Evaluation of the microcirculation in hypertension and cardiovascular disease

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The ability to investigate the microvascular structure and function is important in improving our understanding of pathophysiological processes in hypertension and related cardiovascular disease. A range of techniques are available or emerging for investigating different aspects of the microcirculation in animals and humans. Techniques such as experimental intravital microscopy and clinical intravital microscopy (e.g., orthogonal polarization spectral imaging) allow visualization at the level of single microvessels. Venous occlusion plethysmography can be used to measure blood flow in organs, and laser Doppler flowmetry to measure red cell flux in small areas of tissue. Positron emission tomography, myocardial contrast echocardiography, and magnetic resonance imaging provide three-dimensional imaging of local blood flow. The current and potential clinical usefulness of these different techniques is evaluated. The technical quality and availability for clinical use of some of the techniques should improve dramatically during the next few years. ‘Molecular imaging’—the combination of these techniques with genetic, molecular, and computational approaches—offers great potential for use in research and in diagnosis and the monitoring of disease progression or the results of therapy. Closer attention to the microcirculation will ultimately improve the treatment and prevention of many of the most important forms of cardiovascular disease.

Introduction

The microcirculation, consisting of resistance arteries, arterioles, capillaries, and venules, has been the focus of increasing research interest in recent years. Previously, many of the most important forms of cardiovascular disease were considered to involve primarily large vessels, particularly the conduit arteries. However, recent advances have highlighted the crucial involvement of the microcirculation in many cardiovascular conditions. Hypertension predisposes to all major forms of cardiovascular disease, and it has long been recognized that distinctive changes in the structure of small vessels, such as an increase in media:lumen ratio, and changes at the microvascular network level, such as arteriolar and capillary rarefaction, accompany many forms of hypertension in humans and animals.1,2 Research has raised the further possibility that inflammation-related changes in the microcirculation may be early, possibly even primary, events not only in the development of target-organ damage in the heart and kidney, but also in the development of hypertension itself.3,4 A similar focus on microvascular changes can be noted in research on target-organ damage in diseases such as heart failure and diabetes.

Investigating the microcirculation

The ability to investigate microvascular structure and function is important in improving our fundamental understanding of pathophysiological processes in many areas of cardiovascular disease, especially those involving hypertension. In clinical research, monitoring the microcirculation could be of great value in assessing the effects of medical or surgical interventions in clinical trials, and in clinical practice it could be helpful to assist in diagnosis, risk stratification, and monitoring disease progression or the results of therapy in individual patients.

These various goals pose different challenges for the study of the microcirculation. There are a large number of

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techniques, which vary widely in the type of information that they can provide, and in their cost and availability. Some of the methods reviewed, for example, provide a lower resolution than microscopy but offer the great advantage of being applicable in vivo. The purpose of the remainder of this article is to review the aspects of the major techniques used for the study of the microcirculation, highlighting their strengths, limitations, and some of their applications. The techniques chosen for discussion and their important features are summarized in Table 1. This review is based upon an expert workshop in which all authors participated. The authors have developed the concepts discussed at this meeting and have drawn on their knowledge of the evolving scientific literature to support the arguments propounded.

### Isolated small arteries

The study of isolated small resistance arteries mounted using a steel wire micromyograph has contributed hugely over many years to our understanding of the contractile properties and other fundamental physiological and pathophysiological processes of microvessels. This technique has been applied to numerous aspects of small artery function and regulation, an area in which there are still many unanswered questions. Much research of obvious clinical relevance is being performed using these techniques. For example, it has been shown that chronic treatment with a non-selective vasodilator improves flow-induced dilation in mesenteric small resistance arteries. A particular strength of this approach is that it can be combined with other powerful techniques, including the use of mutant and transgenic animals. Specific microvascular abnormalities have been described, for instance, in mice lacking the gene coding for dystrophin. Such studies in resistance arteries (in contrast to the majority of studies, which have been performed in large arteries) may also give rise to new hypotheses regarding many pathologies—such as a possible vascular contribution in myopathies. In support of this, mice lacking desmin present marked changes in resistance arteries but not in large arteries such as the aorta.

The study of isolated resistance arteries requires a sample of tissue and is most often performed with animals reared for use in the laboratory. However, samples from humans can sometimes be used. A limitation of this approach is that ex vivo-obtained data on biopsies have to be extrapolated to the clinical situation. Biopsies of subcutaneous fat from the gluteal region have been used to investigate the function of small arteries 100–280 μm in diameter using the wire micromyograph technique. Rizzoni et al. showed that small arteries taken from patients with essential hypertension showed a different form of remodelling from those in patients with type 2 diabetes. Additionally, this team was able to correlate changes in small artery structure with risk for cardiovascular morbidity and mortality.

### Intravital microscopy

Microscopy has been widely used in animal studies to examine the microvasculature in situ. Originally, the technique could only be used with inherently thin tissues that allowed trans-illumination, such as the bat wing, the tadpole tail, or the mesentery of the bowel after exteriorization, and such preparations continue to yield fundamental information concerning blood flow in small vessels. The range has been extended by the use of epi-illumination combined with fluorescent dyes, although safety concerns have limited the use of such dyes in humans. The microscopic study of the microcirculation without the use of dyes in humans has been largely restricted to the capillaries of the nailfold, where it has been used to investigate microcirculatory abnormalities in various types of patients.

The technique of clinical intravital microscopy may greatly extend the range of human tissues amenable to

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<td>Vessel diameter, perfusion pressure and flow</td>
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<td>Single microvessels, small microvascular networks</td>
<td>Vessel diameter, flow velocity, vessel density, permeability, leucocyte function, tracer appearance times</td>
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<td>Standard intravital microscopy, capillaroscopy</td>
<td>Single microvessels, small microvascular networks</td>
<td>Vessel diameter, flow velocity, vessel density, permeability, leucocyte function, tracer appearance times</td>
<td>Skin, internal surfaces</td>
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<td>Clinical intravital microscopy (e.g. orthogonal polarization spectral imaging microscopy)</td>
<td>Single microvessels, small microvascular networks</td>
<td>Vessel diameter, flow velocity, vessel density, permeability, leucocyte function, tracer appearance times</td>
<td>Skin, internal surfaces</td>
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<td>Regional measurements</td>
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<td>Plethysmography</td>
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| Surface measurements | Tissue volume elements | Local blood flow and metabolic state | Organs, tissues | ++++
| Laser Doppler flux measurement | Tissue volume elements | Local blood flow | Organs, tissues | ++
| Three-dimensional imaging | Tissue volume elements | Local blood flow | Organs, tissues | +

Table 1 Methods to assess abnormalities of the microcirculation
microscopic analysis without the use of fluorescent dyes. One approach used for clinical intravital microscopy is orthogonal polarization spectral (OPS) imaging. OPS imaging makes use of polarized reflected light, and contrast is achieved using the absorbance of light by haemoglobin.\(^{13}\) OPS imaging can produce trans-illumination quality images from the surface of solid organs, down to a depth of approximately 300 \(\mu\)m. The technique has been implemented using a small, hand-held device.\(^{14}\) This device allows the measurement of parameters such as arteriolar and venular diameters and venular red blood cell velocity. OPS measurements have been validated against intravitral fluorescence microscopy in experimental models of skin wound healing\(^{15}\) and inflammatory bowel disease,\(^{16}\) and in humans OPS imaging has been validated against conventional nailfold capillaroscopy.\(^{17}\) Various relevant clinical applications have recently been demonstrated, including in sepsis,\(^{18}\) surgery of tumours,\(^{19}\) assessment of shock states,\(^{20}\) as well as the investigation of the microcirculation of the liver.\(^{21}\) A particularly interesting possibility is its use during surgery, when the surfaces of internal solid tissues become accessible.\(^{17}\)

One part of the microcirculation that has been accessible for optical evaluation for many years is the microvasculature of the retina. Structural features of the retinal microcirculation can be examined using analogue or digital fundus photography, or more recently by scanning laser ophthalmoscopy.\(^{22}\) The relative simplicity of retinal photography means that it can be employed in large-scale epidemiological studies. For example, the Atherosclerosis Risk in Communities Study has shown associations between retinal microcirculatory abnormalities, such as arteriolar narrowing, and the risk of incident stroke.\(^{23}\)

### Laser Doppler flowmetry

Laser Doppler flowmetry is used to assess microvascular function by measuring the red cell flux in small-volume samples (0.5 mm\(^3\)) of body and organ surfaces, e.g. the skin.\(^{24}\) The quantity measured by laser Doppler is usually referred to as perfusion, defined as the product of local speed and concentration of blood cells, and the laser Doppler perfusion monitor records the integrated perfusion within the sampling volume. Because the laser Doppler flowmeter operates on the basis of characterizing a shift in frequency from a particular reference, it is important that the reference source is both highly stable and of single frequency.

The penetration depth of the most common laser Doppler flowmeters is about 0.6 mm with a sensitivity that gradually decreases in relation to the depth in the dermis, thus inducing an average measurement depth of about 0.3 mm. The local heterogeneity of the measured parameters is overcome by generating two-dimensional maps of perfusion, using laser Doppler imaging.\(^{25}\) The two-dimensional maps are made by systematic \(X-Y\) scanning of a low-power laser beam allowing horizontal mapping of the perfusion in a large area based on a digital image composed of many single points. One of the major advantages of laser Doppler perfusion imaging is that it allows an estimate of both temporal and spatial heterogeneity. Furthermore, it is possible to identify areas of interest in individual images for successive measurements. Image resolution is limited by the laser beam diameter and the distance between two consecutive measurement sites.

A major limitation of laser Doppler measurements is that the resulting signal is expressed in relative numbers (perfusion units). Methods of calibration have been developed but, even with these, results are expressed in percentage of change rather than absolute terms.\(^{25}\) Laser Doppler imaging is possible when assessing responses to physical stimuli, such as change of body posture, temperature changes, or hyperaemia. A particularly useful application has been in measuring the response to pharmaceutical stimuli.\(^{25}\) Drugs can be applied locally by means of iontophoresis. Thus, drug effects can be studied without systemic actions.

Altogether, laser Doppler perfusion is a widely applied method to explore the microcirculation. It is a relatively simple and inexpensive method. Laser Doppler perfusion imaging is an important step in the further development of this approach.

### Venous occlusion plethysmography

Venous occlusion plethysmography (VOP) is the longest established non-invasive method for investigating the microcirculation in humans.\(^{26}\) It involves measuring tissue blood flow, usually in the upper or lower limb, by measuring volume increases after inflation of a cuff around the proximal part of the limb to a pressure that occludes venous return but not arterial inflow. The volume change can be measured by displacement of fluid or using a strain gauge around the calf or forearm. Technical advances in this method include computer control and the use of an electromagnetic sensor with automated calibration instead of the conventional mercury-in-Silastic strain gauge.\(^{27}\)

VOP is widely used in many areas of vascular research, including research into mechanisms of vasodilation and vasoconstriction, the effects of vasoactive drugs, and the role of the vascular endothelium. A variation of the technique, venous congestion plethysmography, has been used to measure microvascular water permeability in patients with septic and non-septic shock,\(^{28}\) and to monitor changes in the peripheral microcirculation in posttraumatic complex regional pain syndrome type 1.\(^{29}\)

The equipment required is cheap and widely available, and the technique has been well validated; indeed, it has been used recently as a reference for validation of an nuclear magnetic resonance-based method for measuring perfusion in human muscles.\(^{30}\) A limitation of the technique is the required assumption that the inflation of the cuff to produce venous occlusion does not alter arterial inflow to the limb; in practice this is usually not the case, although the error is minimized if the lowest possible pressures and adequate data analysis are used.

### Positron emission tomography

Positron emission tomography (PET) involves the detection of pairs of photons produced during the annihilation of positrons emitted from a tracer injected into the body. PET has numerous potential applications in medicine; in this review we focus on its use in the measurement of regional myocardial blood flow (MBF) and coronary flow reserve (CFR) as indices of the function of the coronary microcirculation.
Modern PET has many of the features of an ‘ideal’ technique for use in healthy humans and patients. It is non-invasive and involves only very low radiation exposure (typically 2.0–2.5 mSv, compared with 15–20 mSv involved in single photon emission computed tomography (SPECT)). PET shows high repeatability and reproducibility, yields absolute values of local perfusion (in mL/min per g or mL/min per 100 g tissue), and has been extensively validated. PET currently offers a spatial resolution of 4–5 mm. Technical difficulties involving movement, attenuation, and the partial volume effect can be effectively corrected. A major limitation of the more widespread use of the technique is the local availability of appropriate positron-emitting tracers. For measurement of MBF, the most widely used tracers are oxygen-15-labelled water (H\textsubscript{2}\textsuperscript{15}O) and nitrogen-13-labelled ammonia (\textsuperscript{13}NH\textsubscript{3}), which have physical half-lives of only 2 and 10 min, respectively. Use of such short-lived tracers requires a particle accelerator and radiochemistry facilities to be situated close to the PET scanner.

PET has enabled the investigation of the effects of clinically relevant factors on the coronary microcirculation in asymptomatic humans, including the demonstration of a significant inverse correlation between CFR and low-density-lipoprotein cholesterol in hypercholesterolaemic patients, and the short-term normalization of CFR by vitamin C in smokers. PET has also been used to explore the impact of aortic stenosis on subendocardial and subepicardial CFR, and to show that impaired CFR improved after 6 months of treatment with a low-dose combination of perindopril and indapamide.

Myocardial contrast echocardiography

Echocardiography is a widely used imaging technique with many applications in cardiology and offers the possibility of excellent spatial (<1 mm) and temporal (30–120 Hz) resolution. The technique is non-invasive and the equipment is familiar to many clinical cardiologists. When combined with the injection of an ultrasound contrast agent, echocardiography can be used to investigate myocardial perfusion, both in ‘experimental’ animals and in humans. Modern ultrasound contrast agents consist of microbubbles containing a high molecular weight gas that is relatively non-diffusible, which means that the microbubbles are relatively stable on the shelf and after injection. Consequently, they can be administered intravenously rather than directly into the coronary arterial circulation. Microbubbles can also be made in highly reproducible sizes; those 3–5 μm in diameter distribute in the vasculature in the same way as red blood cells. Because microbubbles produce signals containing harmonics of the applied ultrasound, imaging using a harmonic frequency can result in an improved signal-to-noise ratio. Some 90% of myocardial blood volume is within capillaries, so myocardial contrast echocardiography (MCE) enables tissue perfusion to be evaluated at the capillary level where oxygen and nutrient transfer occurs.

MCE applied to the acute myocardial infarction (AMI) patient can provide information concerning infarct size, collateral circulation, and myocardial viability. In particular, MCE has played a major role in elucidating the ‘low-reflow’ phenomena that have become apparent since the widespread introduction of recanalization techniques following AMI.

Studies have demonstrated the feasibility of performing serial MCE evaluation of myocardial perfusion in the emergency room or coronary care unit before and after primary percutaneous transluminal coronary angioplasty. A significant reduction in the size of the initial perfusion defect within 24 h was found to predict functional ventricular recovery after 4 weeks, and the size of the persistent perfusion defect is a predictor of left ventricular remodelling.

However, MCE in this setting is demanding and requires up-to-date ultrasound equipment and expert sonography personnel.

There is still considerable scope for the technical development of MCE. Intermittent imaging, in which microbubbles are destroyed by the ultrasound applied during imaging, then replenished by perfusion during pauses, can improve contrast, and, if high cycle rates are used, permits real-time visualization. ‘Flash’ MCE allows an image recorded after microbubble destruction to be subtracted from a primary image recorded a few milliseconds earlier with bubbles present, avoiding the need for image alignment to correct for movement between images.

A potential concern with MCE is that destruction of microbubbles by the ultrasound beam could cause microvascular damage and impair left ventricular performance. Exposure of isolated rabbit hearts to ultrasound and any of several different contrast agents has been shown to result in capillary rupture and a transient decrease in ventricular performance. However, this damage occurred at ultrasound energies unlikely to be reached during conventional imaging procedures in patients. Interestingly, an experimental study has suggested that capillary rupture by microbubble destruction can stimulate local arteriogenesis and lead to increased arterial density in skeletal muscle.

Magnetic resonance imaging

Through a combination of static high-power magnetic fields, changing low-power magnetic fields, and radiofrequency pulses, magnetic resonance imaging (MRI) allows the three-dimensional visualization of intravascular blood flow and tissue perfusion over time, as well as in any plane chosen by the operator. Paramagnetic contrast agents, gadolinium chelates, are used when conducting MRI in clinical practice to achieve a high-quality image. MRI has found wide application in the assessment of cardiac microcirculation, in particular in relation to the study of microvascular reperfusion following AMI. MRI is capable of obtaining data about microvascular flow, regional myocardial wall motion, and viability in one single examination and without the administration of pharmacological stress. The application of cardiac MRI (CMR) is highly accurate in assessing left ventricular function.

Over the past decade new modalities based on MRI have been developed. Methods based on differences in the magnetic resonance signal from oxygenated and deoxygenated blood, such as blood oxygenation level dependent, flow-sensitive alternating inversion recovery, contrast-enhanced dynamic MRI, or arterial spin labeling, can be used to estimate global or local levels of blood flow. The main advantage of MRI is the absence of a requirement for radioactive tracers, thus allowing the option of multiple repetitive measurements. The CFR data obtained with MRI are comparable to those obtained with PET or invasive techniques, such as a Doppler wire.
Measurement of blood flow and myocardial perfusion

Blood flow velocity or the volume of flow can be quantified within large vessels through the phase-contract technique of velocity mapping.47 Both ultrafast and echo-planar imaging have been shown to be feasible methods of assessment of myocardial perfusion in both animals51 and humans.52–54 To ascertain the extent of perfusion of cardiovascular tissues, beat-to-beat ultrafast imaging can be used to examine the passage of a contrast medium within the intracardiac and vascular blood pools and, subsequently, through the cardiovascular tissues themselves.47 It is possible to achieve the three-dimensional time-resolved, contrast-enhanced magnetic resonance angiography for coronary arteries through this type of image acquisition.47

The use of CMR is particularly an important method of assessing myocardial perfusion compared with other imaging techniques, because of the high level of detail that it provides the clinician. A recent prospective study involving 20 patients who had undergone emergency percutaneous coronary intervention for AMI used CMR to assess the patients’ patterns of myocardial perfusion.48 Through CMR the investigators revealed that although angiography showed that patency had been restored to the infarct-related artery, microvascular perfusion was still impaired in the majority of patients. When patients experienced a severe impairment of perfusion as detected by CMR, there was an associated lack of recovery of wall motion in these patients.48

Future prospects

Central to future improvements in the treatment of microvascular abnormalities will be advances in understanding of the physiology, pathophysiology, and pharmacology of small vessels. These advances will hinge on the further development and wider use of research techniques such as the study of isolated vessels and intravital microscopy. Recent developments include contrast-enhanced in-vivo video microscopy,55 fluorescence microscopy,56 microangiography using synchrotron radiation,57 and electron beam computed tomography.58 Further refinements in instrumentation will continue and an area of great potential is the combination of these techniques with genetic, molecular, and computational approaches. This development is usually referred to as ‘molecular imaging’. The basis of molecular imaging is the use of specific ligands, such as antibodies, that can serve as markers for the underlying disease, and that provide the opportunity to monitor the progress of the disease or its treatment. Most of the early results in molecular imaging have been obtained with PET and, to a lesser extent, with SPECT. Other developments have suggested a potential high clinical impact of molecular imaging on the basis of MRI and ultrasound.59 In experimental animal models of cardiovascular disease and target-organ damage, optical fluorescence imaging is rapidly becoming the state-of-the-art approach to assess target-organ damage. The development of very stable fluorochromes, in particular in combination with two-photon excitation, now allows analysis of cellular structures in intact thick tissues with a spatial resolution better than 1 μm.

Until these innovations find their way to routine use in the clinic, refinement of the more classical approaches will be needed. OPS imaging probably offers the best opportunity to complement nailfold capillaroscopy for the application of microscopy to at least some vascular beds in humans. Widespread use of OPS imaging would be encouraged by the availability of software to permit ‘turn-key’ operation, and for the convenient calculation of clinically relevant parameters such as functional capillary density. Technical improvements, such as the use of stroboscopic illumination to minimize blurring, will improve the quality and reproducibility of the data obtainable with the currently available OPS device. In the medium term, such a device could have a role in clinical decision making.

Modern forms of VOP will continue to play an important, perhaps unglamorous, role in microvascular research, as will retinal photography. In our view, the relative simplicity and availability of these techniques should allow their wider application in large-scale clinical trials and epidemiological studies in the future, particularly in the fields of hypertension, diabetes, and dyslipidaemia.

PET and harmonic MCE offer enormous scope for monitoring disease progression and the effects of treatment, both in clinical trials and clinical practice. PET monitoring of CFR gives indirect but highly relevant information about the function of the coronary microcirculation. A major limitation is the local availability of the tracers and apparatus required. The present decade should see dramatic improvements in the quality and range of data obtained by MCE, leading to a greatly expanded role in cardiovascular research and treatment.

Conventionally, MCE exploits the fact that contrast microbubbles behave in a similar way to red blood cells. However, recent work is opening up further possibilities. Microbubbles tend to be retained in the microcirculation in diseased or inflamed tissues, and retention can be enhanced and made more specific by conjugation of ligands, such as antibodies to endothelial adhesion molecules, to the microbubble surface.60 Given the crucial role of inflammation-related processes in the early stages of many forms of cardiovascular disease, this molecular approach may become an important application. Finally, the targeted permeabilization of microvessel walls by microbubble destruction could be used for local delivery of drugs or genes introduced into the bloodstream, but not bound to the microbubbles themselves.45 These developments could take MCE into entirely new areas of research and therapeutics in the longer term.

Conclusion

Appreciation of the importance of the microcirculation has been hampered by the perceived lack of appropriate techniques for its study. In this review, we have shown that a range of techniques are available or are emerging for the investigation of different aspects of the microcirculation in animals and humans. Some of these techniques are likely to show dramatic improvements during the next few years in terms of technical quality and availability for clinical use. It is important that the academic and clinical research communities develop and nurture close links with biomedical engineers and commercial companies to ensure that technical progress is rapid. Nonetheless, these exciting possibilities should not distract us from making greater use
of techniques, such as plethysmography and retinal photography, which are already widely available, cheap, and simple enough to be included in large-scale clinical trials and in clinical practice. Closer attention to the microcirculation will ultimately improve the treatment and prevention of many of the most important forms of cardiovascular disease.

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References
An unusual complication of a pericardial window

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A 59-year-old man, with known metastatic non-small cell lung cancer presented with a 3-week history of increasing dyspnoea and clinical features of cardiac tamponade. Echocardiography confirmed a large pericardial effusion with diastolic right ventricular collapse. The effusion re-accumulated despite prolonged pericardial drainage. Therefore, a subxiphoid pericardial window was performed. The patient became increasingly breathless and hypotensive on the first post-operative day. Transthoracic echocardiography was unable to produce any interpretable sono-graphic images of the heart, despite excellent pre-operative windows (Panel A). Chest radiograph (Panel B) and subsequent computed tomographic scan (Panels C and D) revealed a bowel loop herniating through the pericardial window into the pericardial space compressing the heart. The patient underwent re-operation with a Marlex mesh repair of the diaphragmatic defect and subsequently recovered uneventfully. This case illustrates an unusual case of cardiac tamponade in patients with malignancy.