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Review Article

Microvascular investigations in diabetes mellitus

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Summary: This paper reviews the current literature concerning the different investigative modalities available to assess the microcirculation in diabetic microangiopathy. The advantages and disadvantages of the different invasive and noninvasive methods available are presented objectively. We have concentrated on the tests that provide a quantitative assessment of the microcirculation, including laser Doppler fluxmetry, capillary microscopy, plethysmography, transcutaneous oximetry and radioactive isotope clearance. Some of the invasive methods described are now being replaced by noninvasive equivalents, providing similar information with less discomfort and risk to the patient.

Introduction

The complications resulting from diabetic angiopathy can be severe and debilitating. An enormous amount of research has been undertaken to try to clarify the mechanisms by which microangiopathy occurs but has so far yielded no clear answer. The development of microangiopathy is probably multi-factorial in origin and includes genetic susceptibility. Factors that are thought to contribute towards the formation of microangiopathy include those shown in Table I(a).

Unfortunately, by the time microvascular changes become clinically evident, there is often little that can be done in the way of treatment. It would be advantageous to identify those patients at risk of developing severe retinal and glomerular impairment and neuropathic or atherosclerotic lesions. Functional microvascular changes may occur early in the development of clinical angiopathy and investigation of the microcirculation might therefore provide a means of detecting angiopathy before it becomes clinically evident. Microvascular measurement techniques are also used clinically in the assessment of sympathtic neuropathy and investigation of the peripheral microcirculation may provide a way of detecting neuropathy in its earliest stages.

In research, microcirculatory investigations might be used to provide an objective test of different modes of treatment. In addition, any information about the nature of the microcirculatory fault in diabetic angiopathy may help in understanding its aetiology and in developing new treatment strategies. Many of the invasive techniques for microvascular measurement have been superseded by noninvasive techniques, which is clearly advantageous for the investigation of microangiopathy in the diabetic patient. This review places more emphasis on the noninvasive techniques available.

Importance of macrovascular assessment

Care must be used in the interpretation of microvascular assessments if macro- and microvascular disease coexist, and this is often the case, diabetic patients being more prone to cardiovascular and peripheral arterial disease than non-diabetics. The reasons for diabetics being more prone to macroangiopathy are not certain but probably include the factors shown in Table I(b). Occlusive macrovascular disease may impede the ability of the microcirculation to respond to a given stimulus. It is therefore important to evaluate the extent of one source of circulatory dysfunction in order to study the other.

Microvascular investigations

An investigation of vessel morphology may be informative about angiopathy in its later stages and can help to assess its progression. However, in order to identify microcirculatory problems earlier on in their development, a functional assessment of the microcirculation may be more useful. This usually consists of measuring blood flow, either in
Table I  Factors of importance in the pathogenesis of diabetic micro- and macroangiopathy

<table>
<thead>
<tr>
<th>(a)</th>
<th>Microangiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>Results in nonenzymic glycosylation of proteins in the vessel walls</td>
</tr>
<tr>
<td>Insulin-immune complexes</td>
<td>Stimulate monocytes and macrophages to produce procoagulant activity</td>
</tr>
<tr>
<td>Platelet activation</td>
<td>Initiates thrombosis, release of angiogenic factors such as PDGF and the transforming growth factors (TGF)-alpha and TGF-beta, and the release of vasoconstrictor substances such as thromboxane A2</td>
</tr>
<tr>
<td>Endothelial activation</td>
<td>Results in increased permeability and release of vasoactive substances</td>
</tr>
<tr>
<td>Macrophage and monocyte activation</td>
<td>Produces free radicals (superoxides, hydroxyl radicals and peroxides) and cytokines and causes vascular damage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(b)</th>
<th>Macroangiopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>A risk factor in atherogenesis which increases adherence of monocytes and macrophages to the vessel walls and may result in local accumulation of vasoactive substances, increased proliferation of endothelium due to the release of growth factors, and damage to the vessel wall by free radicals</td>
</tr>
<tr>
<td>Free radicals</td>
<td>Increased free radical activity is seen in diabetes7,8 and may be involved in microvascular damage11,12</td>
</tr>
<tr>
<td>Lipoproteins</td>
<td>Concentrations of low density lipoproteins and very low density lipoproteins are high in patients with poorly controlled diabetes13,14 and this may be important in atherogenesis. High density lipoproteins are said to have a protective role in atherogenesis and are lower in some diabetics15</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Not considered a ‘very important factor in vascular disease in diabetes’ by most authors</td>
</tr>
<tr>
<td>Other factors</td>
<td>Including: hyperinsulinaemia, rheological factors, growth factors, reduced physical activity, obesity and genetic factors</td>
</tr>
</tbody>
</table>

PDGF = platelet-derived growth factor.

the steady state or in response to some provocation. The resting skin blood flow in diabetic patients is often shown to be normal and yet the maximal flows are impaired.16,17 Since there has been some difficulty in finding abnormal data at rest (possibly because of some redundancy in the control of local flow18) many studies use some kind of provocation in order to expose a latent problem, for example, looking at blood flow either during exercise, while raising body temperature, after administering vasoactive substances19 or following tissue ischaemia. The actual pattern of the blood flow response to a challenge such as ischaemia may be important.20 In diabetes mellitus, return of blood flow after ischaemia is impaired in the skin of the toes21 and in the nailfold22 (although it occurs more rapidly in leg muscle23). The cold recovery time of skin blood flow is also longer.23

Another way to study the function of the microcirculation is to evaluate reflexes such as the reduction of blood flow normally seen on standing (the veno-arteriolar reflex). This is impaired in patients with diabetic neuropathy.24 Similarly, in the retina, the vasoconstriction normally caused by high oxygen tension is blocked by hyperglycaemia.16,25 Care must be taken in interpreting the changes in blood flow induced by such stimuli since there are various controlling influences that may be at work. These include sympathetic nerve activity, local autoregulatory mechanisms, venous reflexes and the status of arterio-venous shunts. Thermal entrainment studies suggest that the central and local regulatory mechanisms provide coarse and fine microvascular control respectively.26 It is therefore important to investigate the different systems separately, using both contralateral and local stimuli. It is also desirable to study flow in both the arterio-venous shunt vessels and the nutritional capillaries in the skin. Unfortunately, most studies to date are unable to distinguish between flow in these different vessels.

It may be meaningful to study the effects of microcirculatory changes on the chemical milieu of the tissues, including oxygen tension, to determine whether observed microvascular alterations have any functional significance. Nuclear magnetic resonance (NMR) spectroscopy may be employed to study this by examining the redox status within the tissues. One approach, which has not been exploited as yet, might be to study the fluorescence of the mitochondria as their metabolic state changes.

Investigative techniques

Blood tests and other nonspecific tests

It would be useful if a simple clinical examination or a laboratory test carried out on the blood or urine samples routinely taken from diabetic patients could show or predict the development of
angiopathy. It is known that hyperglycaemia has at least a permissive role in the aetiology of diabetic lesions, such as retinopathy and nephropathy. Monitoring the levels of glucose or glycosylated haemoglobin in the blood and attempting optimal glycaemic control may therefore help in preventing the development of microvascular complications. However, the relationship between these factors is not strict and metabolic control is of little use once microangiopathies have developed. One of the standard tests for diabetic microangiopathy is microalbuminuria, resulting from glomerular dysfunction. Early elevation of transcapillary leakage of albumin in the kidney (incipient nephropathy) is said to be the first sign of microvascular disease. If performed regularly in all diabetic patients, this test might facilitate the detection of angiopathy in its earliest clinical stages, but there are obvious financial and practical limitations. Another marker for angiopathy is a slight increase in blood pressure, although this is not very specific. An increased level of plasma von Willebrand factor has been proposed as an indicator of microangiopathy since its elevation is associated with retinal hyperpermeability. Angiotensin converting enzyme (which cleaves angiotensin I to angiotensin II and inactivates bradykinin) is also high in some diabetic patients and these have a higher incidence of retinopathy. Angiotensin converting enzyme was therefore thought to indicate widespread endothelial damage in microvascular disease. However, it is increased in only a small percentage of patients with microangiopathy and is a less reliable indicator than von Willebrand factor. Increased plasma levels of inactive renin may also be a marker for microvascular complications. Although in diabetic patients without microvascular complications, plasma inactive renin concentrations lie within the normal age-adjusted range, in those patients with retinopathy or albuminuria it is nearly always above this range. Similarly, limited joint motility in childhood diabetes mellitus indicates an increased risk for microvascular disease. The problem with many of these tests is that they indicate the presence of some process which accompanies angiopathy, rather than measuring it directly. They may therefore be useful as epidemiological pointers but are of little help in predicting and following angiopathy in an individual patient.

Invasive techniques

Many of the microcirculatory changes in diabetic microangiopathy were originally discovered using invasive techniques. Although in some cases these techniques have since been replaced by noninvasive methods, in others there is no substitute for the invasive approach. Instead, the methods have been made as atraumatic as possible. For example, in order to study capillary permeability and blood–tissue exchange, it is usually necessary to introduce labelled tracer substances invasively. However, their movement can now be monitored noninvasively, so reducing the trauma presented by the investigation.

Histology

Histological tissue measurement techniques show that blood vessel walls are thicker in diabetes mellitus and vascular lumina are narrower, especially in those patients with vascular complications. Capillary basement membrane thickening has been said to be the hallmark of microvascular disease. However, it occurs in parallel with microangiopathy, rather than being a cause, and tissue biopsy for investigation of basement membrane thickness is a poor substitute for a functional assessment of the microcirculation.

Local clearance (blood flow)

Clearance of radioactive isotopes such as $^{133}$Xe and Na$^{31}$I can be used to measure perfusion. By injecting $^{133}$Xe into muscle or skin its rate of disappearance can be used to measure local blood flow. $^{133}$Xe clearance is thought to reflect blood flow since it is freely diffusible and fat soluble and crosses all vascular barriers. In contrast, the clearance of Na$^{31}$I may be limited by capillary permeability rather than blood flow. This means that in diabetes, where capillary thickening is often seen, rates of blood flow may be underestimated by Na$^{31}$I clearance rates alone. Using combined xenon and sodium clearance measurements it is possible to study vessel–tissue exchange as well as blood flow.

Skin perfusion pressures

In this technique, an intradermal injection of a radioactive tracer mixed with histamine (to promote vasodilatation) is given and the washout measured with a scintillation counter. A blood pressure cuff is applied over the injection site and the pressure in it increased until washout stops. This cuff pressure is taken as the skin perfusion pressure (SPP). A number of different radioactive tracers, including $^{131}$I-antipyrine and $^{99m}$Tc pertechnate, have been used. This technique has its disadvantages, as it is time consuming, especially if the SPP is to be determined at more than one site, and painful enough to require analgesia. An alternative new approach using either a photoplethysmography transducer or a laser Doppler probe (see laser Doppler fluxmetry below) underneath an inflatable cuff may be more useful.

Capillary filtration and permeability

Increased capillary diffusion capacity (CDC) has been demonstrated by various investigators in different tissues (such as skeletal muscle, retina and nerves) for small ions, dopamine, fluor-
escin, albumin, IgG and 131I. Microvascular permeability is related to the metabolic state and may be reduced by metabolic regulation. The permeability of the vascular diffusion barriers, i.e. the capillary wall and pericapillary collagen sheath, can be measured using the 'relatively atraumatic technique' of intravital fluorescence videomicroscopy, especially in the eye and nailfold. Sodium fluorescein passes the capillary wall and pericapillary space faster in diabetic patients. However, the results of such studies should be interpreted with caution, since there may be effects due to, for example, the lymphatic return of the tracers or to the labelled substances being handled differently from unlabelled ones.

Measurement of capillary pressure using micropipettes Capillary pressure can be measured directly using a microinjection technique. Using this method the pressure in the arteriolar end, the loop and the venular end of the capillary can be measured, and an assessment of the pressures responsible for fluid filtration and reabsorption evaluated. Nailfold capillary pressure have been found to be elevated in young insulin-dependent diabetics in the early stages of disease. The regulation of pressure in relation to skin temperature is also disturbed and the pressure during postocclusive reactive hyperaemia is less than in normal subjects.

Noninvasive techniques

It is preferable that any routine investigations be noninvasive. Some of the tests described above have been abandoned since the information needed can be obtained using the noninvasive tests described below. Such tests are less traumatic to the patient and can be repeated as necessary to assess the development and progression of angiopathy.

Vessel morphology Abnormalities in vessel morphology can be investigated using in vivo microscopy as well as by histological methods. Dilated nailfold capillaries have been found, and well defined in diabetes mellitus. However, there is a difference in capillary morphology even between toes on the same foot and so care must be taken in making measurements. The first retinal lesions in diabetic retinopathy can be seen noninvasively by fundoscopy or even earlier using fluorescein angiofluorography.

Skin temperature and thermal clearance The temperature of the skin tends to increase as the blood flow increases. It can be measured most simply using thermocouples, although many studies use thermography which is useful for showing gross changes, such as the cessation and recommencing of flow. However, skin temperature has a nonlinear relationship with blood flow, especially at higher levels (above 28°C) and responds slowly to flow changes, lagging behind them. Skin temperature may be useful for demonstrating large changes in the perfusion of skin after drug therapy or surgery. The maximum increase in finger skin temperature following ischaemia is decreased in diabetes mellitus and is still less in those patients with vascular complications.

Thermal clearance probes have been used to measure blood flow noninvasively in the skin. The probes consist typically of a heated central copper disc with an unheated copper annulus. The temperature difference between these is measured using thermocouples and decreases as the blood flow beneath the probe increases. Although, in muscle, the measurement depends greatly on the proximity of the probe to a blood vessel, in the skin, thermal clearance probes measure total skin blood flow including flow through arterio-venous anastomoses in the microcirculation and not nutritive flow only. The technique can give important information about flow distribution, especially if used in conjunction with a measure of total flow, such as laser Doppler flowmetry. An alternative method is to measure the power consumption of a thermostatically controlled heating element. The higher the blood flow, the more rapidly heat will be removed from the skin under the heating element and the more power will have to be supplied to maintain a fixed temperature. This approach is particularly attractive when the heating element used is that of a tcPO₂ electrode or thermostatically controlled laser Doppler probe holder. Oxygen tensions and blood flow measurements have been made simultaneously in this way.

Venous occlusion plethysmography Various techniques of plethysmography have been used for the measurement of limb blood flow. The method is able to give quantitative values after calibration and is said to be accurate and reproducible. It relies on measuring volume changes, the rate of increase in limb volume following release of occlusion being used to measure blood flow rates. The usual volumetric techniques are water displacement or a mercury-in-Silastic strain-gauge. In the hand and foot, values from venous occlusion plethysmography are assumed to reflect skin blood flow since there is little muscle present. However, in the arm and leg, the technique cannot distinguish between skin and muscle flow (unless used in conjunction with adrenaline ionophoresis). In normal subjects, under thermoneutral conditions, the muscle and skin contribute similarly to total limb blood flow so that changes in total flow are assumed to reflect changes in skin and muscle flow equally, but this may not hold true for diabetic
patients. In addition, whilst a thermal stress in a non-diabetic patient results in changes in skin blood flow only, this may not be the case in diabetes. Additional problems with the technique are that alterations in tissue compliance occur with each pulse and that a veno-arteriolar reflex may be induced by cuff compression if it is high or prolonged.

Strain gauge plethysmography has been used to study blood flow and capillary diffusion coefficients in the forearm. Following release of occlusion, the initial slope of the volume/time curve represents venous filling, and is used to calculate blood flow. Vascular resistance and venous capacity can also be calculated. The shallower slope that follows after a few minutes represents capillary filtration. This method is simple, quick and noninvasive.

Photoelectric plethysmography Using this technique, light is shone onto the skin where it is absorbed by both skin and blood. As the volume of blood in the skin increases, it absorbs more light and less is received by the detector. The method cannot distinguish between nutritive and shunt flow and is sensitive to movement and to the orientation and packing of the red cells. If the light source used also produces heat, it may cause vasodilatation which will interfere with the measurements. It can therefore only be used for qualitative comparisons. The technique has now been largely superseded by other methods.

Laser Doppler fluxmetry

Many observations of blood flow, especially in the skin, have been made using laser Doppler fluxmetry (LDF). This involves shining a laser light into the skin and measuring the back scattered light. Some of the incident light will strike moving red blood cells and be reflected with a shift in its frequency, caused by Doppler broadening, which is related to the speed of the cells. Studies in vitro show that the mean Doppler frequency is proportional to the rate of blood flow. In vivo studies in skin using Xe washout techniques confirm this linearity and show that stable recordings can be achieved. A laser Doppler flowmeter provides a signal, used as a measure of blood flow, which is proportional to the number of red cells in the volume penetrated by the laser beam and to the integrated red cell velocity. The laser beam penetrates through the skin and measures flow in a volume of several cubic millimeters. Although the beam is supposed to reach a depth of 0.6 mm, it maintains half of its sensitivity at a depth of 1.2 mm and can still pick up some cell movement deeper than this. This means that flow in small arterioles and arterio-venous anastomoses may be included so that LDF does not give a measure of flow in the nutritional capillaries alone. The dependence of LDF readings on depth of penetration means that care must be taken when comparing readings from diabetic patients in whom there may be epidermal thickening, with normal subjects. Synchronous measurement using LDF and microscopy in muscle and skin gives broadly comparable results but not under all conditions. In the skin there are differences in the timing of spontaneous oscillations, the time course of reactive hyperaemia and the response to venous hypertension between the two measurement techniques. In addition, LDF cannot distinguish between capillary flow and shunt flow and it is therefore now regarded as a measure of total blood flow in the skin. LDF may be a particularly useful technique in diabetes where there is thought to be increased non-nutritive flow in the skin due to sympathetic denervation.

The laser Doppler flowmeter does not provide absolute quantitative values relating to blood flow and calibration is difficult. The measurements show marked variations over distances of less than 1–2 cm and readings are generally regarded as not repeatable, although one series of measurements demonstrated a coefficient of variation of less than 12%. Although it may be valid to examine the relative changes in flow within an individual subject, comparisons of absolute blood flow rates between groups are of doubtful validity, especially when there are changes which may affect the laser Doppler signal (such as the glycosylation of connective tissues or thickening of capillary basement membranes seen in diabetic angiopathy).

In spite of its limitations, LDF is better validated as a measure of superficial microvascular volume flow rate than its predecessor photoelectric plethysmography. Using LDF it has been demonstrated that basal blood flow in the skin is not altered in diabetes mellitus but that maximal flows are impaired. Blood flow has also been measured in the retinal arterioles in diabetes mellitus using LDF.

Capillary microscopy Microscopy facilitates the direct and noninvasive study of the capillaries in the upper layers of the skin and in this way morphological abnormalities can be observed. In addition to such static investigations, blood flow in the capillaries can be measured. Some work has involved tracers such as fluorescein to measure retinal blood flow. In other studies, the capillary blood velocity itself is measured and along with capillary morphometry and estimation of the relative haematocrit, this allows volume flow patterns to be studied. Because the capillaries are under direct observation, microscopy is the only technique in which it is certain that nutritive blood flow alone is being measured. Simultaneous LDF and capillary blood velocity measurements have
been used to demonstrate discrepancies between total and nutritional flow in skin.\textsuperscript{77,78}

Early studies used time-consuming frame-by-frame analysis of capillary images recorded on video tape.\textsuperscript{88} This involves locating the position of a cell group or plasma gap, advancing the tape by several frames and measuring the new position of the cells and gaps. The velocity can be calculated from the distance moved in a set time (which is the number of frames multiplied by 1/25 or 1/30 seconds). In the simpler ‘flying spot’ technique,\textsuperscript{89} the speed of a moving spot superimposed on the video image is adjusted until it moves at the same rate as the red cells. The analysis can be carried out in real time but is subject to user-error and cannot detect rapid changes in velocity.

More sophisticated techniques have also been developed, based on early photodetector methods.\textsuperscript{90} They rely on the principles of cross-correlation, in either the space\textsuperscript{85} or the time\textsuperscript{83} domains, to match up the patterns created as dark red cells and light plasma gaps pass the photodetectors (or a window in the video image).

Subject movement presents a significant problem when these techniques are applied in humans. If the area being studied moves even slightly underneath the microscope objective, then the capillaries will move within the video image. Attempts have been made to immobilize the area under study using special casts or brackets\textsuperscript{91} but these do not always completely eliminate movement and may interfere with blood flow. Newer systems compensate for the movement by either tracking a capillary as it moves around in the image,\textsuperscript{86,87} or by performing a two-dimensional cross-correlation on a small area of the image (‘CapiFlow system for the evaluation of video recorded dynamic capillary blood flow parameters’, CapiFlow AB, Sweden). Using such tracking methods, velocimetry can be carried out in real time on capillary microscopy images in which there is subject movement. The technique is still time consuming, especially when several capillaries are studied, but is much less so than earlier methods.

Unfortunately the technique of velocimetry using noninvasive capillary microscopy is only applicable to certain sites such as the nailfold and only a small sample of capillaries can be studied at a time. The velocity of blood flow in the different capillaries may differ substantially. Since there are differences in capillary morphology even between the toes of the same foot,\textsuperscript{90} it is important to standardize the site of measurement. Capillary microscopy does, however, permit characterization of the size, shape and number of vessels present so that the influence of these parameters on blood flow can be studied.

In spite of its limitations, microscopy is still regarded as the ‘gold standard’ for measuring capillary blood flow against which other techniques must be judged.\textsuperscript{78} Capillary microscopy has been used to demonstrate dilated capillaries and delayed return of local blood flow after ischaemia in diabetes mellitus.\textsuperscript{22}

Noninvasive measurement of capillary filtration

The invasive measurement of capillary filtration coefficients (CFCs) has been described above. Capillary filtration can also be measured noninvasively by venous occlusion plethysmography (described above). The slower part of the volume/time curve represents extravasation of plasma into the tissues as a result of elevated venous pressure. The CFC is normal or depressed early on in diabetes\textsuperscript{92} but increases with duration and becomes elevated in long-standing diabetes.\textsuperscript{93} Although part of this increase may be an artefact,\textsuperscript{93} due to impairment of the veno-arteriolar reflex in diabetic patients,\textsuperscript{94} such effects are not entirely responsible for increased filtration\textsuperscript{94} and so there is a real increase in the CFC in long-duration diabetes.

Noninvasive measurement of xenon clearance

As has been discussed, clearance of the radioactive isotope \textsuperscript{133}Xe has been used to measure blood flow in the skin.\textsuperscript{38} In order to avoid the initial hyperaemia due to injection trauma, \textsuperscript{133}Xe can also be introduced epicutaneously via a small chamber attached to the skin.\textsuperscript{95} Since its molecular weight and solubility are similar to those of oxygen, \textsuperscript{133}Xe uptake has been used as an indicator of vascular permeability in assessing the oxygen diffusion barrier in chronic venous disease.\textsuperscript{95}

Transcutaneous oxygen tension

Transcutaneous oxygen pressures have been used to study the end result of perfusion and diffusion effects in diabetes mellitus by monitoring tissue oxygenation. Some studies show that the transcutaneous pressure of oxygen (tcPO\textsubscript{2}) is slightly lower in patients with diabetes mellitus than in normal subjects.\textsuperscript{96} However, it is not clear how well skin oxygen pressures reflect the normal levels of oxygen in the tissues.

The technique of measuring tcPO\textsubscript{2} was originally developed for monitoring arterial oxygenation in neonates. In order to make these measurements, it is necessary to ‘arterialize’ the skin by heating it to 43 or 44°C.\textsuperscript{97} This produces a local hyperaemia, so that excess oxygen diffuses across the skin to a modified Clarke electrode in the tcPO\textsubscript{2} probe where it is chemically reduced and measured. TcPO\textsubscript{2} measured using a heated probe thereafter does not show actual tissue oxygenation under normal physiological conditions. When arterial PO\textsubscript{2} is adequate, tcPO\textsubscript{2} changes with blood flow and when blood flow is adequate, tcPO\textsubscript{2} reflects the arterial oxygen saturation.

Heating the skin to 44°C produces a 20-fold
increase in blood flow in diabetic patients compared with a 40-fold increase in normal subjects as measured by LDF. Care must therefore be taken in choosing the electrode temperatures and in interpreting the results since any differences may reflect an inability to increase the nutritional blood flow at 44°C. When skin oxygen tension in venous disease is measured at 37°C, there is no difference between patients and controls at rest, whereas there is at 44°C. The poor oxygenation of the tissues sometimes found using tcPO2 measurements in diabetes mellitus may therefore be a result of the method of measurement rather than a true pathophysiological feature. Furthermore, although the capacity for the microvessels to vasodilate and increase their flow to supply oxygen to the tcPO2 probe may be reduced in diabetes, there is no evidence that this has any functional significance and patients with diabetes mellitus are probably still able to supply their tissues with sufficient oxygen.

Although few studies actually show a significantly lower tcPO2 in diabetics at rest, possibly because of redundancy in control of local flow and metabolic accommodation to modest hypoxia, more pronounced differences can be evinced using an oxygen inhalation test. In Breuer et al.'s study, although the basal tcPO2 is only slightly lower in diabetics, there are more significant differences when breathing 5 and 10 litres of oxygen per minute. However, what is actually being measured is the system's maximal capacity to supply oxygen under conditions of hyperaemia and hyperoxia. Nevertheless, the rate of rise of oxygen concentration is slower in diabetics, whilst the time to the maximum level is the same and such functional studies are able to show differences between diabetic patients and controls before there are any clinical or morphological signs of microangiopathy.

In measuring tcPO2, a control electrode is often used, placed in the subclavicular area. The tcPO2 in the area of interest is then related to this, the ratio being used to give a regional perfusion index. Such indices may provide better discrimination than single tcPO2 values.

tcPO2 readings are dependent on arterial and venous blood pressures, arterio-venous pressure differences and changes in venous PO2, and are linearly related to the blood flow under the electrode. Epidermal thickness also has an influence, tcPO2 falling as the thickness increases. In addition, tcPO2 measurements depend on capillary density and the number of perfused superficial capillaries and may also be affected by angiopathy in these capillaries. Other factors have also been shown to affect tcPO2, including inflammation, oedema and the skin's oxygen consumption. Care must be therefore used when making comparisons of absolute tcPO2 levels, especially when studying diabetic subjects, who are known to differ in some of these variables.

tcPO2 may be better for measuring induced responses such as postocclusive hyperaemia than basal blood flow. However, great care must be taken when using the heated tcPO2 to monitor microvascular responses in this way, since it has been shown that heating the skin to 43 or 44°C abolishes both periodic changes in blood flow and the normal blood flow regulation by local reflexes or vasodilatory substances.

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