Current Perspective

Microcirculation in Hypertension
A New Target for Treatment?

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The number of effective agents available for the treatment of hypertension is now substantial. However, in spite of this, most would agree that there is still considerable scope for improvement in the way hypertension is managed. In many countries, the great majority of hypertensive subjects still show imperfect blood pressure control. Furthermore, the reductions or improvements in end-organ damage seen during antihypertensive therapy do not always correlate well with the reduction in arterial blood pressure achieved. Thus, there seems to be a need for new therapeutic perspectives in the treatment of hypertension. One important new perspective might be provided by an enhanced appreciation of the importance of the microcirculation in the pathophysiology and treatment of hypertension.

Description of the Microcirculation

The microcirculation is widely taken to encompass vessels <150 μm in diameter. It therefore includes arterioles, capillaries, and venules. However, there is no universally accepted definition of the microcirculation, and it is not clear whether vessels that would be defined as small arteries on the basis of anatomical criteria but have diameters >150 μm should also be included. A definition based on arterial vessel physiology rather than diameter or structure is therefore proposed, depending on the response of the isolated vessel to increased internal pressure. By this definition, all those arterial vessels that respond to increasing pressure by a myogenic reduction in lumen diameter would be included in the microcirculation, as well as the capillaries and venules. Such a definition would include the smallest arteries and arterioles in the microcirculation and would be in line with the recent suggestion that the small arterial and arteriolar components should be considered a continuum rather than distinct sites of resistance control. Several aspects of the physiology of arterial vessels, including flow-dependent responses, are not restricted to particular vessel categories (Figure 1). A primary function of the microcirculation is to optimize nutrient and oxygen supply within the tissue in response to variations in demand. A second important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries causing disturbances in capillary exchange. Finally, it is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs. The microcirculation is therefore extremely important in determining the overall peripheral resistance. It is also the site where the earliest manifestations of cardiovascular disease—in particular, inflammatory processes—occur. There is now a very high level of clinical and research interest in the microcirculation, as demonstrated by the fact that over the last 3 years, >800 articles per year have been published in MEDLINE-listed journals on this topic.

The Microcirculation in Hypertension

In hypertension, the structure and function of the microcirculation may be altered in at least 3 ways. First, the mechanisms regulating vasomotor tone may be abnormal, leading to enhanced vasoconstriction or reduced vasodilator responses. Second, there may be anatomic alterations to the structure of individual precapillary resistance vessels, such as an increase in their wall-to-lumen ratio. Finally, there may be changes at the level of the microvascular network, perhaps involving a reduction in the density (rarefaction) of arterioles or capillaries within a given vascular bed. It is likely that the relative contributions of these factors will be different in different vascular beds and may vary between different forms and models of hypertension. Nevertheless, it is possible to discern a historical shift in the focus of antihypertensive therapy between these different mechanisms. Initially, antihypertensive therapy was directed mainly toward altering vasomotor tone and promoting vasodilation. More recently, attention was directed toward reducing or reversing changes in resistance vessel structure, and in the last few years, there has been a further evolution toward reducing or reversing microvascular network rarefaction. Interestingly, several antihypertensive agents that act acutely to reduce vasomotor tone are now known to have additional chronic actions on vessel and network structure, which may be more important in the long-term treatment of hypertension.
In this article, we review the animal and human evidence available for the role of the microcirculation during hypertension and the effects of therapy, focusing on those aspects that are likely to be common to most forms of hypertension and most organ systems.

The Increased Vascular Resistance of Hypertension Is Located Largely in the Microcirculation

The Normal Hydrostatic Pressure Profile

The profile of the fall in hydrostatic pressure along the various vascular elements between the heart and capillaries has been determined in numerous studies. There is general agreement that there is relatively little pressure loss within the large conduit arteries and that although the pressure profile varies somewhat between studies and for different vascular beds (Figure 2),7 the drop in pressure occurs predominantly in precapillary vessels ranging from 10 to 300 μm in diameter. It has been suggested that differences in methodology may be responsible for at least some of the variation between studies.5 In particular, the use of exteriorized muscles may underestimate the pressures delivered to the microcirculation. Pressures recorded with minimal surgical intervention have indicated that as much as 70% to 90% of the systemic pressure is delivered to the microcirculation in many skeletal muscles.8

The Pressure Profile in Hypertension

In most forms of experimental and clinical hypertension, the cardiac output is close to normal and the peripheral vascular resistance is increased in proportion to the increase in blood pressure. Several studies of skeletal muscle in spontaneously hypertensive rats (SHR) have concluded that pressure is elevated approximately proportionally throughout the precapillary vasculature. For example, DeLano et al8 found that if the measured pressures were normalized by the systemic arterial pressure, pressures were virtually identical in normotensive rats and in SHR at all the locations studied. These results suggest that because the major pressure drop occurs in the smallest arteries and arterioles, these vessels also represent the principal site of the increased resistance in hypertension, at least in SHR.

Microcirculatory Abnormalities in Hypertension: Both Cause and Effect?

It has been known for many years that the diameter and structure of small resistance arteries can alter in response to changes in blood pressure and flow. There have been numerous reports of decreases in arteriolar diameters in experimental secondary hypertension.4 Increases in the media-to-lumen ratio of small arteries have also been widely documented in several forms of hypertension,4 consistent with the classic view that vessels maintain constant wall stress in the face of changing pressure. However, it is not clear whether similar changes occur in arterioles in primary hypertension. In SHR, arterioles have not been reported to show consistently reduced luminal diameter or wall thickening (reviewed by Struijker Boudier et al).4

A more consistent observation has been microvessel rarefaction. A reduction in the number or density of microvessels has been reported for many years in most forms of clinical and experimental hypertension. Several studies have documented microvessel rarefaction in SHR and after the experimental induction of secondary hypertension.4

It has been suggested that rarefaction may occur in 2 phases.9 The first phase of functional rarefaction involves microvessel constriction to the point of nonperfusion, possibly as a result of increased sensitivity to vasoconstrictor stimuli. The nonperfused vessels may then disappear, leading to the second phase of structural or anatomic rarefaction, which cannot be reversed by maximal vasodilation. In patients with primary hypertension, the reduction in density of capillaries in the skin of the dorsum of the fingers has recently been shown to be mainly a result of anatomic rather than functional rarefaction.10

It is therefore possible to view microvessel abnormality and rarefaction as responses to increased vascular pressure. However, this is clearly not always the case, because microvascular changes similar to those observed in hypertension can be found in conditions such as scleroderma, syndrome X, and hypertrophic cardiomyopathy in the absence of any elevation in arterial blood pressure. Furthermore, there is
A “Vicious Cycle” in Hypertension?

If, as seems likely, microvascular abnormalities can both result from and contribute to hypertension, a “vicious cycle” may exist in which the microcirculation maintains or even amplifies an initial increase in blood pressure. Thus, an increase in blood pressure might cause resistance in the microcirculation to rise, leading to a further elevation of blood pressure. Pries and colleagues\(^3,16\) have used computer simulation techniques to study the long-term effects of increased blood flow and pressure on the resistance and structural adaptation of microvascular networks. These models show how an initial small increase in pressure can lead to larger structural increases in pressure and flow resistance by a mechanism involving the tendency of vessels to reduce their luminal diameter in response to increased intraluminal pressure.

There is evidence that this argument could be taken a step further to suggest that microvascular abnormality might initiate the pathogenic sequence in primary hypertension. In this way, primary hypertension is seen as a developmental abnormality of the microcirculation. There is now direct evidence for a reduced angiogenic potential in SHR. Serum from 6-week-old SHR has less ability to induce angiogenesis in the chick embryo chorioallantoic membrane than serum from normal rats.\(^2\) This suggests that an unknown angiogenic compound is underexpressed in young SHR.

A possible mechanism by which microcirculatory abnormality could produce a predisposition to primary hypertension in humans has been suggested by the epidemiological work of Barker et al.\(^17\) These authors found that blood pressure and the risk of hypertension among men and women \(\sim 50\) years of age were predicted by a combination of their birth weight and placental weight. The highest blood pressures were found among people who had been small babies with large placentas. Barker et al.\(^17\) suggested that reduced blood flow in the trunk of a fetus that is small in relation to its placenta could lead to reduced microcirculatory growth and a predisposition to hypertension in later life. An alternative interpretation is that a primary deficit in the development of the microcirculation could lead to impaired growth of the fetus.

Microvascular rarefaction will tend to both reduce the vessel surface area available for oxygen delivery and increase the diffusional distance between vessels and their target cells. The resulting ischemia may be responsible for much of the end-organ damage associated with hypertension.

Therapeutic Implications

Targeting the Microcirculation to Prevent End-Organ Damage: Beyond Blood Pressure Reduction?

Numerous trials have demonstrated that antihypertensive therapy is effective in reducing major vascular events, including stroke and coronary heart disease. However, several forms of specific end-organ damage that primarily involve the microcirculation are thought to be secondary to hypertension, including nephropathy, retinopathy, lacunar infarction, and microvascular angina. Thus, it is to be expected that there will be additional benefits from targeting the microcirculation during antihypertensive therapy in terms of the prevention of or reduction in end-organ damage.

Microalbuminuria

One of the most intensively studied forms of end-organ damage with microvascular involvement is microalbuminuria or increased urinary albumin excretion. Microalbuminuria is known to be a risk factor for cardiovascular disease and mortality in nondiabetic and diabetic individuals. In the Framingham study, proteinuria was 3 times more common in hypertensive than in normotensive individuals and was associated with a 3-fold increase in mortality.\(^18\) Importantly, hypertensive patients with microalbuminuria have an increased cardiovascular risk compared with normoalbuminuric patients with similar blood pressure.\(^19\)

Although microalbuminuria may be an early marker of renal dysfunction, it is now clear that it can be reversible. A recent large-scale study of 6000 nondiabetic hypertensive patients showed that microalbuminuria can be reversed in many cases by antihypertensive therapy.\(^20\) In SHR, different antihypertensive agents have different effects on renal afferent arteriolar structure. ACE inhibition produced a greater increase in the diameters of distal afferent arterioles than a calcium antagonist of equivalent hypotensive effect.\(^21\)

Microcirculation in the Myocardium

The heart is another organ that may suffer end-organ damage, and numerous studies have reported changes in myocardial microvessel structure and density in hypertension. During normal development, myocardial microvascular density increases during the first few postnatal weeks but then decreases, probably because angiogenesis fails to match the growth in myocyte volume.\(^22\) During the pressure-overload hypertrophy that often accompanies hypertension, the picture that emerges from studies in both animals and human patients is that microvessel growth is insufficient to prevent dilution...
because of the greater increase in other myocardial components; hence, microvascular density decreases.\textsuperscript{22} It has been argued that microvascular changes may make a substantial contribution to the development of cardiac failure in hypertensive patients.\textsuperscript{23}

**Cerebral Microcirculation**

The risk of stroke is greatly increased by hypertension. Although there are multiple causes of stroke, the form that is perhaps most closely associated with small-vessel abnormality is lacunar infarction, the occurrence of small, deep infarcts thought to be caused by the occlusion or rupture of small vessels, largely as a result of hypertensive changes.

Hypertensive changes in cerebral arteriolar structure have been documented in animal models. In SHR, reductions in the external diameter and increases in the media-to-lumen ratio of cerebral arterioles have been reported.\textsuperscript{24} However, most reports conclude that neither cerebral arterioles nor capillaries undergo rarefaction in SHR or in other experimental models of hypertension. At least some forms of antihypertensive therapy can reverse structural changes in cerebral microvessels\textsuperscript{25} and can dramatically increase the lifespan of stroke-prone SHR.\textsuperscript{26,27}

**Therapeutic Strategies and the Microcirculation in the Treatment of Hypertension**

Targeting the microcirculation to prevent end-organ damage and treat hypertension involves 2 structural goals: the reversal of microvascular rarefaction and the reduction of small arterial wall-to-lumen ratio. Most of the widely used classes of antihypertensive agents have been investigated with regard to both structural parameters, at least in animal studies, and clear differences have emerged between them.

**Diuretics**

There have been very few studies of the long-term effects of diuretic therapy on the microcirculation. Hydrochlorothiazide therapy was reported to have no beneficial effect on structural changes in precapillary resistance vessels in hypertensive patients.\textsuperscript{28}

**β-Blockers**

Although β-blockers are widely used antihypertensive agents, there is little evidence that they exert a marked beneficial action on microvascular structure or rarefaction. Treatment with propranolol had no effect on the cross-sectional area of the vessel wall or the external diameter of maximally dilated cerebral arterioles in stroke-prone SHR.\textsuperscript{25}

In hypertensive patients, treatment with atenolol for 1 year produced no significant improvement in the media-to-lumen ratio of small gluteal subcutaneous arteries.\textsuperscript{29}

**Calcium Antagonists**

Calcium antagonists have been shown to increase microvessel density in several animal models. Three different calcium antagonists—nifedipine, nimodipine, and verapamil—were all shown to increase vascular density on the chick chorioallantoic membrane.\textsuperscript{30} In SHR, nifedipine induced growth in the coronary capillary network,\textsuperscript{31} and in Goldblatt 2-kidney, 1-clip hypertensive rats, the long-acting calcium antagonist benidipine increased the density of capillaries and reduced the wall-to-lumen ratio of arterioles in the left ventricle.\textsuperscript{32}

**ACE Inhibitors**

The situation regarding the effects of ACE inhibitors on microvessel structure and density is complex and has been the subject of numerous recent studies. A marked increase in ACE activity has been demonstrated in the arteriolar walls of peripheral muscle in SHR, and ACE inhibitor treatment has been shown to largely but not totally inhibit this local ACE activity.\textsuperscript{33} It seems clear that ACE inhibition can reduce the media-to-lumen ratio of resistance vessels in SHR\textsuperscript{25,36} and renal afferent arterioles in genetically hypertensive rats.\textsuperscript{37} In previously untreated patients with essential hypertension, ACE inhibitor treatment but not β-blocker treatment caused a reduction in the media-to-lumen ratio of small arteries in gluteal biopsies.\textsuperscript{26}

The effects of ACE inhibition on microvessel rarefaction, however, are more controversial. Angiotensin II is known to have angiogenic effects, so blockade of its production or action might be expected to induce rarefaction. Consistent with this, ACE inhibition was found to block neovascularization in the rat cornea\textsuperscript{38} and to induce a significant decrease in the density of both small arterioles and venules in the cutaneous maximus muscle in SHR.\textsuperscript{29} On the other hand, recent studies have reported increased myocardial capillary densities in hypertensive rats after ACE inhibition.\textsuperscript{40,41} Some ACE inhibitors have also been reported to stimulate angiogenesis in vivo in the ischemic hind limb of the rabbit.\textsuperscript{42} In several studies, there was evidence that the effects on microvessel structure and density were independent of the lowering of arterial blood pressure.\textsuperscript{25,36,40,41} It has also been suggested that the action of ACE inhibitors on microvessel structure might be independent of the renin-angiotensin system and involve inhibition of zinc-dependent metalloproteinases\textsuperscript{38} or stimulation of bradykinin receptors.\textsuperscript{40}

A further complication is that angiotensin II may independently affect arteriolar and capillary densities. In rats, angiotensin II–induced hypertensive cardiac hypertrophy was associated with an 18% decrease in capillary density but a 54% increase in arteriolar density.\textsuperscript{53} Further evidence for independent regulation of capillary and arteriolar density has been obtained recently\textsuperscript{44} in Goldblatt 1-kidney, 1-clip rats. After 4 weeks of renovascular hypertension, there was a significant increase in myocardial arteriolar density and a decrease in capillary density. Treatment with the ACE inhibitor perindopril normalized arteriolar density but did not improve the low myocardial capillary density, despite the complete normalization of blood pressure. The combination of perindopril and
the diuretic indapamide, however, resulted in normal arteriolar and capillary densities.44

In spite of all the complexities, it seems clear that blockade of the renin-angiotensin system with ACE inhibitors, perhaps in combination with other therapies, including diuretics, offers considerable promise for reducing microcirculatory abnormalities in hypertension.

Angiotensin II Receptor Blockers

Fewer data are available for the effects of angiotensin II receptor (AT) blockers on microvessel structure and rarefaction, and conflicting results have been obtained. AT blockers were found to increase left ventricular capillary density in stroke-prone SHR45 and to normalize angiotensin II–induced changes in cardiac arteriolar and capillary densities.46 The AT blocker losartan also decreased the media-to-lumen ratio of renal afferent arterioles in genetically hypertensive rats.37 On the other hand, losartan treatment from an early age failed to significantly increase cardiac capillary length density in stroke-prone SHR, despite attenuating the development of hypertension.40

Combination Therapy

Two recent studies have examined the effects of combinations of antihypertensive agents on microvascular structure and function. The combination of a low-dose ACE inhibitor and a β-blocker was more effective than either therapy alone in reducing the wall cross-sectional area of cerebral arterioles in stroke-prone SHR.25 However, the combination was no more effective than the ACE inhibitor alone in increasing arteriolar internal and external diameters. A low-dose combination of the ACE inhibitor perindopril and the diuretic indapamide has recently been shown to increase capillary density and arteriolar internal and external diameters in the venules of stroke-prone SHR.27 In this case, the combination was more effective than either agent given alone for most of the microvascular parameters studied.

Conclusions

Abnormalities of microvessel structure and microvascular network density often accompany, and may be an important cause of, primary hypertension. Microcirculatory abnormalities are also likely to be central to many forms of hypertensive end-organ damage, including those involving the kidneys, heart, and brain. Optimal antihypertensive therapy should therefore be targeted at both large and small vessels. Available evidence suggests that the 2 longest-established classes of antihypertensive agents, diuretics and β-blockers, have no specific beneficial actions on the microcirculation. However, the results of numerous animal studies and a much smaller number of clinical studies indicate that the newer classes of antihypertensive agents and some combinations of agents offer considerable potential for improving microvessel structure and network density. It would therefore be predicted that more widespread use of these agents and combinations would enable substantial reductions in end-organ damage to be achieved, with consequent reductions in morbidity and mortality. Much further clinical research is needed to assess the extent to which this potential can be realized in clinical practice.

References


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