14 Microvascular Structural Alterations and Tissue Perfusion in Hypertension/Diabetes

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14.1 Microvascular Structure in Hypertension

Resistance arteries are key elements in the control of blood pressure. The main drop in hydrostatic pressure occurs at the level of the resistance vasculature: i.e. small resistance arteries (<350 μm of lumen diameter), arterioles (<100 μm of lumen diameter) and capillaries (about 7 μm of lumen diameter) [1, 2]. Total peripheral resistance in terminal arteries and arterioles amounts to 45–50%, in capillaries to 23–30%, in venules to 3–4%, and to 3% in veins [2]. 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, 3–5]. A thickened arterial wall together with a reduced lumen (a process known as remodelling) may play an important role in the increase of vascular resistance, and may also be an adaptive response to the increased haemodynamic load. As described by Poiseuille's law, resistance is inversely proportional to the radius to the forth power; therefore, slight alterations in arterial lumen result in significant effects on vascular resistance. In addition, hypertension seems to be associated with a reduction (rarefaction) in the number of capillaries [6–8].

In the last few years, several evidences have suggested that hypertensive injury of small arteries may participate also in the pathophysiology of its complications.

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Hence, the study of structural alterations of resistance vessels in essential hypertension, the possibility of their regression with antihypertensive treatment as well as their contribution to the prognosis of patients with essential hypertension should be considered of great clinical and scientific interest.

14.2 Microvascular Structure in Diabetes Mellitus

Microvascular complications are major contributors to morbidity, mortality and costs of both non-insulin-dependent (NIDDM) and insulin-dependent diabetes mellitus (IDDM) [9]. Damage of the small vessels in the kidney can lead to end-stage renal disease, structural alterations of the smaller vessels that supply nutrients and oxygen to peripheral nerves contribute to neuropathy while damage of the microvasculature of the eye is the leading cause of loss of vision in working-age adults. The clinical manifestations of microvascular disease are so characteristic of the disease that diabetes itself is defined primarily by the level of hyperglycaemia which causes microvascular complications.

Alterations in the microcirculation involve small resistance arteries, arterioles, capillaries and post capillary venules. A relevant role in the impairment of vascular distensibility may be played by advanced glycosylation end products (AGE), which may be involved in the formation of collagen cross-links [10]. While there is a huge number of data about microangiopathy (capillary and arterioles), quite few data about morphology of small resistance arteries (diameter ranging from 100 to 350 μm) in diabetes mellitus are presently available. In one study [11], no difference in subcutaneous small artery structure was observed between control subjects and patients with insulin-dependent diabetes mellitus (IDDM). On the contrary, it has been demonstrated that, in both hypertensive and normotensive patients with NIDDM, marked alterations in small artery structure are present [12], and that these alterations are more pronounced in hypertensive patients with NIDDM than in patients with essential hypertension or in normotensive diabetics (Fig. 14.1) [12]. In addition, in diabetic patients a clear increase in the media cross-sectional area of the vessels was observed, thus suggesting the presence of hypertrophic remodelling (vascular smooth muscle cells hypertrophy or hyperplasia) [12, 13] (Fig. 14.1). This was not the case of patients with essential hypertension. A weak, but significant correlation between circulating levels of insulin and media-to-lumen ratio of subcutaneous small arteries was observed in diabetic patients, thus suggesting a possible role of insulin or insulin-like growth factor-1 in the genesis of hypertrophic remodelling in these patients [12] However, an alternative explanation for the presence of hypertrophic remodelling in these vessels has been proposed [13]. In fact, a possible stimulus for hypertrophic remodelling could be the increased wall stress, as a consequence of the impaired myogenic response. Myogenic response is a pressure-induced vasoconstriction, which is the key component of blood flow autoregulation and stabilization of capillary pressure. The observation by Schofield et al. [13] of the lack of such a myogenic response in diabetic patients may therefore be responsible for the development of hypertrophic

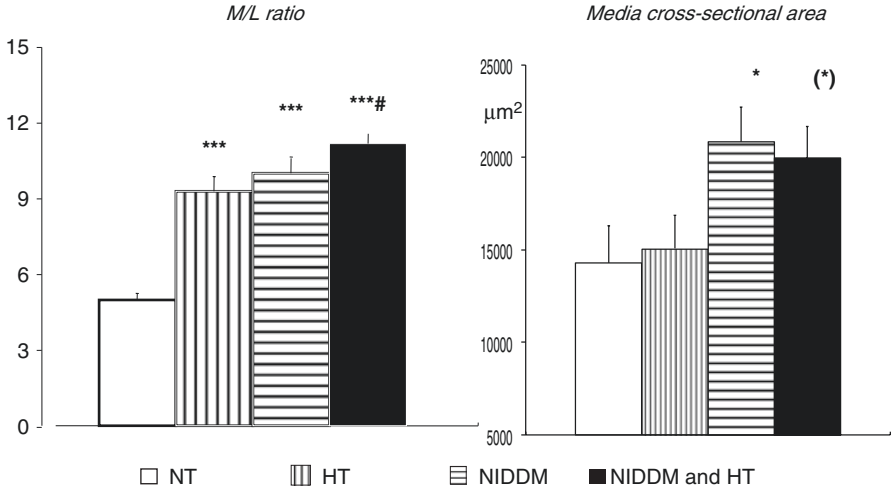

Fig. 14.1 Subcutaneous small resistance arteries structure in hypertensive and diabetic patients. Left: Media-to-lumen ratio in subcutaneous small resistance arteries from normotensive subjects (NT), essential hypertensive patients (HT), normotensive patients with non-insulin-dependent diabetes mellitus (NIDDM) and hypertensive patients with NIDDM (NIDDM and HT). A clear increase may be observed in all the three pathologic groups, which is more evident in hypertensive patients with NIDDM. Right: Medial cross-sectional area in subcutaneous small resistance arteries from normotensive subjects (NT), essential hypertensive patients (HT), normotensive patients with NIDDM and hypertensive patients with NIDDM (NIDDM and HT). An increase may be observed in the diabetic patients, which is more evident in normotensive patients with NIDDM. (*)$p = 0.06$, *$p < 0.05$ vs. Normotensives. Mean ± SEM. (re-drawn, data from [12])

remodelling of small arteries (Fig. 14.2) [13]. As mentioned, while small resistance arteries and arterioles may undergo a remodelling process and fibrosis in pathological conditions, capillaries may undergo a functional or structural rarefaction, with consequent reduction in the density per area units of tissue. This process of vascular rarefaction was previously observed in patients with hypertension [7, 8] but also in patients with NIDDM [14, 15].

On the contrary, in other vascular districts such as the retina, microvascular proliferation may also be observed. In fact, diabetic retinopathy results either from capillary leakage or from new vessel formation (neovascularization, angiogenesis), caused by capillary closure and retinal ischaemia. The capillaries leak lipid products and fluid in the area around the fovea and thicken the retina, which may lead to macular oedema. Angiogenesis is the result of retinal ischaemia, and retinal haemorrhages are the consequence of the fragility of neovessels. The haemorrhage can enter the vitreous and cause sudden loss of vision. Several mechanisms and metabolic abnormalities, acting alone or in concert with each other, may lead to capillary death, leakage and occlusion and to the release of growth factors, finally resulting in new vessel formation and increase vascular permeability. A relevant role is played by vascular endothelial growth factor (VEGF). Whereas VEGF is involved in

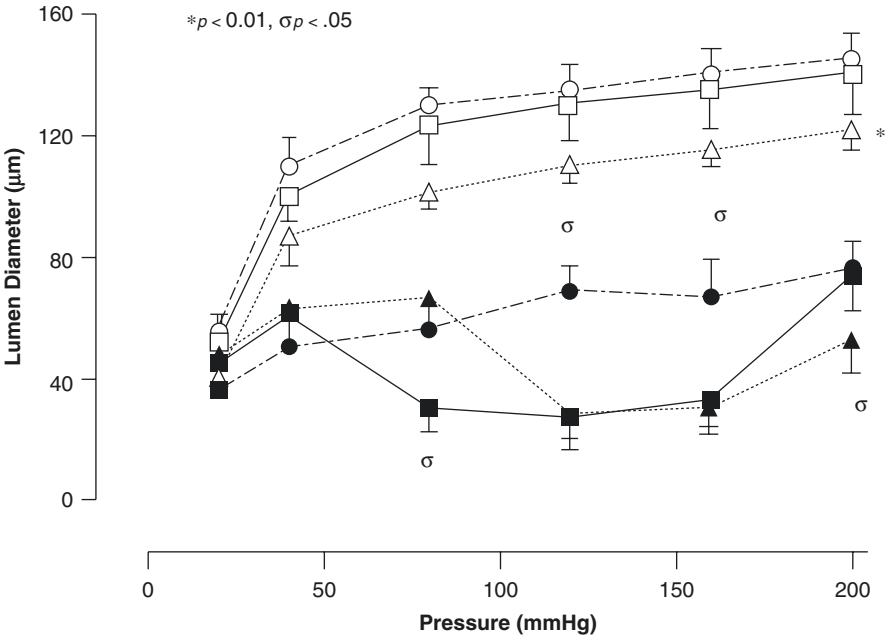

Fig. 14.2 Myogenic response in subcutaneous small resistance arteries in patients with NIDDM. Passive pressure–lumen diameter relations for arteries from control subjects (square), patients with EH (triangle), and hypertensive patients with NIDDM (circle). * = $p < 0.05$, ANOVA, vs. control. Active pressure–lumen diameter relations for arteries from control subjects (filled square), patients with essential hypertension (filled triangle), and hypertensive patients with NIDDM (filled circle). σ = $p < 0.05$ vs. control vessels (from [13])

vascular leakage and angiogenesis, growth hormones and the insulin-like growth factor-1 (IGF-1) are involved, as mediators, in angiogenesis.

14.3 Microvascular Structural Alterations and Organ Perfusion

As previously mentioned, the extent of structural alterations in small resistance vessels is more pronounced in patients with both diabetes mellitus and hypertension, thus suggesting that clustering of risk factors may have synergistic deleterious effects on the vasculature [12, 13]. An important pathophysiological and clinical consequence of the presence of structural alterations in small resistance arteries and arterioles may be an impairment of vasodilator reserve [16]. In fact, as previously reported, remodelling of small resistance arteries is characterized by a narrowing of the lumen, which leads to an increase of flow resistance even at full dilatation, i.e. in the absence of vascular tone. A significant correlation between coronary flow reserve and subcutaneous small resistance artery remodelling has been observed in hypertensive patients, suggesting that structural alterations in

small resistance arteries may be present at the same time in different vascular districts, including those of paramount clinical importance, such as the coronary circulation [17]. 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 (Fig. 14.3), thus, again, suggesting that more pronounced alterations of small vessels may be associated to an impaired tissue perfusion [18]. Cerebral autoregulation, a mechanism aimed at maintaining constant brain flow in the presence of changes in mean blood pressure is shifted rightward in hypertension [19], and this may have a consequence in terms of excessive reduction in cerebral perfusion during abrupt reductions in blood pressure [19, 20].

It was observed also that a relatively close correlation exists between structure of subcutaneous small resistance arteries of normotensive subjects and hypertensive patients and microvessel density in the derma, as evaluated by an immunohistochemical approach (immunostaining for CD 31), thus suggesting that structural changes in the microcirculation may be present simultaneously at different levels [21] (Fig. 14.4).

An impaired microvascular hyperaemic response (which may reflect an altered flow reserve) has been observed in children with diabetes mellitus [22] as well as in adult patients with NIDDM [23]. Thus, alterations in the microcirculation may play an important role in the development of organ damage not only in hypertension but also in diabetes mellitus. In fact, a relevant prognostic role of an increased media-to-lumen ratio of subcutaneous small resistance arteries in a high-risk population (including normotensive and hypertensive diabetic patients) has been previously demonstrated [24]. Also the characteristics of the vascular remodelling, i.e. eutrophic vs. hypertrophic remodelling was taken into account. For the same values of internal diameter, those subjects who suffered cardiovascular events had a greater

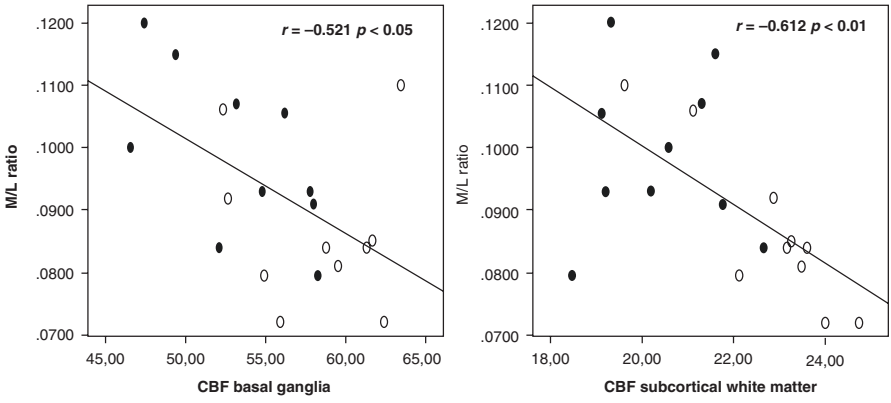

Fig. 14.3 Left graph: correlation between cerebral blood flow (CBF) in the basal ganglia and media-to-lumen (M/L) ratio of cerebral arteries. Right graph: correlation between CBF in the subcortical white matter and M/L ratio of cerebral arteries. Empty circles normotensive subjects, full circles hypertensive patients (from [18])

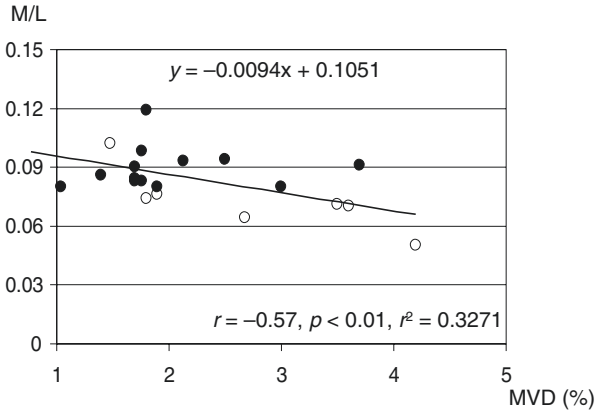

Fig. 14.4 Correlation between media-to-lumen ratio (M/L) of subcutaneous small resistance artery and microvessels density (MVD) in the derma of normotensive subjects (empty circles) and hypertensive patients (full circles). Reprinted from [21], with permission from IOS Press

media-cross-sectional area, in comparison with those without cardiovascular events [25]. Therefore, it seems that, for the same size of the vessels explored, a more consistent cell growth (hypertrophic remodelling, such as that observed in diabetic patients) means an even worse prognosis. It has been also suggested, as previously reported, that an impairment of myogenic response may have a relevant role in the development of hypertrophic remodelling in patients at high cardiovascular risk. In addition, an impaired myogenic response in small vessels may also induce an increase of high blood pressure flow to target organs and downstream increase in capillary pressure, with consequent increased permeability and capillary leakage. Fluid extravasation may induce organ damage. Some data support the presence of an increased capillary pressure in patients with diabetes mellitus [26], especially if they have increased blood pressure values [27], although at present time there is no general agreement about this issue.

The increase in capillary pressure seems to be related to the extent of clinical complications as well as to metabolic control [28]. Also vascular rarefaction per se may have important consequences in terms of tissue perfusion. In fact, it has been demonstrated that in patients with NIDDM, the mechanisms through which insulin is able to increase total limb flow or achieve optimal microvascular perfusion is impaired [14].

As mentioned, hypertension seems to be also associated with a reduction (rarefaction) in the number of parallel-connected arterioles and capillaries [6, 29], with possibly important consequences in terms of tissue perfusion [6]. Microvascular density may be evaluated non-invasively by videomicroscopy/capillaroscopy in specific cutaneous regions or in the nailfold [7, 8, 29]. 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 [6, 29]. Therefore, capillary rarefaction observed in hypertension is very likely a permanent anatomical change rather than a functional one. Whether it is pathologically important in terms of worsening the disease or generating complications is still a matter of debate, although it is probable that it might be associated to increased peripheral resistance and impaired tissue

perfusion, thus, consequently, to organ damage [30]. At present, however, we do not have convincing evidence of a prognostic value of a decreased capillary density in hypertension [29], at difference to what demonstrated for small resistance artery remodelling [24].

Tissue perfusion might be altered, especially in diabetes mellitus, also due to impaired myogenic properties of small vessels [13] (Fig. 14.2). In normal controls and in essential hypertension, an increase in intraluminal or transmural pressure 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 [13] (Fig. 14.2), and an excessive transmission of flow and energy to the periphery might be involved in the development of hypertrophic remodelling, 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.

In any case, it is well accepted that cerebral lacunar infarctions [34], or large white matter hyperintensities [35], are usually expression of cerebral microvascular disease. Pulsatility index was associated with lower memory scores and worse performance on tests assessing executive function. When magnetic resonance imaging measures (grey and white matter volumes, white matter hyperintensity volumes and prevalent subcortical infarcts) were included in cognitive models, haemodynamic 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 [36]. 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 [36].

Therefore, it seems that a close relationship has been established between brain microvascular damage and indices of age and large artery stiffness (pulse pressure, aortic pulse wave velocity, and augmentation index) [36]. 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 three- to fourfold with age. Exposure of small vessels to highly pulsatile pressure and flow explains microvascular damage, renal insufficiency and intellectual deterioration [36].

Finally, another issue possible relevant in respect with impaired tissue perfusion in pathological conditions is represented by the loss of anticontractile activity of perivascular fat.

A large body of evidence has accumulated suggesting that adipose tissue is probably highly metabolically active [37, 38]. 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, nitric oxide, hydrogen sulphide and palmitic acid methyl ester [36]. In patients with metabolic syndrome there is clear evidence that this anticontractile function is lost [39]: the perivascular environment becomes inflamed with increased oxidative stress, macrophage activation [40] and the release of a number of cytokines that can influence the bioavailability of key vasodilator molecules such as adiponectin [39]. The lack of a vasodilator effect mediated by perivascular fat might expose peripheral tissue to hypoperfusion [36].

14.4 Effect of Treatment on Microvascular Structural Alterations

Since changes in microvascular structure have a profound and direct effect on the development of hypertension complications and cardio-cerebrovascular events [24], it is expected that prevention/regression by appropriated treatment of these alterations may be associated with a better prognosis [41, 42].

In hypertension, some intervention studies with specific drugs have demonstrated an improvement or even an almost complete normalization of the structure of subcutaneous small resistance arteries with angiotensin converting enzyme (ACE) inhibitors (cilazapril, perindopril, lisinopril), calcium channel blockers (nifedipine, amlodipine, isradipine), angiotensin II receptor blockers (losartan, irbesartan, candesartan, olmesartan and valsartan) [3, 29, 43]. On the contrary, the β-blocker atenolol and the diuretic hydrochlorothiazide had limited effects on resistance vessels**,** despite a similar blood pressure reduction [3, 29, 43]. ACE inhibitors proved to be significantly more effective than the β-blocker atenolol in terms of changes in media-to-lumen ratio [43]. The same result was obtained comparing dihydropyridinic calcium channel blockers and atenolol, or angiotensin receptor blockers and atenolol [43]. It should also be noted that, during antihypertensive treatment, the regression of microvascular structural alterations in the subcutaneous small arteries of hypertensive patients is paralleled by an improvement of coronary flow reserve [42, 44].

Basal and total capillary density is increased in effectively treated antihypertensives [45–47]. Hypertensive patients with their blood pressure well controlled with the combination perindopril/indapamide [45, 46] or lercadipine/enalapril [47] showed an improvement/normalization of capillary density, whereas other antihypertensive treatments, including the combination lercanidipine/hydrochlorothiazide, had less effect despite similar blood pressure control [45, 47]. An improvement

in retinal capillary rarefaction was observed recently after valsartan treatment in hypertensive patients [48].

Inhibitors of angiogenesis, extensively used in oncology, may induce an increase in blood pressure values also through a reduction in capillary density [49]. This effect might have a clinical relevance in terms of cardiovascular risk and/or management of these patients [49].

Few data are presently available about the possibility to improve or restore the anticontractile effect of PVAT in humans. Blockade of the renin-angiotensin system [50] or antioxidants such as melatonin [51] seem to be effective, while also bariatric surgery seems to reverse the obesity-induced alteration to PVAT anticontractile function [52]. This reversal is attributable to reductions in local adipose inflammation and oxidative stress with improved adiponectin and nitric oxide bioavailability [52].

Similarly, there are not many data about the effect of treatment on structural and functional alterations in the microcirculation of patients with diabetes mellitus. In the United Kingdom Prospective Diabetes Study (UKPDS), a large randomized controlled trial that included almost 5000 patients, it has been demonstrated that a tight haemodynamic and metabolic control is associated with a lower incidence of microvascular disease [53], and, in general, of clinical endpoints related to microvascular disease [54].

Even fewer data are presently available about the effects of antihypertensive drugs on small artery structure in hypertensive diabetic patients. Despite effective antihypertensive treatment, resistance arteries from hypertensive diabetic patients showed marked remodelling, greater than that of vessels from untreated, nondiabetic, hypertensive subjects, in agreement with the high cardiovascular risk of subjects suffering from both diabetes and hypertension [55]. A study has compared the effects of 1 year treatment with the ACE inhibitor (enalapril) or the angiotensin II receptor blocker (candesartan), on subcutaneous small artery structure in hypertensive patients with NIDDM [56]. The two drugs were equally effective in reducing media-to-lumen ratio of small arteries (Fig. 14.5), however, candesartan was more effective than enalapril in normalizing vascular collagen content, probably through a more pronounced stimulation of the local production of metalloproteinase 9 (a collagen-degrading enzyme). At variance to what is observed in the majority of studies in normoglycaemic hypertensive patients, media-to-lumen ratio of small arteries in treated diabetic patients did not reach the values observed in normotensive controls, therefore suggesting that a complete regression of vascular hypertrophic remodelling is probably more difficult to obtain [56]. Angiotensin II receptor blockers seem to be effective in diabetic hypertensive patients also when given on top of an ACE inhibitor treatment [57].

It has been recently proposed that drugs that may stimulate PPARα or PPAR γ receptors (such as fibrates of glitazones) may be useful in terms of vascular protection and regression of structural alterations in the microcirculation although no convincing data is presently available. The sodium-glucose cotransporter 2 inhibitor, dapagliflozin was demonstrated to be able to favourably affect microvascular and macrovascular circulation [58].

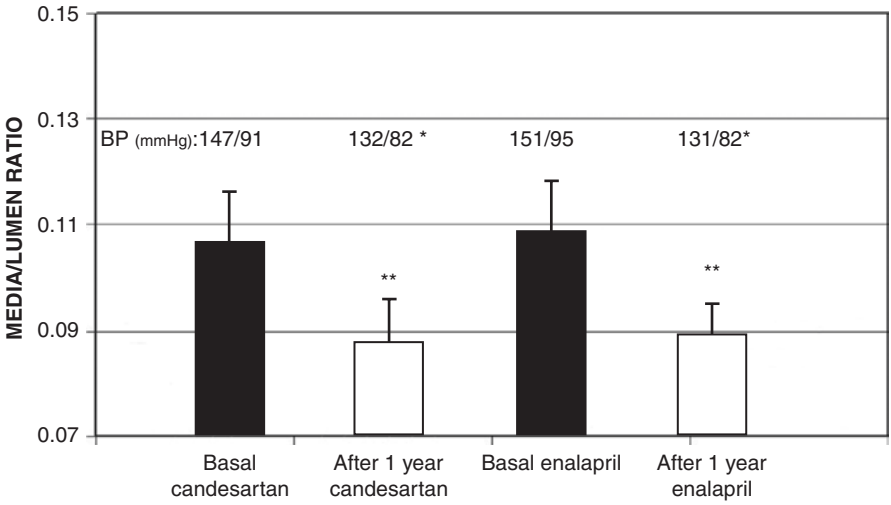

Fig. 14.5 Media-to-lumen ratio in subcutaneous small resistance arteries from hypertensive patients with NIDDM, before and after 1-year treatment with the ACE inhibitor enalapril or the angiotensin II receptor blocker candesartan. A significant and similar reduction was observed with both drugs. *BP* blood pressure. ** = $p < 0.01$ vs. Basal. (re-drawn, data from [56]

Few data about patients with type 1 diabetes mellitus are presently available. A study from Greenstein et al. [59] suggests that, with poor metabolic control, small arteries from patients with type 1 diabetes mellitus show hypertrophic growth in response to elevated blood pressure, similar to that seen in type 2 diabetes mellitus. However, metabolic improvements enable eutrophic remodelling to occur in response to an increase in blood pressure [59].

Conclusion

Probably, more than affecting resistance, microvascular rarefaction has the potential to disturb the cellular delivery of nutrients and oxygen, thus contributing to hypertensive end-organ damage [60]. 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, a muscle in which rarefaction was consistently demonstrated, but not the spinotrapezius, a muscle in which no rarefaction was found [60]. The theoretical impact of rarefaction on tissue oxygenation was also investigated by modelling 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 [60].

Alterations in the microcirculation represent a common finding, and microangiopathy is one of the most important mechanisms involved in the development of organ damage as well as of clinical events in patients with diabetes mellitus [61, 62]. Both patients with essential hypertension and those with NIDDM are characterized by alterations in the resistance vasculature, i.e. an increased

media-to-lumen ratio, that in diabetics is the consequence of the so-called hypertrophic remodelling [61, 62]. Structural alterations of small arteries are associated with an increased cardiovascular risk in hypertensive and diabetic patients, perhaps as a consequence of an impaired organ flow reserve in several vascular districts, including the coronary vascular bed [61, 62]. In fact, it has been observed that the presence of an increased wall-to-lumen ratio in the subcutaneous resistance arteries is associated with a worse prognosis in high-risk patients [61]. Hypertrophic remodelling, such as that observed in diabetic patients, seems to be associated with an even worse prognosis [25]. Data about the effect of therapy on microvascular structure in diabetic patients are scarce; however, renin-angiotensin system blockade seems to be effective in regressing, at least in part, the microvascular structure [61]. Blockers of the angiotensin-aldosterone system and calcium antagonists are effective in regressing small resistance artery remodelling in hypertension [43], and this regression seems to be clinically advantageous [41]; the same drug classes together with the diuretic indapamide were also able to improve microvascular density [45–47], however, in this case we do not know whether this improvement is associated with a better clinical prognosis.

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