Hemodynamic Consequences of Changes in Microvascular Structure

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In hypertension, an increased media-to-lumen ratio of small resistance arteries might play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased hemodynamic load. The presence of morphological alteration in the microvasculature may be associated to an impaired tissue perfusion and/or to the development of target organ damage. Structural alterations in the microcirculation might represent a predictor of the onset of cardio-cerebrovascular events and hypertension complications. A cross-talk between the small and large artery may exaggerate arterial damage, following a vicious circle. Therefore, in the present review, possible hemodynamic consequences of the presence of microvascular structural alterations will be considered, in terms of their time of onset, role in the development and/or maintenance of high blood pressure values, and interrelationships with structural/mechanical alterations of large conductance arteries.

Keywords: blood pressure; hypertension; hemodynamics; microcirculation; remodeling; small arteries.

doi:10.1093/ajh/hpx032

MICROVASCULAR STRUCTURE IN HYPERTENSION

Resistance arteries (internal diameter <350 μm) and capillaries (internal diameter <7 μm) are key elements in the control of blood pressure.[1] Thus, structural changes in the microcirculation may directly and strongly affect blood pressure values. In fact, it is now widely accepted that structural abnormalities of microvessels are common alterations associated with chronic hypertension.[1,2] The majority of the available data indicates that, in patients with essential hypertension, the resistance arteries show a greater media thickness, a reduced lumen and external diameter with increased media-to-lumen ratio, without any significant change of the total amount of wall tissue, as indicated by an unchanged media cross-sectional area (a process known as eutrophic remodeling: rearrangement of the same amount of wall material around a smaller vessel lumen, without net cell growth).[3–5] A thickened arterial wall together with a reduced lumen (with increased media-to-lumen ratio) might play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased hemodynamic load.

TIME COURSE OF MICROVASCULAR STRUCTURAL ALTERATIONS AND BLOOD PRESSURE VALUES

It is not clear whether an increase in blood pressure values precedes or follows the onset of microvascular alterations. Some data in animal models of hypertension, in particular in the spontaneously hypertensive rat (SHR) suggest that an alteration in microvascular structure, namely an increase in the media-to-lumen ratio of mesenteric small resistance arteries might be present in a prehypertensive phase,[6–9] when blood pressure values are, substantially, similar to those of normotensive control animals.

Data in humans are obviously scarce and relatively difficult to obtain, since there is no certainty about what could be considered as a true prehypertensive condition, and no longitudinal data are presently available.

An increase in forearm minimal vascular resistance (an indirect index of microvascular structure) in young subjects with positive family history of hypertension was observed[10]; however, when resistance vessels from offspring of essential hypertensive patients were investigated with direct approaches (micromyography), no morphological alterations was observed, compared with controls.[11] According to Park and Schiffrin, small artery remodeling is the most prevalent and probably the earliest form of target organ damage in human mild essential hypertension.[12] In a review, Ernesto Schiffrin addressed the issue of the time course of changes in morphologic and mechanical aspects of resistance arteries as hypertension evolves in time.[2] He suggested that an increase in the media-to-lumen ratio in small resistance arteries might be present very early, but its severity parallels the increase in blood pressure values[2] (Figure 1).

INTERRELATIONS BETWEEN MICROVASCULAR STRUCTURAL ALTERATIONS AND BLOOD PRESSURE VALUES

Bjorn Folkow hypothesized that alterations in the microvessels might have a relevant impact in terms of

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Initially submitted January 11, 2017; date of first revision February 8, 2017; accepted for publication February 19, 2017; online publication March 10, 2017.

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resistance to flow, and, thus, in the determination of blood pressure values. In fact, he postulated that for the same amount of shortening of vascular smooth muscle cells, in hypertension, due to the presence of an increase media-to-lumen ratio of the vessels, the increase in vascular resistance is far more evident than in normotensive controls[13,14] (Figure 2). This has provided the basis for the hypothesis of the "vascular amplifier"[15]: an increase in the media-to-lumen ratio of small resistance arteries may increase the effect of any hypertensive stimulus.[13,15–17]

It seems that the effect of some vasoconstrictor agents is more pronounced in the presence of an increased media-to-lumen ratio both in animal models of hypertension[18] and in humans.[3,11] Vascular contractions to norepinephrine or other vasoconstrictor agents are increased both in the prehypertensive[6,8,9,20] and in the hypertensive phase[6] in SHR and in the hypertensive rabbit.[21]

However, Izzard and Heagerty challenged the amplifier hypothesis, suggesting that available data do not support the hypothesis that an increased wall-to-lumen ratio may act as an amplifier in hypertension, since vessels from the SHR demonstrated a reduced diameter across all pressures in the absence of tone but, in the presence of myogenic tone, no difference in diameter was observed across the physiological range of pressures, and myogenic tone was not enhanced in hypertension despite an increase in wall-to-lumen ratio.[22,23] Also looking at the data from Mulvany and Aalkjaer obtained in an experimental condition in which vessels do not develop myogenic tone (wire micromyography),[20] there is a constant difference in terms of lumen diameter of mesenteric small arteries between SHR and normotensive Wistar-Kyoto control rats (WKY), at different levels of transmural pressure, thus possibly suggesting a minor role of an amplification of the effects of hypertension in terms of vascular resistance (Figure 3, part b).[20] However, internal diameters of WKY remained around 150, 175, and 200 μm, at 3 progressively increased levels of transmural pressure, while in SHR the corresponding values of internal diameter were around 125, 150, and 175 μm (Figure 3, part b). Since, according to Poiseuille's law, the effect of changes in the internal diameter impact on resistance according to the 4th power of radius, there is, actually, a progressively increasing difference in resistance between the 2 strains (Figure 3, part b), thus supporting the presence of a certain amount of "amplification."

There is some evidence suggesting that, also in humans, the presence of structural alterations at the level of small resistance arteries could increase vascular responses, and, at maximum vasodilatation, could decrease organ flow reserve.[24]

It has been also suggested that alterations in the microcirculation may be involved in the abrupt rise of blood pressure during the early morning hours, which is, in turn, associated to an increased incidence of cardiovascular events[25]; in addition, systolic blood pressure after 6 minutes of exercise (600 kpm/min) correlated with minimal forearm vascular resistance, an indirect index of structural alteration in the forearm microcirculation.[26]

Recently, we have observed a correlation between media-to-lumen ratio of cerebral small resistance arteries and cerebral blood flow in the cortical grey matter, basal ganglia, thalami and subcortical white matter, thus, again, suggesting that more pronounced alterations of small vessels may be associated to an impaired tissue perfusion.[27] Therefore, is seems reasonable that alterations in the microvascular structure may translate into an increased cardiovascular risk.[28] In addition, it was also demonstrated that the severity of structural alterations in subcutaneous small resistance arteries might predict the outcome after adrenalectomy in patients with primary aldosteronism, since the presence of vascular remodeling imply lower chances of blood pressure normalization at long-term follow-up postadrenalectomy.[29]

Tissue perfusion might be altered, especially in diabetes mellitus, also due to impaired myogenic properties of small vessels.[30] In normal controls and in essential hypertension, an increase in intraluminal or transmural pressure

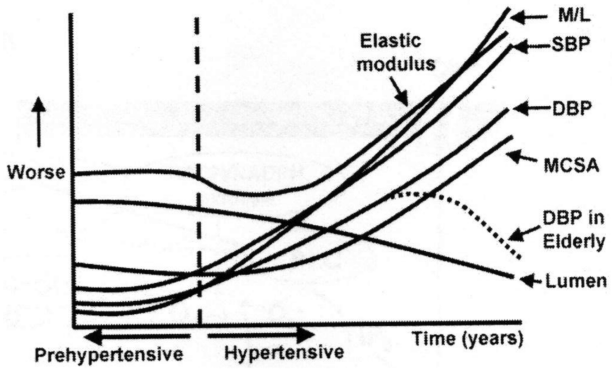

Figure 1. Changes in morphologic and mechanical aspects of resistance arteries as hypertension evolves in time. Abbreviations: DBP, diastolic blood pressure; MCSA, media cross-sectional area; M/L, media/lumen ratio; SBP, systolic blood pressure. (Adapted from the study of Schiffrin[2]).

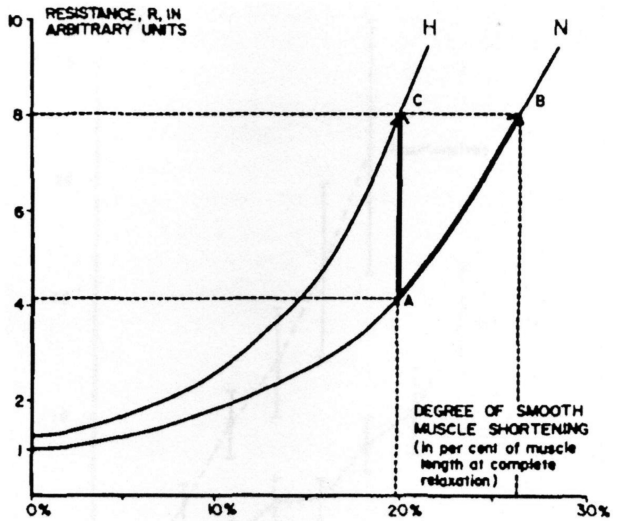

Figure 2. Relationships between vascular resistance and degree of vascular muscle shortening in normotensives (N) and hypertensives (H). For a 20% of shortening, hypertensives show a greater increase in resistance compared with normotensives, due to the presence of microvascular structural alterations. (From: Folkow B "Structural factor" in primary and secondary hypertension. Hypertension. 1990; 16:89–101).

is associated with vasoconstriction, in order to protect tissues from an overperfusion. This autoregulatory function is also vital to ensure stabilization of distal capillary pressures and, hence, to prevent, or limit, organ damage. Indeed in any animal model studied, when myogenic autoregulation is affected, target organ damage ensues.[31]

Myogenic autoregulation is damaged in diabetes mellitus,[30] and an excessive transmission of flow and energy to the periphery might be involved in the development of hypertrophic remodeling, usually seen in the vasculature of diabetic patients.[31] An impaired myogenic tone was also observed to be present in the cerebral or cardiac vasculature,[32,33] at least in animal models.

On the other hand, it should be noted that, in some experimental and clinical conditions, clear dissociations between microvascular structural alterations and hemodynamic effects were observed. As previously mentioned, structural alterations of small arteries are present in young SHR, when blood pressure values are within normal limits.[6] In addition, in SHR treated for a short period of time with antihypertensive drugs, blood pressure progressively increased, although to a lower rate, despite a persistent reduction of structural alterations[34–36] (Figure 4).

Similar dissociations between vascular structural alterations and blood pressure values were observed in 1-kidney 1-clip rats after declipping,[37] and in SHR after withdrawal of a prolonged infusion of angiotensin II[38]: in both cases, a rapid fall in blood pressure was observed, despite a persistent increase in the media-to-lumen ratio of small arteries. In addition, the F2 generation, obtained by a crossbreed between SHR e WKY no difference was observed in terms of media-to-lumen ratio of mesenteric small arteries between rats with high or low blood pressure values.[39]

In hypertensive humans, drug classes with similar effects on brachial blood pressure have different effects on microvascular structure,[2,40–42] and changes in blood pressure and systemic vascular resistance do not predict microvascular structure during treatment of mild essential hypertension.[43] Despite these dissociations, there is hardly any doubt that changes in microvascular structure have a profound and direct effect on the development of hypertension complications and cardio-cerebrovascular events.[28,44,45]

An early treatment with dihydropiridinic calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors is anyway able to delay the development of hypertension after treatment withdrawal in SHR[34,36] (Figure 4), while the angiotensin II receptor blocker candesartan was demonstrated to be able, at least in part, to prevent the transition from prehypertension to hypertension in humans.[46]

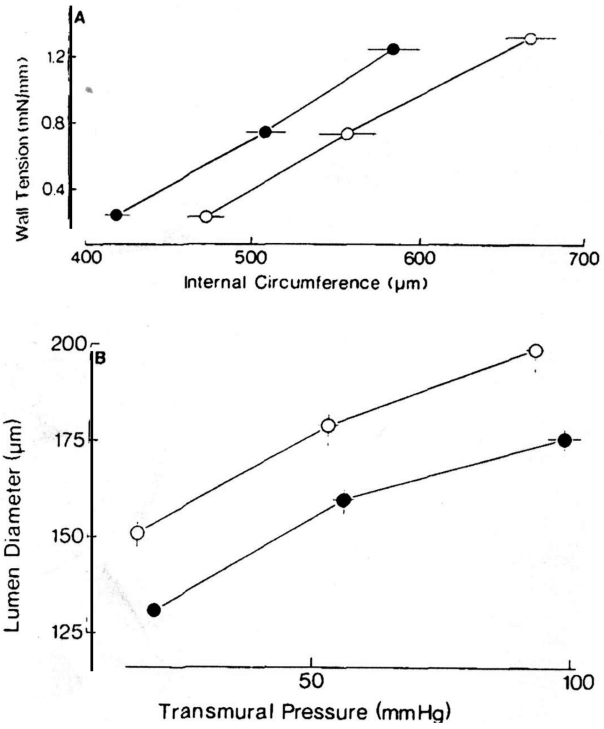

Figure 3. (**a**) Average resting wall tension plotted against internal circumference for 13 spontaneously hypertensive rat (SHR) vessels (filled circles) and 13 Wistar-Kyoto rat (WKY) vessels (unfilled circles). (**b**) Estimated average transmural pressure-lumen diameter relationship in 10 SHR vessels (filled circles) and 10 WKY vessels (unfilled circles). The data have been grouped according to the calculated transmural pressure level. (Adapted from the study of Mulvany *et al.*[20]).

ANTICONTRACTILE ACTIVITY OF PERIVASCULAR FAT TISSUE

A large body of evidence has accumulated suggesting that adipose tissue is probably highly metabolically active.[47,48] This has important implications for the vasculature where the perivascular adipose tissue (PVAT) exerts an anticontractile effect through the paracrine actions of vasodilator adipokines. These adipose-derived vasodilators act independently of the endothelium and include adiponectin,[49] NO,[35] hydrogen sulfide,[50] and palmitic acid methyl ester.[51]

In obese patients as well as in experimental models of weight gain there is clear evidence that this anticontractile function is lost[49]: the perivascular environment becomes inflamed with increased oxidative stress, macrophage activation,[52] and the release of a number of cytokines that can influence the bioavailability of key vasodilator molecules such as adiponectin.[49]

In fact in 2009, Greenstein *et al.*[49] performed the first human small artery study of PVAT and showed that subcutaneous gluteal PVAT from lean healthy individuals reduced adrenergic constriction in adjacent arteries (anticontractile effect). However, in patients with metabolic syndrome the vasodilatory effect of the PVAT was entirely lost, due to dual processes of adipose tissue hypoxia and inflammation, both of which are established sequelae of obesity in fat depots.[48]

In addition, there is increased activation of the locally generated components of the renin–angiotensin–aldosterone axis that contribute to the inflammatory reaction.[53,54] Indeed this situation can be reproduced *in vitro* by the induction of local hypoxia or the application of exogenous aldosterone in segments of artery surrounded by PVAT.[52] Hypoxia or exposure to $CoCl_2$ leads to an increase in the hypoxia-sensitive transcription factor, HIF-1alpha, and to

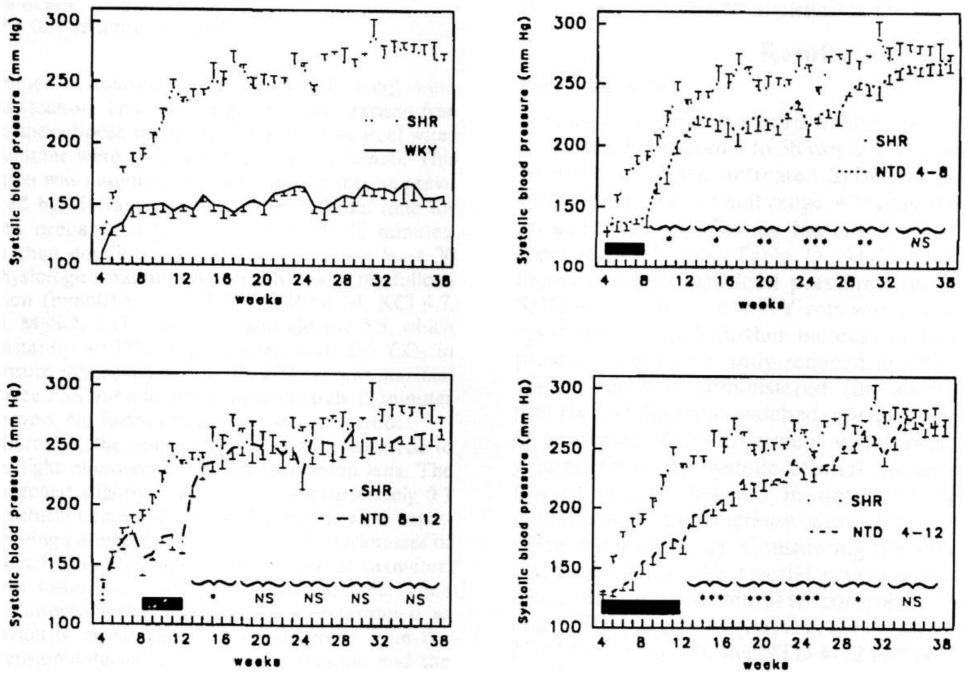

Figure 4. Line graphs show time course of systolic blood pressure from 4 to 38 weeks in rat groups killed at 38 weeks. Wistar-Kyoto (WKY) rats (top left) and rats treated with nitrendipine from 4 to 8 weeks of age (NTD 4–8) (top right), from 8 to 12 weeks of age (NTD 8–12) (bottom left), and from 4 to 12 weeks of age (NTD 4–12) (bottom right) are compared with untreated spontaneously hypertensive rats (SHR). Data are mean values ± SEM; $n = 6$ in each group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ by ANOVA vs. untreated age-matched SHR. (Adapted from the study of Rizzoni *et al.*[34]).

a reduction in adiponectin levels in human adipocytes with an increase in the production of several proinflammatory adipokines.[55] It has also been demonstrated, at least in animal models, that the loss of PVAT-associated anticontractile function with hypoxia or aldosterone can be restored using eplerenone, a mineralocoticoid receptor antagonist,[52] as well as with the ACE inhibitor captopril or the angiotensin-receptor blocker telmisartan,[56] or giving a long-term treatment with melatonin, an endogenous hormone with antioxidant and vasculoprotective properties.[57] A reduced expression of adiponectin and adiponectin receptor was observed in the perivascular fat of untreated obese mice, whereas a significant increase was observed in mice treated with melatonin.[57]

In small arteries of obese patients, PVAT-derived tumor necrosis factor-alpha excess and an increased vascular expression of endothelin-1 and endothelin-A receptors contribute to the endothelin-1/nitric oxide (NO) system imbalance, by impairing tonic NO release.[58] Reactive oxygen species excess may induce the endothelial nitric oxide synthase uncoupling, which, in turn, may generate superoxide anions and impairs NO production.[58]

Few data are presently available about the possibility to improve or restore the anticontractile effect of PVAT in humans. Bariatric surgery seems to reverse the obesity-induced alteration to PVAT anticontractile function.[59] This reversal is attributable to reductions in local adipose inflammation and oxidative stress with improved adiponectin and nitric oxide bioavailability.[59]

In general, relationships exist between functional properties and structural alterations in the microvascular district, in the course of the natural history of hypertension, although it is difficult to establish properly the causal link. As mentioned, changes in the myogenic responsiveness may play a relevant role in this regard, while endothelial dysfunction, frequently present in small arteries of hypertensive/obese patients[12,60] might be both a promoter of vascular remodeling through concomitant low-grade inflammation/oxidative stress or might be a consequence of an altered vascular structure or of increased blood pressure values *per se*. Some data however suggest that endothelial dysfunction seems to be, at least in part, independent from the degree of vascular structural alterations and from the etiology of hypertension.[60] This issue was specifically addressed in a recent paper form Bruno *et al.*,[61] which demonstrated that hypertension anticipates and enhances the "physiological" age-related increase in the media-to-lumen ratio of subcutaneous small arteries, but the impact of essential hypertension on structural and functional age-related vascular changes (media-to-lumen ratio, oxidative stress, collagen deposition, endothelial dysfunction, etc.) is quite heterogeneous.[61]

RELATIONSHIPS BETWEEN STRUCTURAL CHANGES IN THE MICROCIRCULATION AND MACROCIRCULATION

Microvascular structure is not only the site of vascular resistance but also, probably, the origin of most of the wave reflections generating the increased central systolic blood pressure in the elderly,[62] although the proper location of a reflection site may be elusive.[63] On the other hand, increased pulsatility of conduit arteries is transmitted to

small arteries and may contribute to vascular injury in the resistance vasculature.[64]

When the possible prognostic role of small artery remodelling in high-risk hypertensive patients was evaluated, only the media-to-lumen ratio of subcutaneous small arteries and pulse pressure (a rough index of large artery stiffness) entered the model, thus suggesting that structural changes in the microcirculation and alterations on mechanical properties of large arteries are 2 most important factors in predicting outcome.[28] In addition, possible relationships between subcutaneous small resistance artery structure, and blood pressure values were investigated in a population of more than 200 normotensive subjects and hypertensive patients.[65] Among the most important predictors of small artery structure, there were clinic systolic, diastolic and mean blood pressure, 24-hour systolic and diastolic blood pressure, and the ratio between pulse pressure and stroke volume, taken as a rough index of large artery compliance.

Recently, possible relationships between indices of large arteries stiffness and media-to-lumen ratio of subcutaneous small resistance arteries have been investigated.[66] The media-to-lumen ratio was significantly related to both brachial systolic pressure and pulse pressure and to central systolic and pulse pressure. A positive correlation was observed between media-to-lumen ratio and carotid-femoral pulse wave velocity; this correlation remained statistically significant after adjustment for age and mean blood pressure. The media-to-lumen ratio was also associated to aortic augmentation index, and these correlation remained statistically significant after adjustment for potential confounders.

Large artery stiffening was also demonstrated to be related to cerebral lacunar infarctions,[67] or to large white matter hyperintensities[68] which are usually expression of cerebral microvascular disease. Elderly subjects with high intracranial pulsatility display smaller brain volume and larger ventricles, supporting the notion that excessive cerebral arterial pulsatility harms the brain.[69] Pulse pressure and pulse wave velocity, hemodynamic markers of arterial stiffness, have been associated with stroke, dementia, and lowered levels of cognitive function, and it was suggested that aggressive treatment of risk factors associated with greater arterial stiffness may help preserve cognitive function with individuals' increasing age.[70]

Also, pulsatility index was associated with lower memory scores and worse performance on tests assessing executive function. When magnetic resonance imaging measures (gray and white matter volumes, white matter hyperintensity volumes, and prevalent subcortical infarcts) were included in cognitive models, hemodynamic associations were attenuated or no longer significant, consistent with the hypothesis that increased aortic stiffness and excessive flow pulsatility damage the microcirculation, leading to quantifiable tissue damage and reduced cognitive performance. Marked stiffening of the aorta is associated with reduced wave reflection at the interface between carotid and aorta, transmission of excessive flow pulsatility into the brain, microvascular structural brain damage, and lower scores in various cognitive domains.[71] Middle cerebral artery pulsatility was also demonstrated to be the strongest physiological correlate of leukoaraiosis, independent of age, and it resulted dependent on aortic diastolic blood pressure and pulse pressure and on aortic and middle cerebral artery stiffness, supporting the hypothesis that large artery stiffening results in increased arterial pulsatility with transmission to the cerebral small vessels resulting in leukoaraiosis.[72]

Therefore, it seems that a close relationship has been established between brain and kidney microvascular damage and indices of age and large artery stiffness (pulse pressure, aortic pulse wave velocity, and augmentation index).[73] A possible pathophysiological explanation of this link can be offered on the basis of differential input impedance in the brain and kidney, compared with other systemic vascular beds: torrential flow and low resistance to flow in these organs exposes small arterial vessels to the high-pressure fluctuations that exist in the carotid, vertebral, and renal arteries. Such fluctuations, measurable as central pulse pressure, increase 3- to 4-fold with age. Exposure of small vessels to highly pulsatile pressure and flow explains microvascular damage, renal insufficiency, and intellectual deterioration.[73] Therefore, the logical approach to prevention and treatment requires reduction of central pulse pressure.[72] Because the aorta and large arteries are not directly affected by drugs, this entails reduction of wave reflection by dilation of conduit arteries elsewhere in the body.[73] This can be accomplished by regular exercise and by drugs such as nitrates, calcium channel blockers, ACE inhibitors, and angiotensin-receptor blockers.[73] This hypothesis may account for greater and earlier vascular damage in diabetes mellitus (relative microvascular fragility) and is similar to that given for vascular changes of pulmonary hypertension caused by ventricular septal defects and other congenital vascular shunts.[73] In summary, microvascular brain damage—the result of age-associated alteration in large arteries and the progressive mismatch of their cross-talk with small cerebral arteries—represents a potent risk factor for cognitive decline and for the onset of dementia in older individuals[74]; loss of cognitive function and hypertension are 2 common conditions in the elderly and both significantly contribute to loss of personal independency.

Recently, a noninvasive approach for the evaluation of retinal arteriolar morphology (Scanning laser Doppler flowmetry) was proposed[75] and validated.[76] The wall-to-lumen ratio of retinal arteries (evaluated noninvasively), is strongly correlated with the gold standard measurement of the media-to-lumen ratio of subcutaneous small arteries, obtained with locally invasive bioptic techniques (wire micromyography).[76,77]

Using this noninvasive approach, Ott *et al.*[78] could recently demonstrate that central pulse pressure and central augmentation index, normalized to a heart rate of 75 beats per minute, correlated with the wall-to-lumen ratio of retinal arterioles. Multiple regression analysis revealed an independent relationship between wall-to-lumen ratio and central pulse pressure, but not with other classical cardiovascular risk factors.

Using the same technique, it was demonstrated that wall-to-lumen ratio of retinal arterioles was significantly related

to clinic systolic and pulse pressure, to 24-hour systolic and pulse pressure, and to central systolic and pulse pressure.[79]

Thus, central pulse pressure, indicative of changes in large conduit arteries is an independent determinant of vascular remodeling in small retinal arterioles.[78,79] Such a relationship indicates a coupling and crosstalk between the microvascular and macrovascular changes attributable to hypertension.[80] In fact, increased wall-to-lumen ratio and rarefaction of small arteries are major factors for an increase in mean blood pressure; then the higher mean blood pressure, in turn, may increases large artery stiffness through the loading of stiff components of the arterial wall at high blood pressure levels; finally the increased large artery stiffness may be a major determinant of the increased pulse pressure, which, in turn, damages small arteries in different organs (heart, brain, retina, kidney) and, in general, favors the development of target organ damage.[80] Thus, the cross-talk between the small and large artery exaggerates arterial damage, following a vicious circle.[80]

As previously mentioned, hypertension may induce an early vascular aging, to some extent similar in large[80] and small[61] arteries. Finally, it should be mentioned that antihypertensive drugs that are particularly effective in the prevention/regression of large artery stiffening, such as calcium channel blockers and blockers of the renin–angiotensin system (ACE inhibitors, angiotensin II receptor blockers)[62] are also most effective in the regression of microvascular remodeling.[41] Specific drug properties, beyond their hemodynamic effects, possibly related to their mechanism of action (calcium entry inhibition, blockade of the deleterious effects of angiotensin II and their consequences on inflammation/oxidative stress), might be involved in this pronounced vascular protection.[41,81,82]

Interrelationships between alterations in the macrocirculation and microcirculation and mechanisms possibly involved represent, therefore, an extremely interesting topic, which deserve further and thorough investigation, also considering its relevant clinic impact, especially in terms of therapeutic targets and possible prevention or regression of such alterations.

MICROVASCULAR RAREFACTION

Hypertension seems to be also associated with a reduction (rarefaction) in the number of parallel-connected arterioles and capillaries,[42,83] with important consequences in terms of tissue perfusion.[83] Microvascular density may be evaluated noninvasively by videomicroscopy/capillaroscopy in specific cutaneous regions or in the nailfold.[42] In general, a functional rarefaction (reduction of capillaries perfused in basal condition) or a structural rarefaction (reduction of capillaries that may be recruited, i.e., after venous congestion) may be observed in essential hypertension.[42,83] Basal and total capillary density is increased in effectively treated antihypertensives.[84] Hypertensive patients with their blood pressure well controlled with the combination perindopril/indapamide had normalized capillary density, whereas other antihypertensive treatments, which did not include ACE inhibitors or diuretics, had less effect despite similar blood pressure control.[84]

Inhibitors of angiogenesis, extensively used in oncology, may induce an increase in blood pressure values also through a reduction in capillary density.[85] This effect might have a clinical relevance in terms of cardiovascular risk and/or management of these patients.[85]

CONCLUSION

In conclusion, in hypertension, an increased media-to-lumen ratio of small resistance arteries might play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased hemodynamic load. The precise time course of the development of microvascular alterations in humans is not entirely clear at present, moreover, their role as amplifier of hypertensive stimuli is still a matter of debate.

However, the presence of morphological alteration in the microvasculature may be associated to an impaired tissue perfusion and/or to the development of target organ damage. Therefore, structural alterations in the microcirculation might represent a predictor of the onset of cardio-cerebrovascular events. A cross-talk between the small and large artery may contribute to enhance arterial damage, with a deleterious synergistic effect.

DISCLOSURE

The authors declared no conflict of interest.

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