposed as a safe, simple and rapid test of skin microcirculatory blood flow. While similar in principle to the use of Doppler ultrasound to detect flow in a single vessel, LDF detects a Doppler shift signal produced when monochromatic laser light is reflected back off red blood cells in the vasculature of the skin. Unlike Doppler ultrasonography in which a single vessel is evaluated, the laser light penetrating the skin encounters many capillaries, and strikes them at varying angles of incidence. To further complicate matters, in the hairpin dermal capillary loops the light will be reflected from cells moving both toward and away from the light source.

The light penetrates to a depth of ~1.5 mm and undergoes significant scattering before reaching the capillary. Similarly, the light undergoes further scattering after reflection, on its way back to the light sensor. The resulting signal produced is the product of the number of red blood cells moving in the sample volume and the mean velocity of the red blood cells. It is therefore a measure of flux and not blood flow.

There are several shortcomings to the use of LDF. The data output of Laser Doppler Fluxmeters is not standardised. Some machines give readings in terms of voltage, while others use arbitrary units (au) or flux units. Attempts have been made by some manufacturers to present the output as blood flow per cm^3. This makes comparison of results from studies using different machines difficult. Another variable in the use of LDH is the absence of true zeroing of the machines. In the model used in our study, a "user confidence test" is offered.

There is also the issue of biological zero. The biological zero is the residual reading above zero obtained with LDF when the blood flow to a limb is occluded with an arterial tourniquet. The biological zero is thought to be due to Brownian motion, but may result in part from retrograde osseous blood flow. It varies with perfusion, vasodilatation, skin temperature and oedema formation. Interpretation of LDF readings may be improved by subtraction of the biological zero from the LDF value. In our study this was not done as we found that attempts to measure Biological zero in patients with severe PVD caused pain, resulting in movement artefacts which affected the readings obtained.

The role of cutaneous heating has been controversial. Several authors have reported the use of unheated LDF for wound healing prediction (Karanfilian, R. G. *et al.*, 1986; Kvernebo, K. *et al.*, 1989), while others maintain the need for cutaneous heating (Matsen, F. A. 3d *et al.*, 1984; Fairs, S. L. *et al.*, 1987).

9.3 Literature review of studies investigating Laser Doppler and $TcpO_2$

Karanfilian, R. G. *et al.*, (1986) combined their data from 20 amputations with that of 37 ischaemic ulcerations or gangrenous changes of the foot and compared $TcpO_2$ with unheated laser Doppler, Doppler ankle pressures and the ABI. A best fit technique was used to analyse the data and determine the level at which each test would yield the greatest accuracy for wound healing. The criteria reached by this method were a $TcpO_2$ greater than 10 mmHg, a laser Doppler skin blood flow of more than 40 mV, a laser Doppler pulsewave amplitude greater than 4 mV (with both criteria having to be met) and an ankle systolic pressure greater than 30 mmHg. The sensitivity or true positive test for predicting healing was best for $TcpO_2$ (100 %) with laser Doppler and Doppler ankle pressures being 79 % and 75 % respectively. The specificity, or true negative, was highest for laser Doppler at 96 %, with $TcpO_2$ being 88 %, and ankle Doppler pressures a very poor predictor of failure at 26 %. The overall accuracy of $TcpO_2$ was 95 %, laser Doppler 87 % and Doppler ankle pressures 52 %.

Fairs looked at unheated laser Doppler, heated laser Doppler (at 42 °C), the LDF flux (relative change in LDF after heating) and $TcpO_2$. Amputation level selection was based on a $TcpO_2$ of 2.7 kPa (20 mmHg). All tests were performed at the BKA level and 14 BKA's were performed, all of which healed. They report the best correlation as being between $TcpO_2$ and LDF flux. A scattergram was produced by pooling the data obtained from the BKA level of the 25 patients and 5 controls. Somewhat confusingly, the scattergram shows 35 pairs of data for the patients and 10 for the controls. Their description of the correlation line produced in

the scattergram states that "$TcpO_2$ rises asymptotically towards the normal levels", yet the figure shows a wide range of $TcpO_2$ ~ (5 – 50 mmHg) associated with a small change in LDF flux (0 – 2 units) (Fairs, S. L. *et al.*, 1987).

Their data could be interpreted as showing that in the dysvascular patient there is reduced vascular reactivity, as reflected by reduced LDF flux, and that this reduced reactivity occurs over a wide range of $TcpO_2$ values. In normal controls there is a wide range of reactivity in controls who have $TcpO_2$ values above 75 mmHg. The correlation is given as $r = 0.7$ ($p < 0.001$). It is not clear as to whether a linear model was used for correlation or whether a model was chosen to accommodate the asymptotic relationship. They conclude that in their recent experience, LDF is far more reliable, simpler and quicker to use and is intrinsically more stable than $TcpO_2$. This conclusion is not supported by the data provided.

Lantsberg, L. and Goldman, M., (1991) found laser Doppler heated to 42 °C to be more discriminatory than $TcpO_2$ for BKA. They studied 24 amputations that all healed. In some patients the $TcpO_2$ value was less than 10 mmHg. While all the BKA's in their series had LDF values above 20 mV, all the AKA's had values below 20 mV and also healed. Despite having healing at LDF values of less than 20 mV, they conclude that primary healing always occurs if the LDF is greater than 20 mV.

Padberg highlighted some of the difficulties associated with interpretation of laser Doppler studies. These included the need to heat the skin, the temperature protocols used, and the lack of standard units for the test. Their data pooled 51 amputations with 29 non-healing ulcers and compared $TcpO_2$ with heated laser Doppler and ABI. Receiver operator curves were constructed, plotting sensitivity against specificity, as opposed to 1 - sensitivity. Based on the areas under the curves, $TcpO_2$ was shown to be superior to heated laser Doppler, which was in turn superior to ABI. The optimal predictive values for healing were given as a $TcpO_2$ of more than 10 mmHg, a heated laser Doppler value of 50 mV or more and an ABI of more than 0.34. They conclude that $TcpO_2$ is a better indicator of wounds that will heal, but that heated laser Doppler is a better predictor of wound failure (Padberg, F. T., Jr. *et al.*, 1992).

9.4 Prospective study comparing Laser Doppler fluxmetry and $TcpO_2$

This has been published as "A comparison of laser Doppler fluxmetry and transcutaneous oxygen pressure measurement in the dysvascular patient requiring amputation" (Mars, M. *et al.*, 1998). See Appendix c.

9.4.1 Method

35 patients undergoing routine evaluation of amputation wound healing potential were studied. The patients were not diabetic and were not on vaso-active medication. Patients lay supine for 20 minutes to acclimatise to the ambient temperature of the Non-invasive vascular laboratory, which ranged from 20 – 23 °C. Laser Doppler measurements were made before $TcpO_2$ measurements to avoid possible confounding effects of skin heating on the Laser Doppler measurements. LDF was performed with a Laserflo BPM2 Blood Perfusion Monitor, Vasamedics, St Paul. The laserflo monitor does not offer a zeroing procedure, but rather a "user confidence test" which checks that the laser and photodetector are within specification. This test was performed before each series of LDF measurements were made.

The measurement sites were prepared by shaving, when necessary, and cleaned with an alcohol solution. The LDF probe was attached to the skin by means of a double sided adhesive ring and unheated LDF measurements were recorded after 3 minutes. The heating element in the probe was then heated to 45 °C and the "heated" LDF reading made after 5 minutes. The difference between heated and unheated was taken as the vascular reserve (VR). All LDF measurements were performed, under supervision, by Mr A.J. McKune.

Probe placement sites were the same as for $TcpO_2$ measurement. Measurements were made on the anterior chest wall, and at the below knee site in all patients. Measurement at the foot was dependent on the clinical decision required. If the clinical choice was between a Foot amputation and a BKA, then the Foot site was measured, and the AKA site was measured if the choice was between a BKA and an AKA.

Data were obtained from the Foot (n = 17), BKA (n = 35), AKA (n = 17 and the Chest (n = 35). One patient presenting with a gangrenous forefoot only had a BKA measurement taken as the Foot site was gangrenous. The data recorded were unheated LDF, heated LDF and the LDF Index which is the limb to chest ratio.

$TcpO_2$ measurements were made as previously described.

All patients underwent amputations, which were performed by members of the Vascular Service according to the standardised procedures of the Unit. Amputation level selection was guided by the $TcpO_2$ value.

9.4.2 Results

The LDF and $TcpO_2$ measurements taken at the different sites are shown in table 9.1.

Table 9.1. $TcpO_2$ (mmHg), unheated and heated LDF (arbitary units = au), $TcpO_2$ Index and unheated and heated LDF indices expressed as means and 1 SD are shown for the different amputation levels.

	Chest	**AKA**	**BKA**	**Foot**
	n = 35	n = 17	n = 35	n = 17
$TcpO_2$ (mmHg)	55.7 ± 11.2	39.2 ± 19.0	36.3 ± 20.3	17.3 ± 13.3
LDF unheated (au)	3.9 ± 2.1	1.7 ± 1.1	1.6 ± 0.9	1.9 ± 1.3
LDF Heated (au)	18.1 ± 4.1	10.0 ± 4.8	7.9 ± 5.0	5.2 ± 5.2
$TcpO_2$ Index		0.73 ± 0.37	0.62 ± 0.31	0.31 ± 0.23
LDF Index unheated		0.61 ± 0.41	0.52 ± 0.41	0.53 ± 0.63
LDF index heated		0.58 ± 0.33	0.46 ± 0.33	0.29 ± 0.30

Correlation of the results at each site was by Spearman's rank correlation. Significance was set at $p < 0.05$. Significant correlation was noted between heated LDF and both absolute $TcpO_2$ and the $TcpO_2$ index and between the heated LDF index and the $TcpO_2$ Index at the Foot and BKA sites.

The data from the various sites was pooled and tests of correlation performed (table 9.2).

Table 9.2. Results of Spearman correlation (r) between unheated and heated LDF indices and $TcpO_2$ and the $TcpO_2$ Index, and LDF Indices and the $TcpO_2$ Index.

	$TcpO_2$ n = 104		**$TcpO_2$ Index** n = 69	
	r =	p	r =	p
LDF unheated	0.31	< 0.001	0.18	0.21
LDF heated	0.63	< 0.0001	0.72	< 0.0001
LDF Index unheated			0.21	0.08
LDF Index heated			0.69	< 0.0001

The strongest correlation was between heated LDF and the $TcpO_2$ Index. The scattergram of the relationship between heated LDF and $TcpO_2$ Index is shown in figure 9.1.

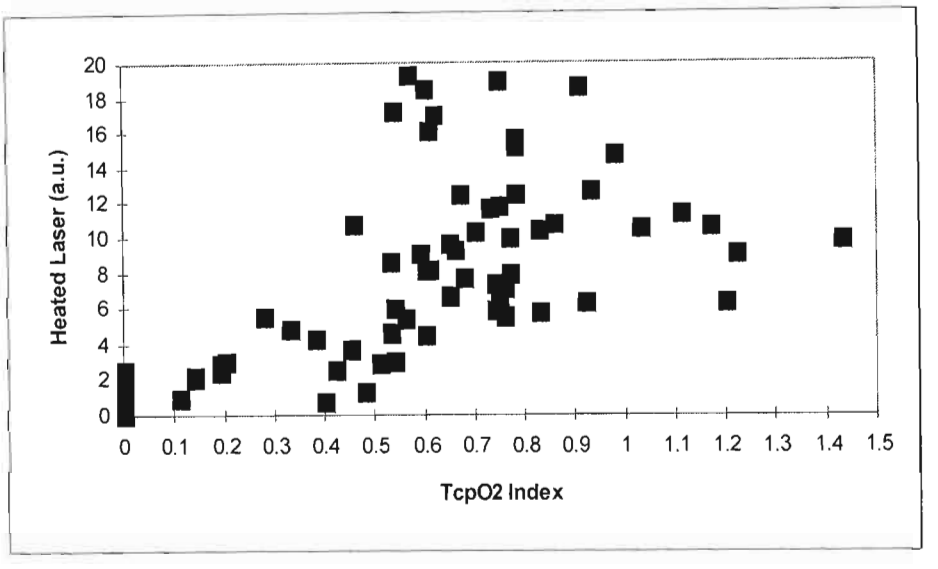


Figure 9.1 Scattergram showing the relationship between the $TcpO_2$ Index and heated LDF (n = 69). The linear regression equation is y = 2.38 +9.4x.

9.5 Clinical outcome

Of the 35 patients, two underwent bypass graft surgery and were excluded from follow-up, one patient refused amputation and 3 patents died peri-operatively. Three patients were transferred back to rural hospitals before wound healing was complete and they have been lost to follow-up. Twenty-six amputations, 4 transmetatarsal, 15 BKA and 7 AKA were available for evaluation. Despite knowing the pre-operative $TcpO_2$ values, 6 amputations were performed at sites with a $TcpO_2$ Index of less than 0.55. Five of these amputations failed to heal, and required revision to a more proximal site. One amputation with a $TcpO_2$ Index of 0.54 and heated flux value of 4.7 au healed after 4 weeks.

The mean $TcpO_2$ Index, heated LDF and LDF VR values for the healed and failed amputations are shown in table 9.3. The differences in mean values for the $TcpO_2$ Index were compared using an unpaired two tailed t-test. The heated LDF and LDF VR data showed significant differences in variance and were compared using Welch's modified t-test

Table 9.3. Mean $TcpO_2$ Index, LDF and LDF VR values and 1 SD, of healed and failed amputations.

	Healed	Failed	p =
n =	21	5	
$TcpO_2$ Index	0.73 ± 0.17	0.33 ± 0.20	0.0001
Heated LDF	9.15 ± 4.28	3.39 ± 1.47	0.0001
LDF VR	7.37 ± 4.14	2.93 ± 1.49	0.0009

The sensitivity, specificity, positive and negative predictive values and the accuracy of the three tests are shown in tables 9.4, 9.5, 9.6 and the ROC curves in figures 9.2, 9.3, and 9.4.

Table 9.4. The sensitivity, specificity, positive and negative predictive values and the accuracy of the $TcpO_2$ Index. The index values with the highest accuracy are highlighted.

Index	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0.00	100.00	20.00	84.00	100.00	84.62
0.05	100.00	20.00	84.00	100.00	84.62
0.10	100.00	20.00	84.00	100.00	84.62
0.15	100.00	20.00	84.00	100.00	84.62
0.20	100.00	20.00	84.00	100.00	84.62
0.25	100.00	20.00	84.00	100.00	84.62
0.30	100.00	60.00	91.30	100.00	92.31
0.35	100.00	60.00	91.30	100.00	92.31
0.40	100.00	60.00	91.30	100.00	92.31
0.45	100.00	60.00	91.30	100.00	92.31
0.50	100.00	80.00	95.45	100.00	96.15
0.55	95.24	100.00	100.00	83.33	96.15
0.60	76.19	100.00	100.00	50.00	80.77
0.65	61.90	100.00	100.00	38.46	69.23
0.70	52.38	100.00	100.00	33.33	61.54
0.75	47.62	100.00	100.00	31.25	57.69

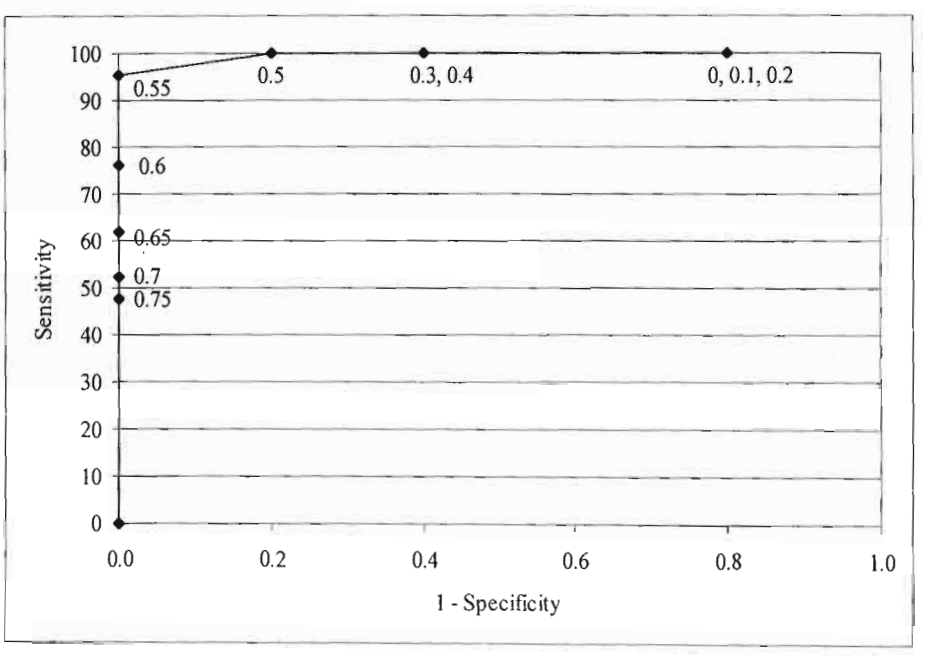


Figure 9.2. Receiver operator characteristic curve based on $TcpO_2$ Index values ranging from 0 – 0.75. The best predictive value based on this curve is 0.55.

Table 9.5. The sensitivity, specificity, positive and negative predictive values and the accuracy of heated LDF (au). The LDF values with the highest accuracy are highlighted.

Heated LDF (au)	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0.00	100.00	0.00	80.77		80.77
1.00	100.00	0.00	80.77		80.77
2.00	100.00	20.00	84.00	100.00	84.62
3.00	100.00	40.00	87.50	100.00	88.46
4.00	95.24	60.00	90.91	75.00	88.46
5.00	85.71	100.00	100.00	62.50	88.46
6.00	71.43	100.00	100.00	45.45	76.92
7.00	71.43	100.00	100.00	45.45	76.92
8.00	57.14	100.00	100.00	35.71	65.38
9.00	42.86	100.00	100.00	29.41	53.85
10.00	33.33	100.00	100.00	26.32	46.15
11.00	23.81	100.00	100.00	23.81	38.46
12.00	19.05	100.00	100.00	22.73	34.62
13.00	14.29	100.00	100.00	21.74	30.77
14.00	14.29	100.00	100.00	21.74	30.77
15.00	9.52	100.00	100.00	20.83	26.92

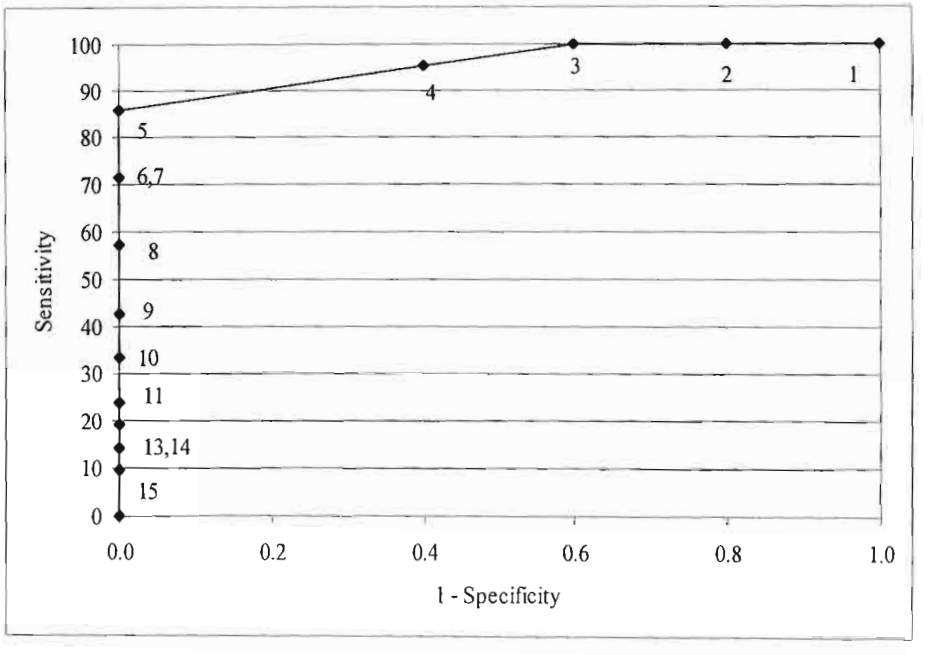


Figure 9.3. Receiver operator characteristic curve based on heated LDF values ranging from 0 – 15 (au). The best predictive value based on this curve is 5 (au).

Table 9.6. The sensitivity, specificity, positive and negative predictive values and the accuracy of heated LDF (au). The LDF values with the highest accuracy are highlighted.

LDF VR	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0.00	100.00	0.00	80.77		80.77
1.00	95.24	20.00	83.33	50.00	80.77
2.00	90.48	20.00	82.61	33.33	76.92
3.00	90.48	60.00	90.48	60.00	84.62
4.00	85.71	80.00	94.74	57.14	84.62
5.00	71.43	100.00	100.00	45.45	76.92
6.00	57.14	100.00	100.00	35.71	65.38
7.00	47.62	100.00	100.00	31.25	57.69
8.00	38.10	100.00	100.00	27.78	50.00
9.00	28.57	100.00	100.00	25.00	42.31
10.00	23.81	100.00	100.00	23.81	38.46
11.00	14.29	100.00	100.00	21.74	30.77
12.00	14.29	100.00	100.00	21.74	30.77
13.00	14.29	100.00	100.00	21.74	30.77
14.00	14.29	100.00	100.00	21.74	30.77
15.00	4.76	100.00	100.00	20.00	23.08

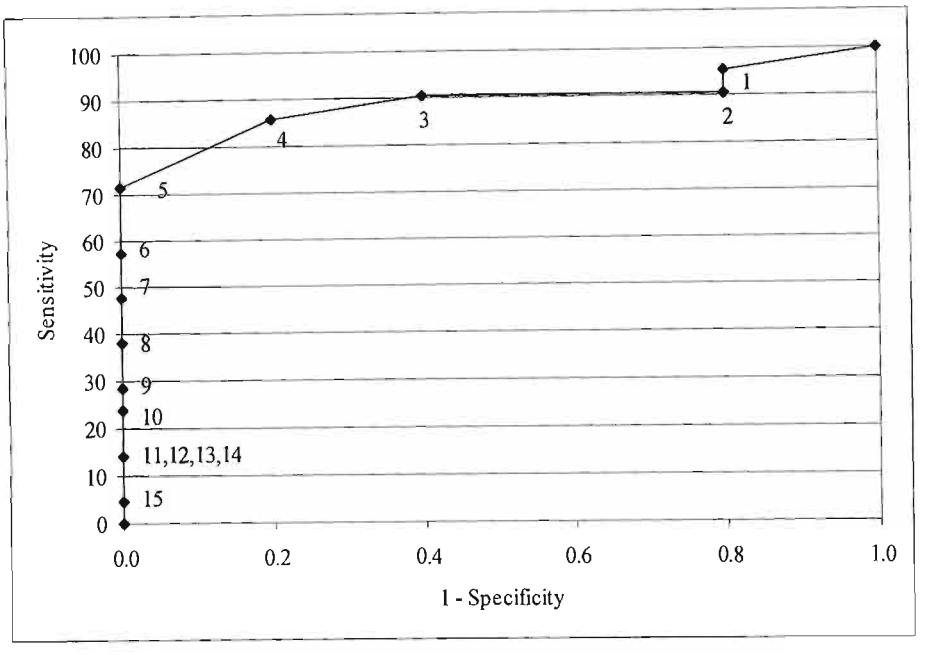


Figure 9.4. Receiver operator characteristic curve based on LDF VR (au) values ranging from 0 – 15 (au). The best predictive value based on this curve is 5 (au).

To compare the three tests a combined ROC was plotted figure 9.5. The best test has the greatest area under the curve.

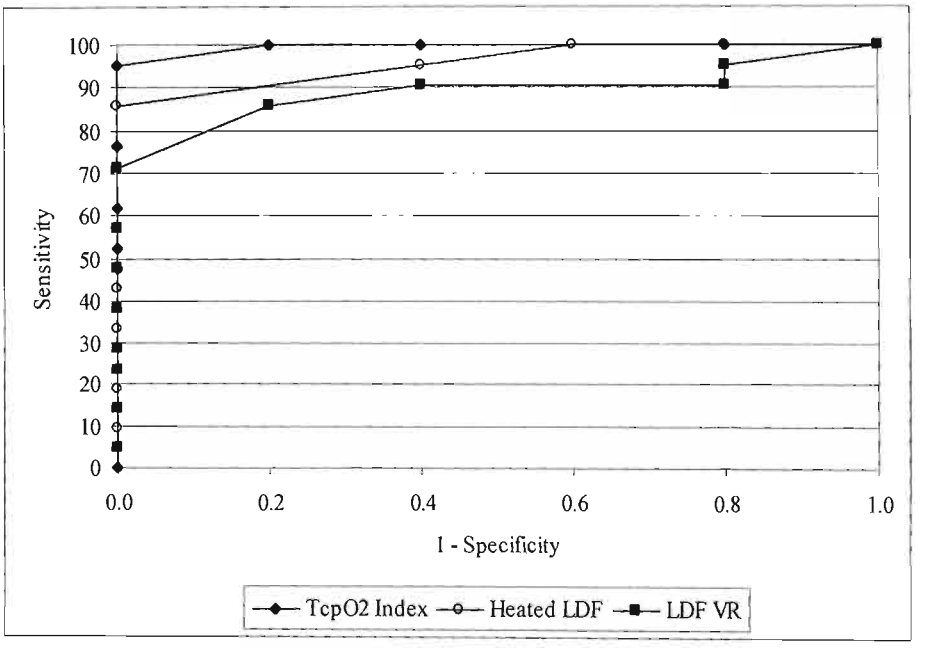


Figure 9.5. Receiver operator characteristic curves for $TcpO_2$ Index, heated LDF and LDF VR.

Figure 9.5 clearly shows that the area under the $TcpO_2$ ROC is greater than that under the heated LDF curve which in turn is greater than that of the LDF VR curve. This suggests that the $TcpO_2$ index is a more accurate method of predicting amputation wound outcome than either heated LDF or the LDF VR. From tables 5.19, 5.20 and 5.21, it can be seen that the best accuracy, 96.2 % was obtained at a $TcpO_2$Index of 0.5 to 0.55. Heated LDF had its accuracy of 88.5 % between 3 and 5 arbitrary units and LDF VR an accuracy of 84.6 % between 3 and 4 arbitrary units.

9.6 Summary

In this series of 26 amputations laser Doppler fluxmetry was found to be inferior to the $TcpO_2$ Index in predicting amputation outcome and the refinement of using the LDF vascular reserve did not add any beneficial additional information to wound prediction.

Despite being less accurate than $TcpO_2$ Index the LDF test takes less than half the time of a $TcpO_2$ investigation to perform. In our setting widespread use of heated LDF may as useful as limited use the $TcpO_2$ Index in reducing the revision rate.

A major limitation to this study is the sample size, and the fact that there were so few failures. This has been a problem in the other studies reporting the use of LDF. The obvious solution of pooling the data and performing a meta-analysis was not feasible because of different heating protocols and the data being reported in different units.

Chapter 10

Transcutaneous Oxygen Pressure Measurement and Amputation Prediction

10.1 Introduction

This chapter will review the literature on the use of $TcpO_2$ and the $TcpO_2$ index to predict amputation wound healing. Possible causes of the variability of results obtained in previous studies will be examined. Criteria for choosing $TcpO_2$ values for amputation level selection will be discussed. Data from a prospective clinical trial will be presented from which criteria were developed for clinical use of $TcpO_2$ in amputation level selection in our laboratory.

10.2 Literature review

What are we looking for from an investigation of amputation wound healing potential? The perfect test would give a single reproducible value, above which healing would always occur and below which failure would always occur. This is presently unobtainable.

When looking at the worth of a test, is it better to be able to predict healing or to predict failure? Conventionally such tests are reported in terms of their ability to correctly predict success. Knowing that there are many factors influencing wound healing, seeking a predictive value that guarantees success results in the risk of setting the predictive value at a very high level to overcome the problem of wound failure due to causes other than insufficient skin perfusion. This means that some amputations will be performed at a more proximal level than necessary. Rather, it might be better to attempt to predict those amputations that will definitely fail, accepting that there will be some amputations that although predicted to heal, will still fail for whatever reason.

After the early reports of Burgess and others of a possible predictive level based on a $TcpO_2$ value, (Franzeck, U. K. *et al.*, 1982; Burgess, E. M. *et al.*, 1982; Dowd, G. S. *et al.*, 1983) Harward and later Wyss found healing to occur when the $TcpO_2$ value was zero (Harward, T. R. *et al.*, 1985; Wyss, C. R. *et al.*, 1988). This should have been the death knell of the investigation, for how can the test be of any value if healing occurs at zero? There were

several other groups working with $TcpO_2$, including Benscoter, Cina, Ito and Ratliff, and their subsequent publications suggest that there are three patterns of results(Cina, C. *et al.*, 1984; Ito, K. *et al.*, 1984; Benscoter, J. L. *et al.*, 1984) (Ratliff, D. A. *et al.*, 1984).

There are those like Dowd who identified definitive, relatively high cutoff values (Dowd, G. S. *et al.*, 1983), those who found low cutoff values with associated overlap "grey areas", (Burgess, E. M. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Katsamouris, A. *et al.*, 1984) and those who had healing at zero (Harward, T. R. *et al.*, 1985; Wyss, C. R. *et al.*, 1988). When a grey area of overlap was found, attempts were usually made to refine the test by using some form of reference or stress.

Following the paper of Wyss, we raised the issue of healing at zero, and questioned the possible differences of equipment, equilibration time, probe placement site and the influence of oedema as causes of the reported variability (Wyss, C. R. *et al.*, 1988; Mars, M., 1988). Falstie-Jensen's 1989 paper, in which he stated that $TcpO_2$ could offer no additional information to the selection of amputation level (Falstie-Jensen, N. *et al.*, 1989), prompted Bacharach to review the Mayo Clinic's experience of the use of $TcpO_2$. They concluded that the $TcpO_2$ test was of use, and their data showed a predictive level at 20 mmHg. In attempting to explain the variability of previously published results, and the issue of healing at a $TcpO_2$ of zero, they again raised the issues of instrument variability, differences in technique, probe placement and probe temperature (Bacharach, J. M. *et al.*, 1992).

Other issues that need to be addressed when comparing the literature are, the definition of healing - which varies, the operative techniques used, the timing of the investigation, the effect of sample size and the disease profile and status.

What emerges, is that most investigators have indicated that the test is of worth. This support of the test needs to weighed up against its subsequent poor support internationally. A cynical approach would be to question whether in the haste to publish, the worth of the test was inflated by enthusiasm and small sample size and that subsequent use has found the test to be flawed, as suggested by Falstie-Jensen, N. *et al.*, (1989), without this new information being published.

This possibility can be explored by looking at reports emanating from the same groups over time.

The Seattle group initially had healing over a range of 27 – 73 mmHg (n = 37) and offered 40 mmHg as the predictive level in 1982 (Burgess, E. M. *et al.*, 1982). Rhodes then found wound breakdown in BKA's where the anterior $TcpO_2$ was less than 25 mmHg in a sample of 12 patients (Rhodes, G. R., 1985) and in 1986, when looking at feet with skin envelope injuries suggested that a foot amputation would not heal if the $TcpO_2$ was below 25 mmHg (n = 5) or 30 mmHg (n = 3) (Rhodes, G. R. and King, T. A., 1986; Rhodes, G. R. and Skudder, P., Jr., 1986). Wyss, reporting on what was the largest series to date, 206 amputations, had healing at 0 mmHg in 4 instances. Despite this they still felt that $TcpO_2$ was the best available predictor of amputation wound healing in the dysvascular patient, as it gave an indication of the relative ischaemia and hence the risk of the amputation failing. Of interest is their statement that a $TcpO_2$ of 20 mmHg "clearly indicates severe ischaemia" and that at the level of the foot only 4 % of amputations performed at $TcpO_2$ levels of less than 20 mmHg healed (Wyss, C. R. *et al.*, 1988).

In 1982, the San Diego group first reported on 35 amputations. Five mmHg was taken to represent the lower limit of healing potential, although 1 patient healed an amputation at 3 mmHg. Twenty mmHg or more indicated good healing potential (Franzeck, U. K. *et al.*, 1982). In their 1985 report of 119 amputations, of which 18 failed, detailed data were provided for 88 cases of BKA and Foot amputation, 9 of which healed despite a $TcpO_2$ of 0 mmHg. On these results they proposed setting the predictive value at 10 mmHg or an increase of 10 mmHg when augmenting the investigation with inhalation of 100 % oxygen. At this predictive level, the investigation had a poor negative predictive value of only 18 % for BKA's (Harward, T. R. *et al.*, 1985). Oishi's 1988 retrospective study of 72 amputations comparing $TcpO_2$ with Doppler pressure studies and skin temperature appears to have included patients reported by Harward with additional patients added to make up the AKA group (Oishi, C. S. *et al.*, 1988). Their data are reported based on a predictive value set at 10 mmHg or an increase in $TcpO_2$ of 10 mmHg or more after 100 % oxygen inhalation. Augmenting the test improved their negative predictive value at the BKA site to 75 %. The data for absolute $TcpO_2$ were not given and thus the sensitivity and specificity could not be calculated.

Christensen, K. S. and Klarke, M., (1986), from Aalburg, reported on 42 amputations in 1986. The amputation level was selected on skin perfusion pressures and 5 amputations failed. A distinct predictive value was apparent at 20 mmHg, with no healing below this level and only one failure above it. Three years later Falstie-Jensen reported on 74 amputations, 14 of which failed, with 11 failures occurring at levels above 20 mmHg. In this study 6 amputations healed at levels between 0 and 20 mmHg. From this they concluded that the failure rates were

unrelated to $TcpO_2$ levels and that $TcpO_2$ offered no worthwhile additional information to that obtained by skin perfusion pressure studies Falstie-Jensen, N. *et al.*, (1989).

Sample size may then have influenced early results.

10.2.1 Does amputation level selection based on $TcpO_2$ outperform clinical judgement and other investigations?

Of the 42 studies on amputation and $TcpO_2$, details are available of 1865 amputations, 332 of which failed, giving an overall failure rate of 17.8 %. Excluding the 3 studies in which $TcpO_2$ was the definitive criterion for level selection, the failure rate rises to 18.7 %. This is in keeping with previous reports of revision rate which range from as low as 10 % (Burgess, E. M. *et al.*, 1971) to 48 % (Fernie, G. R., 1981). Keagy's "definitive control series" had revision rates of 19 % for BKA's and 9 % for AKA's (Keagy, B. A. *et al.*, 1986). It should be remembered that authors use different definitions of failure, and this will be dealt with under test variability.

Ito, Dowd and Fairs report the only three studies in which level selection was based solely on $TcpO_2$ levels. Ito used isobaric lines based on 30 mmHg to predict amputation outcome. They report healing of 31 amputations in terms of primary healing and state that 3 amputations did not undergo primary healing. It appears, although it is not stated, that 2 of these amputations failed, giving a failure of primary healing rate of 9.7 % and a failure rate requiring revision of 6.5 % (Ito, K. *et al.*, 1984). Dowd performed 50 amputations based on a $TcpO_2$ level of 40 mmHg of $TcpO_2$. Despite this selection criterion one amputation was performed at 35 mmHg and failed. Another amputation failed at 45 mmHg. Therefore based on the predictive level of 40 mmHg, he had only a 2 % failure rate (Dowd, G. S., 1987). Fairs reports on 14 BKA's performed at levels above 20 mmHg, all of which healed (Fairs, S. L. *et al.*, 1987). The combined failure rate of these three studies is 3.2 %.

Our study reporting the use of the $TcpO_2$ index in which the surgeon was advised on the amputation level but could perform the amputation at a more distal level if clinical evidence supported this, showed that the $TcpO_2$ index outperformed clinical judgement (Mars, M. *et al.*, 1993). Revision rates of as low as 1.6 % *per annum* were achieved in patients whose amputations were based on this selection criterion.

It could be argued that these $TcpO_2$ based studies have merely resulted in some amputations being performed at a more proximal level than was necessary.

As has been stated previously, because of the multifactorial nature of wound healing in the dysvascular patient it is unlikely that there will be any one test that will successfully predict healing with a high degree of sensitivity and specificity. It may be that individual laboratories have to establish their own $TcpO_2$ norms using their techniques and equipment to be able to make the test useful, and that the test is neither readily "exportable" nor easily implementable. In institutions performing large numbers of amputations for peripheral vascular disease, the time spent establishing norms may well be of ultimate benefit to the patients.

Detailed review of the literature pertaining to $TcpO_2$ and amputation wound healing has been divided into those studies suggesting predictive values above 20 mmHg, those which propose levels below 20 mmHg and studies which report on the use of the $TcpO_2$ index.

10.2.2 Studies reporting useful $TcpO_2$ predictive values between 20 and 40 mmHg

An initial case report on the use of $TcpO_2$ in level selection was presented by Matsen, F. A. 3d *et al.*, in 1980, in which a transmetatarsal amputation was performed at a $TcpO_2$ of 0 mmHg. This failed and was successfully revised to a BKA which was performed at a $TcpO_2$ level 49 mmHg. In addition they report on a range 25 to 65 mmHg within which healing occurred. The number of patients is however not reported.

Burgess, E. M. *et al.*, (1982) retrospectively reviewed their BKA outcome based on a predictive value of 40 mmHg. Above this level all amputations healed, however 15 amputations below this level also healed. Their data show that the lowest healing occurred at 26 mmHg. No amputations at levels below this (n = 5) healed. The possible usefulness of $TcpO_2$ as a predictor of amputation wound failure was not commented upon.

White, R. A. *et al.*, (1982) reported on 9 amputations, 6 AKA and Hip disarticulations and 3 BKA's. Six of the nine amputations healed. Above 20 mmHg, 4 amputations healed primarily and one after revision. This was a Guillotine amputation with a $TcpO_2$ of 40 mmHg, which was recorded as a failure. Below 20 mmHg, 2 amputations healed and 2 failed. No predictive level for failure was seen. They concluded from this, that a $TcpO_2$ of 50 mmHg predicts success for amputations and that 40 mmHg or less is associated with ongoing wound

problems. Their results need to be viewed with caution as they may have made some of the measurements with the patients on oxygen therapy, for they state that the "same inspired oxygen concentration was maintained for the duration of each patient's evaluation". In addition it is not clear as to whether the $TcpO_2$ measurements were made at the margins of the proposed flaps, or at the margins of persistent cellulitis or gangrenous lesions.

Dowd, G. S. *et al.*, (1983) compared the $TcpO_2$ of 91 volunteers with 63 patients with PAOD and found a $TcpO_2$ gradient from proximal to distal in the PAOD patients which was not present in the controls. In addition, in the normal volunteers $TcpO_2$ was not affected by age. Twenty-four amputations were reported, 6 of which failed and 1 which healed after a delay. All amputations performed at a level of 40 mmHg or more healed, except for a TMA that failed at 40 mmHg. The delayed healing occurred in a BKA with a $TcpO_2$ of 49 mmHg. They noted that the lower limit of normal at the foot was 45 mmHg and suggested that oxygenation below 40 mmHg is always associated with severe circulatory disturbance, associated stump breakdown and failure to heal. They demonstrated a clear level of 40 mmHg below which healing did not occur.

Mustapha (1983) reported fourteen patients who underwent BKA, 9 of which healed. The average absolute $TcpO_2$ values of the healed amputations was 51.9 ± 13.1 mmHg. For the failed amputations the absolute values averaged 28.4 ± 8 mmHg. The ranges are not given so it is not possible to assess overlap and cutoff values. They concluded that an absolute value 40 mmHg was associated with healing and below 35 mmHg they suggest that amputation wound healing is unlikely (Mustapha, N. M. *et al.*, 1983).

Benscoter (1984) reported a series of 16 amputations. All 13 amputations performed at $TcpO_2$ levels above 37 mmHg healed. Two of 5 BKA's failed, and both were 35 mmHg or less. One amputation at the foot healed with a $TcpO_2$ of 6 mmHg, and it was noted that there was marked local oedema (Benscoter, J. L. *et al.*, 1984).

Cina (1984) reported on 22 amputations, 17 of which healed. All those that healed had a value of 38 mmHg or more, while 4 of the 5 failures were at levels below 38 mmHg. There was one failure at 42 mmHg. They also evaluated the use of the $TcpO_2$ index and found that it offered no additional information (Cina, C. *et al.*, 1984).

In the first prospective study using $TcpO_2$ to predict amputation level selection, Ito mapped multiple points on the anterior and posterior aspects of the leg and mapped isobars of partial pressure. Amputation was performed at the 30 mmHg isobar with the proviso that sufficient

stump length remained for prosthetic fitting. 28 of 31 amputations (90.3 %) healed (Ito, K. *et al.*, 1984). The process is laborious and it is interesting to note that readings were taken 10 – 15 minutes after probe application, a shorter stabilisation time than is generally accepted.

Katsamouris, A. *et al.*, (1984) retrospectively reviewed the outcome of 29 amputations and compared the usefulness of absolute $TcpO_2$ and the $TcpO_2$ Index. Some of the patients may have already been reported by Cina from the same group (Cina, C. *et al.*, 1984). Primary healing was achieved in 22 of the amputations and delayed healing in 2. The lowest $TcpO_2$ at which healing was achieved was 32 mmHg and the lowest Index value was 0.51. Of the 5 amputations that failed, the highest absolute value was 42 mmHg with an index of 0.56. No amputation performed at a level below 0.51 healed.

Ratliff, D. A. *et al.*, (1984) felt, based on their observations of declining absolute $TcpO_2$ towards the periphery of limbs with PVD and its correlation with ankle systolic pressure, that $TcpO_2$ accurately reflected the degree of limb ischaemia and would therefore be of use in predicting amputation healing. They report on 56 amputations, 33 of which were BKA's. Their paper only reports in detail on the BKA's, and gives 35 mmHg as a predictive value, above which a BKA will heal. The data presented in their figures suggest a large area of overlap and a less than conclusive predictive value. All BKA's performed at a level greater than 35 mmHg healed, while all the BKA's that failed to heal were performed at $TcpO_2$ values of less than 35 mmHg. However, 10 BKA's undertaken at values of 9 – 33 mmHg also healed. The data reflect no clear level which would predict failure of an amputation and a very broad "grey area" of overlap. They note that 9 of their 19 AKA's may well have healed a BKA based on $TcpO_2$ values at the BKA level of 35 mmHg or more.

Christensen, K. S. and Klarke, M., (1986) selected amputation level based on skin perfusion pressure in 42 patients undergoing 28 BKA and 14 AKA's. Failure occurred in 5 amputations, 4 with values below 20 mmHg and 1 at 58 mmHg. Above 20 mmHg wound healing occurred. They are the first to report on the problems associated with choosing a $TcpO_2$ level for amputation level selection, pointing out that had they chosen the 40 mmHg level for amputation, 11 healed BKA's would have been performed at the AKA site. They noted that while skin perfusion pressure was the best available test of healing potential available at the time, it was associated with 50 % failure rates at perfusion pressures between 20 – 30 mmHg, emphasising the need for a more sensitive investigation (Holstein, P., 1982). They concluded that $TcpO_2$ is a simpler method which needs to be prospectively compared to skin perfusion pressure.

McCollum, P. T. *et al.*, (1986) studied 39 amputations and reported primarily on 29 BKA's. They augmented their absolute $TcpO_2$ study with inhalation of 100 % O_2 and calculated the rate at which the $TcpO_2$ rose. They report a wide range of values for those patients undergoing BKA (0 – 70 mmHg) and an area of overlap with failed and healed amputations. This overlap was reduced by basing the selection level on a rate of increase in $TcpO_2$ of 9 $mmHg.min^{-1}$ or more, reducing the error to 1 false negative, that is one amputation that would be predicted to fail, which ultimately healed. They note that all BK amputations with an absolute $TcpO_2$ of 35 mmHg or more healed while 12 of 16 BK amputations with a value of less than 35 mmHg healed. The range of these 12 amputations was not given. They conclude that there is no simple relationship between $TcpO_2$ and the healing potential of BKA skin flaps and that as a low $TcpO_2$ is an unreliable indicator of tissue viability, the test is of minimal worth to the surgeon. It needs to be remembered that level selection in this study was based on radio-isotope study information, thermography and clinical judgement. That 5 (12.8 %) amputations still failed is somewhat surprising. Unfortunately insufficient data are presented in the paper to be able to fully analyse the significance of the comments made regarding the usefulness of absolute $TcpO_2$.

Rhodes measured $TcpO_2$ in 8 patients who underwent distal tibial bypass for limb salvage. Successful bypass was associated with an increase in $TcpO_2$ 5 – 8 days after surgery. Earlier post-operative measurement reflected a decrease in $TcpO_2$ in 2 patients and a moderate rise in the remaining 6 patients despite demonstrable pedal pulses. The delay in full revascularisation is attributed to an ischaemic reperfusion injury. The mid foot values increased from 11 ± 11 mmHg preoperatively to 22 ± 6 mmHg in the early postoperative period, rising to 39 ± 13 in the late postoperative period. Amputation was based on clinical grounds and a $TcpO_2$ of more than 25 mmHg. 4 amputations around the foot were performed and all healed (Rhodes, G. R. and King, T. A., 1986).

Rhodes also used multiple $TcpO_2$ mapping around skin envelope injuries after distal bypass procedures to predict outcome. Three patients went on to have BK amputations. All 3 healed and the $TcpO_2$ values at these sites were all greater than 30 mmHg (Rhodes, G. R. and Skudder, P., Jr., 1986).

In the Hunterian lecture given by Dowd, he reviewed his experience with $TcpO_2$ measurement. In an initial retrospective series of 51 AKA and BKA's, no amputation with a $TcpO_2$ value of less than 35 mmHg healed, with 2 failures occurring above this level. Again it was noted that about 50 % of the AKA's performed had the potential to heal at the BK level (Dowd, G. S., 1987). This was followed by a prospective study of 50 amputations in which he

states that level selection was made on the basis of a $TcpO_2$ of more than 40 mmHg. Despite this one amputation was performed at 35 mmHg and failed while a second failed at above 45 mmHg. The 96 % healing achieved, while impressive, should be looked at in the knowledge that there had been healing at the 35 – 40 mmHg level in the retrospective study. Some patients may have had the ability to heal a more distal amputation. He concluded that further studies were required to see if high rates of healing can be achieved at lower $TcpO_2$ levels.

Fairs compared laser Doppler and $TcpO_2$ and reported below knee $TcpO_2$ data on 25 amputations. Amputations level selection was based on a BKA $TcpO_2$ of 20 mmHg ie patients with values above this underwent a BKA and those with values less than 20 mmHg at the BKA level had an AKA. All 14 BKA's selected in this way healed (Fairs, S. L. *et al.*, 1987).

Oh mentions, in response to questioning of their paper, that they had performed a prospective study using $TcpO_2$ to predict BKA healing. They found that 25 mmHg predicted outcome with almost 100 % accuracy (Oh, P. I. *et al.*, 1987). Their group does not appear to have published this.

Mars, M. *et al.*, (1990) reported a series of 10 amputations of which 6 failed to heal. The study looked at the relationship of $TcpO_2$ at the amputation level and antibiotic concentration in the muscle at the level of amputation. Healing occurred in patients with a $TcpO_2$ above 40 mmHg.

Following Falstie-Jensen's conclusion that $TcpO_2$ was of no help in predicting amputation wound healing, Bacharach *et al* reviewed the Mayo Clinic's experience with $TcpO_2$ use. They reported on 90 amputations, 21 (23.3 %) of which failed. The amputation level was selected on clinical and other unstated criteria. They found an absolute $TcpO_2$ value of 40 mmHg or greater to be predictive of healing, with only one amputation performed at more than 40 mmHg failing to heal. In addition 20 mmHg was given as a level below which failure was predicted. Of 20 amputations performed at levels between 20 – 40 mmHg, 14 healed and 6 failed. As a stress test to improve discrimination they used a leg elevation test in which the leg was elevated at 30° for 3 minutes and the reduction in $TcpO_2$ noted. A fall of less than 15 mmHg was associated with healing and failure with a fall of more than 15 mmHg. The combined investigation of a $TcpO_2$ of 20 mmHg or more and an inclination test fall of less than 15 mmHg had a combined sensitivity of 85 %, with a specificity of 97 %, a positive predictive value of 89 % and a negative predictive value of 96 %. In discussing the spectrum of predictive ranges reported in the literature they suggest that some of this variation may be due to testing methods, citing as we did, factors such as the type of instrumentation, the

equilibration time, electrode placement sites and electrode probe temperature (Bacharach, J. M. *et al.*, 1992; Mars, M., 1988).

Pinzur reported on 38 amputations of the foot including Symes. $TcpO_2$ measurements were made at on the dorsum and the sole of the foot for TMA, ray and toe amputations, and on the medial and lateral malleolus for Symes' amputations. It appears that they then took the average of the two readings obtained at either of the levels as being the $TcpO_2$ level. The equilibration time was 10 min which is very short. Amputation level selection included nutritional evaluation and was made on clinical examination, an ABI of 0.5 or more, a minimum serum albumin of 3.0 $gm.dl^{-1}$ and a total lymphocyte count of 1500 or more. Six of the 38 amputations failed (15.8 %) despite standardising nutritional status to meet the minimum requirements. Two amputations healed at "averaged" levels below 20 mmHg and 2 failed at levels above 30 mmHg. They report 8 patients with "pipe-stemming", an ABI of more than 1.0, two of whom had $TcpO_2$ values of less than 20 mmHg, and subsequent wound failure. The authors conclude that a $TcpO_2$ of more than 30 mmHg is highly predictive of wound healing (Pinzur, M. S. *et al.*, 1992).

In a follow-up study Pinzur measured the $TcpO_2$ of 8 insulin dependent diabetics admitted with deep foot infections and signs of systemic sepsis. Again the equilibration time was only 10 min. The patients were then taken to theatre for surgical decompression of the infection where they either underwent partial ray resection or open midfoot amputation. All wounds were left open, the patients given nutritional support, culture sensitive antibiotics, and their diabetes controlled. Three days after surgery the $TcpO_2$ measurements were repeated at the same sites. Definitive surgery was undertaken after the infection appeared to be controlled. Three patients with mid foot amputations and low post decompression foot $TcpO_2$ values underwent Symes amputations. All 8 amputations healed and the $TcpO_2$ at the amputation level ranged from 30 – 52 mmHg. They note that in 3 patients the $TcpO_2$ showed an appreciable increase after resolution of cellulitis (Pinzur, M. S. *et al.*, 1993).

10.2.3 Studies reporting useful $TcpO_2$ predictive values between 0 and 20 mmHg

Franzeck, U. K. *et al.*, (1982) reported on 35 amputations at different levels, 6 of which failed to heal. Of the failed group, the highest $TcpO_2$ was 3 mmHg. Healing occurred at all values above 8 mmHg, and in one amputation with a $TcpO_2$ of 1 mmHg. They suggested that below 5 mmHg healing was unlikely and that above 20 mmHg healing potential was good.

The use of 100 % oxygen as a supplemental test was proposed by Harward, based on the observations of plastic reconstruction flap survival made by Achauer (Achauer, B. M. *et al.*, 1979; Achauer, B. M. and Black, K. S., 1984; Harward, T. R. *et al.*, 1985). After absolute $TcpO_2$ measurement the patient breathes 100 % oxygen and the change in $TcpO_2$ reading is noted. They studied 119 amputations, and measured $TcpO_2$ on the medial gastrocnemius at the BKA site and on the foot. 23 AKA's are reported but the pre-operative investigations were performed at the BKA site. These have been excluded, as they do not represent the value at the level of amputation, leaving 87 surviving amputations. Their conclusion was that an amputation would heal if the resting value at that level was greater than 10 mmHg or if after 100 % O_2 supplementation, the value rose by 10 mmHg or more. 17 BKA and Foot amputations healed with a $TcpO_2$ of 10 mmHg or less and three amputations failed at levels above 10 mmHg. Healing occurred with a value of 0 mmHg in 9 cases. Absolute $TcpO_2$ was able to predict healing in 83 % of BKA's and 80 % of foot amputations while prediction of failure was 67 % at the BKA and 66 % at the foot. The addition of the O_2 supplementation test improved the prediction of healing to 95 % and that of failure to 100 % at the BKA. Of importance is the observation, similar to that of Ratliff that the $TcpO_2$ values indicate that 50 % of the patients would in all likelihood have healed an amputation at a more distal level (Ratliff, D. A. *et al.*, 1984).

Rhodes, G. R., (1985) used multiple readings to perform skin mapping around ischaemic skin envelope injuries. At the conventional BKA, site 11 of 12 amputations healed but 4 subsequently broke down anteriorly with prosthetic fitting and weight bearing at 4 – 6 weeks. These four all had $TcpO_2$ values of less than 25 mmHg. In this small series, 25 mmHg appeared to be a good prognosticator of outcome. They also looked at post amputation $TcpO_2$ levels 1 – 2 weeks after surgery and noted an increase in anterior flap $TcpO_2$ in 9 of 12 patients. These changes did not relate to the final outcome however. Although the chest reference $TcpO_2$ value was measured, the Index was not reported. There are insufficient data to be able to calculate the indices associated with healing and failure.

Twenty mmHg was assessed as a suitable selection level by Depairon, M. *et al.*, (1986). The French abstract reports 35 amputations, 30 of which healed. If the amputation was performed at a site with a $TcpO_2$ of more than 20 mmHg there was a 92 % chance of healing. Amputations at less than 20 mmHg still had a 66 % chance of healing. Despite this, they advocate the use of a $TcpO_2$ level of 20 mmHg as a selection criterion.

Karanfilian, R. G. *et al.*, (1986) studied ischaemic, ulcerative and gangrenous lesion of the feet in 37 diabetics and 22 PVD patients, and compared $TcpO_2$ with laser Doppler fluxmetry and ankle brachial pressure indices. Amputation at the foot was performed in 20 patients, 18 of which healed. The data on the amputations was pooled with that of ulcers that were debrided and or skin grafted. The combined data show wound healing prediction based on a $TcpO_2$ of 10 mmHg to be superior to laser Doppler fluxmetry which was in turn superior to ABI. $TcpO_2$ was shown to have an accuracy of 95 %, laser Doppler 87 % and ABI 52 %. There was no significant difference between the accuracy of $TcpO_2$ in diabetics, 91 % and non-diabetics, 100 %.

Campbell, W. B. and Morris, P. J., (1987), investigated healing in through knee and Gritti-Stokes amputations, recording the $TcpO_2$ values at the BKA site. Eighteen of 19 amputations healed, with a range of (3 – 64 mmHg). They concluded that TKA's have more problems with healing than Gritti-Stokes amputations. This may in part be explained by the average $TcpO_2$ of the TKA group which was 22.9 ± 25.1 (3 – 64 mmHg) while that of the Gritti-Stokes group was 34.9 ± 17.5 (10 – 61 mmHg). Three of the amputations healed with $TcpO_2$ levels of 10 mmHg or less.

Oishi, C. S. *et al.*, (1988) of the San Diego group of Franzek, Harward and Fronek, reviewed 72 amputations in which the surgeon knew the $TcpO_2$ values and the effect of oxygen supplementation, but still selected the amputation level on clinical grounds. They set a positive test, healing predicted, as a $TcpO_2$ of more than 10 mmHg or an increase with O_2 supplementation to 10 mmHg or more. This gave a 98 % sensitivity, 88 % specificity and 97 % accuracy. The positive predictive value was 98 % and the negative predictive value 88 %, with only one false positive and false negative in the study. The false negative study, in a BKA, was attributed to the patient having severe congestive cardiac failure at the time of measurement. The healing potential and the severity of the congestive cardiac failure may have been established through the use of the $TcpO_2$ index. The sensitivities and specificities varied slightly at the different amputation levels.

It is interesting to note that the $TcpO_2$ studies were performed up to 6 months before the amputation. The justification for this was that in their "previous experience the $TcpO_2$ does not change significantly within this period unless the signs or symptoms have suddenly changed." The addition of the O_2 supplementation test identified 7 patients with an initial $TcpO_2$ of less than 10 mmHg who were predicted to heal after administration of O_2. Clinical assessment at time of surgery correctly identified these sites as having the potential to heal. Based on this they conclude that an increase in $TcpO_2$ of 10 mmHg or more is the most

sensitive predictor of healing being superior to absolute $TcpO_2$, clinical judgement, segmental blood pressure and cutaneous skin temperature.

Wagner (1988) compared $TcpO_2$ with thermometry, flourescein angiography and Doppler ABI in 102 amputations at the AK and BK levels, 10 of which failed to heal. The lowest $TcpO_2$ level at which healing occurred was 5 mmHg. Using a receiver operator curve, a $TcpO_2$ of 16 mmHg was proposed as a selection level. Based on this value the test had a 94 % positive predictive value and a 70 % negative predictive value for BKA's. Receiver operator curves were plotted for the other investigations and optimal selection levels determined. $TcpO_2$ was found to be superior to the other investigations and better than clinical judgement (Wagner, W. H. *et al.*, 1988).

Wyss, C. R. *et al.*, (1988) report a retrospective study in which they measured $TcpO_2$ and ankle systolic blood pressure in a large cohort of 162 patients who underwent 206 amputations to 181 limbs. While they had healing of four amputations with a $TcpO_2$ of 0 mmHg they suggest that a $TcpO_2$ of 20 mmHg clearly indicates severe ischaemia. They approach the issue of the search for a single investigation with a definitive cutoff value in a different way, suggesting that the value obtained should be viewed as an additional risk factor. This additional risk factor should be considered when reviewing the proposed amputation site, taking into account other factors such as motivation, mobility, nutrition, age and the patient's prospects of rehabilitation.

Falstie-Jensen (1989) followed up the previous report by their group, with a report of 74 amputations, 58 BKA and 16 AKA . Again they based the amputation level selection on skin perfusion pressure. Unlike their first study in which they found a predictive level at an absolute $TcpO_2$ of 20 mmHg, they could find no such predictive level. Primary healing occurred in 3 amputations performed at levels below 10 mmHg and 3 at levels between 10 and 20 mmHg (Christensen, K. S. and Klarke, M., 1986; Falstie-Jensen, N. *et al.*, 1989). Their data on delayed healing are made more difficult to interpret because they included local revisions in this healed group. What is surprising in this study is that even although amputation level was selected on skin perfusion pressure, 14 (20.3 %) of the amputations failed to heal. Only 3 of the failed amputation had $TcpO_2$ values below 20 mmHg level and only 4 were at levels less than 30 mmHg. They note the confounding influence of oedema on interpretation. $TcpO_2$ values measured at oedematous sites are low, and these sites may subsequently go on to heal an amputation once the oedema settles. They state that they did not look for oedema in this study. In contradistinction to their previous study they conclude, "no further information is acquired by measuring $TcpO_2$.

Padberg expanded on the work of Karanfilian which had shown 10 mmHg to be the best predictive value in a study comparing $TcpO_2$ and laser Doppler in wound healing. They again compared $TcpO_2$ and laser Doppler and the outcome of 51 amputations and pooled the results with data from 29 non healing ulcers. The definition of healing allowed for debridemant and skin grafts, and took on average 3.6 months with a range of 0.78 – 14 months. The optimal $TcpO_2$ value for prediction of wound healing derived from a receiver operator characteristic curve was found to be > 10 mmHg with 3 amputations healing at 0 mmHg. Six of their amputations failed and they had a very high AKA:BKA ratio of 3.7:1. They conclude that "$TcpO_2$ excels in the prediction of wound healing, but is less precise at low values" (Padberg, F. T., Jr. *et al.*, 1992). This is somewhat surprising as $TcpO_2$ has been held to be more sensitive to change in blood flow in its lower range (Wyss, C. R. *et al.*, 1981).

Lantsberg, L. and Goldman, M., (1991) studied laser Doppler fluxmetry and $TcpO_2$ in 24 amputations. All healed with values ranging from 2 – 50 mmHg.

10.2.4 $TcpO_2$ Index and amputation healing

Evaluation of the peripheral systemic circulation by the use a second reference point is well established, as in the Ankle brachial Doppler pressure index or ischaemic ratio. It is therefore not unexpected that the use of such an index for the evaluation of the data obtained from $TcpO_2$ measurement would follow.

Burgess noted the fall in segmental $TcpO_2$ measurements from the anterior chest wall to the AKA level, the BKA level and the foot of those patients with PVD whose BKA's healed (Burgess, E. M. *et al.*, 1982). While not presenting the index, the average $TcpO_2$ associated with healing, calculated from his data was 0.80. To estimate the lowest Index that healed, the ratio of the average value obtained at the BKA site (43 $\pm$ 4 mmHg) minus two standard deviations was divided by the average value at the chest (54 $\pm$ 4 mmHg) plus two standard deviations. This gives a possible lowest Index of a healed BKA as ~ 0.57. In this study, healing occurred at all BKA sites with an absolute $TcpO_2$ of 27 mmHg or more, with 2 amputations with values of 32 mmHg and 36 mmHg failing. Failure occurred in all amputations performed at less than 27 mmHg. Again this predictive value for failure was not reported.

In 1983 the first two studies reporting the use of a $TcpO_2$ Index in prediction of amputation wound healing were reported. Esato, K. *et al.*, (1983) reported on the use of a $TcpO_2$ Index at

the foot, in 33 patients with PVD or thromboangiitis obliterans. They noted that the absolute $TcpO_2$ of the chest decreased with age and that the Index fell with increasing Fontaine grade. The difference between Grades 2 and 4 being significant. Three patients underwent amputation at an average Foot index value of 0.08 ± 0.04. The level of amputation and outcome were not stated in the English abstract of the Japanese paper.

Mustapha, N. M. *et al.*, (1983) compared $TcpO_2$ indices in young and old normal volunteers, and patients with PVD and found a fall in $TcpO_2$ at the chest and anterior leg with age and disease. Fourteen patients underwent BKA, 9 of which healed. The average $TcpO_2$ Index of the healed amputations was 0.83 ± 0.23 with absolute $TcpO_2$ values of 51.9 ± 13.1 mmHg. For the failed amputations the $TcpO_2$ Index was 0.43 ± 0.14 with the absolute values averaging 28.4 ± 8 mmHg. The ranges are not given so it is not possible to assess overlap and cutoff values. An index of 0.8 or greater was considered likely to be associated with a successful outcome, as was an absolute value of 40 mmHg. Below 35 mmHg they suggest that amputation wound healing is unlikely. They concluded that the index did not appear to offer any further advantage over absolute $TcpO_2$ in terms of predicting amputation healing, but rather that it was of use in "eliminating central circulatory failure".

Cina, C. *et al.*, (1984) showed that use of the Index abolished the effect age. In a study of 22 amputations they report that the index added no additional information to that obtained by measurement of absolute $TcpO_2$. They question the use of the Index as the parameter on which healing should be predicted as it is their contention that local oxygenation is the major influence on wound healing. Their amputee cohort did not exhibit a marked grey area. All patients with a $TcpO_2$ of 38 mmHg or more healed, bar one patient with a $TcpO_2$ of 42 mmHg. Unfortunately no index data are presented in the paper. They state that the use of the Index may lead to errors in interpretation of wound healing potential.

Katsamouris, A. *et al.*, (1984) retrospectively reviewed the outcome of 29 amputations and compared the usefulness of absolute $TcpO_2$ and the $TcpO_2$ Index. Some of the patients may have already been reported by Cina from the same group (Cina, C. *et al.*, 1984). Primary healing was achieved in 22 of the amputations and delayed healing in 2. Of the 5 amputations that failed, the highest index was 0.56. No amputation with an absolute value of less than 32 mmHg healed, with only one failing above this level. Based on this they suggest predictive levels of 40 mmHg and 0.59. Data are provided for 20 of the amputations in which $TcpO_2$ measurements were also made on the posterior calf and sole of the foot. In this cohort, both an absolute $TcpO_2$ 37 mmHg and an index of 0.57 perfectly discriminated between healing and

failure. Sensitivity and specificity at the various cutoff levels are not presented, but the authors state that the index offers slightly better discrimination than the absolute value.

Hauser, C. J., (1987) conducted a "prospective" study of wound healing and amputation wound healing. In effect the study was a retrospective audit of the relationship of a $TcpO_2$ Index and ABI to outcome. 66 amputations were reviewed of which 21 (32 %) failed, by far the largest series of failed amputations to date. A Regional Perfusion Index (RPI) was used instead of absolute $TcpO_2$. This is derived in the same way as the $TcpO_2$ Index, being the value at the test site divided by a reference value. In this study the reference site was described as either the chest wall or the forearm. No supporting data are given to confirm that forearm values are the same as chest values. It is not stated whether the majority of reference readings were made at the chest or on the forearm.

The BKA measurements were initially made at four sites 10 cm distal to the tibial tubercle, over the medial, lateral and posterior calf and over the tibia. An additional measurement was taken 20 cm distal to the tibial tubercle over the distal gastrocnemius muscle. The 20 cm posterior site was the one that was finally chosen as being of most use. The anterior site over the tibia was noted to be frequently very low. The stabilisation time was also not stated, but the method as referenced describes a stabilisation time of 5 – 10 minutes which is very short (Hauser, C. J. and Shoemaker, W. C., 1983; Hauser, C. J. *et al.*, 1984).

No amputation with an index of less than 0.4 healed while failure was noted at indices of up to 0.44. (There are some discrepancies between the data provided in their tables and the text. In a table, the range of indices for healed amputations is given as 0.40 – 0.98 while in the discussion two AK amputations are reported to have healed at RPI's of 0.30 and 0.35). The lowest absolute $TcpO_2$ of a healed amputation was 19 mmHg with a chest $TcpO_2$ of 40mmHg, giving an index of 0.48. Two predictive levels for "pooled" wound healing of amputations and ulcers are suggested, 0.4 which would have an associated 13 % failure rate and 0.6 with a 5 % failure rate.

Malone, J. M. *et al.*, (1987) investigated the use of $TcpO_2$, the $TcpO_2$ index, $TcpCO_2$, a $TcpO_2$: $TcpCO_2$ index, ^{133}Xenon, ABI and Popliteal artery systolic pressure in 51 amputations. $TcpO_2$ and the $TcpO_2$ index were shown to be statistically reliable indicators of healing at the AKA, BKA, and TM sites, while ABI, ^{133}Xe and systolic pressures were not. This held true for diabetics and non-diabetics. Interestingly, in this patient cohort, an absolute $TcpO_2$ of 20 mmHg clearly separated those that healed from those that did not. A method similar to a receiver operator curve was used to determine the best cutoff point for each

investigation. Absolute $TcpO_2$ set at 20 mmHg gave no false positives or false negatives. The $TcpO_2$ index cutoff point of 0.44 was associated with 9 % false positives and 2.6 % false negatives. Somewhat surprisingly, Malone, whose group had previously advocated the use of intradermal ^{133}Xe to predict skin blood flow and wound healing potential concluded that ^{133}Xe skin blood flow test was not statistically reliable as a prospective test for amputation level selection.

Kram, H. B. *et al.*, (1989) studied absolute $TcpO_2$ and the $TcpO_2$ index in 40 patients requiring BKA. The amputation level was selected on clinical criteria. They used multiple sensors, and measured the anterior mid upper arm over the mid anterior portion of biceps as a reference point. The arm was chosen in preference to the chest because of its easier standardisation in terms of probe placement. No mention is made of possible variability between the chest and the arm. Seven of the amputations failed. All but one amputation with a value of more than 20 mmHg healed. However, of 12 with values from 8 – 20 mmHg, 6 (50 %) healed, giving a sensitivity of 82 %, specificity of 86 % and an overall accuracy of 83 % based on a cut-off level of 20 mmHg. Effectively a grey zone existed between 8 and 12 mmHg. The $TcpO_2$ index proved to be a better test with a clear distinction at 0.20. No amputation performed at levels with values below this, healed, and all but 1 amputation performed at levels above 0.20 healed. This improved the sensitivity to 100 %, the specificity to 86 % and the overall accuracy to 98 %. In this study anterior and posterior readings were taken at the BKA level and the lesser of the two values used to compute the index. They conclude that the "calf/brachial index improves the overall predictive accuracy by identifying patients with a low calf $TcpO_2$ as a result of causes other than local ischaemia, in whom a BKA may still be successful".

We reported the use of absolute $TcpO_2$ and the $TcpO_2$ index in 10 patients undergoing amputation for PVD. Six amputations failed. The levels obtained were compared to a ratio of the antibiotic cefoxitin in muscle from the amputated limb to the plasma concentration. No amputation with a $TcpO_2$ of less than 40 mmHg and index of 0.76 healed (Mars, M. *et al.*, 1990).

In a second study we reviewed the outcome of 270 amputations, performed over 4 years, in which amputation level was advised based on a $TcpO_2$ index of 0.55. The surgeon was aware of the $TcpO_2$ index value but could perform the amputation at a more distal level if clinically suggested at surgery. Over the 4 years the revision rate for patients undergoing $TcpO_2$ investigation dropped from 40.3 % to 8.2 %. No amputations performed at a $TcpO_2$ index level of less than 0.55 healed. The revision rate in amputations performed at $TcpO_2$ index

levels of greater than 0.55 ranged from 16.6 % to 1.6 %. The amputations were performed by several surgical trainees of differing experience (Mars, M. *et al.*, 1993).

In a comparative study of the use of $TcpO_2$ index and laser Doppler fluxmetry, we reported the outcome of 26 amputations. While amputation level selection was guided by an index value of 0.55, the level was ultimately selected at surgery. Five amputations failed, all with index values below 0.55. One amputation performed at an index value 0.54 healed (Mars, M. *et al.*, 1998).

10.2.4.1 Summary

Of the 6 papers reporting the use of the $TcpO_2$ Index in amputation wound healing prediction, 3 papers dismiss the Index as being no better than absolute $TcpO_2$ measurement. The studies on the use of the Index do not report any amputation to have healed at an absolute $TcpO_2$ of 0 mmHg.

10.2.5 Variability of test results

After Falstie-Jensen's assertion that $TcpO_2$ added nothing to amputation wound healing prediction (Falstie-Jensen, N. *et al.*, 1989), Bacharach *et al.* tried to explain the variability in the predictive values offered in the literature. The 4 factors which they identified were

(i) the type of equipment and instrumentation used,
(ii) the time allowed for equilibration,
(iii) electrode placement
(iv) electrode surface temperature.

In their discussion they address only electrode surface temperature. They based their argument on Rooke's work on the effect of sympathetic nerve activity on $TcpO_2$ measurement, in which the probe temperature was set at 42 °C and 45° C. The $TcpO_2$ values measured at the same site with the different probe temperatures averaged 30.3 mmHg and 62.1 mmHg respectively. They contend that the small difference in probe temperature in reported studies can explain much of the variation between the studies Bacharach and Rooke (Rooke, T. W., *et al.*, 1987; Bacharach, J. M. *et al.*, 1992) .

Jaszczak, P., (1988) used the blood flow cessation method to assess the effect of temperature conduction on capillary blood flow and $TcpO_2$ at different probe temperatures. At probe temperatures of 43, 44 and 45 °C he showed the temperature gradient to the capillary layer to be 2.1, 2.4 and 2.7 °C respectively. These differences resulted in increased $TcpO_2$ and increased ^{133}Xe skin blood flow with increasing probe temperature. In another study in which the probe temperatures were set at 43 and 45 °C, the difference in $TcpO_2$ between probe temperatures of 43 and 45 °C ranged from 11 – 29 mmHg (Jaszczak, P. and Poulsen, J., 1983). These differences are not unexpected, and can be predicted from the Lubbers and Grossman model of capillary loop blood flow and the effect of heating on the oxygen haemoglobin dissociation curve (Chapter 2).

In the literature, 4 papers give no information on probe temperature or do not cite a reference giving the heating protocol followed. In 3 papers the heating protocol involved heating the probe to 45 °C for 10 minutes followed by reducing the temperature to 44 °C for 10 minutes or until stable. 44 °C was the fixed probe temperature in 9 papers and 45 °C in the remaining 22 papers (Tables 10.1, and 10.2).

Table 10.1. Probe temperature, equilibration time, and make of oximeter use in studies in which the probe temperature was 44 °C.

Author	Probe Temperature (°C)	Equilibration Time (min)	Make
Matsen	45-44	20	Not stated
Burgess	45-44	20	Radiometer TCM 1
Dowd	44	20	Radiometer TCM 1
Ratliff	44	20	Kontron
McCollum	45-44	stable	Radiometer TCM2
Dowd	44	Not stated	Radiometer
Hauser	44	5 - 10	Novametrix and Kontron
Malone	44	15 - 20	Novametrix 800
Bongard	44	20	Kontron
Wyss	44	20	Radiometer TCM1
Kram	44	15	Kontron
Johnson	44	15	Kontron 632

(Matsen, F. A. 3d *et al.*, 1980; Burgess, E. M. *et al.*, 1982; Dowd, G. S. *et al.*, 1983; Ratliff, D. A. *et al.*, 1984; McCollum, P. T. *et al.*, 1986; Hauser, C. J., 1987; Malone, J. M. *et al.*, 1987; Dowd, G. S., 1987; Bongard, O. and Krahenbuhl, B., 1988; Wyss, C. R. *et al.*, 1988; Kram, H. B. *et al.*, 1989; Johnson, W. C. *et al.*, 1997)

Table 10.2. Probe temperature, equilibration time, and make of oximeter use in studies in which the probe temperature was 45 °C.

Author	Probe Temperature (°C)	Equilibration Time (min)	Make
Franzeck	45	20	Hellige transoxode
White	45	15	Novametrix Tcomette
Mustapha	45	35	Radiometer Tcm1
Benscoter	45	10,15,20	Novametrix TcO2M 816
Cina	45	stable + 5 -10	Kontron
Ito	45	15 - 20	Hellige
Katsamouris	45	stable + 5 -10	Kontron
Harward	45	stable	Litton
Christensen	45	20	Radiometer TCM1
Karanfillian	45	20	Litton
Fairs	45	15	Kontron
Oh	45	10 - 15	Kontron
Oishi	45	20	Litton
Wagner	45		Novametrix 808
Falstie-Jensen	45	20	Radiometer TCM2
Mars	45	20	Hellige
Lantsberg	45		Medictachnique
Bacharach	45	20	Novametrix 811
Padberg)	45	stable	Litton
Pinzur	45	10	Kontron 632
Pinzur	45	10	Kontron 632
Padberg	45	stable	Litton

(Franzeck, U. K. *et al.*, 1982; White, R. A. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Cina, C. *et al.*, 1984; Ito, K. *et al.*, 1984; Benscoter, J. L. *et al.*, 1984; Katsamouris, A. *et al.*, 1984; Harward, T. R. *et al.*, 1985; Karanfilian, R. G. *et al.*, 1986; Christensen, K. S. and Klarke, M., 1986; Fairs, S. L. *et al.*, 1987; Oh, P. I. *et al.*, 1987; Oishi, C. S. *et al.*, 1988; Wagner, W. H. *et al.*, 1988; Falstie-Jensen, N. *et al.*, 1989; Mars, M. *et al.*, 1990; Lantsberg, L. and Goldman, M., 1991; Padberg, F. T., Jr. *et al.*, 1992; Pinzur, M. S. *et al.*, 1992; Bacharach, J. M. *et al.*, 1992; Pinzur, M. S. *et al.*, 1993; Padberg, F. T. *et al.*, 1996)

For those studies in which probe temperature was 44 °C, equilibration time varied from 5 to 10 min in Hauser's study (Hauser, C. J., 1987), to the more accepted 20 minutes. McCollum, P. T. *et al.*, (1986) merely reported the reading as having been taken when the value was stable. At 45 °C, equilibration times ranged from 10 to 35 minutes.

While slightly lower values may be obtained at 44 °C, the equilibration time probably has as much, if not more influence on the $TcpO_2$ value. As has been shown in (Chapter 3) there is

variability between readings at the same site at 10, 15 and 20 minutes. Furthermore at ischaemic sites the response time of the oximeters is slower, requiring longer to reach stability. A reading taken early will thus be lower than one taken when true steady state has been reached. The index does not negate this problem, but rather accentuates it. The reading at the "normal" reference site rises to steady state faster than the measurement at the ischaemic site, thereby giving a lower index value than would be achieved if both reached steady state simultaneously.

10.2.5.1 Site of measurement

Where are TcpO2 measurements made? Most papers refer to standard amputation levels and quote $TcpO_2$ values with respect to AKA, BKA and TM sites. It is well documented that $TcpO_2$ values fall progressively the more distally the measurement is made in the dysvascular limb (Franzeck, U. K. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Dowd, G. S. *et al.*, 1983; Marshall, T. A. *et al.*, 1984). It is also clear that the $TcpO_2$ measured at any level on a limb is not constant around the circumference of the limb but rather there are lines of oxygen pressure, or isobars that ran obliquely from proximal ventral to distal dorsal and from medial to lateral in the leg in most patients. The concept of isobaric lines demarcating healing levels was proposed by Ito. In the dysvascular patient requiring amputation the longitudinal distance between the 0 mmHg isobar and the 30 mmHg isobar was usually several centimetres, but 10 cm at the most (Ito, K. *et al.*, 1984). (This highlights the importance of placing the probe as near the proposed flap margin as possible.) This pattern is very similar to the pattern of temperature distribution seen in thermograms (Spence, V. A. *et al.*, 1984). Several authors also note the low $TcpO_2$ values recorded over pre-tibial skin (Hauser, C. J., 1987). The implication in the majority of papers is that $TcpO_2$ has been measured at a proposed flap margin, but this may not always be the case and may explain some of the variability in the results obtained.

Smith has noted the paradoxical reduction in $TcpO_2$ measured over the plantar surface of the great toe and over the plantar surface of the sole over the head of the 2nd metatarsal, when assessing vascular reserve in diabetic patients. This reduction in $TcpO_2$ at these sites occurred when probe temperature was increased from 37 °C to 44 °C, and was found both in diabetic and non diabetic control subjects (Smith, D. G. *et al.*, 1995).

The different probe placements reported in studies using the $TcpO_2$ Index for wound healing are shown in table 10.3.

Table 10.3. Probe placement sites in studies reporting the use of the $TcpO_2$ Index. MC = mid clavicular line, SC = sub clavicular, MAxL = mid axillary line.

Author	Reference Point	Above Knee	Below Knee	Foot
Mustapha	MC		10 cm below knee joint line anteriorly	
Katsamouris	SC	Anterior thigh	Anterior aspect of leg at level of amputation also posterior flap	Dorsum and sole
Hauser	Chest or forearm	10 and 20 cm above knee medial and lateral	10 cm distal to tibial tubercle, medial, anterior, lateral and 20 cm posterior. Later in study only 10 cm medial and 20 cm posterior used	Not stated
Malone	SC in MAxL	Anywhere between a hands breadth above the patella and a hands breadth below the groin crease.	10 cm below the tibial tubercle, medial and lateral	Midway between ankle crease and base of toes
Kram	Biceps, anteriorly		6 – 8 inches below knee joint line anterolateral calf over tibialis anterior and posteromedial calf 2 – 4 inches posteromedial to tibia	

Similarly, although the chest is usually given as the central reference point, there are different points on the chest wall at which $TcpO_2$ has been measured, and in two of the papers reporting on the $TcpO_2$ index, the reference point used was on the biceps and the forearm. Hauser used either the chest or the forearm and did not distinguish between the sites in the results presented (Hauser, C. J., 1987). It is interesting to note that the lowest index reported to be associated with healing was in Kram's study where the reference point was the anterior mid biceps (Kram, H. B. *et al.*, 1989). In normal lower limbs it has been shown that the $TcpO_2$ index usually exceeds 1.0 in both young and old controls and the same may occur in the upper limb. If so this would result in a lower Index than that obtained on the chest (Mustapha, N. M. *et al.*, 1983).

The various reference probe placements, heating protocols and equilibration times described in the literature are shown in table 10.4. Several of the papers cited did not report $TcpO_2$ Index but described the reference point used.

Table 10.4. The reference point measurement site, probe temperature, equilibration time and proposed amputation prediction value in studies reporting the use of a reference point.

Author	Reference Point	Probe Temp. (°C)	Equilibration Time (min)	Predictive Value
Matsen	Left 4th intercostal space anteriorly	45-44	20	
Burgess	4th intercostal space at anterior axillary line	45-44	20	
Franzeck	Right subclavicular region	45	20	
Mustapha	5 cm below the midclavicular line Right or Left	45	35	0.8
Benscoter	4th intercostal space in midclavicular line	45	10,15,20	
Cina	Chest	45	stable + 5 - 10	
Katsamouris	Subclavicular area of the chest	45	stable + 5 - 10	0.59
Rhodes	Infraclavicular Right			
Rhodes	Infraclavicular Right		15 - 20	
Hauser	Chest or forearm	44	5 - 10	0.4 or 0.6
Malone	5-7cm infraclavicular in midaxillary line	44	15 - 20m	0.44
Wagner	5cm below midclavicular line	45		
Wyss	Chest	44	20m	
Kram	Biceps, midway between axilla and antecubital fossa, anteriorly	44	15	0.2
Johnson	Medial part of upper part of arm	44	15	

Of the 5 papers proposing an Index value for use in predicting amputation wound healing two were based on $TcpO_2$ values obtained with a probe temperature of 45 °C, both appear to have had adequate stabilisation periods and both use the anterior chest wall as the reference point. The proposed $TcpO_2$ Indices are relatively high, 0.59 and 0.8. The 3 papers proposing Index values below 0.5, all used a heating protocol of 44 °C and the equilibration time was relatively short in two of the studies. The lowest two $TcpO_2$ Indices proposed for prediction of amputation wound healing were both derived from studies which used the biceps or forearm as the reference point.

10.2.5.2 Oedema

10.2.5.2.1 What is the effect of oedema on $TcpO_2$?

The metabolically active cells in the skin consume oxygen, setting up an oxygen diffusion gradient from the capillary to the mitochondrion. The $TcpO_2$ electrode adds an additional demand by also consuming oxygen. Any factor that impairs diffusion will then influence the availability of O_2 to both the cell and the probe. Diffusion rate through a cell membrane is generally described as

$$\text{Diffusion rate} \propto \frac{\text{Concentration difference x Cross-sectional area x Temperature}}{\text{Molecular weight x Distance}}$$

In the skin of an ischaemic, oedematous limb, the total oxygen delivery is reduced due to decreased perfusion and a reduction in the number of capillary loops per unit area. This effectively reduces the concentration difference. Likewise, the total cross-sectional area over which diffusion can occur is reduced by the decrease in capillary loops thereby lowering the total oxygen diffusion per unit time. Oedema serves to increase the distance that the O_2 molecules will have to travel to reach the mitochondrion. This further diminishes O_2 flux.

10.2.5.2.2 Is there evidence in the $TcpO_2$ literature to support this?

Dooley investigated the effect of breathing air, 100 % oxygen and hyperbaric oxygen therapy at 2.36 atmospheres on $TcpO_2$ measured in oedematous wounds. Wounds were categorised into non oedematous, moderately and markedly oedematous. $TcpO_2$ values around markedly oedematous wounds, when breathing air, were significantly lower than in the other wounds. Administration of 100 % oxygen or hyperbaric oxygen significantly increased the $TcpO_2$ values suggesting that peri-wound oedema is an O_2 diffusion barrier under normal conditions (Dooley, J. *et al.*, 1996).

An opposing view was presented by Nemeth who felt that oedema may not constitute a barrier to oxygen diffusion through the skin and does not account for the low $TcpO_2$ values in the ulcerated leg. This conclusion was reached after using a pneumatic compression device to reduce oedema in 8 patients with leg ulcers. $TcpO_2$ was not significantly affected by oedema removal (Nemeth, A. J. *et al.*, 1989).

Kolari, P. J. *et al.*, (1988) studied 10 patients with post traumatic leg ulcers and 9 control subjects asymptomatic of PVD. All subjects received intermittent pneumatic compression at 50 mmHg for 60 minutes. $TcpO_2$, skin temperature and oedema were measured before and after treatment. In 9 of the 10 patients, the $TcpO_2$ increased from 26.2 $\pm$ 7.0 mmHg to 42.7 $\pm$ 6.4 mmHg. The increase in $TcpO_2$ correlated with the reduction in oedema and an increase in skin temperature.

Rithalia, S. V. *et al.*, (1988) also studied the effects of intermittent pneumatic compression of 50 mmHg on 14 healthy controls and 14 elderly people. With the probe temperature set at 37 °C they showed reactive hyperaemia and a non significant increase in $TcpO_2$ in some subjects after treatment. This led them to conclude that the symptomatic improvement noted after intermittent positive pressure treatment "was more likely due to enhanced removal of metabolites than to improvement in leg oxygenation."

Carnochan used an intradermal model in which histamine, or saline or prostaglandin E_2 was injected into forearm skin. While $TcpO_2$ values were not affected at the injection sites, the rate of recovery of $TcpO_2$ following forearm circulation occlusion was delayed when compared to undisturbed skin. They concluded that the increased diffusional distances in mediator-induced oedema are unimportant for the respiration of otherwise normal tissues, but that oedema may contribute appreciably to the hypoxia of inflamed tissue infiltrated with metabolically active cells by reducing oxygen flux (Carnochan, F. M. *et al.*, 1990).

In the microangiopathy associated with chronic venous insufficiency, skin capillary loops are reduced in number and those remaining become elongated, dilated and coiled, and are surrounded by an enlarged pericapillary space. The skin lymphatics become occluded while at the same time there is an increase in capillary permeability leading to local oedema as demonstrated by increased transcapillary diffusion of sodium flourescein (Bollinger, A. *et al.*, 1995). In the ischaemic limb, the combination of reduced oxygen delivery secondary to reduced perfusion and capillary number with associated oedema is considered by Bollinger to be the cause of the associated reduction in $TcpO_2$ (Bollinger, A. *et al.*, 1996).

In a comprehensive study of the events leading to ulceration in patients with deep vein thrombosis Partsch again highlighted oedema formation, reduced lymphatic drainage, local hypoxia due to a reduction in the number of capillaries and the "impermeable" capillary cuffs as factors leading to ulceration and associated decreased $TcpO_2$ readings (Partsch, H., 1988).

The role of oedema is seldom mentioned in the $TcpO_2$ amputation literature except when its presence is used to attempt to explain an apparently anomalous result. The presence of oedema as a contra-indication for the use of $TcpO_2$ wound healing prediction has not been stated.

Franzeck, U. K. *et al.*, (1982) noted that one patient in their study who healed an amputation with a $TcpO_2$ of less than 10 mmHg had presented with "...severe oedema of the entire leg..." which they assumed influenced the $TcpO_2$ measurement.

A case report in Benscoter's paper describes a patient who had undergone what appeared to be a successful femoral to anterior tibial artery bypass. Success was documented by relief of ischaemic pain, increased $TcpO_2$, PVR and ABI. A month after discharge the foot was oedematous, with a black toe and markedly reduced $TcpO_2$ values, while the PVR and ABI were not decreased. They suggest that oedema was the cause of the reduction in $TcpO_2$ in their patient and that oedema "or other confounding factors" may explain the healing at low $TcpO_2$ values obtained in Franzeck's study (Benscoter, J. L. *et al.*, 1984).

Cina noted that marked oedema was a limitation of $TcpO_2$ measurement and that it may in part explain their finding of 4 patients with low $TcpO_2$ values inconsistent with their clinical status of ischaemia (Cina, C. *et al.*, 1984). Rhodes described a delay in improvement in $TcpO_2$ following distal revascularisation which he attributed to either a form of revascularisation injury or operative oedema, and suggested that amputation after bypass should be delayed until the $TcpO_2$ had risen to more than 30 mmHg. He also reported that oedema, cellulitis and hyperkeratosis can "limit the accuracy" of $TcpO_2$, as in the case of a patient who healed a toe amputation despite $TcpO_2$ values of 0 - 25 mmHg adjacent his amputation site (Rhodes, G. R., 1985).

Malone and Padberg give oedema as a local factor influencing $TcpO_2$ (Malone, J. M. *et al.*, 1987; Padberg, F. T., Jr. *et al.*, 1992), citing Byrne and Nemeth (Byrne, P. *et al.*, 1984; Nemeth, A. J. *et al.*, 1989). Oedema was not however mentioned as a factor affecting outcome in their studies.

Post femoro-popliteal bypass oedema is given as a reason for "failure" of $TcpO_2$ tests in 3 patients in Falstie-Jensen's study (Falstie-Jensen, N. *et al.*, 1989). It is not clear as to what is meant by failure other than that the patients were excluded from the study. In the discussion it is stated that in these 3 cases extremely low $TcpO_2$ values were observed and that healing subsequently took place in 2 of the 3 patients. This was probably an example of what Rhodes'

described as either a revascularisation syndrome or post-operative oedema (Rhodes, G. R., 1985). They go on to say that oedema was not specifically looked for in their series. It would appear then that these 3 patients had post bypass $TcpO_2$ values that the authors did not consider consistent with their clinical status or other investigations. On the basis of this they were declared to have had a failed test, when in fact the values were probably a true reflection of the $TcpO_2$ at that time.

Although not referring to oedema, Pinzur showed the benefit of decompressing deep abscesses of the foot in 8 diabetic patients, with resultant increases in pedal $TcpO_2$. Deep infection with accompanying increased muscle compartmental pressure results in increased venous pressure. This reduces the arterio-venous gradient and local perfusion. The raised venous pressure impairs fluid return to the venular end of the capillary and results in interstitial oedema which may be exacerbated by lymphatic blockage (Pinzur, M. S. *et al.*, 1993). Post traumatic raised compartment pressures in the foot are well documented (Mars, M., and Hadley, G. P., 1998).

10.2.5.2.3 Summary

The issue of oedema and its effect on $TcpO_2$ are raised under two circumstances in the $TcpO_2$ amputation literature. Oedema is cited as a possible local factor which may affect the value obtained and influence the accuracy of the test, or it is given a reason for what appears to the author to be an anomalous result. The anomaly being healing at a low $TcpO_2$ value. We believe that oedema affects the $TcpO_2$ value and have referred patients with oedema at a proposed amputation site back to the attending surgeon, with the warning that the test results cannot be interpreted with confidence in the presence of oedema. Correction of oedema through local therapy or by treatment of a central cause such as congestive cardiac failure has always been associated with an increase in peripheral $TcpO_2$.

10.2.5.3 Timing of $TcpO_2$ investigation

For how long is a $TcpO_2$ value valid?

As has been discussed, the $TcpO_2$ value is dependent on central and local factors, any of which may change oxygenation of skin cells. Clearly it will fluctuate slightly on a daily basis as central factors such as cardiac output and respiration change. In the absence of a new occlusion, congestive cardiac failure, pulmonary pathology, anaemia, polycythaemia and

oedema, are probably the conditions that will cause the most fluctuation in $TcpO_2$ in our patient population. The test can take several hours to perform with skin mapping or multiple sites including a reference point This places stress on the investigator to complete each measurement as quickly as possible while retaining clinical accuracy. If the $TcpO_2$ value is to be taken into account when planning amputation the information should be available during the pre-operative workup period. In the majority of studies $TcpO_2$ has been an additional non-invasive test which has been added to the battery of test being performed.

It is interesting to note that the timing of the pre-operative $TcpO_2$ investigation with respect to surgery is very seldom given.

Ratliff, D. A. *et al.*, (1984) performed the tests within 24 hours of surgery as did Dowd, G. S., (1987) in his retrospective study. For his prospective study in which amputation level selection was based on the $TcpO_2$ value, the timing of the test is not stated. Pinzur too, measured $TcpO_2$ within 24 hours of surgery in his semi-emergent group of 8 diabetic patients with deep foot abscesses and signs of systemic sepsis (Pinzur, M. S. *et al.*, 1993).

The Seattle group measured $TcpO_2$ "within the two weeks prior to operation" (Burgess, E. M. *et al.*, 1982; Wyss, C. R. *et al.*, 1988). At the extreme, Oishi, C. S. *et al.*, (1988) entered patients into their study if they had had their non-invasive vascular tests within 6 months of the amputation. They support this practice by stating that in their experience$TcpO_2$ values do not change significantly unless the signs or symptoms suddenly change.

No other information on the interval between test and amputation is available.

10.2.5.4 The definition of healing

The Oxford English Dictionary gives the following definition: "*heal*"; 1. (of sore or wounded part) to form healthy flesh again, to unite after being cut or broken; 2. to cause to do this; 3. to cure.

Results other than merely formed healthy flesh are desirable in a successfully healed amputation stump. These include that the stump be pain free, mobile and of sufficient quality to allow prosthetic fitting and subsequent rehabilitation.

The use of investigative tests to predict wound healing focus on muscle and skin healing and the "reconstitution of healthy flesh". Franzeck was the first to present a detailed explanation

of healing for evaluation of wound outcome using $TcpO_2$ which we have modified slightly by expanding the last criterion in category B. In category B, Franzeck had , "no need for additional amputation", which we modified to "no need for additional *surgery or* amputation." (Table 10.5).

Table 10.5. Classification of wound healing after amputation. (After Franzeck) (Harward, T. R. *et al.*, 1985))

Successful Amputation (A)	Per primum healing in 4 weeks Granulation complete No need for additional amputation
Delayed healing (B)	Delayed healing of more than 4 weeks Granulation not yet complete Eventual healing in more than 4 weeks No need for additional surgery or amputation
Failure (C)	Necrosis / gangrene No granulation Additional amputation

This change although small has major implications in interpreting and comparing the published data. As will be described, some authors have strict criteria regarding healing while others allow amputations which require local debridement, drainage, skin graft and even re-amputation at a slightly more proximal level to be included in their "healed" group.

The definitions of healing used can be broadly grouped into four categories. Healing has been defined either in terms of primary and delayed healing, or as definitive healing, with or without additional local surgery. The time allowed for primary healing to occur varied from 4 – 6 weeks. In 11 studies, local procedures were performed to accomplish delayed or definitive healing, while in 3 studies the performance of any such procedure classified the wound as having failed to heal. Local procedures included debridement, drainage, local wound care, secondary suture, and in three papers, local revision. In 14 studies no mention was made of the use of local procedures to facilitate healing. Four papers report only primary healing with no wound failure occurring, and in 2 studies no definition of wound healing is given (Table 10.6).

Table 10.6. Definitions of wound healing. The n = the number of papers using the definition, and the headings describe the criteria used in the definition.

Group		**Definition of Healing**			**Additional Surgery**		**Definition of Failure**
	n =	Primary Healing	Delayed Healing	Definitive Healing	Local Procedure	Local Revision	
A	3	Yes	Yes		Yes	Yes	Proximal revision
B	4	Yes	Yes		Yes	Not stated	Revision
C	4			Yes	Yes	Not stated	Revision
D	8	Yes	Yes		Not stated	Not stated	Revision
E	6			Yes	Not stated	Not stated	Revision
F	1	Yes			No	No	Further operative procedure
G	2			Yes	No	No	Further operative procedure
H	4	Yes					All healed
I	2	No definition of healing given					

References: Group A (Karanfilian, R. G. *et al.*, 1986; Christensen, K. S. and Klarke, M., 1986; Falstie-Jensen, N. *et al.*, 1989) Group B (Ratliff, D. A. *et al.*, 1984; Rhodes, G. R. and Skudder, P., Jr., 1986; Wagner, W. H. *et al.*, 1988; Bacharach, J. M. *et al.*, 1992) Group C (Wyss, C. R. *et al.*, 1988; Kram, H. B. *et al.*, 1989; Padberg, F. T., Jr. *et al.*, 1992; Padberg, F. T. *et al.*, 1996) Group D (Franzeck, U. K. *et al.*, 1982; Dowd, G. S. *et al.*, 1983; Cina, C. *et al.*, 1984; Ito, K. *et al.*, 1984; Benscoter, J. L. *et al.*, 1984; Katsamouris, A. *et al.*, 1984; Harward, T. R. *et al.*, 1985; Oishi, C. S. *et al.*, 1988) Group E (Burgess, E. M. *et al.*, 1982; Mustapha, N. M. *et al.*, 1983; Rhodes, G. R., 1985; Hauser, C. J., 1987; Campbell, W. B. and Morris, P. J., 1987; Pinzur, M. S. *et al.*, 1992) Group F (Johnson, W. C. *et al.*, 1997) Group G (Malone, J. M. *et al.*, 1987; Dowd, G. S., 1987) Group H (Matsen, F. A. 3d *et al.*, 1980; Rhodes, G. R. and King, T. A., 1986; Fairs, S. L. *et al.*, 1987; Lantsberg, L. and Goldman, M., 1991) Group I (White, R. A. *et al.*, 1982; McCollum, P. T. *et al.*, 1986).

Not unexpectedly, the two studies which defined failure as any surgical intervention and which provided proposed $TcpO_2$ predictive levels had clearly defined levels above and below which healing occurred, 20 mmHg and 35 mmHg. The effect that the different definitions of healing may have on the overall interpretation of the studies is difficult to quantify. It adds another variable to an equation already complicated by problems of probe placement, probe temperature, local oedema and timing of assessment.

10.2.5.5 Amputation technique

Wound healing may be influenced by many factors as has already been stated. There are several events during the intra and perioperative phases that may alter outcome. Surgical technique such as tissue handling, myocutaneous flap shape, myodesis, myoplasty, suture tension, the use of skin sutures, post operative drainage, postoperative bandaging, peri-operative antibiotics, the use of post operative oxygen therapy and postoperative nutritional supplementation may all affect outcome. Only 9 papers describe the amputation technique used (Table 10.7).

Table 10.7. Papers reporting the amputation technique used at the different levels.

Author	AKA Type	BKA Type	Foot
Burgess		Burgess	
Katsamouris	Circular incision or slight fishmouth	Burgess	McKittrick for TM
Ratliff		Burgess	
Christensen	Equal anterior and posterior flaps	Burgess and equal sagittal flaps	
Campbell		Gritti-Stokes and Through Knee	
Dowd	Equal flaps	Longer posterior flap	
Falstie-Jensen	Equal anterior and posterior	Equal sagittal flaps and long posterior flap	
Lantsberg	Equal anterior and posterior flaps	Burgess	
Johnson		Burgess and skew flap according to Ruckley	

10.2.5.6 Repeatability and reproducibility

Variability in terms of repeatability and reproducibility has not been discussed and is never quoted in the literature on amputation wound healing prediction. Its importance cannot be overlooked. The influence of such variability is greatest in longitudinal studies of, for example, the effect of drug therapy or success of a revascularisation procedure. In studies determining amputation wound healing prediction levels, the influence of variability is going

have the most effect in studies of small sample size. In large studies the effect of the variability should become apparent and may account for the "grey areas" of overlap reported.

Hauser reported that "whereas chest and limb $TcpO_2$ in normal subjects varied significantly both with position and with momentary fluctuations in cardiorespiratory status, RPI ($TcpO_2$ Index) in a given position was stable to within 1 – 2 % per hour." They noted that this was compatible with machine drift. Repeatability was assessed by re-measurement of the $TcpO_2$ Index in 12 patients within 3 to 5 days after first measurement. In 8 patients with severe PVD requiring limb salvage procedures the foot $TcpO_2$ Index was 0.25 ± 0.14 at first measurement and 0.29 ± 0.11 when repeated. In 4 patients with claudication, the initial measurement was 0.75 ± 0.3 with follow-up values of 0.69 ± 0.32. The differences were not significantly different (Hauser, C. J. *et al.*, 1984).

Wyss, C. R. *et al.*, (1984) studied a group of 28 patients with PVD of differing severity. Measurements were made at the foot, BKA, AKA and Chest sites and were repeated within 1 month of the original test. The average difference at all sites was 11 mmHg. The standard deviation is not given, so the coefficient of variation cannot be calculated. This is similar to the findings of Eickhoff, J. H. and Engelman, E., (1981) who reported Foot $TcpO_2$ measurements varying by 11 mmHg over 24 hours in 5 patients with intermittent claudication.

Olerud, J. E. *et al.*, (1987) measured $TcpO_2$ at 7 sites in 10 elderly normal subjects, on 3 occasions at 2 weekly intervals. The measurement to measurement variation of the pooled data was relatively low, 8 mmHg and the coefficient of variation 14.4 %. Although measurements were made at the chest, the variability in $TcpO_2$ Index was not mentioned.

Coleman, L. S. *et al.*, (1986) measured $TcpO_2$ daily for 3 weeks in normal controls. They found results to vary by almost 10 % from the mean for each individual. They did not interpret this as being clinically significant.

Casparay looked at reproducibility of $TcpO_2$ measured at probe temperatures of 37 °C and 44 °C on six different days over a fortnight. The patients studied had severe claudication and measurements were made at the foot. At 37 °C, coefficients of variation were high 74 ± 27 %. At 44 °C they found the coefficients of variation to still be high, averaging 42 ± 24 %. They concluded that single $TcPO_2$ measurements are of low value in patients with severe claudication (Caspary, L. *et al.*, 1993).

Rosfors, S. *et al.*, (1994) investigated $TcpO_2$ repeatability before, during and after an exercise stress test. They found resting $TcpO_2$ to be highly reproducible, while $TcpO_2$ measurements obtained during and after exercise were not. Mouren, X. *et al.*, (1996) repeated an exercise stress test, on 3 consecutive days and found the found the coefficient of variation for $TcpO_2$ 21 %.

Melillo, E. *et al.*, (1994) investigated the reliability of $TcpO_2$ over time in patients with PVD. To exclude the possible confounding effects of PVD they only analysed $TcpO_2$ data from the right infraclavicular position. The median time between repeated tests was 24 days in 34 patients. Three patients had 10 tests done over a period 2.25 years. Intra-patient coefficients of variation ranged from 11 – 16 %. The initial and final $TcpO_2$ values did not differ significantly over time. They concluded that $TcpO_2$ values at the Chest are constant over time.

Rooke, T. W. and Osmundson, P. J., (1989) measured $TcpO_2$ in 43 limbs of 23 subjects, at two sites on the Foot and on the Chest. $TcpO_2$ measurements were repeated within forty-eight hours, and foot values differed on average by 6.9 mmHg. They compared this with ankle brachial indices and concluded that in the short-term reproducibility of $TcpO_2$ between studies is comparable to that for ABI's. In a subsequent paper, Rooke describes the reproducibility of $TcpO_2$ measurements as being "very good... and thus relatively small changes in $TcpO_2$ produced by disease progression or therapeutic interventions can be detected." (Rooke, T. W., 1992).

Lukkari-Rautiarinen, E. *et al.*, (1989) measured $TcpO_2$ at the foot in 21 patients with PVD on 3 consecutive days and found the coefficient of variation to be 37 %, which is relatively high. They felt that this would explain the difficulty in determining a single predictive value for the prediction of amputation wound healing.

Stein used generalisability analysis to investigate whether $TcpO_2$ accurately and consistently measured peripheral oxygen delivery. Measurements were made at the Foot, BKA and Forearm on 3 consecutive days in a control group of 9 subjects and a study group of 15 patients with PVD. They concluded that measurements of $TcpO_2$ were dependable for patients with PVD for absolute $TcpO_2$ at the Foot and BKA sites and for the $TcpO_2$ index at the Foot. The poorer reliability of the Index at the BKA level was ascribed to the variability noted at the forearm site. They did not feel that the investigation was a dependable method of non-invasive investigation in healthy individuals (Stein, M. *et al.*, 1989).

Franzeck reported on the reproducibility of $TcpO_2$ at the BKA level in 15 control subjects. After 20 minutes of $TcpO_2$ measurement the probe was removed for 10 minutes and then reapplied to the same site and a second reading taken after a further 20 minutes. The average difference between readings was 4.7 ± 6.3 mmHg, with a range of 0 – 14 mmHg (Franzeck, U. K. *et al.*, 1982).

10.2.5.7 Summary of variability

That there have been several studies confidently reporting the worth of $TcpO_2$ to predict amputation wound healing potential, and that these studies have reported different predictive values over a wide range of values is not really surprising, considering the lack of standardisation of the investigation. What emerges from the literature is that in individual laboratories, methodological techniques tend to be relatively standard, and meaningful information can be gained from the use of $TcpO_2$ measurement. It would be convenient if studies that used probe temperatures of 44 °C resulted in lower predictive values than those which have used the probe at 45 °C. This has not always been the case, as shorter equilibration times and different sites of probe placement also affect the resultant $TcpO_2$ value.

Patient variables, especially those related to systemic oxygen delivery can be reduced by the use of the $TcpO_2$ Index. Again, predictive values proposed appear to be influenced by probe temperature, equilibration time and the reference site used. The fact that there are only 6 papers suggesting the use of the Index may be due to healing at low values and even zero, which would make the index meaningless, and hence not worth reporting. Oedema is an important variable that may also account for some of the reports of healing at low $TcpO_2$ values.

The literature on the repeatability and reproducibility of $TcpO_2$ and the $TcpO_2$ Index in both normal controls and in patients with different degrees of PVD is contradictory. Again one of the problems is the relatively small size of the studies. Probably the most sophisticated study in terms of statistical methodology is that of Stein *et al.* which used generalisability modelling and found $TcpO_2$ and the $TcpO_2$ Index to be dependable in patients with PVD, but not in normal controls.

The day to day variability noted in the various studies may account for the "grey areas" noted in studies seeking a predictive value for amputation wound healing potential. As part of the

daily variation in $TcpO_2$ is due to changes in systemic oxygen delivery, it might be expected that the $TcpO_2$ Index would be a better test than absolute $TcpO_2$ to predict amputation wound healing based on a one off assessment.

Based on review of the available literature at the time, we chose to heat the $TcpO_2$ thermistor to 45 °C. We took stabilisation time to be 20 minutes. This was based on a series of pilot studies in normal volunteers and patients with peripheral vascular disease, described in chapter 3.

Chapter 11

Clinical Studies To Determine $TcpO_2$ Criteria For Amputation Level Selection

11.1 Introduction

In this chapter, a retrospective review of amputation outcome in a defined cohort of patients will be compared with prospectively gathered $TcpO_2$ data. From this, criteria for clinical use of $TcpO_2$ in amputation level selection will be developed.

At the outset of our investigation of the use of $TcpO_2$ for amputation level selection, the predictive level proposed by Burgess, White and Dowd ranged from 20 - 40 mmHg (White, R. A. *et al.*, 1982; Burgess, E. M. *et al.*, 1982; Dowd, G. S. *et al.*, 1983) which subsequently fell, with healing being reported at 0 mmHg (Harward, T. R. *et al.*, 1985). As we gathered data on amputations it became apparent that while most amputations performed at levels with an absolute $TcpO_2$ of more than 40 mmHg healed, there appeared to be a grey area between 20 and 40 mmHg in which absolute $TcpO_2$ was not predictive of outcome. The concept of using an index similar to that of the ankle brachial pressure index was attractive as it would "normalise" the blood flow. On the other hand, it could be argued that there should exist a level of oxygenation below which healing could not occur (Cina, C. *et al.*, 1984).

When investigating the use of $TcpO_2$ as an indicator of the success of revascularisation procedures we had noted that measurements made in the immediate post-operative period were sometimes lower than pre-operative values, a finding subsequently published by Rhodes, G. R. and King, T. A., (1986). We also noted that in some patients the postoperative $TcpO_2$ rose slowly over several days after surgery. Our interpretation of this at the time was linked to the observation of mild postoperative oedema. Rhodes has suggested that it is the result of a reperfusion injury. During early evaluation of $TcpO_2$ measurement in an ICU setting, pedal $TcpO_2$ was noted to improve in oedematous patients undergoing diuresis. It was also noted that $TcpO_2$ measurements made on oedematous limbs of patients with vascular disease increased as the oedema settled. For these reasons we felt that interpretation of $TcpO_2$ measurements made within 2 weeks of surgery or on oedematous limbs should be viewed with caution.

11.2 Preliminary study on the use of $TcpO_2$ to predict amputation wound healing, in which the surgeon was not told the $TcpO_2$ value

In 1987 a prospective study was commenced to evaluate the use of $TcpO_2$ in amputation wound healing. The details of this study have been published as part of "The potential benefit of pre-operative assessment of amputation wound healing potential in peripheral vascular disease" (Mars, M. *et al.*, 1993) see appendix d.

11.2.1 Method

Patients with peripheral vascular disease who were considered candidates for an amputation were referred to the non-invasive vascular laboratory for pre-operative measurement of $TcpO_2$ at the proposed amputation site and the adjacent sites. In addition chest measurements were made. All measurements were made as described in chapter 3.

221 patients underwent $TcpO_2$ measurement, and the values were recorded on the $TcpO_2$ summary form and the surgeon was not informed of the $TcpO_2$ value. Amputation level selection was based on standard clinical criteria. The patients were followed until either wound healing occurred or further surgery was required. 193 patients underwent an amputation, 17 died and 24 were referred back to their original hospital before healing was complete and were this lost to the study.

The outcome of 152 amputations were available for review. These were a then checked against the following inclusion criteria :

i) that the patient undergo a definitive amputation and not a Guillotine amputation
ii) that the patient had not undergone a revascularisation procedure in the affected limb within 2 weeks of the pre-amputation $TcpO_2$ measurement
iii) that the amputation was not a revision at the same level of a previous definitive or Guillotine amputation stump
iv) that the limb was not oedematous at the site of measurement.

With the exit criterion being that the patient survived the amputation and either left the hospital with a healed stump or underwent revision surgery or a local surgical procedure.

11.2.2 Results

The outcome of 122 amputations performed in 1987 and 1988 that met these criteria were studied. Of these, no amputation with a $TcpO_2$ of less than 27 mmHg healed. Between 27 and 40 mmHg, absolute $TcpO_2$ was an unreliable indicator of outcome with 4 wounds failing and 11 healing. The wounds that failed had absolute $TcpO_2$ values of 30, 32, 33 and 39 mmHg.

The $TcpO_2$ index was a better prognosticator. No amputation healed with a $TcpO_2$ index of less than 0.55. Of the 15 amputations performed at sites with absolute values between 25 and 40 mmHg, the 11 that healed had indices from 0.56 to 1.25. Three of the 4 that failed had values of less than 0.55 and only 1 had an index value predictive of healing. This one false positive test had a $TcpO_2$ index of 0.76 and an absolute $TcpO_2$ of 39 mmHg and may have failed for reasons other than inadequate skin perfusion.

11.3 Study to evaluate the potential use of $TcpO_2$ Index to predict amputation wound healing

Based on the above data, a $TcpO_2$ index of value of 0.55 was then proposed as being predictive of amputation wound healing. In 1989 and 1990, surgeons were advised of the most distal level at which an amputation would be expected to heal using this value. 148 patients met the criteria for study in 1989 and 1990. The surgeon chose to perform the amputation at a more distal site with an index value of less than 0.55 in 21 of these patients. All of these amputations performed at more distal sites failed to heal. In the range 27 to 40 mmHg, 4 amputations failed, all at $TcpO_2$ index of less than 0.55 and 17 healed, all with an index greater than 0.55.

While this gave a very precise discriminatory level at an index of 0.55 one must question whether the exclusion criteria were too strict, resulting in the predictive level being set too high, as in Dowd's studies. If the criteria are relaxed to include

i) patients undergoing Guillotine amputations
ii) amputations performed on stumps of previous amputations and Guillotine stumps
iii) amputations based on $TcpO_2$ measurements made more than 1 week after revascularisation or a Guillotine amputation,

an additional 190 amputations are available for review giving a total sample of 338 amputations. The inclusion of these additional amputations reveals 7 amputations that healed at indices of less than 0.55, with the lowest index at which healing occurred being 0.49. Three of these 7 amputations were in patients in whom measurements made in the second week after a Guillotine amputation, 3 were patients who underwent a Guillotine amputation and subsequently healed a definitive amputation without another $TcpO_2$ measurement and 1 patient who had $TcpO_2$ measurements made 8 days after an Aorto-bifemoral bypass.

The sensitivity, specificity, positive and negative predictive values and accuracy of absolute $TcpO_2$ and the $TcpO_2$ index are over a range of values are given in tables 11.1 and 11.2.

Table 11.1. The sensitivity, specificity, predictive values and accuracy of the $TcpO_2$ index set at values ranging from 0 to 1.

Index	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0.00	100.00	22.48	67.64	100.00	70.41
0.05	100.00	27.91	69.21	100.00	72.49
0.10	100.00	32.56	70.61	100.00	74.26
0.15	100.00	37.98	72.32	100.00	76.33
0.20	100.00	42.64	73.85	100.00	78.11
0.25	100.00	46.51	75.18	100.00	79.59
0.30	100.00	48.84	76.00	100.00	80.47
0.35	100.00	55.04	78.28	100.00	82.84
0.40	100.00	60.47	80.38	100.00	84.91
0.45	100.00	65.12	82.28	100.00	86.69
0.50	99.04	70.54	84.49	97.85	88.17
0.55	96.65	79.84	88.60	93.64	90.24
0.60	89.00	83.72	89.86	82.44	86.98
0.65	82.78	87.60	91.53	75.84	84.62
0.70	72.73	88.37	91.02	66.67	78.70
0.75	61.72	88.37	89.58	58.76	71.89
0.80	52.63	89.92	89.43	53.95	66.86
0.85	43.06	93.02	90.91	50.21	62.13
0.90	37.80	94.57	91.86	48.41	59.47
0.95	29.67	95.35	91.18	45.56	54.73
1.00	21.05	95.35	88.00	42.71	49.41

As can be seen from these tables, as the predictive value increases the sensitivity falls and the specificity increases. What then constitutes the optimal predictive value? The first step in setting the predictive value would be to choose the value that has the best accuracy, where accuracy is defined as the number of true positive and true negative tests expressed as a

percentage of the total number of tests. In this case the best accuracy of 90 % is achieved at an index value set at 0.55 and 87 % at a $TcpO_2$ of 30 mmHg.

Table 11.2. The sensitivity, specificity, predictive values and accuracy of absolute $TcpO_2$ set at values ranging from 0 to 60 mmHg.

$TcpO_2$ mmHg	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0	100.00	28.15	68.71	100.00	72.13
5	100.00	31.85	69.84	100.00	73.56
10	100.00	37.78	71.72	100.00	75.86
15	100.00	46.67	74.74	100.00	79.31
20	100.00	54.81	77.74	100.00	82.47
25	100.00	65.93	82.24	100.00	86.78
30	97.18	71.11	84.15	94.12	87.07
35	91.08	77.78	86.61	84.68	85.92
40	77.46	82.96	87.77	70.00	79.60
45	60.09	88.15	88.89	58.33	70.98
50	43.19	91.11	88.46	50.41	61.78
55	31.92	91.11	85.00	45.90	54.89
60	21.60	92.59	82.14	42.81	49.14

The next method is to weigh up the interplay between sensitivity and specificity by constructing a receiver operator characteristic curve (ROC), which plots the true positive fraction (sensitivity) against the true negative fraction (1 – specificity) (Zweig, M. H. and Campbell, 1993) (figures 11.1 and 11.2).

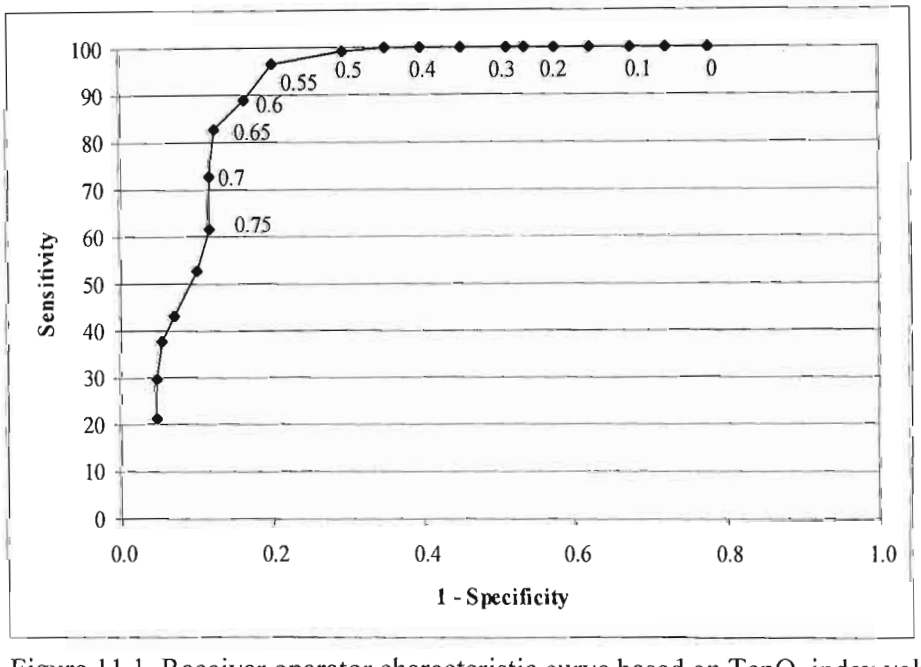


Figure 11.1. Receiver operator characteristic curve based on $TcpO_2$ index values ranging from 0 to 1. The best predictive value based on this curve is 0.65.

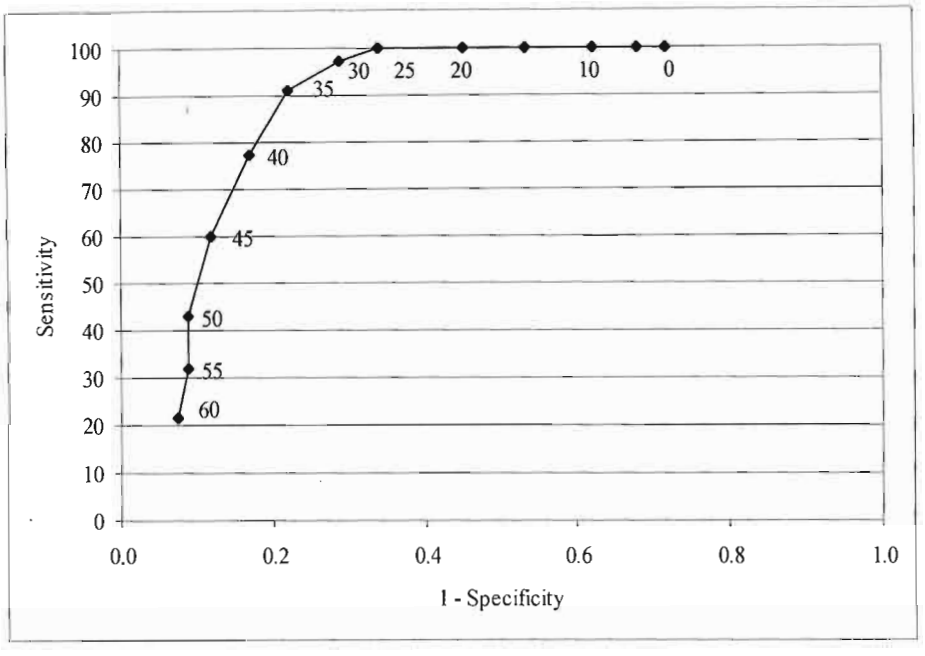


Figure 11.2. ROC curves for absolute $TcpO_2$ over a range of 0 – 60 mmHg.

The ideal predictive value for which there are neither false positives nor false negatives would result in an ROC curve that starts at 0 on the x and y axes, ascends the y axis vertically to the top and then runs horizontally at y = 100, from x = 0 to x = 1. Deviation from this ideal occurs because of false positives and false negatives. Under such circumstances, the point nearest x = 0 and y = 100 is considered to be the test value that will give greatest accuracy or the least false positive and false negatives. This however needs to be assessed in terms of morbidity associated with either too many false positives or false negatives. For amputation level selection we aim to avoid unnecessary ablation of a joint which would occur with false negatives. To avoid this the predictive value chosen should have a high sensitivity (Zweig, M. H. and Campbell, 1993).

In figures 11.1 and 11.2 the best trade off between sensitivity and specificity is at a $TcpO_2$ index of 0.65 while 0.45 provides the first point at which sensitivity is 100 %. Similarly for the absolute $TcpO_2$ 35 mmHg provides the best trade off while 25 mmHg is the highest value with a sensitivity of 100 %. While this may be statistically correct, clinically setting the predictive level at 0.65 or 35 mmHg would result in a number of amputations being performed at unnecessarily proximal sites. In this enlarged series, 42 amputations (12 %) healed at $TcpO_2$ indices below 0.65 while 30 healed at absolute $TcpO_2$'s of less than 35 mmHg.

While the $TcpO_2$ index appeared to be a better prognosticator than absolute $TcpO_2$ in the initial series, is this true of the larger series? A method of comparing two tests is to plot both as ROC curves with the test that has the larger area under the curve being considered to be more accurate. The ROC curves for absolute $TcpO_2$ and the combination of Absolute $TcpO_2$ and the $TcpO_2$ index are shown in figure 11.3.

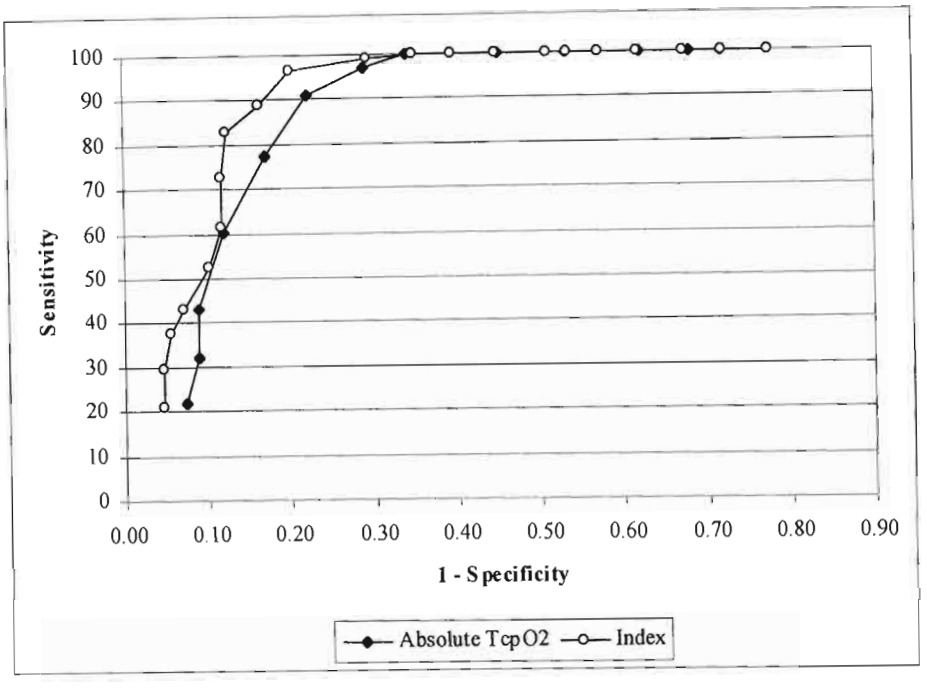


Figure 11.3. ROC curves for absolute $TcpO_2$ and the $TcpO_2$ index.

The area under the Index curve is greater than that under the absolute $TcpO_2$ curve indicating that the Index is more accurate than absolute $TcpO_2$ in predicting amputation outcome.

If avoidance of unnecessary sacrifice of functional joints is the goal of using the test, then the lowest value at which healing occurred should be the criterion. In this instance the lowest index at which healing occurred was 0.49 and an absolute $TcpO_2$ of 27 mmHg, which would suggest that the predictive value be set slightly lower at 0.45.

Combinations of criteria can also be used to set the predictive value. This can be visualised by plotting the absolute $TcpO_2$'s and indices of healed and failed amputations (figure. 11.4). In figure 7.4, all amputations above the 0.55 line would be expected to heal, as would all amputations to the right of the 40 mmHg line. Combined, prediction could be made in the following way. All amputations with an absolute $TcpO_2$ of more than 40 mmHg would be expected to heal, and there is no need to measure the Chest value to derive an index. For those

sites with an absolute value below 40 mmHg, an index of 0.55 or more would be expected to heal.

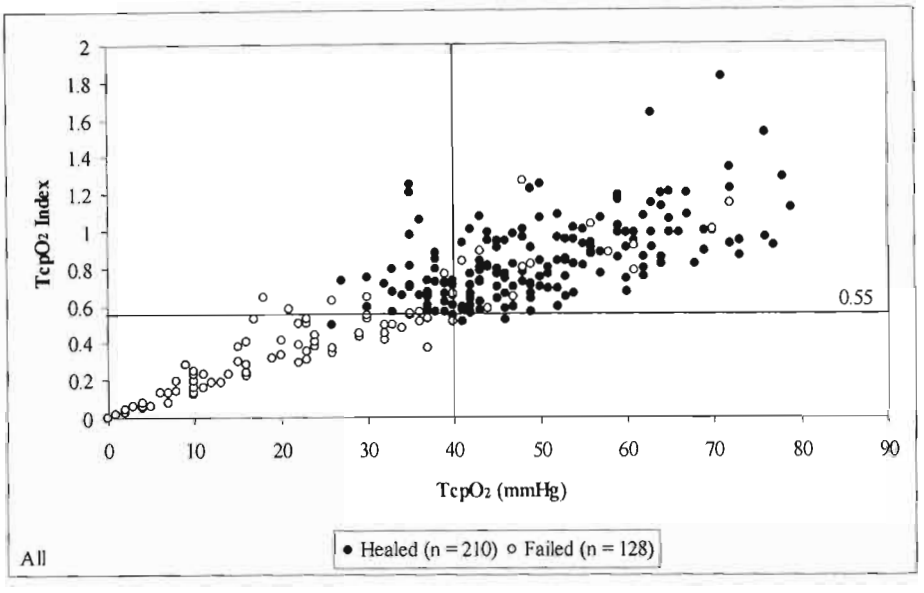


Figure 11.4. Scatterplot of the absolute $TcpO_2$ measurements in mmHg and the $TcpO_2$ indices of healed and failed amputations. Lines representing predictive values set at an absolute TcpO2 of 40 mmHg and an index of 0.55 are shown.

The effect of this over the grey zone 25 – 40 mmHg is shown in figure 11.5, in which lines have been drawn in for $TcpO_2$ Index values of 0.5 and 0.55.

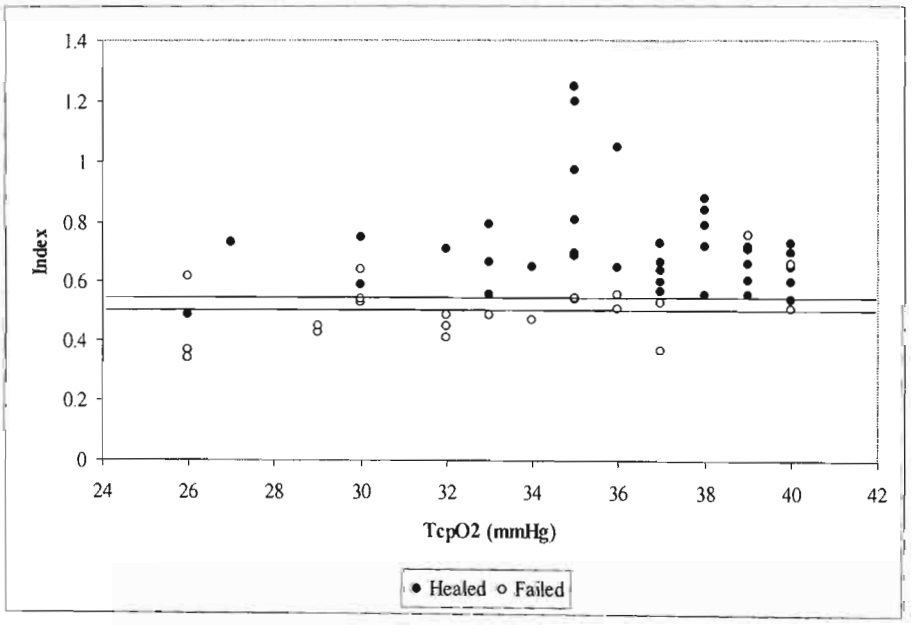


Figure 11.5. Scatterplot of the outcome of 81 amputations performed at sites where the absolute $TcpO_2$ was between 25 and 40 mmHg. Lines representing $TcpO_2$ values of 0.5 and 0.55 have been drawn.

It is this grey zone in which the best discrimination is required. Within this zone of 25 – 40 mmHg the sensitivity and specificity was calculated using different index values from 0.4 to 0.7 (table 11.3) and different absolute $TcpO_2$ values from 28 to 42 mmHg (table 11.4). The ROC curves were then plotted in figure 11.6.

Table 11.3. The sensitivity, specificity, predictive values and accuracy of the $TcpO_2$ Index set at values ranging from 0.4 to 0.7, for the amputations performed on patients with absolute $TcpO_2$'s of 25 to 40 mmHg.

Index	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
0.40	100.00	11.54	69.33	100.00	70.51
0.45	100.00	19.23	71.23	100.00	73.08
0.50	96.15	46.15	78.13	85.71	79.49
0.55	92.31	73.08	87.27	82.61	85.90
0.60	82.69	80.77	89.58	70.00	82.05
0.65	71.15	92.31	94.87	61.54	78.21
0.70	50.00	96.15	96.30	49.02	65.38

Again the $TcpO_2$ Index of 0.55 has the best accuracy of 85.9% and the best combined sensitivity and specificity.

Table 11.4. The sensitivity, specificity, predictive values and accuracy of absolute $TcpO_2$ set at values ranging from 28 to 42 mmHg, for the amputations performed on patients with absolute $TcpO_2$'s of 25 to 40 mmHg.

$TcpO_2$ mmHg	Sensitivity %	Specificity %	Positive Predictive Value %	Negative Predictive Value %	Accuracy %
28	92.31	15.38	68.57	50.00	66.67
30	92.31	15.38	68.57	50.00	66.67
32	86.54	26.92	70.31	50.00	66.67
34	75.00	38.46	70.91	43.48	62.82
36	50.00	57.69	70.27	36.59	52.56
38	36.54	65.38	67.86	34.00	46.15
40	15.38	84.62	66.67	33.33	38.46
42	1.92	88.46	25.00	31.08	30.77

The results of the predictive value set at 28 and 30 mmHg are the same, and offer the best accuracy at 66.7 % with the highest sensitivity. From this it would be expected that the area under the $TcpO_2$ ROC curve would be less than that under the $TcpO_2$ Index ROC curve.

This is confirmed by the data in figure 11.6.

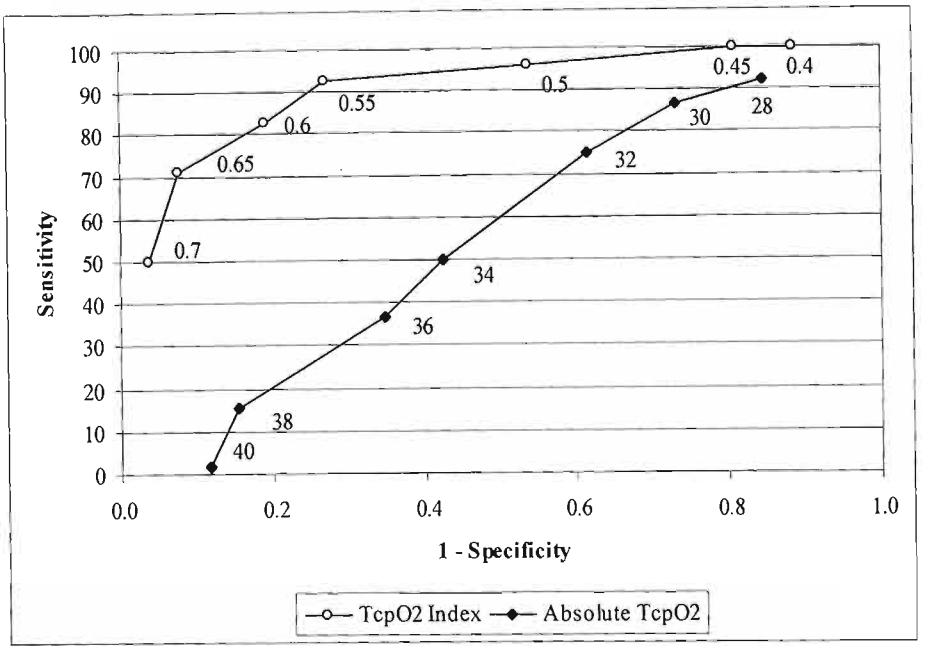


Figure 11.6. Receiver operator characteristic curves for $TcpO_2$ and $TcpO_2$ Index in the "grey zone" 25 – 40 mmHg.

The problem now is to select the best $TcpO_2$ predictive value. What is at issue? Amputation at the most distal site with the potential to heal, results in the chance of preserving an additional joint and may lead to better rehabilitation and a better quality of life. The risk however with any amputation, is that it will fail and require revision. The data presented in chapter 12 show that over 15 years the average mortality rate per amputation performed at our hospital is 15.1 %. A patient who survives the first amputation and undergoes a second amputation has a 28 % chance of dying in hospital after the second procedure.

Choosing the amputation prediction level then becomes a matter of weighing up the risk of unnecessarily sacrificing a joint, by operating too proximally, against the risk of the patient dying after a revision amputation.

Selecting a $TcpO_2$ amputation prediction level of 0.45 would, based on our data, suggest that the level selected has the potential to heal an amputation. It does not however guarantee that healing will occur. The positive predictive value is 82 % (Table 1.8) and therefore 18 % of patients undergoing an amputation based on this level can be expected to require at least 1 revision procedure with the attendant morbidity and mortality. Put another way, 1 in 6

patients would face an additional operation with a 28 % chance of dying. The comparison of the risk of unnecessary sacrifice of a joint, against the risk of revision, is shown in table 11.5.

Table 11.5. The chance of unnecessarily sacrificing a joint by performing an amputation at a site above that which has the potential to heal, is expressed as a percentage and as a patient risk ratio, the percentage of patients who would require revision, and the risk ratio of requiring a revision amputation is shown for various $TcpO_2$ Index values. The data is based on Table 11.1.

$TcpO_2$ Index Predictive Value	**Chance of Operating More Proximally Than May Heal**		**Chance of Requiring a Revision Amputation**	
	%	Risk Ratio	%	Risk Ratio
0.45	0	0	18	1 in 6
0.5	1	1 in 100	15	1 in 7
0.55	3	1 in 33	11	1 in 9
0.6	11	1 in 9	10	1 in 10
0.65	17	1 in 6	8	1 in 13

Based on the receiver operator characteristic curve (Figure11.1), 0.65 is the best $TcpO_2$ Index for amputation level selection. While this would offer the least risk of requiring a revision, 1 in 6 patients would be undergoing an amputation at a site more proximal than might heal. The slight benefit of choosing 0.6 over 0.55 in terms of the risk of revision is more than off set by the large difference in the number of joints that would be sacrificed. The choice between 0.55 and 0.5 is more difficult.

Is the morbidity associated with unnecessary loss of 2 joints per 100 amputations offset by the advantage of sparing 4 people per 100 amputations a revision procedure? In terms of associated mortality and morbidity, a reduction in the revision rate outweighs the unnecessary loss of a joint. Based on this data 0.55 has been proposed as the predictive level.

Chapter 12

Amputation for Peripheral Vascular Disease at KEH – a 15 Year Survey

12.1 Introduction

The goals of implementing a programme of pre-operative assessment of wound healing potential are to reduce patient morbidity and mortality, and to improve the chances of rehabilitation by providing the best possible functional stump. Morbidity and mortality may be reduced by performing amputations more proximally, with minimal risk of failure and re-amputation. Proximal amputation, however, compromises the second goal of rehabilitation.

In 1979, Malone showed that using ^{133}Xe skin clearance to select amputation level, combined with immediate post operative prosthetic fitting could result in a saving of $80,000,000 over a 5 year period to the Veteran's Hospital Administration system. The potential saving was achieved through shorter hospital stay secondary to a reduction in amputation revisions (Malone, J. M. *et al.*, 1979).

12.2 Initial study on amputation healing at King Edward VIII Hospital

In 1993 we investigated the extent of the problem of revision surgery in our hospital (King Edward VIII) and examined the potential savings that might accrue from a programme of pre-operative assessment of amputation wound healing potential using $TcpO_2$. This was published as "The potential benefit of pre-operative assessment of amputation wound healing potential in peripheral vascular disease." (Mars, M. *et al.*, 1993). See appendix d.

12.2.1 Method

The centralised computer records of all patients admitted to the hospital for the 5 year period 1984 – 1988 were reviewed. This yielded 965 patients who underwent 1,563 lower limb amputations for peripheral vascular disease.

12.2.2 Results and discussion

The primary revision rate, ie the number of first time amputations that required revision was 51 %. This very high revision rate is skewed by the unit's policy of performing an initial Guillotine amputation and subsequent definitive amputation in patients with septic non-salvageable limbs (Desai, Y., *et al.*, 1986). From the available data it was not possible to determine how many Guillotine amputations were performed. The figure was approximated by counting the number of foot and below knee amputations that were revised at the same level and considering the initial amputation to have been a Guillotine amputation. Above knee amputations that were revised at the AKA level were considered to have failed, although on occasion an above knee guillotine was known to have been performed. Considering the Guillotine amputations as a planned two stage amputation reduced the primary revision rate (failure rate) to 34.8 %. There were 222 deaths in hospital, giving an overall mortality rate of 23.0 % and a mortality rate per amputation of 14.2 %.

The total number of days spent in hospital was available for 1987 and 1988. From this the average number of days spent in hospital following an amputation that healed primarily was obtained for each amputation level. The number of extra days spent in hospital after revision was then calculated. The extra days of hospitalisation resulting from revision surgery is shown in figure 12.1.

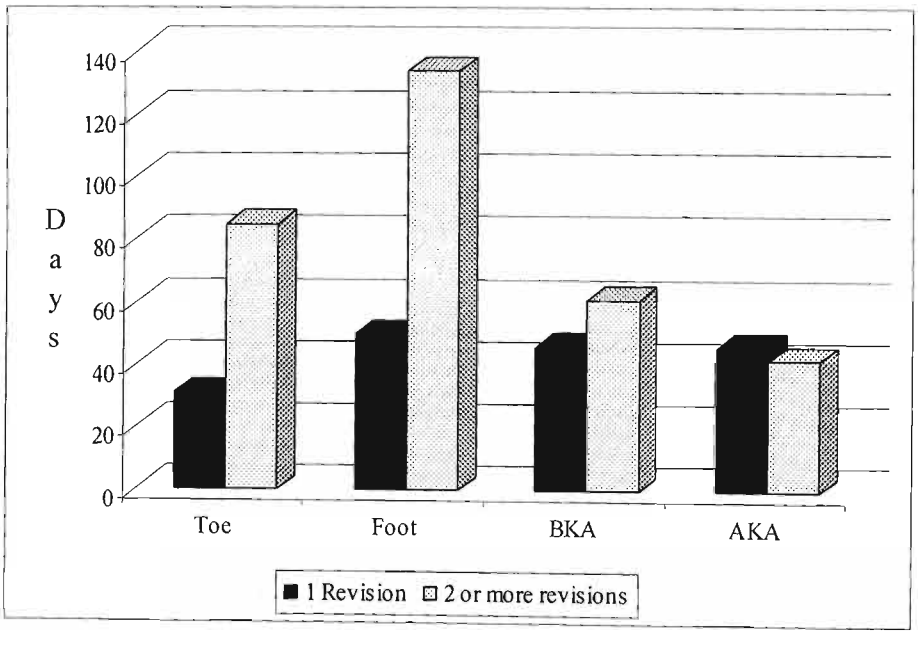


Figure 12.1. Average number of extra days spent in hospital following one or several revision amputations, based on the site of the initial amputation (1987 and 1988).

The total increase in hospital stay following revision surgery for patients who survived was 4,980 days per year. The extra days spent in hospital by those patients who died following revision surgery was 1,371 days per year. In total, patients who underwent revision surgery occupied 17.4 hospital beds per day per year. At an approximate bed cost at the time of R200 per day, failed amputations in King Edward VIII hospital cost the local Provincial Health Services R1.27 million per year.

It should be noted that the long periods of hospitalisation for an amputation are a reflection of the State health care services provided in the country. Most patients are unable to access clinics for wound dressing and as a result are kept in hospital until their amputations have healed.

12.3 Study to determine amputation $TcpO_2$ criteria

Between 1987 and 1990, $TcpO_2$ investigations were performed pre-operatively on 392 patients with peripheral vascular disease who were being worked up for amputation. The measurements were made at the standard amputation sites and on the anterior chest wall. Data from 270 patients who met the following criteria were reviewed:

(i) that the patient undergo a definitive amputation and not a Guillotine amputation

(ii) that the patient had not undergone a revascularisation procedure in the affected limb within 2 weeks of the pre-amputation $TcpO_2$ measurement

(iii) that the amputation was not a revision at the same level of a previous definitive or Guillotine amputation stump

(iv) that the limb was not oedematous at the site of measurement.

In 1987 the primary revision rate of patients who underwent pre-operative $TcpO_2$ was 40.3 %. Of all the amputations performed in 1987, 35.5 % were undertaken at sites with a pre-operative $TcpO_2$ of less than 0.55. Based on the $TcpO_2$ index of 0.55 being predictive of amputation wound failure, these sites would be considered to be inappropriate and healing would not have been expected. None of the amputations performed at sites with a $TcpO_2$ of less than 0.55 healed.

Of the amputations performed at sites with a $TcpO_2$ index of 0.55 or more 4.8 % failed to heal and required revision. In 1989, after informing the surgeon of the most distal site at which

healing could be expected, based on the $TcpO_2$ index, the advice was overruled and a more distal amputation performed based on clinical criteria in 16.4 % of patients in 1989 and 6.6 % in 1990. All the amputations performed at more distal sites failed to heal. Informing the surgeon of the most distal amputation site at which healing could be expected significantly reduced the revision rate in these patients from 40.3 % in 1987 to 8.2 % in 1990 ($p < 0.0001$) (Table 12.1).

Table 12.1. Percentage of amputations requiring revision in patients who underwent pre-operative $TcpO_2$ measurement.

	Percentage Amputations Revised			
	1987	1988	1989	1990
Total revision rate	40.3	38.8	20.0	8.2
$TcpO_2 < 0.55$	35.5	22.2	16.4	6.6
$TcpO_2 > 0.55$	4.8	16.6	3.6	1.6

The reduction in revision rate in 1989 and 1990 may reflect growing acceptance of the $TcpO_2$ index as a better prognosticator of outcome than the surgeon's own clinical judgement. It could be argued that the use of the $TcpO_2$ index would result in too proximal an amputation in a small percentage of patients. Even if this is so, and while some joints may then have been unnecessarily sacrificed, morbidity for the patient cohort has been reduced and a significant number of patients have been spared further surgery.

The data presented in table 12.1 showing the percentage of amputations with a $TcpO_2$ index of more than 0.55, that would be expected to heal but which failed to heal, is of particular interest. It most probably reflects those amputations that will fail for reasons other than inadequate skin perfusion. While less than 5 % for 3 of the years, it reached 16.6 % in 1989. On review, a possible cause identified for this was poor surgical technique of a trainee performing the majority of the amputations in that year.

Has the use of $TcpO_2$ in the Durban Metropolitan Vascular Service had any effect on the outcome of amputation surgery? Routine $TcpO_2$ testing was implemented in late 1988. $TcpO_2$ measurement is time consuming and it is not available on an emergency basis, after hours or over weekends. In addition the Non-invasive Vascular laboratory at King Edward VIII performs $TcpO_2$ measurements for the other Hospitals in the Metropolitan Service. As a result, not all patients requiring amputation are sent for the investigation.

12.3 Effect of implementation of $TcpO_2$ prediction of amputation wound healing on amputation revision rates at King Edward VIII Hospital

To investigate whether the use of the $TcpO_2$ index has had any effect on the outcome of amputation surgery, similar data were gathered for the following 10 years, 1989 – 1998.

12.3.1 Method

The data were derived from the central hospital records and reflect all patients at King Edward VIII Hospital undergoing lower limb amputation for peripheral vascular disease. Of these, a subset had $TcpO_2$ measurements made pre-operatively, and again, of this subset not all amputations were necessarily performed at the level indicated by the test.

The raw data acquired were based on the international coding for amputations and consisted of all amputations of the lower limb, codes 5845 – 5849, irrespective of aetiology. The data consisted of the patient's hospital number, age, sex, survival, e-code and up to 3 ICD codes for both aetiology and surgical procedures. Data were also gathered for the code 5850, revision amputation surgery. From this the total number of amputations performed on a patient in a year was calculated. The data were entered in a database and a program was written, based on the disease codes, to filter out only those amputations performed for peripheral vascular disease. In the first study, additional data giving the duration of hospital stay were also obtained for 1987 and 1988. For the period 1989 to 1998 data on the hospital stay were only available for 1994 – 1998. (The Provincial Administration surprisingly destroys data more than 5 years old).

12.3.2 Results and discussion

The combined data for the 15 year period 1984 to 1998 are shown in figure 12.2 and table 12.2. Introduction of $TcpO_2$ to the surgeons' decision making occurred in 1989. Associated with this was a significant decline in the primary revision rate from an average of 52.2 % between 1984 and 1988 to an average of 35.9 % for the following 10 years (Fishers exact test, $p < 0.0001$). Accompanying this was the reduction in the corrected primary revision rate, based on Guillotine amputations, which dropped from an average of 32.7 % for the 5 years 1984 – 1988 to 22.0 % (Fishers exact test, $p < 0.0001$). While a decline in amputation revision rates has occurred, this has had little influence on the peri-operative mortality.

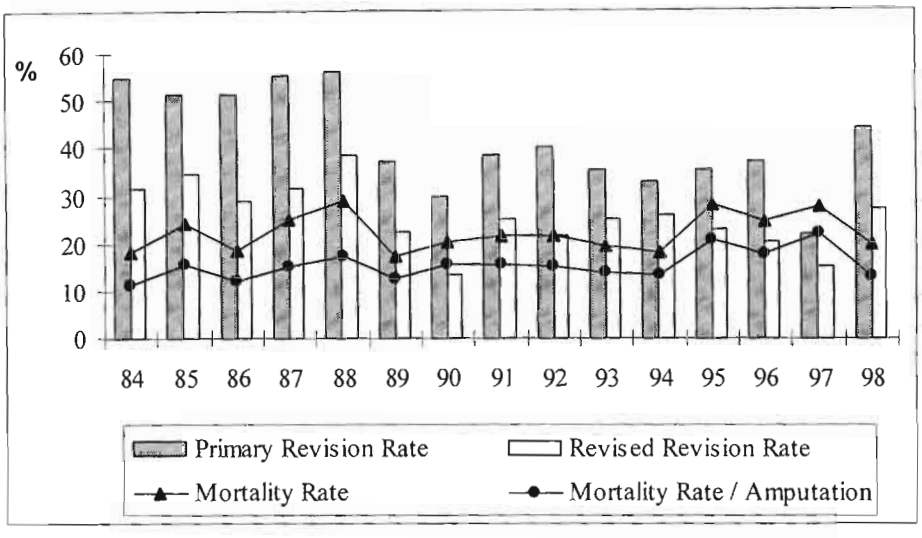


Figure 12.2. The percentage of amputations that required revision (primary revision rate), the rate corrected for BKA Guillotines, mortality rate and the mortality rate per amputation for the period 1984 – 1998.

Table 12.2. The total number of patients undergoing lower limb amputation for peripheral vascular disease, with the revision and mortality rates expressed as percentages for the 15 years 1984 – 1998. The data are presented as three 5 year cycles, and aggregated over the 10 years 1989 – 1998 and over the full 15 years.

	84-88	**89-93**	**94-98**	**89 - 98**	**Total 15y**
Total number of patients	895	1116	837	1953	2848
Total number requiring revision	577	547	422	969	1546
Total number of amputations	1438	1547	1159	2706	4144
Deaths	207	222	196	410	632
In-hospital mortality (%)	23.1	19.9	23.4	21.4	21.9
Mortality per amputation (%)	14.4	14.4	16.9	15.4	15.1
Survivors	688	894	643	1537	2225
Primary revision rate (%)	53.8	36.4	35.8	36.0	45.0
BKA revised at the same level	145	134	81	215	360
Revised revision rate (%)	32.7	21.4	22.9	22	25.3

When a new test or investigation is the focus of a unit's research, the patients' outcome may be beneficially influenced by extraneous factors such as increased care or attention to detail. To interrogate this possibility, the data have been divided into three 5 year cycles. The first of these predates the use of $TcpO_2$ in clinical decision making, the second may be biased by

knowledge that the test was under review, and the third should represent its use as an ongoing routine investigation (figure 12.3).

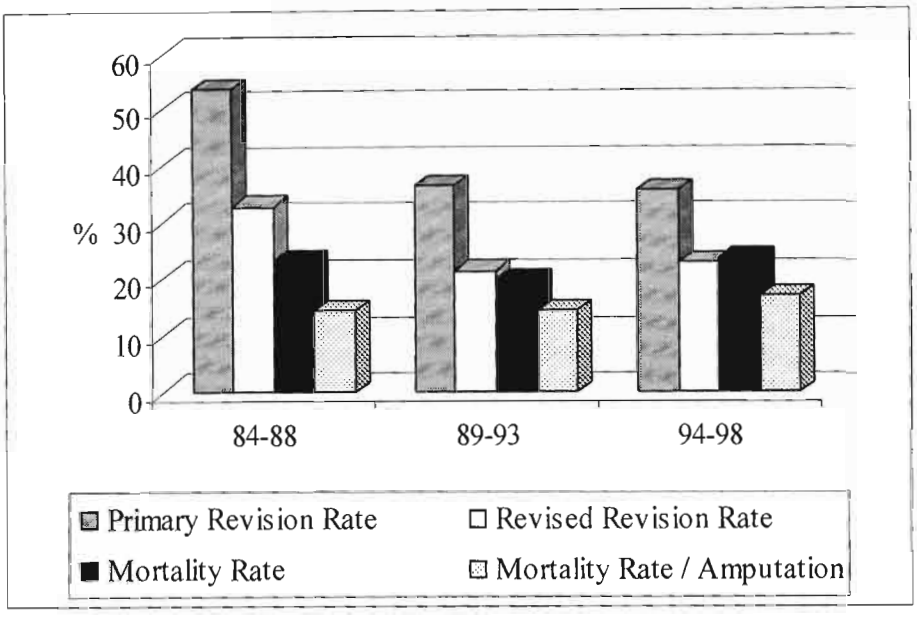


Figure 12.3. The primary revision rate, revised revision rate based on BKA's revised to the same level, the mortality rate and mortality rate per amputation for the three 5 year cycles from 1984 – 1998. The primary and revised revision rates were significantly higher during the first 5 years ($p < 0.0001$). The mortality rate was not significantly different between groups.

The uncorrected primary revision rate fell from 53.8 % in 1984 – 1988, to 36.4 % for the second cycle and 35.8 % for the third cycle. Similarly, the amputation rate corrected for Guillotine amputations fell from 32.7 % between 1984 – 1988 to 21.4 % and 22.9 % in the subsequent cycles. The decrease in both rates following the introduction of $TcpO_2$ to decision making in amputation level selection was significant (Fishers exact test, $p < 0.0001$). Analysis of variance with post hoc testing showed the 1984 – 1988 rates to be significantly greater than both the subsequent cycles ($p < 0.0001$) with no statistical difference between the second and third cycles.

The data presented thus far have been cumulative for all amputation sites and do not investigate any possible differences at the different amputation levels. The number of amputations performed at each level and their outcome is shown in table 12.3. The outcome of amputations performed at each level, expressed as a percentage is shown in figure 12.4.

Table 12.3. The total number of amputations performed between 1984 and 1998, at each of the standard amputation levels, the number that healed primarily and those that required 1 or more revisions in patients who survived. This is not corrected for Guillotine amputations.

	Toe	Foot	BKA	AKA	Hip	Total
Total	583	153	956	532	1	2225
Primary Healing	425	76	411	390	0	1302
1 Revision	108	54	501	136	1	800
2 Revisions	50	22	44	6	0	122
3 Revisions	0	1	0	0	0	1

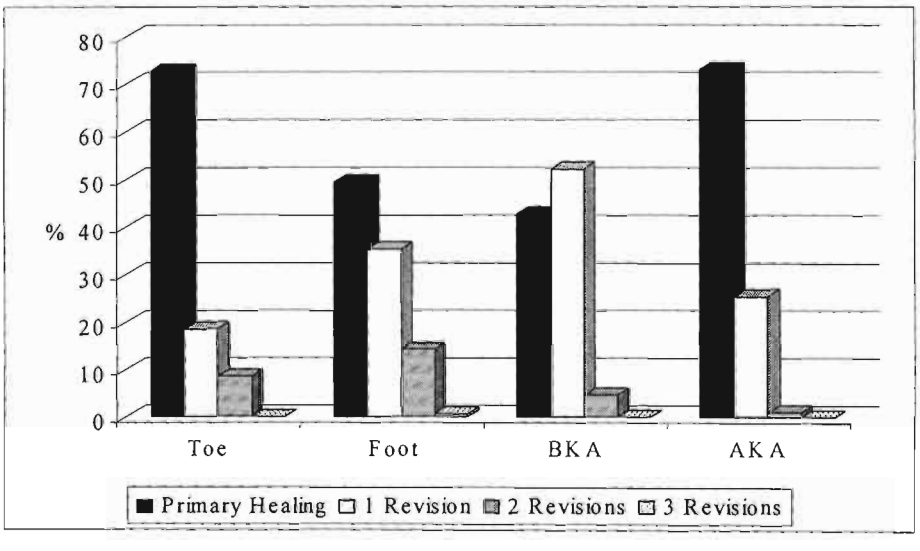


Figure 12.4. Percentage of amputations at each level that healed primarily or which required revision in patients who survived for the period 1984 - 1998. Toe (n = 583), Foot (n = 153), BKA (n = 956) and AKA (n = 532). These data are not corrected for Guillotine amputations.

The primary healing rate and need for additional amputations based on the site of initial amputation (figure 12.4) is the aggregate of the 15 years and conceals any changes that may have occurred with the introduction of $TcpO_2$ testing. The pattern of amputations for the period 1984 – 1988 and 1989 – 1998 are shown in figures 12.5 and 12.6.

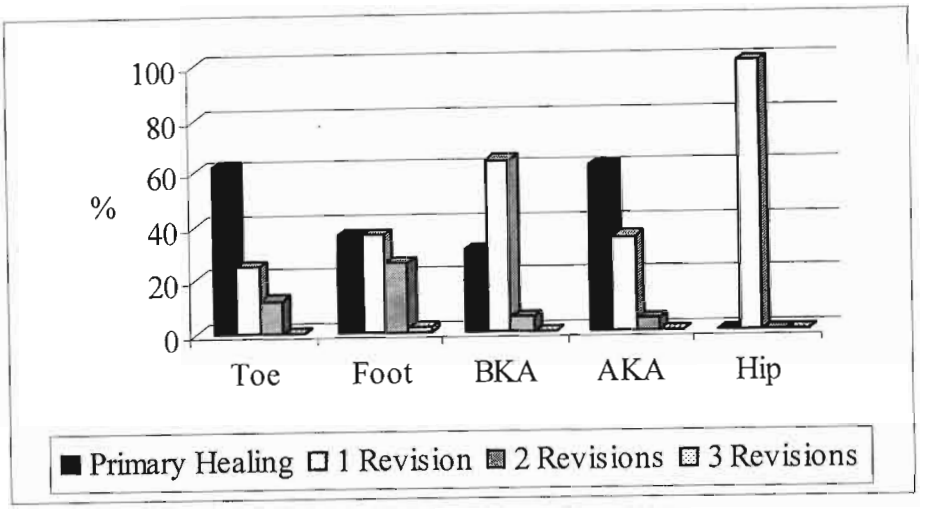


Figure 12.5. Percentage of amputations at each level in patients who survived, that healed primarily or which required revision between 1984 and 1988.

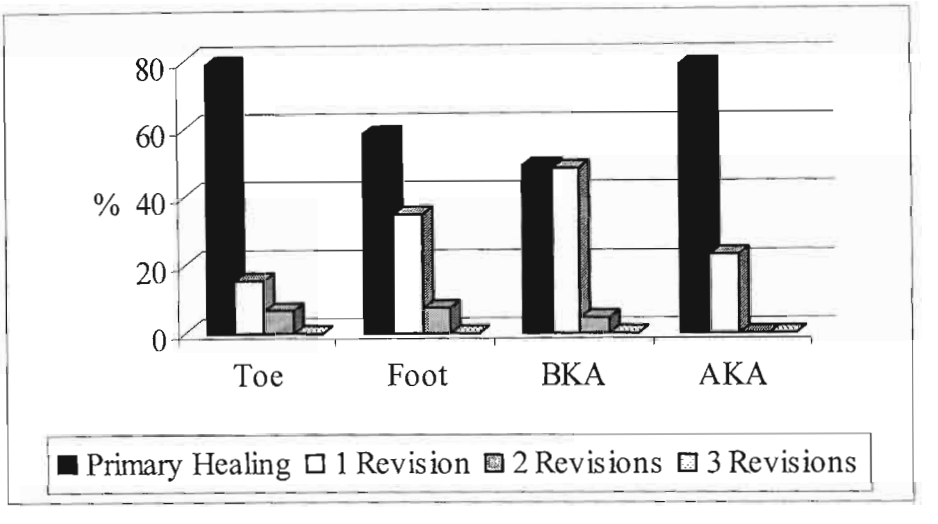


Figure 12.6. Percentage of amputations at each level that healed primarily or which required revision between 1989 and 1998, in patients who survived.

Statistically significant increases in healing were noted at all levels from 1989 onwards. These differences occurred in both five year cycles, 1989 – 1993 and 1994 – 1998, except at the level of the foot where there was no improvement in healing between 1989 and 1993. When comparing these latter two five year cycles no difference in healing rate was noted except again at the foot, where significantly better healing was achieved between 1994 and 1998 (Table 12.4).

Table 12.4. Results of two tailed Fishers exact tests comparing the ratio of primary healing to failure between the results obtained in 1984 – 1988 with the subsequent 10 years and the two five year subsets. The results of 1989 – 1993 are then compared with those of 1994 – 1998.

	Toe	**Foot**	**BKA**	**AKA**
1984 – 88 compared to	p	p	p	p
1989 – 98	< 0.0001	0.0123	< 0.0001	0.0002
1989 – 93	0.0002	0.3488	< 0.0001	< 0.0001
1994 – 98	0.0166	0.0001	< 0.0001	0.0104
1989 – 93 and 1994 – 98	0.4361	0.0027	1.0000	0.2239

The BKA:AKA ratio is often cited as an indicator of the success of a unit's approach to amputation level selection and a ratio exceeding 1:1 is given as the goal. While useful, it does not take into account the pattern of presenting pathology, which may vary in different patient populations. The definition of the BKA:AKA ratio is seldom stated. Is it the ratio of amputations based on the level of the first amputation, irrespective of outcome, or is it the ratio based on the outcome level of amputations performed initially at the BKA and AKA levels? These two approaches do not take into account amputations performed more distally that have failed and require revision to these more proximal levels. Probably the most useful and least ambiguous definition of the BKA:AKA ratio would be the ratio of the total number of amputations which ultimately heal at these two levels irrespective of the site of the primary amputation (Table 12.5).

Table 12.5. BKA:AKA ratio over the 15 years using three definitions in patients who survived.

BKA:AKA Based on	**84-88**	**89-93**	**94-98**		**84-98**
initial site selected	2.26	1.86	1.57		1.80
outcome of BKA and AKA amputations	1.34	1.14	0.98		1.11
amputation level at discharge	1.50	1.30	1.00		1.22

Knowing the high revision rate at King Edward VIII, it is not unexpected that the aggressive approach to joint salvage has resulted in a ratio above equity. The pattern over the three cycles based on the initial site selected (primary amputation performed at the BKA or AKA level) shows a decline in the ratio with time, suggesting that more AKA's were performed initially than BKA's in an attempt to reduce the failure rate. The percentage of amputations

performed as a primary amputation at each of the levels is shown in figure 12.7. It is should be noted that while the percentage of primary AKA's increased from 20 % between 1984 and 1988, to 27.5 % between 1993 and 1998, the percentage of primary BKA's remained constant at 42.6 % and 43.9 %. This implies that the percentage of primary amputations at the lower levels of the foot and the toes decreased on average 5 – 7 % over the cycles from 1989 – 1998.

It is interesting that this 5 % proximal shift to the BKA level and the 5 % shift to the AKA level approximates the 10 % reduction in revision rate corrected for guillotine amputations between 1989 – 1998 (table 12.2).

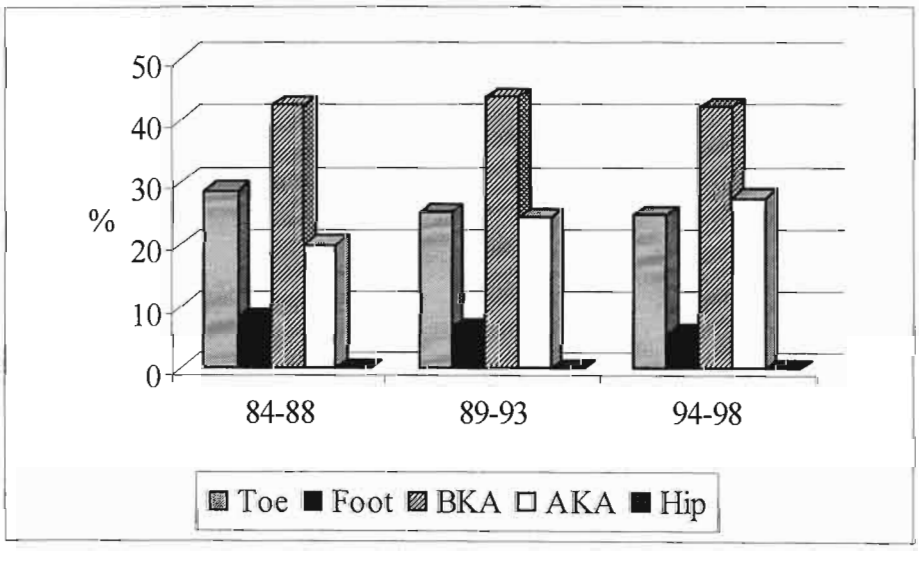


Figure 12.7. The percentage of amputations performed at the different levels based on the level of primary amputation in patients who survived.

Of the 2845 patients undergoing amputation for peripheral vascular disease 625 people died, giving a mortality rate of 22 %. These patients underwent 4144 amputations, with a mortality rate of 15.1 % per amputation. The mortality rate and the mortality per amputation is shown in table 12.6.

There was no statistical difference between either the mortality rate or the mortality rate per amputation for the three 5 year cycles. As no measurable change in peri-operative patient management has been implemented during the 15 years, the constant mortality rate suggests that the patient population requiring amputation and severity of the their illness has not undergone major change.

Table 12.6. The mortality rate expressed as a percentage, for patients undergoing amputation and the mortality rate per amputation at the different levels for each of the three 5 year cycles.

	84 – 88 Mortality %		89-93 Mortality %		94-98 Mortality %	
	/Patient	/Amputation	/Patient	/Amputation	/Patient	/Amputation
Toe	9.6	6.1	9.2	7.0	13.6	10.3
Foot	17.1	9.0	15.7	10.1	21.7	16.9
BKA	26.6	15.6	23.7	15.7	25.9	16.8
AKA	31.7	23.0	23.0	19.8	27.5	22.4
Hip	80.0	66.7	100.0	50.0	0	0
Total	23.1	14.4	19.9	14.4	23.4	16.9

Information on hospitalisation time was available for 1987 and 1988, and 1994 –1998. In all 1239 people were in hospital for 83604 days at an average of 67.5 days per person. This includes those who died before discharge and reflects a shorter than expected hospital stay. The 933 people who survived averaged 77.2 days in hospital. The average stay based on the number of amputations performed is shown in table 12.7.

Table 12.7. The average hospital stay based of people who were discharged from hospital, and the number of amputations that they underwent.

	Primary Healing	1 Revision	2 Revisions
Total days	30728	31078	10259
Total patients	541	318	74
Average	56.8	97.7	138.6
Extra days		40.9	40.9

The average hospitalisation for an amputation that heals without need for revision is surprisingly long at 8 weeks. Each additional amputation adds almost 6 weeks to the stay. In effect, 9 revision procedures will result in 1 hospital bed being occupied for a year.

To quantify the effect of the reduction in primary revision rate in terms of the number of amputations that would not have been performed per year the amputation data needs to "normalised" to reflect an average year. Over the 15 year period the average number of people who survived amputation and were finally discharged was 148 per year. The percentage of operations performed on survivors as primary and repeat amputations is shown in table 12.8.

Table 12.8. The percentage of amputations that healed primarily or required second or third amputations, in patients who survived.

	84-88	89-93	94-98	89-98
Primary Healing	46.2 %	63.6 %	63.4 %	63.5 %
1 Revision	44.5	33.4	31.6	32.7
2 Revision	9.2	2.9	5.3	3.9
3 Revision	0.1	0.0	0.0	0.0

Using this data the theoretical average number of people undergoing primary and revision amputation can be calculated by taking the percentage for each group in table 12.8, as a percentage of 148 (the average of number of survivors per year). The results are shown in table 12.9.

Table 12.9. The predicted number of amputations and their outcome for an average year in each of the three 5 year cycles. The total number of amputations is the sum of the products of the number of people undergoing more than one amputation and the number of amputations performed on them.

	84-88	89-93	94-98	89-98
Primary Healing	68.4	94.2	93.8	94.0
1 Revision	65.8	49.5	46.8	48.4
2 Revision	13.6	4.3	7.9	5.8
3 Revision	0.2	0.0	0.0	0.0
Total amputations	241.6	206.1	211.1	208.1

Comparing the theoretical total number of amputations performed in an average year in the 1984 – 1988 cycle prior to the introduction of $TcpO_2$ measurement with the results from 1989 – 1998, shows an average reduction of 33.5 (13.9 %) amputations per year. Each additional amputation adds approximately 40 days to hospital stay. Since 1988 there has been an approximate saving of 1337 hospital bed days per annum or 3.7 hospital beds freed of amputation revision patients per year. This is a long way short of the 17 beds based on our predictions in 1993 (Mars, M. *et al.*, 1993).

Possible explanations for this are that the $TcpO_2$ test is not proving as successful as had been predicted, or that not all patients are having $TcpO_2$ measurements performed. As we have noted, the measurement of $TcpO_2$ is time consuming, and the service is available only during weekday office hours. To investigate this the number of patients undergoing $TcpO_2$ measurements in the Non-Invasive Vascular Laboratory was determined from a $TcpO_2$ record

book commenced in 1989. Accurate records appear to have been kept between 1989 and 1995 and again in 1998.

Over the 8 years of available records, 1988 sets of $TcpO_2$ investigations were performed of which 970 were on patients admitted to King Edward VIII hospital. The remainder of the tests were performed on patients from other centres and outpatients. The tests performed on in-patients have been used to estimate the number of $TcpO_2$ investigations that may have been performed as part of the pre-operative assessment of wound healing. In the years that accurate $TcpO_2$ records were kept, 1658 people underwent 2312 amputations. If all the tests performed on in-patients were pre-operative tests to predict wound healing, 42 % of the amputations performed would have had a $TcpO_2$ performed before surgery. Not all the $TcpO_2$ tests were for pre-operative healing potential assessment. A number were for assessment of failed wounds, healing potential of patients who had already undergone Guillotine amputation, and in the early years, 1989 and 1990 included patients who were part of other trials in which $TcpO_2$ use was being evaluated.

If hypothetically all the tests were pre-operative assessment of amputation wound healing, and if all the amputations had been performed at the appropriate level and if all had subsequently healed, a reduction in the primary revision rate, of approximately 40 % would be expected. This would be expected to reduce the primary revision rate revised for Guillotine amputations from the 1984 – 1988 level of ~ 33 % to ~ 20 % in the subsequent years. The average achieved for the period 1989 – 1998 was 22 %.

Reworking this to see the effect on primary revision rate, suggests that the revision rate of survivors should have dropped from ~ 54 % to ~ 32 %. The actual reduction achieved was to 36 %. Both these approaches are flawed as they are based on survivors and it is not known how many patients undergoing $TcpO_2$ measurement survived.

12.4 Limitations

There are many limitations to this audit of amputation surgery for peripheral vascular disease at King Edward VIII Hospital. These include the dependence on the clerical staff to code the patients correctly for both disease and amputation surgery. The hospital stay data may reflect some patients who were discharged for a brief time to attend to personal affairs. Every effort was made to check admission and re-admission dates to overcome this. The data were gathered from the central Provincial records on 5 different occasions, and each time the data supplied was in a slightly different format, despite requests for uniformity. This explains for

example the absence of data on hospital stay for all years. A major limitation is that the assumption is made that all patients are discharged with a healed stump. Some patients will have been discharged with an unhealed stump and or transferred back to a peripheral hospital for wound management. The final outcome can only be assessed by checking readmissions for revision. While this was done, the already high primary failure rate is in all likelihood a percentage point or two higher than calculated above.

The filters used to gather the subset of vascular patients from the overall amputation data may have been overly strict and omitted some patients who required amputation following failed infected prosthetic grafting, as the disease coding for this appears to have variable.

The $TcpO_2$ records do not reflect which patients were undergoing testing for pre-operative assessment of wound healing and certain assumptions had to made, which have been stated previously.

12.5 Summary

Despite these limitations it does appear that $TcpO_2$ measurement has influenced the healing rate of amputation surgery at King Edward VIII, confirming the original hypothesis. While the expected benefits are not as large as had been hoped this appears to be in part due to the inability to assess all patients pre-operatively. The reduction in primary revision rate achieved bears a relationship to the number of tests performed.

Chapter 13

Conclusion

Transcutaneous oxygen measurement using a miniaturised Clark electrode and heating thermistor was developed independently by Huch e*t al.* and Eberhardt *et al.* in 1972. It was initially used to non-invasively monitor arterial oxygen partial pressure (PaO_2) in neonates. The relationship of PaO_2 and $TcpO_2$ does not always hold in the adult and especially the adult with altered blood flow due to peripheral vascular disease. $TcpO_2$ was then shown to follow changes in arterial oxygen partial pressure when blood flow was adequate, changes in blood flow when flow is compromised but PaO_2 is adequate, and to follow oxygen delivery when PaO_2 and blood flow are compromised. $TcpO_2$ has become an accepted test of skin blood flow. In the vascular surgery setting, $TcpO_2$ reflects the metabolic sequelae of a stenotic lesion. $TcpO_2$ has been investigated as a potential test of wound healing potential in the dysvascular patient requiring amputation. A search for one $TcpO_2$ value that will predict wound healing or failure has been sought and many different values have been offered. Additional manoeuvres have been used in attempts to refine the investigation. One of these is the use of a $TcpO_2$ Index, which is the ratio of the limb $TcpO_2$ to a central reference point $TcpO_2$. The Index reduces the effect of central problems of oxygen delivery on the interpretation of limb $TcpO_2$.

The literature on $TcpO_2$ development and its use in assessing peripheral vascular disease and amputation wound healing has been reviewed. Potential causes of variability between research groups were discussed. These include differences in heating protocols, stabilisation time, probe placement, definitions of healing and amputation surgical technique. The influence on $TcpO_2$ measurement and its interpretation of, oedema, recent revascularisation surgery, amputation, and the timing of the investigation relative to subsequent surgery have been discussed.

A series of studies investigating the use of $TcpO_2$ in the clinical setting of the Durban Metropolitan Vascular Service were presented. The methodology was standardised and routine $TcpO_2$ measurements were made with the patient supine and breathing room air. Measurement sites were, the chest in the mid-clavicular line, 10 cm above the patella in the midline, 10 cm distal to the tibial tuberosity and 2 cm lateral to the tibial margin, and on the mid dorsum of the foot. Absolute $TcpO_2$, and $TcpO_2$ Index values of control subjects ($n = 30$),

clinically free of peripheral vascular disease, were not different to the pooled data from the literature.

Data derived from a prospective study of 527 patients with peripheral vascular disease undergoing $TcpO_2$ evaluation in the non-invasive laboratory were available for study. Significant reduction in both absolute $TcpO_2$ and the $TcpO_2$ Index occurred as the measurements were made more distally in the limb. These changes were also significant for patients presenting with gangrene, ischaemic ulcers and pre-gangrenous changes ($p < 0.0001$). Patients presenting with claudication showed significant differences between the AKA and Foot levels but not between the BKA level and the other two levels. These results were compared with the pooled data from the literature and differed in that the literature data shows a significant difference in $TcpO_2$ between the BKA and foot sites in claudicants. This difference may be explained by the relatively small sample of patients presenting only with claudication in our study.

$TcpO_2$ was compared with pulse status in 367 limbs. A significant reduction and gradient in $TcpO_2$ was noted at sites distal to the lowest palpable pulse. The percentage fall in $TcpO_2$ from AKA to Foot sites ranged from 28 % in patients with pedal pulses to 79 % in patients with absent limb pulses. $TcpO_2$ values were found to be no different in patients with peripheral vascular disease and diabetes mellitus ($n = 127$).

$TcpO_2$ measurement was compared with other investigations. Doppler pressure measurement at the popliteal artery and at the foot, and the ankle brachial pressure index (ABI) were found to be significantly higher in diabetic patients ($n = 107$) than in non diabetic patients ($n = 399$). Absolute $TcpO_2$ and the $TcpO_2$ Index were not different. The outcome of 164 amputations for which full data sets of Doppler pressures were available were evaluated and receiver operator characteristic curves were used to select optimal predictive values for amputation selection and to compare Doppler pressure measurement with the $TcpO_2$ Index. The $TcpO_2$ Index of 0.55 gave the best accuracy 92.1 % while a Doppler pressure measurement of 70 mmHg gave an accuracy of 72.6 %.

$TcpO_2$ was correlated with the ^{133}Xenon radio-isotope skin washout test. The best correlation ($r = 0.46$) was obtained with a logarithmic curve $y = 10.862\text{Ln}(x) + 38.751$. Ten patients who had ^{133}Xe measurement underwent amputation. Based on a ^{133}Xenon predictive level of 2.0 ml / 100 g tissue / min, the ^{133}Xe test had an accuracy of 50 %.

$TcpO_2$ was compared with antibiotic (Cefoxitin) concentrations obtained from muscle at the site of amputation, as an indication of the relationship of skin $TcpO_2$ to muscle blood flow (n = 10). The antibiotic concentration in the muscle was expressed as the ratio of muscle antibiotic concentration to plasma antibiotic concentration (Cefoxitin Index). The Cefoxitin Index of healed amputations was significantly higher than that of failed amputations. The mean inhibitory concentration of the antibiotic for anaerobes was not achieved in 5 patients at the time of amputation. Four of these patients failed to heal their amputations.

$TcpO_2$ and the $TcpO_2$ Index were compared with heated and unheated laser Doppler fluxmetry (LDF) in 35 patients undergoing pre-amputation assessment of wound healing potential. Heated LDF and the heated LDF Index showed a significant correlation with the $TcpO_2$ Index ($r = 0.63$ and $r = 0.69$ respectively, with $p < 0.0001$ in both instances). The outcome of 26 amputations, 5 of which failed to heal, was available for evaluation. Differences between the mean values of healed and failed amputations were significant for the $TcpO_2$ Index and heated LDF ($p < 0.0001$). The LDF vascular reserve (LDF VR), the difference between unheated and heated LDF values at a given site was also significantly different ($p = 0.0009$). $TcpO_2$ Index values of 0.5 and 0.55 showed an accuracy of 96.2 %, and heated LDF values of 3, 4 and 5 arbitrary units gave an accuracy of 88.5 %. Receiver operator curves showed a $TcpO_2$ Index of 0.55 and a heated LDF of 5 (au) to give the best predictive values, with the $TcpO_2$ Index as the better test.

$TcpO_2$ data gathered on 122 patients who underwent amputation in 1987 and 1988, and who met the following entry criteria were reviewed with respect to amputation outcome. The inclusion criteria were, that:

(i) the patient undergo a definitive amputation and not a Guillotine amputation

(ii) the patient had not undergone a revascularisation procedure in the affected limb within 2 weeks of the pre-amputation $TcpO_2$ measurement

(iii) the amputation was not a revision at the same level of a previous definitive or Guillotine amputation stump

(iv) the limb was not clinically oedematous at the site of measurement.

No amputation with an absolute $TcpO_2$ of less than 27 mmHg healed. Between 27 and 40 mmHg, 4 of 15 amputations failed. A $TcpO_2$ Index of 0.55 gave a definitive predictive value below which no amputation healed. Of the 15 amputations with absolute $TcpO_2$ values between 27 and 40 mmHg, 3 of the failed amputations had $TcpO_2$ Index values of less than 0.55. Receiver operator characteristic curves showed the $TcpO_2$ Index to be a better test than

absolute $TcpO_2$. The $TcpO_2$ Index 0f 0.55 had a sensitivity of 96.7 %, a specificity of 79.8 %, and an accuracy of 90.2 %.

Based on this information, a $TcpO_2$ Index of 0.55 was selected as a level predictive of amputation outcome, with failure predicted below this level and likely success predicted for amputations performed at sites with an Index value above this. Surgeons were informed of the lowest amputation level that had the potential to heal. They could however decide on the amputation level based on a clinical decision should they so wish. The total amputation revision rate in patients undergoing pre-amputation $TcpO_2$ measurement fell from 40.3 % in 1987 to 8.2 % in 1990. The percentage of amputations performed on clinical criteria at levels predicted to fail, based on $TcpO_2$ Index, fell from 35.5 % in 1987 to 6.6 % in 1990.

The effect of implementation of a programme of pre-amputation $TcpO_2$ measurement on amputation revision rates, mortality and morbidity was assessed over a 15 year period. During the first 5 years the test was not available, during the second 5 years it was available as part of an active research programme and during the third 5 year period it was a routine laboratory investigation. The revision rates dropped significantly with the introduction of the investigation and were no different during the active research period and when part of routine laboratory work-up. The amputation revision rate dropped from 32.7 % to 21.4 % and 22.9 %. Mortality rates were unchanged. This decline in revision rates was less than expected and is probably due problems in getting all the patients to the laboratory during working hours, with approximately only 42 % of patients undergoing $TcpO_2$ investigation.

As with all clinical studies there are limitations to every study and these have been described where appropriate. Despite the limitations, these studies have confirmed the usefulness of $TcpO_2$ measurement in the non-invasive vascular laboratory. The $TcpO_2$ Index is shown to be superior to absolute $TcpO_2$ as a predictive test of amputation wound healing. The introduction of several criteria to define when $TcpO_2$ use is appropriate, has refined the investigation and made it clinically useful in our setting. A $TcpO_2$ Index of 0.55 in the appropriate patient with peripheral vascular diseases is shown to be a useful test to predict amputation wound healing. The effect of its routine use in reducing amputation revision rates over a 10 year period has been demonstrated, confirming the original hypothesis. The test is however time consuming and as a result less than half the patients in our hospital undergo the test. Differences in test methodology may require individual laboratories to establish their own normative data and amputation predictive levels.

Further work is required to find a less time consuming test of amputation wound healing potential. The possibility of using near infrared spectroscopy to determine muscle ischaemia, on its own or in combination with $TcpO_2$ to reflect the adequacy of skin blood flow, shows theoretical potential. Until then, the use of the $TcpO_2$ Index is clinically justifiable and appears to be better than other investigations.

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Name: Age Hosp: Add KEH Other
IP No Sex
DOA File : Date Green Card : Date
DOD Summary : Date
History:

PMH:	Cardiac:	MI	CCF	Murmurs		Angina				
	Respir:	Asthma		Bronchitis		TB	Emphysema		COAD	
	Diabetes:	Juv	Adult	Diet	Oral	Insulin				
	Vasc:									
	H/T:	Y	N	Rx						
	Smoker	Y	N	<5	<10	<15	<20	<25	>25	
	Surgery:			Allergy						
Medications:										

Sx:	Dyspnoea	Y	N	Grade						
	Claudication	R	<10	<50	<100	<250	<500	<1Km		
		L	<10	<50	<100	<250	<500	<1Km		
	Site	R	Butt	Thigh	Calf	Foot	w	m	y	
		L	Butt	Thigh	Calf	Foot	w	m	y	
	Rest Pain	R	Foot	Calf	Thigh	Stand	Better	Same	Worse	
		L	Foot	Calf	Thigh	Stand	Better	Same	Worse	
	Ulcer	R	Toe	Foot	Ankle	Leg	A	P	M	L
		L	Toe	Foot	Ankle	Leg	A	P	M	L
		R	<2.5 cm	<5 cm	<7.5 cm	<10 cm	>10 cm			
		L	<2.5 cm	<5 cm	<7.5 cm	<10 cm	>10 cm			
	Ischaemic les	R	Toe	Foot	Ankle	Leg	A	P	M	L
		L	Toe	Foot	Ankle	Leg	A	P	M	L
	Gangrene	R	Toe	Foot	Ankle	Leg	A	P	M	L
		L	Toe	Foot	Ankle	Leg	A	P	M	L
	Sensory Change	R	Toe	Foot	Ankle	Leg	A	P	M	L
		L	Toe	Foot	Ankle	Leg	A	P	M	L

Examination Date BP
H+N Chest CVS
Abdo CNS MsSk

Pulses	R	L	Bruit			**Tests**		
Carotid				Wcc	RBC		GGT	
Aorta				HB	Hct		AST	
Fem				Plt	Creat		ALT	
Pop				Na	K		Alk Phos	
DP				Cl	AR		Bili	
PTib				Urea	Gluc		TPrt	
Peron				Trig	Chol		Alb	
				Glob	Creat		Cl	
				PI	PTT		Lymph	

Diagnosis Angio No Date

Doppler	Date		Brachial			TcpO2		Date	
	Fem	Pop	PT	PP	DP	Foot	BKA	AKA	Chest
R						R			
L						L			
R Ind						R Ind			
L Ind						L Ind			

Management 1. Date
2. Date
3. Date
4. Date

Opsomming

Prognose in esofageale kanker hou direk verband met diepte van indringing en limfkliermetastases. Dit is egter welbekend dat sonder chirurgiese eksplorasie die beraming van die verspreiding van esofageale kanker onakkuraat is, en dat daar 'n behoefte is aan 'n ander objektiewe maatstaf vir prognose. In hierdie studie is die verwantskap tussen DNA-ploïdiestatus en tumorduur, histologiese voorkoms, ekstra-esofageale verspreiding en oorlewing in 42 pasiënte met esofageale plaveiselkarsinoom ondersoek. Geen korrelasie is gevind tussen DNA-ploïdiestatus en tumorduur of histologiese voorkoms nie. DNA-aneuploïdiekoers in kankers met ekstra-esofageale verspreiding was egter beduidend hoër as die koers in tumore wat tot die esofagus beperk was ($P = 0,038$). Korttermynoorlewing was laer in pasiënte met DNA-aneuploïede kankers as in dié met 'n DNA-diploïede patroon. DNA-analise kan dalk 'n meer akkurate riglyn wees vir prognose in esofageale kanker as kliniese of operatiewe stadiëring.

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Do pre-operative antibiotics reach the operative field in amputation surgery for peripheral vascular disease?

A pilot study

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Summary

Amputation surgery in patients with peripheral vascular disease is associated with high revision and mortality rates. A prospective pilot study examined the intra-operative delivery of cefoxitin sodium to the amputation site, and used pre-operative transcutaneous oxygen pressure measurement to try to predict the tissue antibiotic levels at the amputation site. Antibiotic concentrations were measured in plasma and muscle from the amputation site at the time of amputation, and a significant difference in antibiotic distribution was found between healed and failed amputations. Transcutaneous oxygen pressures correlated with the antibiotic distribution.

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Amputation surgery in the dysvascular patient is viewed by many as an admission of failure, i.e. no more can be done to try to save the limb or, in some cases, the patient. With this negative perception, limb ablation is often relegated to the end of the surgical list as a minor procedure, and in large institutions is often performed by a relatively junior member of the surgical staff. To the patient it is a major psychological, physical and often financial assault. Ideally, the trauma of this event should be lessened by an uneventful postoperative recovery and early rehabilitation. This is, however, as often the exception as the norm.

A retrospective review of all lower-limb amputations undertaken for peripheral vascular disease at King Edward VIII Hospital in 1987 showed that of the 351 amputations performed, 1 in 3 were revisions to a more proximal level. The addition of the in-hospital mortality of 36% for these patients indicates that only every second patient had an uneventful amputation.

A feature of those amputations that failed was that most of the limbs had become infected, despite our practice of routine peri-operative antibiotic prophylaxis.[1] The following questions were posed, for which no answers were found in published reports: (*i*) do prophylactic antibiotics reach the site of surgery in patients with peripheral vascular disease? (*ii*) does the disease process in the vessels affect the uptake of the antibiotic? and (*iii*) is there any way of predicting pre-operatively what the muscle antibiotic level will be at the amputation site?

A prospective pilot study was undertaken to compare amputation healing with the antibiotic level both in the patient's plasma and in muscle from the site of amputation, taken at the time of surgery; and also to establish if there was any correlation between pre-operative transcutaneous oxygen pressure ($TcPo_2$) measurement and the tissue antibiotic levels. $TcPo_2$ measurement was chosen because it is a simple non-invasive investigation that reflects skin blood flow, and has been used to predict amputation wound healing in patients with peripheral vascular disease.[2,3] The $TcPo_2$ index, being the ratio of the limb to chest $TcPo_2$, was also examined, since it has been shown to be a more discriminatory test of amputation wound healing than absolute $TcPo_2$ measurement.[3]

Patients and methods

Ten patients who required lower limb amputations for peripheral vascular disease were studied. There were 8 men and 2 women with an average age of 55,4 years (range 36 - 70 years). They were not diabetic, and all had serum creatinine clearance values within the normal range of 70 - 100 ml/min.

On the day before surgery, $TcPo_2$ measurements were taken at the routine amputation sites: (*i*) the mid dorsum of the foot; (*ii*) 10 cm below the tibial tuberosity over the anterior compartment of the leg; (*iii*) 10 cm proximal to the patella over the anterior midline; and (*iv*) on the anterior chest wall 5 cm below the clavicle in the mid-clavicular line.

$TcPo_2$ was measured using a commercially available oxygen monitor (Hellige Servomed). After a 20-minute warm-up period, the probes were calibrated against air and a zeroing solution, and corrected for barometric pressure. The sites to be measured were shaved, if necessary, and cleaned with an alcohol solution. The probe was attached to the skin with a double-sided adhesive disc, over a drop of contact solution. The heating element of the probe was set at 45°C and readings were made after the probe had been in place for 20 minutes, and hyperaemic stabilisation had occurred.

$TcPo_2$ values were recorded and the surgeon performing the amputation was not given the results since he had to select the level of amputation on standard clinical criteria. All the amputations were performed by the same surgeon, using the same techniques of a long posterior flap and myoplasty for below-knee amputations, and equal anterior and posterior flaps with myodesis for above-knee amputations. In all cases the deep fascia were sutured and the skin approximated with Steristrips.

All amputations were performed under general anaesthesia, and immediately after induction, a 2 g bolus dose of cefoxitin sodium was administered intravenously. At the moment of dividing the limb, a 5 ml venous blood sample was taken from a peripheral arm vein and collected in a heparinised tube. The blood sample was immediately centrifuged and the plasma removed.

Cubes of muscle (2 cm) were taken from each of the compartments of the most proximal part of the amputated limb. Both plasma and tissue samples were frozen and stored at −20°C.

Plasma and muscle antibiotic levels were measured using high-pressure liquid chromatography.[4] All assays were performed in duplicate and the mean antibiotic level of the compartment with the lowest antibiotic level was taken as the muscle antibiotic level.

The patients were followed up for 1 year to assess wound healing.

Results

There were 5 above-knee and 5 below-knee amputations. Four amputations healed — 2 from each group. Successful amputation healing was defined as an amputation that healed without further surgery to the stump. All the amputations that failed to heal had become infected. Muscle antibiotic levels ranged from 6 μg/ml to 40 μg/ml (Fig. 1). There was no antibiotic level that could be used to predict the outcome of an amputation.

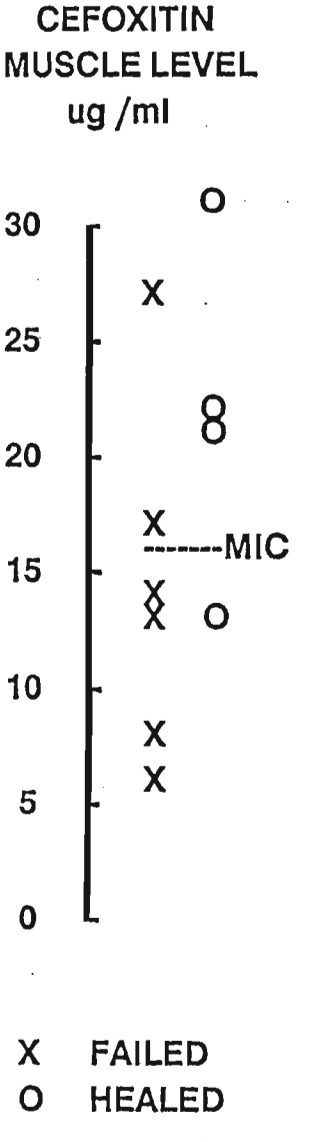

Fig. 1. The cefoxitin concentration in muscle at the time of amputation, with respect to subsequent wound healing. In 5 of the amputations the antibiotic concentration had not reached the MIC for anaerobic organisms at the time of surgery.

The plasma antibiotic levels were high, ranging from 57,2 to 134,2 μg/ml. A trend was shown of a difference in the distribution of the antibiotic between the two groups. Amputations that healed had lower plasma antibiotic levels and higher muscle antibiotic levels than those that failed. This

TABLE I. COMPARISON OF MEAN ANTIBIOTIC LEVELS IN PLASMA AND MUSCLE TAKEN AT THE MOMENT OF AMPUTATION IN SUCCESSFUL AND FAILED OPERATIONS

	Healed	Failed	*P* value
Plasma (μg/ml)	70,3 ± 3,8	106,3 ± 11,1	< 0,03
Muscle (μg/ml)	21,6 ± 3,7	14,3 ± 3,02	= 0,055
Cefoxitin index	0,31 ± 0,05	0,12 ± 0,02	< 0,006

The antibiotic distribution is expressed as the cefoxitin index, being the ratio of muscle to plasma antibiotic levels.

difference in the antibiotic distribution is expressed as the ratio of muscle antibiotic level to plasma antibiotic level and is called the cefoxitin index (Table I).

There was a significant difference between the mean $TcPo_2$ and $TcPo_2$ index of the healed and failed groups (Table II).

TABLE II. COMPARISON OF THE MEAN TRANSCUTANEOUS OXYGEN PRESSURE MEASUREMENTS AND TRANSCUTANEOUS PRESSURE INDICES IN SUCCESSFUL AND FAILED AMPUTATIONS

	Healed	Failed	*P* value
$TcPo_2$ (mmHg)	56,5 ± 5,97	26,2 ± 7,6	< 0,03
$TcPo_2$ index	0,94 ± 0,18	0,31 ± 0,05	< 0,02

There was no correlation between the muscle antibiotic levels and either the absolute $TcPo_2$ or the $TcPo_2$ index. There was, however, a significant correlation between the cefoxitin index and the $TcPo_2$ index ($r = 0,64$; $P < 0,05$; Fig. 2) and between the cefoxitin index and the absolute $TcPo_2$ ($r = 0,66$; $P < 0,05$; Fig. 3). Statistical analysis was by the F-test followed by Student's *t*-test or the Mann-Whitney *U*-test, as appropriate.

Discussion

Based on the plasma levels of cefoxitin at the time of amputation the assumption could have been made that all the patients had an adequate antibiotic concentration at the time of surgery, the minimum inhibitory concentration (MIC) of cefoxitin being 16 μg/l for anaerobes[5] and from 3 to 12,5 μg/ml for aerobic organisms.[6] The muscle antibiotic levels show a different picture, with 5 patients having cefoxitin levels lower than the MIC at the site of amputation. In 4 of the 5 patients whose cefoxitin levels were below the MIC the wounds subsequently became infected and needed revision.

Possible reasons for the failure to achieve the MIC in the muscle at the time of surgery were: (*i*) there may have been insufficient time for antibiotic uptake between administration and surgery, since the average time from cefoxitin administration to plasma sampling was 28,5 minutes, with a range of 25 - 36 minutes; the half-life of cefoxitin is 45 - 60 minutes,[7] thus the steady state of plasma to muscle antibiotic equilibrium had not been reached, and antibiotic uptake was probably still occurring at the time of surgery; (*ii*) possibly the dosage was inadequate — the dose of cefoxitin was 2 g as an intravenous bolus over 3 minutes, which is as recommended for patients with normal renal function; (*iii*) there may have been a loss of antibiotic receptor binding sites — cefoxitin is thought to bind to the cell membrane and, in ischaemic areas with resultant

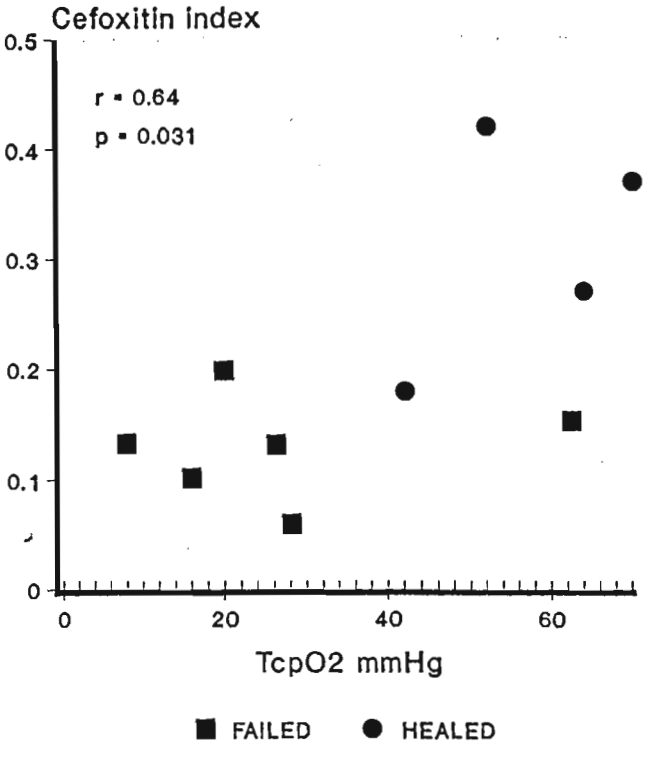

Fig. 2. The relationship between the transcutaneous oxygen pressure measurement and the distribution of cefoxitin, as expressed by the cefoxitin index, being the ratio of muscle to plasma cefoxitin concentrations at the time of amputation. The regression equation is $y = 0,065 + 0,0035 \times x$.

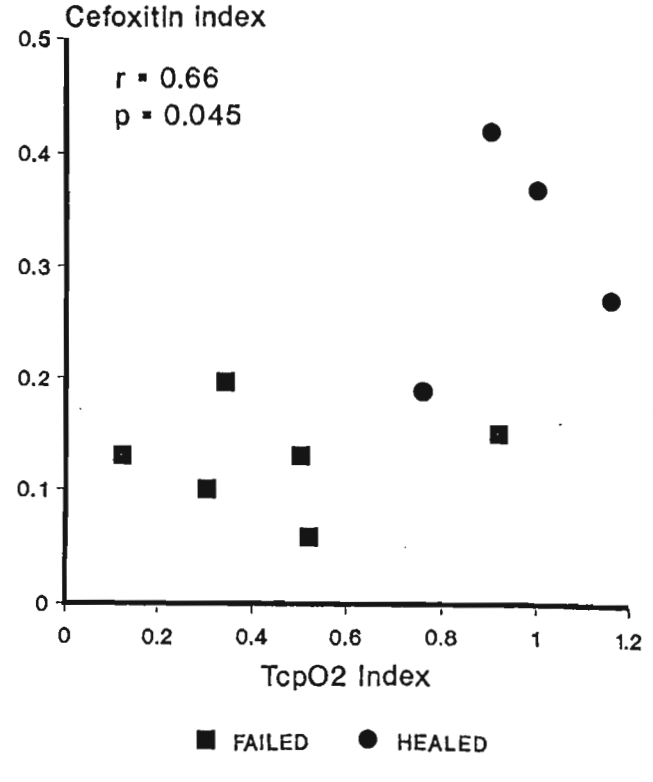

Fig. 3. The relationship between the transcutaneous oxygen pressure index and the cefoxitin distribution as expressed by the cefoxitin index. The regression equation is $y = 0,059 + 0,22 \times x$.

cell damage, a decrease in the total number of functional receptors may occur; and (*iv*) diminished blood flow to the area might have resulted in less antibiotic being delivered to the tissue, slower antibiotic uptake because of increased diffusion distances, and fewer viable cells to bind the antibiotic.

The difference in antibiotic distribution (cefoxitin index) between the two groups, suggests that in those patients whose amputations healed there was better delivery and/or extraction of the antibiotic. The cefoxitin index may thus reflect differences in muscle perfusion.

Wound healing in patients with peripheral vascular disease is multifactorial, with the essential prerequisite being adequate tissue blood flow and oxygenation. Several investigations based on tissue blood flow have been used to try to predict amputation wound healing in these patients. Of these, Xenon skin clearance,[8] $TcPo_2$ measurement[2] and laser Doppler flow measurement[9] have been relatively successful.

$TcPo_2$ measurement has been shown to reflect changes in skin blood flow if the partial arterial pressure (Po_2) is constant and if cutaneous oxygen consumption is constant.[10-12] The $TcPo_2$ index is dependent on total systemic oxygen delivery (Do_2), and should reflect local limb oxygen supply and demand.[13]

We have previously defined two values below which wound healing is unlikely to occur, a $TcPo_2$ of 35 mmHg and a $TcPo_2$ index of 0,65.[3] Based on these cut-off levels, we correctly predicted that the surgeon chose his amputation level too distally in 5 of the 10 patients. The 6th amputation that failed had a high $TcPo_2$ of 61 mmHg and a high $TcPo_2$ index of 0,91, both of which in our experience signify more than adequate skin blood flow for wound healing to occur. Possibly muscle perfusion was inadequate in this case, and if the cefoxitin index reflects muscle perfusion, it might be useful in predicting amputation wound healing.

Both $TcPo_2$ and the $TcPo_2$ index showed a significant correlation with the cefoxitin index. From the respective regression equations, cefoxitin index values were extrapolated below which wound healing would not be expected to occur. These were 0,2 and 0,19, based on a $TcPo_2$ value of 35 mmHg and a $TcPo_2$ index value of 0,65. No amputation with a cefoxitin index of less than 0,19 healed.

The failed amputation with the cefoxitin index of 0,2 had a $TcPo_2$ of 20 mmHg and a $TcPo_2$ index of 0,33, which would indicate insufficient skin blood flow for skin healing to occur. The patient whose amputation healed with a cefoxitin index of 0,19 had a $TcPo_2$ of 42 mmHg and a $TcPo_2$ index of 0,76, levels at which we would have expected wound healing to occur. What of the patient with the high $TcPo_2$ and $TcPo_2$ index whose amputation failed? The cefoxitin index was 0,15, which indicates that despite good skin blood flow, there may have been insufficient muscle perfusion at the amputation site, and hence subsequent wound failure.

An argument against the usefulness of $TcPo_2$ measurement for predicting amputation wound healing has been that it reflects only skin blood flow and gives no indication of the state of muscle blood flow. The correlation of $TcPo_2$ and $TcPo_2$ index with the cefoxitin index suggests that there may well be a relationship between $TcPo_2$ and perfusion of the underlying muscle.

This prospective pilot study on antibiotic levels in patients undergoing lower-limb amputations for peripheral vascular disease shows that while the plasma cefoxitin levels were high in all patients, the MIC of cefoxitin was not achieved at the level of amputation in 5 of the 10 patients. Pre-operative $TcPo_2$ measurement, which is useful in the selection of the amputation site, may also reflect muscle blood flow. Amputation-wound healing is dependent on many factors, and any investigation that might aid in the correct selection of amputation site and thereby improve the patient's chances of an uneventful recovery should be used, since peri-operative prophylactic antibiotics are not going to 'save' an amputation performed on ischaemic tissue at too distal a level.

Opsomming

Amputasie-chirurgie in pasiënte met perifere vaskulêre siekte word met hoë hersienings- en mortaliteitskoerse geassosieer. 'n Prospektiewe loodsstudie het die intraoperatiewe lewering van sefoksitien natrium na die amputasieplek ondersoek, en het preoperatiewe transkutane suurstofdrukmetings gebruik om die antibiotikumvlakke in weefsel by die amputasieplek te probeer voorspel. Die konsentrasie van antibiotikum is gemeet in plasma en spiere van die amputasieplek ten tye van die amputasie, en 'n beduidende verskil in antibiotikumverspreiding tussen geneesde en gefaalde amputasies is aangetoon. Transkutane suurstofdruk het met die antibiotiese verspreiding gekorreleer.

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A Comparison of Laser Doppler Fluxmetry and Transcutaneous Oxygen Pressure Measurement in the Dysvascular Patient Requiring Amputation

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Objective: To determine the predictive power of laser Doppler fluxmetry (LDF), both heated and unheated, as a preoperative investigation of wound healing potential in dysvascular patients requiring amputation, by comparison with transcutaneous oxygen pressure measurement ($TcpO_2$) and the limb to chest $TcpO_2$ index.

Methods: Thirty-five non-diabetic patients with peripheral vascular disease were investigated before amputation. Heated and unheated LDF and heated $TcpO_2$ measurements were taken on the chest wall and at the routine above-knee, below-knee and mid-foot amputation levels. Wound healing potential was evaluated against a $TcpO_2$ index value of 0.55 and on clinical outcome.

Results: A heated LDF value of 4.9 arbitrary units (au) was shown by receiver-operator characteristic curve to have the best predictive power, with an overall accuracy for preoperative prediction of wound healing of 91.4%, and a predictive value for wound failure of 89%. Based on the heated LDF of 4.9 au, review of 26 amputations performed shows the overall accuracy for preoperative prediction of wound healing of 92.3%, a predictive value for wound healing of 100%, and a predictive value for wound failure of 62.5%.

Conclusion: A heated LDF value of 4.9 au appears to be a useful predictor of the potential of an amputation site to heal.

Key Words: Laser Doppler fluxmetry; Blood gas transcutaneous; Amputation.

Introduction

Peripheral vascular disease is the most common cause of lower limb amputation.[1,2] Amputation in these patients is associated with high morbidity and mortality.[3] Primary wound healing is more likely the more proximally the amputation is performed. While proximal amputation with primary wound healing reduces initial morbidity, the additional energy cost required to use a larger and heavier prosthesis makes total rehabilitation more difficult.[4] Preservation of the knee or ankle joint improves the chance of successful rehabilitation, but increases the risk of delayed or failed wound healing with consequent morbidity and mortality. The problem facing the surgeon is determination of the most distal site at which an amputation will heal.

The benefits to both patients and hospital administrations of using routine preoperative evaluation of amputation wound healing potential have been reported.[3,5] Despite this, routine evaluation of preoperative wound healing potential has not been widely implemented. A reason for this is that there is no single investigation which has gained universal acceptance. This is not surprising as there are many factors in addition to the adequacy of regional blood flow which influence wound healing. Investigations such as Doppler ankle-brachial pressure indices, Xenon[133] skin clearance, thermography, fluorescein dye angiography, transcutaneous oxygen pressure measurement ($TcpO_2$) and laser Doppler fluxmetry (LDF) have been tried. While each test has its proponents, it has not always been possible to reproduce the results reported in different settings.

Of these tests, $TcpO_2$ measurement is presently held to be the most useful investigation of preoperative wound healing potential.[6,7] The use of the ratio of $TcpO_2$ measurement obtained at the amputation level to that of the anterior chest wall, the $TcpO_2$ index, has improved the sensitivity and specificity of the test.[3] The index gives a better indication of oxygen delivery as it takes into account variation caused by central factors of oxygen delivery, such as cardiac and respiratory function. It has been our practice to use the

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$TcpO_2$ index to select the most distal amputation site which will heal by primary intention. An amputation site with a $TcpO_2$ index greater than 0.55 is considered likely to heal and is associated with an amputation revision rate of less than 5%.[3]

Transcutaneous oxygen pressure measurement is however time consuming. With patient acclimatisation to the environmental temperature of the laboratory, probe calibration, and measurement at the four routine sites, the average test time is approximately 2 h. A test is required which is as sensitive and specific as the $TcpO_2$ index, but which can be performed more rapidly.

Laser Doppler fluxmetry (LDF), a test of skin microperfusion, has found a place in the evaluation of diabetic microangiopathy.[8] It has also been proposed as a test of amputation wound healing potential.[9–11] If the test is performed on unheated skin, readings can be obtained 3 min after application of the probe and with the heated probe after 5 min. Routine testing at the four sites would then take less than 30 min. There is however controversy as to whether skin heating is required.[10–14] In addition, several shortcomings of LDF are documented.[15,16] These include problems with zeroing, variations in biological zero and the various ways in which the output of the LDF is expressed, which range from voltage (mV), arbitrary units, flux units, to blood flow per cm^3. In view of this it is probably necessary for each laboratory to validate the use of LDF in its own setting.[17]

The aim of this study was to compare readings obtained from both an unheated and heated LDF with $TcpO_2$ measurement in non-diabetic patients with peripheral vascular disease requiring amputation.

Materials and Methods

Thirty-five patients with atherosclerotic peripheral vascular disease undergoing routine evaluation of amputation wound healing potential were studied at the Non-invasive Vascular Laboratory, King Edward VIII Hospital. The patients were not diabetic and were not on vasoactive medication. Informed consent was obtained and the study was performed with the approval of the University of Natal, Faculty of Medicine Bioethics Committee.

Prior to testing, each patient lay supine for 20 min to acclimatise to the ambient temperature of the laboratory, which ranged from 20 to 23 °C. To avoid the possible confounding effects of previous heating of the skin, laser Doppler measurements were made before $TcpO_2$ measurement.

LDF was performed with a Laserflo BPM2 Blood Perfusion Monitor, Vasamedics, St Paul. The laserflo monitor does not offer a zeroing procedure, but rather a "user confidence test" which checks that the laser and photodetector are within specifications. This test was performed before each series of LDF measurements were made.

Measurement sites were shaved and cleaned with an alcohol solution when necessary. The laser probe was attached to the skin by means of a double sided adhesive ring and the unheated LDF measurements recorded 3 min after probe application. For the heated readings, the probe was then heated to 45 °C and recordings made after 5 min of heating. The LDF index, the ratio of limb to chest LDF reading was calculated for the amputation sites.

The chest and the below-knee sites were measured in all patients. Measurements at the foot or above-knee site was based on the clinical decision required. Where the choice was between below-knee amputation and an amputation about the foot, the foot site was measured and similarly, the above-knee site was measured when clinically the choice was between a below-knee and an above-knee amputation. Data were obtained from the foot ($n=17$), the below-knee site ($n=35$), the above-knee site ($n=17$) and the anterior chest wall ($n=35$). One patient presenting with a gangrenous forefoot, had only a below-knee measurement taken, and no measurement made at the foot.

Transcutaneous oxygen pressure measurement was made using a Hewlett Packard Transcutaneous Oxygen Monitor. The monitor was calibrated against air and a zeroing solution, according to the manfacturers' instructions. Calibration was performed before use on each patient. The probe was attached to the skin by a double sided adhesive ring, over a drop of contact solution. The heating thermistor was set to 45 °C Hyperaemic stabilisation occurred within 20 min and readings were taken after 20 min. $TcpO_2$ measurements were taken at the same sites as the LDF measurements. The $TcpO_2$ index, the ratio of limb to chest $TcpO_2$ was calculated for the amputation sites.

Amputations were performed according to standardised procedures by members of the Vascular Service. Although guided by the preoperative assessment of wound healing potential, the final decision as to the level of amputation in patients in this study, was made intraoperatively by the surgeon.

Statistical analysis was performed using Spearman's rank correlation. The sensitivity and specificity, and positive and negative predictive value of LDF relative to $TcpO_2$ were calculated. Sensitivity was defined as the ability of LDF to predict wound healing failure and specificity as the ability of the test to predict

Table 1. $TcpO_2$ and laser Doppler values at the chest and amputation levels.

	Chest $n=35$	Above-knee $n=17$	Below-knee $n=35$	Foot $n=17$
$TcpO_2$ (mmHg)	55.7±11.2	39.2±19.0	36.3±20.3	17.3±13.3
Laser unheated (au)	3.9±2.1	1.7±1.1	1.6±0.9	1.9±1.3
Laser heated (au)	18.1±4.1	10.0±4.8	7.9±5.0	5.2±5.2
$TcpO_2$ index		0.73±0.37	0.62±0.31	0.31±0.23
Laser index unheated		0.61±0.41	0.52±0.41	0.53±0.63
Laser-index heated		0.58±0.33	0.46±0.33	0.29±0.30

$TcpO_2$, unheated and heated laser Doppler fluxmetry, $TcpO_2$ index, and unheated and heated laser Doppler indices expressed as means and one standard deviation are shown for the different measurement sites. The indices are the limb to chest ratios. Correlation of the results at each site was by Spearman's rank correlation which was considered significant when $p<0.05$. Significant correlation was noted between heated LDF and both absolute $TcpO_2$ and the $TcpO_2$ index and between the heated LDF index and the $TcpO_2$ index at the foot and below-knee sites.

wound healing. Receiver-operator characteristic (ROC) curves were constructed to determine the LDF value which would be most useful for preoperative prediction of wound healing.

Results

The absolute LDF and $TcpO_2$ measurements, and the LDF index and the TcpO2 index at the different sites are expressed as means and one standard deviation are shown in Table 1. The ranges of the readings were, unheated LDF 0–12 arbitrary units (au), heated LDF 0–27.8 au, $TcpO_2$ 0–77 mmHg, the unheated LDF index 0–2.9, the heated LDF index 0–14, and the $TcpO_2$ index 0–1.43. The highest mean readings for LDF and $TcpO_2$ were measured at the chest. Significant correlations were found between heated LDF and $TcpO_2$ absolute and index values at the foot and below-knee sites.

Pooling the heated LDF data for the various sites there was a significant correlation between heated LDF and $TcpO_2$ ($n=104$), $r=0.63$, ($p<0.0001$), heated LDF and the $TcpO_2$ index, ($n=69$), $r=0.72$ ($p<0.0001$), heated LDF index and the $TcpO_2$ index, ($n=69$), $r=0.68$, ($p<0.0001$) and between unheated LDF and $TcpO_2$, with a low correlation co-efficient ($n=104$), $r=0.31$, $p<0.001$. There was poor correlation between the unheated LDF index and the $TcpO_2$ index, ($n=69$), $r=0.21$, $p=0.08$ and between unheated LDF and the $TcpO_2$ index ($n=69$), $r=0.18$, $p=0.21$. The relationship between heated LDF and $TcpO_2$ index is shown in Fig. 1.

Various $TcpO_2$ values have been suggested as predictive of amputation wound healing. These range from 0–40 mmHg.[18–20] Despite a significant correlation between absolute unheated LDF and $TcpO_2$ readings, the correlation co-efficient is low and there is poor linearity. There is no unheated LDF level which has a high predictive power when compared to $TcpO_2$.

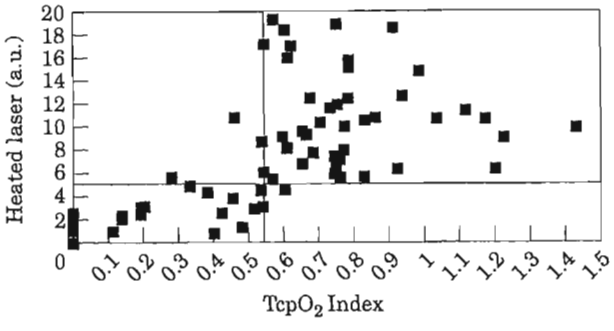

Fig. 1. Scattergram showing the relationship between the $TcpO_2$ index and heated LDF ($n=69$). The Spearman rank correlation coefficient is $r=0.72$, ($p<0.0001$). The linear regression equation is $y=2.38+9.4x$. No amputation site with a $TcpO_2$ index of less than 0.55 would be expected to heal. A heated LDF value of 4.9 au is shown as a potential predictive value.

Receiver-operator characteristic (ROC) curves were constructed to determine the LDF value which would be most useful for preoperative prediction of wound healing.[21] This is a graphic way of portraying the trade-offs involved between improving either the LDFs sensitivity or its specificity. Sensitivity and specificity were calculated for unheated and heated LDF at $TcpO_2$ indices of 0.50, 0.53, 0.55, 0.57 and 6. Sensitivity was then plotted against 1-specificity for unheated and heated LDF against each of the $TcpO_2$ indices. The diagnostic accuracy based on the area under the curve was also calculated.[22] For the $TcpO_2$ index of 0.55 the best predictive level was found to be at a heated LDF of 4.9 au (Fig. 2).

Twenty-five readings fall below a heated LDF = 4.9 au and all but one have a $TcpO_2$ index of less than 0.55. Of the 44 readings above LDF = 4.9 au, 40 are above the $TcpO_2$ index of 0.55 and would be expected to heal. The four sets of readings above LDF = 4.9 au and below a $TcpO_2$ of 0.55 would be expected to fail. This has a sensitivity of 97.6%, specificity of 82.8%, an LDF >4.9 au has a predictive value of 88.9% in identifying sites that will heal and an LDF <4.9 au has

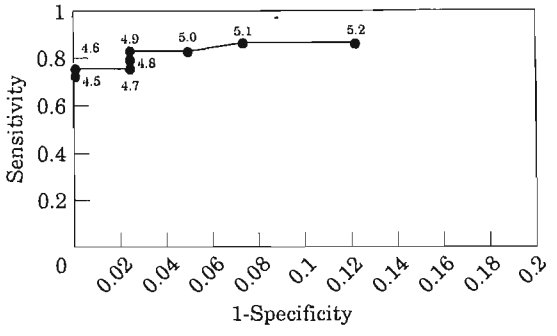

Fig. 2. Receiver-operator characteristic curve displaying sensitivity and 1-specificity of absolute LDF values from 4.5 to 5.2 based on a $TcpO_2$ index of 0.55.

a predictive value of 96% in identifying sites that will fail to heal, with an overall accuracy for preoperative prediction of wound healing or failure of 91.4%.

Clinical outcome

Of the thirty-five patients, two underwent bypass graft surgery and were excluded from follow-up, one patient refused surgery and three patients died perioperatively. Three patients were transferred back to rural hospitals before wound healing was complete and have been lost to follow-up. Twenty-six amputations, four transmetatarsal, 15 below-knee and seven above-knee amputations were available for evaluation. Six of these amputations were performed at sites with a $TcpO_2$ index of less than 0.55, five of which failed to heal and required revision to a more proximal site. One amputation with a $TcpO_2$ index of 0.54 and a heated LDF of 4.7 au healed after four weeks.

A heated LDF of 4.9 au had a sensitivity of 100%, specificity of 90%, and LDF >4.9 au has a predictive value of 100% in identifying sites that will heal and an LDF <4.9 au has a predictive value of 62.5% in identifying sites that will fail to heal, with an overall accuracy for preoperative prediction of wound healing or failure of 92.3%.

Discussion

The microvascular bed of the skin is composed of superficial nutritional capillary loops containing approximately ~5% of the cutaneous bloodflow and the subpapillary, thermoregulatory vascular bed comprised mainly of venules, containing ~95% of the skin bloodflow.[23] The $TcpO_2$ reading is the reduction current produced when surplus oxygen molecules diffuse from the cutaneous nutritional capillary loops under maximal hyperaemia.[24] LDF has a measuring depth of 1–2 mm and the predominant part of the signal comes from the subpapillary thermoregulatory vessels. LDF therefore evaluates total skin microcirculation while $TcpO_2$ evaluates skin nutritional circulation.

The findings of the present study show a significant but poor correlation between unheated LDF and $TcpO_2$ ($r=0.31$). Belcaro *et al.*, reported similar results with the correlation of $TcpO_2$ to resting LDF being $r=0.4$.[8] These findings contradict those of Matsen *et al.*, who in a relatively small sample found that non-heated LDF measurements did not correlate with local skin perfusion.[25]

The signs and symptoms of peripheral vascular disease, intermittent claudication, rest pain, ulceration and finally gangrene are all manifestations of insufficient oxygen and nutrient delivery at a cellular level, secondary to relative degrees of arterial occlusion. It is therefore expected that tests of perfusion of both the macro- and microcirculation should reflect a fall in perfusion as the tests are performed more distally in the atherosclerotic patient. The magnitude of the segmental fall in perfusion parameters is dependent on the site and severity of the disease process. While both the absolute $TcpO_2$ measurements and the $TcpO_2$ index and the heated LDF reflect a fall in mean values as the site of measurement moves distally, the reduction in unheated LDF results is less apparent because of the large range of readings.

Unheated LDF readings may be high around the margin of diabetic ulcers.[26,27] The rise in LDF in these patients with microangiopathy has been attributed to shunting of blood to the thermoregulatory plexus or the dermal capillary loops. The very wide range of unheated LDF readings obtained at the foot, 0–10.9 au may be due to a similar phenomenon. Ischaemia is associated with increasing peripheral vasodilatation in an attempt to improve oxygen and nutrient supply to the tissues. In the ischaemic foot the LDF value may be high when compensation is successful — maximal vasodilatation in the presence of an adequate inflow, or it may be low if the inflow is insufficient despite maximal vasodilatory compensation.

A large variability in resting unheated LDF has been reported.[28,29] This variability has been attributed to physiological variation in skin perfusion, the structure of the anatomical microvasculature under the probe, [30] methodological factors (e.g. penetration depth of the laser, and probe configuration) and environmental factors.[29] This wide variation is seen in the values obtained at an essentially normal segment of the vasculature, the anterior chest wall, where the co-efficient

of variation of the unheated LDF was 74.4%. Heating reduced the co-efficient of variation to 22.7% which is similar to that of $TcpO_2$, 23.6%.

Another factor which influences LDF variability is the biological zero.[31] The biological zero is the residual reading, above zero, obtained with LDF when the blood flow to a limb is occluded with an arterial tourniquet. The biological zero is thought to be due to Brownian motion, but may result in part from retrograde osseous bloodflow. Biological zero varies with perfusion, vasodilatation, skin temperature and oedema formation.[31] While the interpretation of LDF readings may be improved by subtraction of the biological zero from the LDF value, or perhaps by the evaluation of biological zero itself, this was not done in this study. In a pilot study, attempts at measuring biological zero in patients with severe peripheral vascular disease caused pain, and the movement artefacts which resulted, affected the readings obtained in most patients.

The addition of cutaneous heating has been reported to improve the predictive power of LDF when evaluating wound healing.[9,10,14,25] Heating of the skin "arterialises" the capillary bed by local vasodilation[12] causing maximal hyperaemia. Direct comparisons of reported LDF values upon which clinical decisions are made are not possible, because of differences in temperature protocols and the different units in which the output of different laser Doppler fluxmeters are expressed.

In the present study heating the LDF probe to 45 °C improved the preoperative prediction potential for evaluating wound healing in PVD patients. Significant correlation was found between heated LDF and $TcpO_2$; heated LDF index and $TcpO_2$ index, and heated LDF and $TcpO_2$ index, $r=0.72$, $p<0.0001$. The degree of the significance obtained is probably due to the comparison being made over the wide range of heated LDF values obtained.

While there is a low but significant correlation between unheated LDF and $TcpO_2$, unheated LDF does not appear to be clinically useful. Heating adds 5 min to each test and using a heated LDF value of 4.9 au gives a theoretical overall accuracy for preoperative prediction of wound healing or failure of 91.4%. In the clinical study, 92.3% accuracy was achieved.

The theoretical predictive value for wound healing is 89%, which was exceeded in the clinical study (100%). Similarly the predictive power of the $TcpO_2$ index for wound healing was 100%, which differs from our previous experience, of 270 amputations in which the $TcpO_2$ index of >0.55 was associated with ±90–95% predictive power of wound healing over 4 consecutive years.[3] This difference is most probably due to the relatively small sample size.

The theoretical predictive value for wound failure of 96% would mean that in 4% of cases a limb would undergo ablation at a site higher than that which has potential to heal. In practice the predictive power for wound failure was found to be 62.5%. Again this may be artificially low because of sample size.

These data suggest that a heated LDF >4.9 au would be a relatively quick and clinically useful preoperative evaluation of an amputation sites' potential to heal. However, basing evaluation of potential wound failure at a site on a heated LDF of <4.9 au could result in up to a third of amputations with a heated LDF <4.9 au being performed at a site more proximal to that which has potential to heal.

It must be remembered, that the predictive LDF value of 4.9 au is based on a $TcpO_2$ "gold standard", which has its own measurement error. Despite this limitation, this study suggests that widespread implementation of heated LDF may be as useful as limited use of $TcpO_2$ measurement for preoperative evaluation of wound healing potential in patients with peripheral vascular disease.

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The potential benefit of pre-operative assessment of amputation wound healing potential in peripheral vascular disease

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Abstract **Choosing the most distal amputation level that will heal is difficult in patients with peripheral vascular disease. From 1984 to 1988, 965 patients underwent 1 563 amputations for lower limb peripheral vascular disease at King Edward VIII Hospital, Durban. The primary amputation revision rate was 51% with a mortality rate of 23,1%. Random pre-operative assessment of amputation wound healing potential using a transcutaneous oxygen pressure index was investigated over the 4-year period, 1987 - 1990. This was responsible for a reduction in the amputation revision rate to 8,2% in patients tested.**

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While peripheral vascular disease is generally thought to be uncommon in the black population of South Africa, its incidence in these patients appears to be increasing steadily. This is in keeping with the worldwide increase in the disease.[1] A feature of the disease in black people is the delay in presentation; 75 - 80% of patients present with threatened gangrene or gangrenous limbs. Many limbs are therefore unsalvageable and require amputation.

Choosing the optimal amputation level can be difficult. A change in the philosophy of amputation surgery now places emphasis on the preservation of as many functional joints as possible to facilitate better rehabilitation. Wound healing can generally be achieved with a proximal amputation, but at the cost of subsequent limb function and rehabilitation. The desire to ablate as distally as possible increases the chances of incorrect site selection, with subsequent wound failure necessitating revision amputation. This increases the likelihood of morbidity and mortality.

In 1978, Malone *et al.*[2] addressed the problem of amputation revision surgery and outlined a programme involving pre-operative assessment of amputation wound healing potential and immediate postoperative prosthetic fitting that would save the Veteran's Administration Hospitals 16 million dollars annually.

The cost of amputation revision surgery in our hospitals is unknown and the concept of pre-operative assessment of amputation wound healing potential has not gained much support in South Africa.

This study investigates the extent and cost of the problem of revision amputation surgery in patients with peripheral vascular disease at King Edward VIII Hospital and examines the potential savings that might accrue from a programme of pre-operative assessment of amputation wound healing potential.

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Method

The Natal Provincial Administration's centralised computer records of all patients admitted to King Edward VIII Hospital between 1984 and 1988 were reviewed. The following data on patients who underwent amputation for peripheral vascular disease were obtained: (*i*) the total number of lower limb amputees; (*ii*) level and number of amputations per patient; (*iii*) in-hospital mortality; and (*iv*) the duration of hospital stay.

Pre-operative assessment

Pre-operative assessment of amputation wound healing potential was investigated using transcutaneous oxygen pressure ($PtcO_2$) measurement. $PtcO_2$ measurements were made using commercially available oxygen monitors (Hellige Servomed and Hewlett Packard). After a 20-minute warm-up period, the probes were calibrated against air and a zeroing solution and corrected for barometric pressure. The sites to be measured were shaved when necessary and cleaned with an alcohol solution. The probe was attached to the skin with a double-sided adhesive ring, over a drop of contact solution. The heating element of the probe was set at 45°C and readings were made after 20 minutes, to allow time for hyperaemic stabilisation to occur.

$PtcO_2$ readings were taken at the routine amputation sites: (*i*) the mid-dorsum of the foot; (*ii*) 10 cm below the tibial tuberosity over the anterior compartment of the leg; (*iii*) 10 cm proximal to the patella over the anterior midline; and (*iv*) on the anterior chest wall 5 cm below the clavicle in the mid-clavicular line. The $PtcO_2$ index, i.e. the ratio of limb to chest $PtcO_2$, was calculated for each site.

In 1987 and 1988 patients with peripheral vascular disease who required lower limb amputation were randomly selected for pre-operative $PtcO_2$ measurement. $PtcO_2$ values were recorded at the routine amputation sites. The surgeon was not told the results, and selected the amputation level on clinical criteria. These were pulse status, general skin condition at the selected site and the amount of skin and muscle bleeding at the time of surgical incision. The patients were followed up postoperatively and a procedure was considered to have failed if revision of the amputation was required either at the same level or at a more proximal level.

From 1989 the surgeon was advised of the most distal amputation level at which wound healing could be expected. This was determined as being the most distal routine amputation site with a $PtcO_2$ index greater than 0,55.[3] The surgeon could, however, still decide to amputate more distally if, on clinical and intra-operative assessment, he considered that the more distal site would heal.

Results

During the 5-year period, 1984 - 1988, 965 patients required 1 563 lower limb amputations for peripheral vascular disease; 222 patients died in hospital. The primary revision rate, i.e. the number of first-time amputations that required revision, was 51%. The in-hospital

mortality rate was 23,1% and the mortality rate per amputation was 14,3%. The number of patients per year who required a lower limb amputation for peripheral vascular disease, the number of patients who required one or more revisions and the number of patients who died in hospital after amputation are shown in Fig. 1.

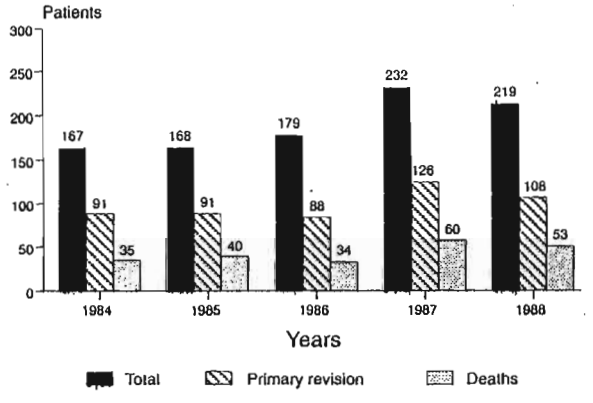

FIG. 1.
Total number of patients per year undergoing lower limb amputation for peripheral vascular disease, number of patients who required one or more revision amputations and number of patients who died after amputation (1984 - 1988).

The anatomical distribution of amputations based on the initial amputation site, the number of patients who required revision at the same or more proximal sites and the number of patients who died are shown in Fig. 2.

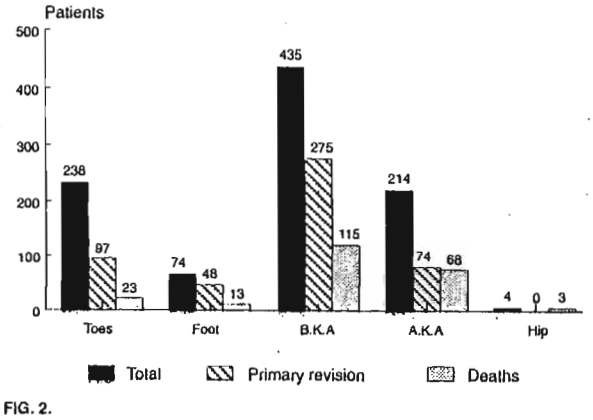

FIG. 2.
Initial site of amputation in 965 patients, number of these patients who required revision amputations and number of patients who died (1984 - 1988).

The primary revision rate is skewed because of the unit's policy of performing an initial guillotine amputation and subsequent definitive amputation in patients with septic non-salvageable limbs.[4] It was not possible from the available data to determine how many guillotine amputations were performed. The figure can, however, be approximated by counting the number of foot and below-knee amputations that were revised at the same level as the initial amputation. This would reduce the primary revision rate in the patients who survived to approximately 35%.

The total number of days spent in hospital was available for 1987 and 1988. The average number of days spent in hospital following an amputation that healed primarily was obtained for the different levels. The number of extra days spent in hospital after revision amputation was then calculated. The average increase in hospital stay is shown in Fig. 3. The total increase in hospital stay following revision amputation surgery in patients who survived was 4 980 days per year. The extra days spent in hospital by patients who subsequently died after one or more revisions was 1 371 days per year. Altogether, patients who underwent revision amputation surgery occupied 17,4 surgical beds per day per year.

In 1987 and 1988 $PtcO_2$ values were measured in 174 patients, 122 of whom met the following criteria: (*i*) the patient was undergoing a definitive amputation and not a guillotine amputation; and (*ii*) the patient had not undergone a revascularisation procedure in the affected

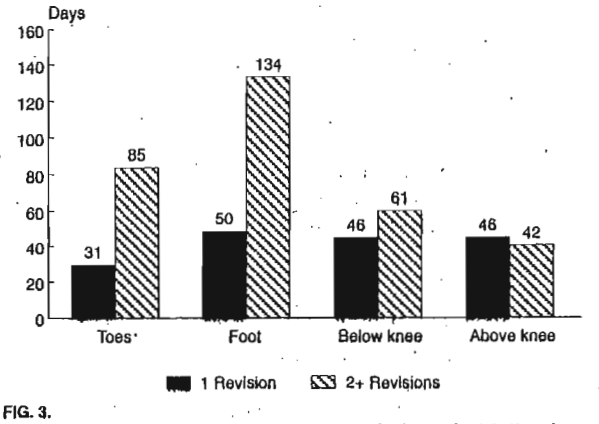

FIG. 3.
Average number of extra days spent in hospital following one or several revision amputations, based on the site of the initial amputation.

limb within the 2 weeks preceding $PtcO_2$ measurement. In 1989 and 1990 $PtcO_2$ measurements were performed in 218 patients, 148 of whom met the above criteria.

In 1987 the primary revision rate of patients who underwent pre-operative $PtcO_2$ investigation was 40,3%. Of all the amputations performed in 1987, 35,5% were performed at sites with a pre-operative $PtcO_2$ of less than 0,55. Based on the $PtcO_2$ index these sites were inappropriate and healing would not have been expected. None of these amputations healed. Of all the amputations, 4,8% failed to heal, despite a $PtcO_2$ index greater than 0,55. After informing the surgeon of the most distal site at which healing could be expected, the advice was overruled and a more distal amputation performed in 16,4% of patients in 1989 and in 6,6% of patients in 1990. All these amputations failed to heal. Informing the surgeon of the most distal amputation site at which healing could be expected significantly reduced the revision rate from 40,3% in 1987 to 8,2% in 1990 ($P < 0,0001$) (Table I).

Discussion

Revision amputation surgery increases morbidity and mortality. Apart from the cost to the patients, both

TABLE I.
Percentage of amputations requiring revision in patients who underwent pre-operative $PtcO_2$ measurement

	Percentage of amputations revised			
	1987	1988	1989	1990
Total revision rate	40,3	38,8	20,0	8,2*
$PtcO_2 < 0,55$	35,5	22,2	16,4	6,6
$PtcO_2 > 0,55$	4,8	16,6	3,6	1,6

*The reduction in revision rate between 1987/88 and 1990 is statistically significant; $P < 0,0001$. The total percentage of amputations that failed is divided into the percentage of all amputations performed at levels at which the $PtcO_2$ index was less than 0,55 and the percentage of all amputations performed at levels with a $PtcO_2$ index greater than 0,55. No amputations performed at a site with a $PtcO_2$ index less than 0,55 healed.

financial and in terms of subsequent rehabilitation, failed amputations are a burden on hospital resources. At an approximate bed cost of R200 per day, failed amputations cost the State an average of R1 270 000 per year.

The primary revision rate of 51%, while high, is in keeping with published figures. The primary revision rate in Ontario was 48% in 1978.[5] Analysis of several series reported by Hunter[6] shows a 46% failure rate for toe amputations, and a combined 33% failure rate for transmetatarsal and Symes amputations. Warren and Kihn[7] reported a 32% failure rate in below-knee amputations in 127 patients and more recently Keagy reported a 19% failure rate in 626 below-knee amputations.[8] It is suggested that a 20% failure rate is now the norm. Revision rates as low as 10%, based solely on clinical evaluation, have been reported.[9]

The solution to the problem, as described by Malone *et al.*[2] is pre-operative assessment of amputation wound healing potential. The difficulty associated with clinical assessment is well known. The most reliable criteria are skin colour and temperature and capillary skin bleeding at surgery. Numerous investigations have been used to try to predict wound healing potential. These include segmental measurement of Doppler pressure, xenon-133 skin clearance, thermographic assessment, measurement of muscle pH, fluorescein dye angiographic examination, pulse volume recording, photoplethysmographic assessment, laser Doppler velocimetry and $PtcO_2$ measurement.

Wound healing is dependent on many factors, both local and systemic. The problem common to all local non-invasive investigations is that information is gained about perfusion or oxygenation of either skin or muscle but not both. The problem is compounded by the fact that the circulation to skin and muscle at the site of amputation does not always originate at the same level of the axial arterial tree. Perfusion of skin and muscle can therefore be different. Because specialised information is gained about only one aspect of the complex healing process, these non-invasive tests are better predictors of wound failure than wound healing. In comparisons of investigations, $PtcO_2$ measurement appears at present to be the most reliable indicator of amputation wound healing potential.[10,11]

In 1987 and 1988 the revision rates in patients undergoing pre-operative assessment of wound healing were 40,3% and 38,8% respectively. At this time, surgeons were selecting the amputation site clinically. Reviewing these revision rates with regard to the $PtcO_2$ index at the site of amputation, it is apparent that the majority of wound failures occurred at sites with a $PtcO_2$ index of less than 0,55. These failures may therefore be attributable to poor site selection. In 1987, 35,5% and in 1988, 22,2% of all the amputations performed were at sites at which wound healing would not be expected. No amputations with a pre-operative $PtcO_2$ index below 0,55 healed.

In 1989, when the surgeon was advised of the most distal site that could heal, the revision rate fell to 20%. The suggested amputation level was ignored, however, and the amputation was performed at a more distal site with a $PtcO_2$ index of less than 0,55 in 16,4% of amputations. All of these amputations failed. Surgeon acceptance of the investigation increased and in 1990 only 6,6% of amputations were at sites more distal than advised. All failed to heal.

The pre-operative use of the $PtcO_2$ index as an aid to level selection has significantly reduced the revision rate in these patients to less than 10%. If this reduction can be carried through to all patients with peripheral vascular disease who require lower limb amputation, 14 - 15 hospital beds would be freed for other use, or if unused, would theoretically generate a potential saving of R1,07 million annually. The associated benefit to the patient in terms of reduced morbidity is unquantifiable.

In summary, the primary amputation revision rate at King Edward VIII Hospital was found to be high. A trial programme of pre-operative assessment of amputation wound healing using a $PtcO_2$ index significantly reduced the revision rate. Routine use of the investigation appears justified.

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