Sociedad Argentina de Hipertension Arterial

Hypertension: A Disease of the Microcirculation?

In the last decade, the pathophysiology of microcirculation has become an actively developing field of hypertension research, which we have felt it useful to review. An exact definition of microcirculation is elusive. It is often taken morphologically, to encompass all of the blood vessels with a diameter <150 µm, that is, some small arteries, arterioles, capillaries, and venules,1 with the morphological distinction between small arteries and arterioles not entirely clear, because some 2 but not all authors 3 limit the concept of arteriole to vessels containing a single layer of smooth muscle cells. Functionally, it is usually accepted that the arterial side of the microcirculation composes most of the resistance vessels, meaning that the largest part of the pressure drop between large conduit arteries and veins takes place in this segment.2,4 The “resistance” property of small arteries and arterioles is intimately, although not exclusively, related to the prevalence of myogenic tone in these vessels.5,6

Myogenic tone is an intrinsic property of vascular smooth muscle, which contracts in response to stretching, independent of any nerve or humoral mediation.5 All arteries have myogenic tone and, therefore, contract in response to an increase in blood pressure. Myogenic tone gains in importance with decreasing vessel caliber,7,8 and only in small arteries and arterioles (diameter: 15 to 300 µm, depending on species and organ) can it provoke substantial luminal narrowing (or even closure) in reaction to an increase in transmural pressure.8,9 In the hamster cheek pouch, for example, control of arterial/arteriolar luminal size by myogenic tone seems minimal in the feeding saccular arteries (diameter 135 µm) but progressively more intense in the A1 (80 µm), A2 (40 µm), and A3 arterioles (28 µm).8

Myogenic tone serves a simple purpose: to protect the distal capillaries against deleterious local hypertension.10 This short-term protection has an immediate result: augmented myogenic tone amplifies arteriolar resistance to blood flow, leading to a proximal increase in blood pressure.

The definition of “capillaries” is unambiguous: they are vessels ranging from 4 to 12 µm in diameter of which the walls are composed exclusively of endothelial cells more or less fenestrated according to the organ and a basement membrane. Usually, each endothelial cell, rolled up in the form of a tube, composes one segment of the capillary.3 Capillaries ensure fluid–metabolite exchange between plasma and tissues, a function requiring a high wall permeability, with consequent high fragility. Except in specialized microvascular beds, such as the renal glomerulus, normal systemic capillary pressure (here, we disregard the pulmonary circulation, which is not relevant to the field of systemic hypertension) is relatively low (10 to 30 mm Hg).11 Elevation of systemic capillary pressure above this range has several potentially deleterious effects, including the following: (1) interstial edema, which can have dramatic effects on the brain as exemplified in hypertensive encephalopathy 12; (2) disruption of capillary wall structure, with extravasation of plasma proteins and blood cells 13; and (3) activation of the microvascular endothelium, which may trigger or amplify an inflammatory cascade,14 of importance, for example, in the pathogenesis of venous ulcers.15

Pleiotropic changes in the functional behavior of arterioles have been noted in both clinical and experimental hypertension, including hyperresponsiveness to vasoconstrictor stimuli,16,17 leading to their constriction or even complete closure,16,18,19 endothelial dysfunction,20,21 and reduced bioactivity of endothelium-derived NO.22 It is being increasingly recognized that endothelial dysfunction in hypertension depends in part on the scavenging of NO by reactive oxygen species, the latter produced in high quantities because of the abnormal activation of membrane-bound reduced nicotinamide dinucleotide phosphate oxidase, mediated in particular by the stimulation of type 1 receptors to angiotensin II.23 Thus, hypertension seems largely associated with an upset balance of vasomotor influences,

which greatly shifts in favor of increased vasoconstriction and, possibly, vessel closure in the microcirculation. In addition to these functional changes, structural alterations seem to take place in the microcirculation of hypertensive animals and humans.

Arteriolar Remodeling and Myogenic Tone

One pathophysiological aspect of resistance arterioles in hypertension is that of arteriolar remodeling. Vascular remodeling occurs as a function of blood pressure according to a simple law of conservation of circumferential wall stress ([sigma]), defined as: [sigma]=P×R/h, where P is transmural pressure, R is vessel radius, and h is wall thickness.24 In large arteries, an acute increase in blood pressure causes distension, an increase in R, a decrease in h, and, therefore, an increase in [sigma]. A growth response of smooth muscle cells is thereby activated until h becomes high enough to normalize [sigma], the classic mechanism of hypertrophic remodeling of large arteries in hypertension (reviewed in Reference 25).

For the same increase in P, arterioles show a completely different behavior, primarily because R/h and, therefore, [sigma] are much lower than in large arteries. For example, R/h is [almost equal to]7 in the thoracic aorta versus 1.25 for a precapillary arteriole in canines.26 Furthermore, myogenic tone at this level leads to a decrease in R in response to the increase in P. In such conditions, there is no augmentation or even a diminution of [sigma] so that hypertension cannot induce any hypertrophy. Instead, the arteriolar wall undergoes a progressive structural change known as eutrophic inward remodeling.27 This process consists of a rearrangement of smooth muscle cells and extracellular matrix, at constant cell number and mass (hence, the eutrophic qualifier), such that luminal narrowing and increased R/h, initially because of the myogenic response, are maintained, although active tone returns to normal.25 The progressive switch in the mechanism of arteriolar luminal narrowing from active myogenic vasoconstriction to eutrophic inward remodeling has been clearly demonstrated in cremaster arterioles from rats with experimental renovascular hypertension.28 In summary, the smaller the arteries/arterioles under study, the less hypertrophic and the more eutrophic inward remodeling is being observed.25,27

Microvascular Rarefaction in Hypertension

A relatively constant finding in both experimental and clinical hypertension has been that of microvascular rarefaction, defined as a reduced spatial density of microvascular networks.6,29

Definitions

Under physiological resting conditions, a substantial part of microvascular networks of most organs remains closed, constituting a flow reserve for adaptation to increased metabolic needs. When merely defined as an abnormally low spatial density of microvessels, rarefaction can be functional, structural, or both.6 Functional rarefaction refers to an abnormal prevalence of anatomically existing but unperfused microvessels. Structural rarefaction can be established either by quantitative histology or by the observation of microvascular beds in vivo under conditions of maximal vasodilation and optimal perfusion pressure.18

Experimental Data

Studies have reported microvascular structural rarefaction in many experimental hypertensive models and tissues, including skeletal muscle,18,30–33 intestine,34 and skin,35 although not the brain.36 Interestingly, structural rarefaction can be detected at a very young age (4 weeks) in spontaneously hypertensive rats.30

Experimental data concerning the myocardial microcirculation deserve a separate mention because of the concomitant myocardial hypertrophy. A reduced myocardial capillary density (ie, a smaller number of vessels per square millimeter of tissue cross-sectional area) has been largely documented in adult hypertensive animals,37–

42 possibly reflecting an inability of microcirculatory growth (through angiogenesis) to keep up with the progressive increase in myocardial mass and myocyte dimensions. In support of such interpretation, young spontaneously hypertensive rats (2.5 months, an age of fast growth in body dimensions with presumably more active angiogenesis than later in life) had a normal capillary density in their already hypertrophic left ventricle, whereas rarefaction was detected in older animals (7 months).43 Consistent with these data, patients with left ventricular hypertrophy because of aortic stenosis only had myocardial capillary rarefaction when the valvular defect was acquired in the adult age but not when it was congenital.44

Rarefaction in Clinical Hypertension

In 1933, Ruedemann 45 noticed that hypertensive patients had an abnormally low number of small conjunctival vessel, an observation later replicated with more sophisticated visualization equipment.46 Using venous occlusion capillaroscopy, Serne et al 47 measured nailfold capillary density in 26 nondiabetic patients with never-treated essential hypertension and an equal number of healthy normotensive control subjects matched for age, sex, and lipid profile. In that study, the mean and SD of capillary counts was 52.5±6.6/mm^2 in hypertensive subjects, significantly lower than in the control subjects (57.2±8.6/mm^2, roughly a 10% difference). Using an identical experimental design, but carrying out venous occlusion capillaroscopy on dorsal finger skin rather than the nailfold, Antonios et al 48 obtained analogous results (never-treated hypertensive subjects: 73±5 capillaries per mm^2; control subjects: 87±7 capillaries per mm^2; 20% difference; 17 subjects per group). Similar data were generated by another group who carried out capillaroscopy on the forearm skin of hypertensive versus normotensive subjects.49 At variance with these reports, rarefaction was not found in dorsal finger skin of elderly subjects with mainly systolic hypertension.11 There is some evidence that capillary rarefaction in the skin may antedate the clinical onset of essential hypertension. In 2 other studies by Antonios et al,50 dorsal finger venous occlusion capillaroscopy revealed an abnormally low capillary density in borderline hypertensive subjects and even in normotensive subjects with a familial predisposition to the disease.51 Noon et al 52 also described microvascular rarefaction in dorsal finger and forearm skin of genetically predisposed normotensive individuals. Finally, we have very recently shown in hypertensive patients, whether treated or not, that the Framingham score for cardiovascular risk was negatively correlated to capillary density, evaluated in the dorsal skin of the second phalanx of finger.53

Mechanisms of Rarefaction in Hypertension

Considering the clinical data detailed above and also supported by some experimental observations,54 it is increasingly speculated that diffuse systemic rarefaction might be a primary defect in essential hypertension.6 In overt disease, on the other hand, rarefaction can also represent a downstream consequence, as clearly shown by its appearance in animal models of secondary hypertension.38,39,41,55

The cause and effect relationships of rarefaction and hypertension are still debated. Whether mechanical forces, in general, and elevated pressure, in particular, can, per se, be responsible, has received an ambiguous answer. In a rat model of secondary hypertension induced by partial ligation of the abdominal aorta upstream from the renal arteries, Boegehold et al 32 noted structural arteriolar rarefaction in hindquarter muscles. Because these vascular beds were not exposed to high pressure in this model, pressure-independent mechanisms were implied. In contrast, the arteriolar rarefaction, which develops along with hypertension in mice genetically deficient in endothelial NO synthase, was prevented in animals whose blood pressure was kept normal by the chronic administration of hydralazine, a vasodilator.56

Microvascular density can decrease because of either vessel destruction or insufficient angiogenesis. Prewitt et al 18 used in vivo videomicroscopy to carefully investigate skeletal muscle microcirculation in spontaneously hypertensive rats at various stages of disease and concluded that nonneural factors (possibly related to the aforementioned hypersensitivity of vascular smooth muscle to vasoconstrictors) first caused reversible closure of arterioles (functional rarefaction), followed by their anatomic disappearance. Very recently, a significant role has been demonstrated for endothelial cell apoptosis caused by oxidant stress,57 the latter possibly related to the abnormal activation of membrane-bound reduced nicotinamide dinucleotide phosphate oxidase by angiotensin II.

The other side of the equation, namely, deficient angiogenesis, has received increasing attention in recent years.[58–61] One reason for this interest lies in the aforementioned evidence that abnormally low microvascular density can be seen at a very young age in animals with genetic hypertension [30] and also exists in normotensive humans with a familial predisposition to the disease,[51,52] suggesting a developmental defect, that is, an inability of vascular growth to keep pace with organ growth. Another powerful reason to link abnormalities in the long-term control of angiogenesis and blood pressure is the crucial role played by NO and the renin–angiotensin system in both processes. NO, the bioactivity of which seems deficient in hypertension, as we have seen, is not only a vasorelaxant, but is also required for appropriate vascular budding in wound healing [62] and stimulates the expression of vascular growth factors, notably vascular endothelial growth factor (VEGF).[63] Impaired angiogenesis has been directly demonstrated in experimental hypertension induced by chronic pharmacological inhibition of NO synthesis.[64] There is no doubt that the renin–angiotensin system is implicated in angiogenesis but probably in a complex fashion involving an interplay of antagonistic and context-dependent influences (Figure). The complete picture is still lacking because of a high level of inconsistency in the literature.[65] Not surprisingly, the pharmacological blockade of the renin–angiotensin system in experimental models of hypertension has manifestly impacted on rarefaction but not always in the same way (see below).

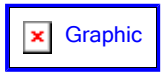

Figure. Possible interactions of the renin–angiotensin system with angiogenesis. Angiotensin II type 1 (AT-1) and type 2 (AT-2) receptors can modulate angiogenesis, but when and how is presently unresolved in view of conflicting data. The figure includes the bradykinin pathway to show that AT-2 receptor stimulation may activate the production of bradykinin, with proangiogenic effects. We have omitted the complexities related to other peptides with potential influence on angiogenesis. Such peptides may be generated in the processing of either angiotensinogen by renin or angiotensin I by neutral endopeptidase.[60] Inhibitors of ACE not only reduce the levels of angiotensin II and, thus, the stimulation of both AT-1 and AT-2 receptors but also promote the bradykinin pathway by inhibiting enzymes responsible for bradykinin degradation. Blockers of the AT-1 receptor (ARB) lead to a compensatory increase in the production of angiotensin II, thus shifting the balance in favor of AT-2 stimulation. Circled lower case letters indicate references: a,[87–89] b,[90–92] c,[90] d,[88,93,94] e,[95] f,[96] and g.[83]

Somewhat paradoxically, essential hypertensive patients without heart failure had high circulating levels of VEGF [66,67] and low concentrations of a VEGF inhibitor (soluble VEGF receptor-1), abnormalities that were corrected by 6 months of intensive cardiovascular risk factor management.[66] This finding suggests desensitization to and compensatory overproduction of vascular growth factors.[60]

The latest player in the field of angiogenesis and hypertension is the circulating bone-marrow-derived endothelial progenitor cell (EPC), first described in 1997.[68] Recruitment of these cells may contribute to the formation of new microvessels in ischemic, malignant, or inflamed tissue.[69] In adult subjects without a history of cardiovascular disease, the number of circulating EPCs was inversely correlated with the Framingham risk score,[70] which includes systolic blood pressure as a major component. Recently, accelerated senescence of EPCs was demonstrated in hypertensive animals and humans.[71] In addition, treatment with olmesartan (and a type 1 angiotensin II receptor antagonist) has increased the number of circulating EPCs in diabetic patients,[72] and administration of angiotensin-converting enzyme (ACE) inhibitors was associated with high levels of these cells in coronary artery disease.[73] Although still speculative, the participation of EPC dysfunction to the pathogenesis of hypertension is now seriously envisioned.[61]

Consequences of Microvascular Rarefaction

Can rarefaction contribute to the increase of peripheral vascular resistance in hypertension? This is a difficult and, in fact, unresolved question. As thoroughly reviewed by Christensen and Mulvany,[4] there is presently considerable uncertainty on the size and anatomic location of resistance vessels because of wild variations

of observations made in different organs, species, and experimental conditions and essential issues include the impact of anesthesia and surgically induced disruption of microvascular physiology.74 In addition, rarefaction of even resistance vessels would be expected to have less impact on global vascular resistance than uniform reduction in their diameter, considering the dependence of the pressure/flow relationship on the fourth power of radius. Finally, most microvascular networks do not conform to a simple model of dichotomous branching where all of the units sharing the same morphofunctional properties would be in parallel, and the global pressure-flow behavior of more complicated arrangements may not be reliably predicted by intuitive–qualitative reasoning alone. In that respect, Greene et al 75 have presented a remarkable, detailed computer simulation of the hamster cheek pouch microcirculation, suggesting that rarefaction of A3 and A4 arterioles can, indeed, augment the global resistance of this vascular bed, although modestly (<=20%). These authors note that changes induced in vivo by rarefaction could be larger than inferred from calculation if a myogenic response occurred in the remaining microvessels because of the fact that they became relatively overperfused.

Other than affecting resistance, rarefaction has the potential to disturb the cellular delivery of nutrients and oxygen, thus contributing to hypertensive end-organ damage. Circumstantial evidence along this line comes from measurements of tissue partial pressure of oxygen in rat models of hypertension, where relative hypoxia occurred in the cremaster,76,77 a muscle in which rarefaction was consistently demonstrated,30,31 but not the spinotrapezius,78 a muscle in which no rarefaction was found.79 The theoretical impact of rarefaction on tissue oxygenation was investigated by modeling the spatial distribution of partial pressure of oxygen with a finite element method; in that simulation, suppression of 25% of microvessels generated extended areas of profound hypoxia, especially in the presence of high cellular demand for oxygen.76

Antihypertensive Treatment and Rarefaction

If rarefaction is, indeed, important in the pathophysiology of hypertension, the question naturally arises of whether it may respond to therapy. Except [beta]-blockers, all classes of antihypertensive drugs in present clinical use have demonstrated an ability both to impact on angiogenesis in specific nonhypertensive models and to influence microvascular rarefaction in experimental hypertension.6,64

Three different calcium antagonists, nifedipine, verapamil, and nimodipine, have increased vascular density on the chick chorioallantoic membrane.80 Calcium antagonists prevented myocardial capillary rarefaction in spontaneously hypertensive rats 37 and in 2 different models of secondary hypertension.39,55

In view of the dual effects of angiotensin II and considering the complexity added by interactions with the bradykinin pathway (Figure), it comes as no surprise that the impact of ACE inhibitors on angiogenesis has varied as a function of experimental conditions. For example, these agents have inhibited vascular growth in tumors 81 while increasing microvascular density in the ischemic skeletal muscle of several species.82,83 In rat hypertensive models, treatment with ACE inhibitors alone had strikingly discordant effects on rarefaction.33,40,41,84,85 For example, treatment increased myocardial capillary density in several 84,85 but not all of these studies 40,41 and could worsen rarefaction in skeletal muscle.33 A similar statement applies to monotherapy with angiotensin II type 1 receptor antagonists.33,38,86

In many of the aforementioned studies, pressure-dependent and pressure-independent effects of therapy on microvascular density are difficult to dissociate. Pressure-independent effects are suggested by some data. In spontaneously hypertensive rats, for example, prolonged treatments with an ACE inhibitor or an angiotensin II type 1 receptor antagonist achieved the same blood pressure reduction; only the former reduced microvascular density in skeletal muscle.33

As another remark, many of the studies cited above have focused on the myocardium, where an increase in the number of vessels per square millimeter of tissue cross-sectional area may reflect a regression of myocardial hypertrophy rather than (or in addition to) a primary effect on vascular structure and growth. Nevertheless, using elaborate morphometry (not restricted to the mere computation of microvascular density), Rakusan et al 37 have concluded that treatment with the calcium antagonist nifedipine reversed rarefaction at least in part by promoting vascular growth in the myocardium of spontaneously hypertensive rats.

Perspectives

There is now abundant data, both clinical and experimental, to indicate that the microcirculation is a major player and target in the pathogenesis of hypertension, notably in the form of microvascular rarefaction. Major issues to be handled by future studies of rarefaction include its mechanisms (still very partially understood), its actual importance for raising peripheral resistance and perpetuating high blood pressure, and its role in the generation of end-organ damage. In a recent cross-sectional study, we found a higher capillary density in the skin of patients with well-controlled, as opposed to poorly controlled, hypertension,53 but the microcirculatory impact of antihypertensive medications remains to be ascertained by longitudinal observation. We may expect that knowledge will rapidly accrue in this field, opening the way to future therapies, which would specifically target the microcirculation of hypertensive patients.

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Hypertension Dec. 2006