Small Artery Remodeling in Hypertension and Diabetes

Damiano Rizzoni, MD, and Enrico Agabiti Rosei, MD

Corresponding author
Damiano Rizzoni, MD
Department of Medical and Surgical Sciences, University of Brescia, c/o 2a Medicina Spedali Civili di Brescia, Piazza Spedali Civili 1, 25100 Brescia, Italy.
E-mail: rizzoni@med.unibs.it

Current Hypertension Reports 2006, **8**:90–96
Current Science Inc. ISSN 1522-6417

The development of structural changes in the systemic vasculature is the end result of established hypertension. In essential hypertension, small artery smooth muscle cells are restructured around a smaller lumen, and there is no net growth of the vascular wall, whereas in some secondary forms of hypertension and in non–insulin-dependent diabetes mellitus, a hypertrophic remodeling may be detected. Indices of small resistance artery structure, such as the tunica media to internal lumen ratio, may have a strong prognostic significance in hypertensive patients. Various antihypertensive drugs seem to have different effects on vascular structure. A complete normalization of small resistance artery structure was demonstrated in hypertensive patients, after prolonged and effective therapy with angiotensin-converting enzyme inhibitors, angiotensin II–receptor blockers, and calcium antagonists. Few data are available in diabetic hypertensive patients; however, blockade of the renin-angiotensin system seems to be effective in this regard.

Introduction

Resistance vessel structure is a difficult quantity to measure. Most of the data available were obtained with histologic studies or by in vitro studies of isolated resistance vessels (wire or perfusion-pressure micromyography) [1]. Histologic studies have the advantage of allowing global analysis, but they may be compromised by unintended activation of artery vessels during fixation and lack of knowledge of the intravascular pressure during the process. Micromyographic techniques have the advantage of providing precise measurements of vascular dimensions without fixation artefacts, but are lacking owing to the difficulty that there is no clear agreement as to the length to which vessels should be set [2]. Therefore, none of the methods used to evaluate morphology of the small arteries is completely devoid of limitations and pitfalls. Nevertheless, if measurements are confined to a comparison of the ratio of wall thickness to lumen diameter "wall:lumen" (or, with measurements of tunica media thickness, "media:lumen") ratios at a given lumen, using a micromyographic approach, there is a more or less general agreement that this parameter is independent of the dimension of the vessels, and, therefore, it may give important insight into the microvascular structure [3••].

Essential hypertension is characterized by increased peripheral vascular resistance to blood flow, which occurs mostly as a result of energy dissipation in small arteries with a lumen diameter of 100 to 350 μm and in smaller arterioles [4•]. Also, a minor decrease in the lumen of resistance arteries may induce significant increase in resistance. It has been proposed, therefore, that this section of the arterial tree may play an important role in the development of hypertension, and may also contribute to its complications. Also, in patients with non–insulin-dependent diabetes mellitus (NIDDM), profound alterations in the microvasculature may be present; they may be directly involved in the development of target-organ damage and complications.

Vascular Structural Alterations

In hypertension

Vascular changes in resistance arteries may be structural, mechanical, or functional; in any case, a decrease in lumen size occurs [1]. It is now widely accepted that structural abnormalities of microvessels are common alterations associated with chronic hypertension [1,3••,5••]. An increased arterial wall thickness together with a reduced lumen may play an important role in the increase of vascular resistance, and may also be an adaptive response to an increased hemodynamic load. In particular, in the past two decades, the presence of structural alterations in subcutaneous and omental small resistance arteries dissected from biopsies performed in essential hypertensive patients has been confirmed with a direct investigation using the micromyographic method [6–8]. In fact, patients with essential hypertension present an increased

tunica media-to-lumen ratio, without any relevant increase of the total amount of wall tissue, as indicated by a media cross-sectional area similar to that observed in normotensive controls. Therefore, the major part of the structural changes observed in essential hypertension is the consequence of eutrophic remodeling (rearrangement of the same amount of wall material around a narrowed lumen) [9–12], without net cell growth. On the contrary, in patients with some forms of secondary hypertension (renovascular hypertension, acromegaly), a more evident contribution of cell growth, leading to the development of hypertrophic remodeling (vascular smooth muscle cell hypertrophy or hyperplasia) was observed [13,14]. In the development of hypertrophic remodeling, a relevant role is probably played by growth factors (eg, endothelin-1, angiotensin II), whereas the mechanisms leading to eutrophic remodeling are less clear.

In diabetes mellitus

In patients with NIDDM, 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 clinical events in diabetes mellitus. However, few data about morphology of small resistance arteries in diabetes mellitus are currently available. In one study [15], no difference in subcutaneous small artery structure was observed between control subjects and patients with insulin-dependent diabetes mellitus (IDDM). More recently, we have investigated subcutaneous small resistance artery structure in hypertensive and normotensive patients with NIDDM [16•]. We could demonstrate that, in both groups, marked alterations in small artery structure are present and that these alterations are more pronounced in hypertensive patients with NIDDM than in patients with essential hypertension or in normotensive diabetics (Fig. 1). In addition, in diabetic patients, a clear increase in the medial cross-sectional area of the vessels was observed, thus suggesting the presence of hypertrophic remodeling [16•]. This was not the case in patients with essential hypertension. A weak, but significant, correlation was observed between circulating levels of insulin, and media-to-lumen ratio of subcutaneous small arteries was observed in diabetic patients, thus suggesting a possible role for insulin or insulin-like growth factor-1 in the genesis of hypertrophic remodeling in these patients [16•]

However, an alternative explanation for the presence of hypertrophic remodeling in these vessels was proposed by Schofield et al. [17•]. A possible stimulus for hypertrophic remodeling may be an increased wall stress, as a consequence of an impaired myogenic response. Myogenic response is a pressure-induced vasoconstriction, which is the key component in blood flow autoregulation and in the stabilization of capillary pressure. The observation of the lack of such a myogenic response in diabetic patients may therefore be responsible for the development of hypertrophic remodeling of small arteries [17•]. Diabetic patients also show the presence of particularly pronounced alterations in the vascular extracellular matrix, as suggested by the observation of an increased collagen to elastin ratio in small arteries of hypertensive patients with NIDDM [16•] (Fig. 1).

Vascular Structural Alterations, End-organ Damage, and Cardiovascular Events

Currently, there is still debate concerning the time course of the vascular structural changes in hypertension, and concerning their role in promoting hypertension. It has been proposed that structural alterations in the resistance vasculature may act as "vascular amplifiers," able to enhance the effects of any hypertensive stimulus [18,19]. In any case, an important consequence of the presence of structural alterations in small resistance arteries and arterioles may be an impairment of vasodilator reserve [20,21]. In fact, as previously mentioned, remodeling of small resistance arteries is characterized by a narrowing of the lumen, which leads to an increase of flow resistance even at full dilatation—that is, in the absence of vascular tone. A significant correlation between coronary flow reserve and subcutaneous small resistance artery remodeling has been detected in hypertensive patients, suggesting that structural alterations in small resistance arteries may be present at the same time in different vascular districts, thus reflecting even clinically more important alterations in other vascular beds, including the coronary circulation [22]. 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 [16•,17•]. Some data suggest that, also in humans, alterations in small resistance artery morphology may represent the most prevalent, and perhaps the earliest form of preclinical target-organ damage in essential hypertension [23•]. In addition, structural alterations in resistance arteries may be closely related to target-organ damage, especially at the cardiac level. In fact, a linear relation between media-to-lumen ratio of subcutaneous small resistance arteries and left ventricular mass index or relative wall thickness has been detected in hypertensive patients; this relation with left ventricular geometry was more evident in patients with activation of the renin-angiotensin-aldosterone system [24]. Therefore, alterations in the microcirculation may play an important role in the development of organ damage in hypertension. It has been proposed that cardiovascular events are the consequence of vascular damage at both the macrocirculatory and microcirculatory level. Hence, the presence of structural alterations in the microcirculation may represent an important

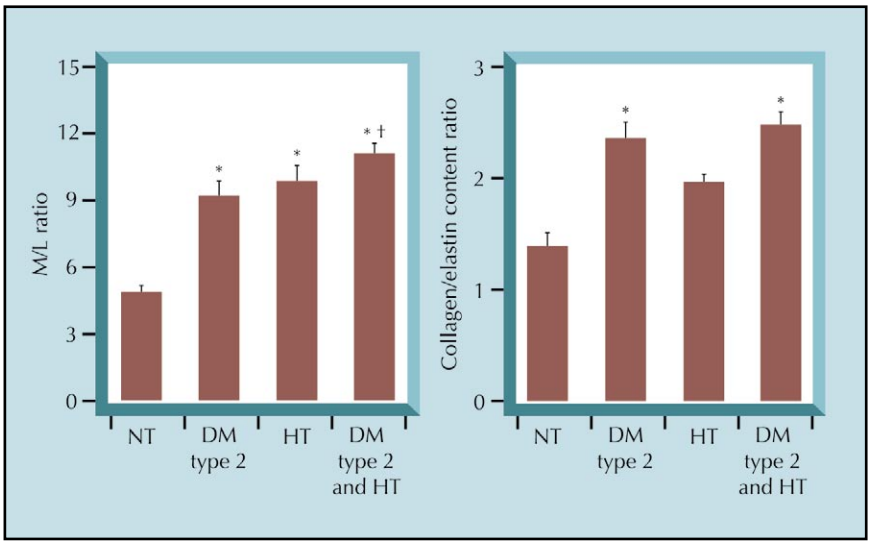

Figure 1. Structural alterations of small resistance arteries in the presence of diabetes and/or hypertension. *Left*, Media-to-lumen ratio in subcutaneous small resistance arteries from normotensive (NT) subjects, essential hypertensive (HT) patients, NT patients with non–insulin-dependent diabetes mellitus (NIDDM), and HT patients with NIDDM. A clear increase may be observed in all three pathologic groups, but is more evident in HT patients with NIDDM. *Right*, Collagen-to-elastin ratio (measured with electronic microscopy in the different groups). An increase was observed in essential HT patients and in HT patients with NIDDM.
*$P < 0.001$ vs NT subjects;
†$P < 0.05$ vs essential HT patients.
(*Adapted from* Rizzoni et al. [16•].)

link between hypertension and ischemic heart disease, cerebral damage, or renal failure. To evaluate the possible presence of a relationship between structural alterations in the subcutaneous small resistance arteries and the occurrence of cardiovascular events, we have investigated 151 hypertensive and/or diabetic patients, together with some normal subjects, in whom a basal evaluation of small artery morphology was available [25••]. The subjects were re-evaluated after an average follow-up time of 5.6 years. Media-to-lumen ratio proved to be the most potent predictor of the occurrence of cardiovascular events in this high-risk population. When our subjects were subdivided according to the presence of a media-to-lumen ratio of small arteries greater or smaller than the mean and median value observed in the whole population, life table analyses showed a highly significant difference in event-free survival between the subgroups (Fig. 2) [25••]. These results strongly indicate a relevant prognostic role of small resistance artery structural alterations in a high-risk population. More recently, we have re-evaluated these data, taking into account also the characteristics of the vascular remodeling. For the same values of internal diameter, those subjects who suffered cardiovascular events had a greater media–cross-sectional area, in comparison with those without cardiovascular events [26•]. Therefore, it seems that, for the same size of the vessels explored, a more consistent cell growth (hypertrophic remodeling) means an even worse prognosis. It has also been suggested that an impairment of myogenic response may have a relevant role in the development of hypertrophic remodeling in patients who are at high cardiovascular risk. Therefore, data available suggest a relevant prognostic role of structural changes in subcutaneous small arteries in patients with hypertension and other cardiovascular risk factors, probably because they are associated with similar changes in the coronary, renal, and cerebral microcirculation.

Effect of Antihypertensive Treatment

In hypertension

According to the previously mentioned observations, the possible regression of vascular alterations in small resistance arteries is an appealing goal of antihypertensive treatment. Some studies have demonstrated an almost complete normalization of the structure of subcutaneous small resistance arteries with angiotensin-converting enzyme (ACE) inhibitors (cilazapril, perindopril) [3••,27–30]. On the contrary, the β-blocker atenolol was devoid of effects on resistance vessels, despite a blood pressure reduction similar to that observed with ACE inhibitors [28–30].

We have investigated the effects on vascular structure of treatment with the ACE inhibitor lisinopril for 3 years [31]. Tunica media-to-lumen ratio in subcutaneous small resistance arteries was significantly lower in treated hypertensives than in matched untreated hypertensives. However, media-to-lumen ratio remained significantly higher than that observed in normotensive subjects. Because blood pressure values also remained higher in treated hypertensives than in normotensives, our data suggest that a persistent and complete normalization of blood pressure is probably mandatory in obtaining a normalization of vascular structure [31]. However, a complete normalization of vascular structure of subcutaneous small resistance arteries was observed after effective treatment with the calcium antagonist nifedipine in an extended-release formulation [32]. Therefore, it seems probable that calcium channel blockers, like ACE inhibitors, have a beneficial effect on vascular structure [3••].

Diuretics seem to be less effective in terms of regression of vascular structural alterations [33]. Recently, it has been demonstrated that the angiotensin II–receptor blockers (ARBs) losartan and irbesartan are also quite effective in normalizing subcutaneous small resistance artery structure in hypertensive patients [34,35]. These findings may have a clinical relevance. It is possible that their favorable effect on small resistance artery structure

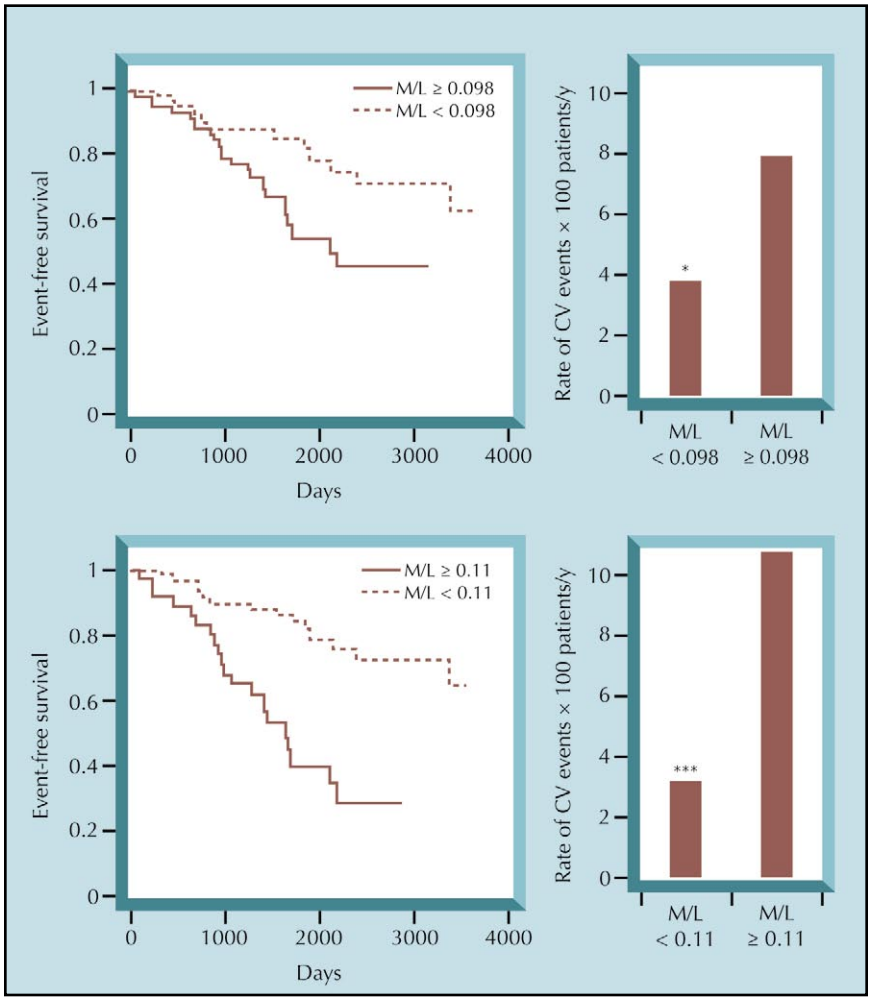

Figure 2. *Top left*, event-free survival (Kaplan-Meier method) in group of patients with an M/L of subcutaneous small arteries ≥ 0.098 (mean and median values observed in whole population) (n = 64, *solid line*) or < 0.098 (n = 64, *dotted line*). Mantel-Cox test between curves, P = 0.015; Breslow test between curves, P = 0.036. *Bottom left*, event-free survival in group of patients with an M/L of subcutaneous small arteries ≥ 0.11 (2 SD above mean value of our normal reference subjects) (n = 36, *solid line*) or < 0.11 (n = 92, *dotted line*). Mantel-Cox test and Breslow test between curves, P = 0.00001. *Top and bottom right*, incidence of cardiovascular (CV) events in subgroups of patients. M/L—media-to-lumen ratio. (*Adapted from* Rizzoni et al. [25••].)

may partially explain the benefits observed with drugs that block the renin-angiotensin-aldosterone system (such as losartan, perindopril, and ramipril) over other drugs, or beyond the decrease in blood pressure, in terms of reduced morbidity and mortality in high-risk hypertensive patients [36]. However, it should be emphasized that the prognostic impact of the regression of vascular structural alterations per se is still unknown, and prospective studies are needed to clarify whether structural alterations in small resistance arteries may be considered an "intermediate" end point in the evaluation of the effects of antihypertensive treatment.

In diabetes mellitus

Very few data are currently available about the effects of antihypertensive dugs on small artery structure in hypertensive diabetic patients. Despite effective antihypertensive treatment, resistance arteries from hypertensive diabetic patients showed marked remodeling, 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 [37].

Recently, a study compared the effects of 1 year treatment with the ACE inhibitor (enalapril) or the ARB (candesartan) on subcutaneous small artery structure in hypertensive patients with NIDDM [38]. The two drugs were equally effective in reducing media-to-lumen ratio of small arteries (Fig. 3); however, candesartan was more effective than enalapril in normalizing vascular collagen, probably through a more pronounced stimulation of the local production of metalloproteinase 9 (a collagen-degrading enzyme). At variance to what is observed in most studies in normoglycemic 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 the regression of vascular hypertrophic remodeling is probably more difficult to obtain [38].

Conclusions

Both essential hypertension and NIDDM are associated with alterations in the resistance vascular district—in particular, to an increased media-to-lumen ratio. It is not clearly established whether structural alterations in the microcirculation precede or are consequences of hypertension. In particular, the causative role of the structure of vessels in hypertension is still a matter of debate, although vascular alterations may act as amplifiers of hypertensive stimuli.

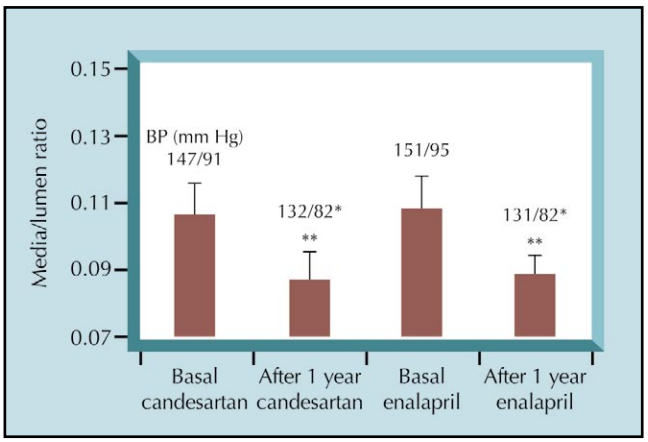

Figure 3. Media-to-lumen ratio in subcutaneous small resistance arteries from hypertensive patients with NIDDM, before and after 1-year treatment with the ACE inhibitor enalapril or the angiotensin II–receptor blocker candesartan. A significant and similar reduction was observed with both drugs. ACE—angiotensin-converting enzyme; BP—blood pressure; NIDDM—non–insulin-dependent diabetes mellitus. $^{**}P < 0.01$ vs basal. (*Adapted from* Rizzoni et al. [38].)

Structural alterations in small arteries are associated with an increased cardiovascular risk in high-risk hypertensive and diabetic patients, perhaps as a consequence of an impaired organ flow reserve in several vascular districts, including the coronary vascular bed. Structural alterations in different vascular regions are probably interrelated. 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 hypertensive patients, and that structural alteration in the microcirculation is probably the most potent predictor of cardiovascular events, together with pulse pressure. Also, the characteristics of vascular remodeling may be relevant in this context, because hypertrophic remodeling seems to be associated with an even worse prognosis. In hypertension, it is possible to obtain an almost full normalization of vascular structure with ACE inhibitors, ARBs, and calcium channel blockers. Data in diabetic hypertensive patients are scarce; however, renin-angiotensin system blockade seems to be effective, although we do not know if this also implies protection from cardiovascular events.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Mulvany MJ, Aalkjaer C: **Structure and function of small arteries.** *Physiol Rev* 1990, **70:**921–971.
2. Mulvany MJ: **Structural abnormalities of the resistance vasculature in hypertension.** *J Vasc Res* 2003, **40:**558–560.

3.•• Schiffrin EL: **Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment.** *Am J Hypertens* 2004, **17:**1192–1200.
A very well-written state-of-the-art paper focused on the mechanism underlying the development of structural alterations of small arteries and on pharmacologic correction of such alterations.

4.• Christensen KL, Mulvany MJ: **Location of resistance arteries.** *J Vasc Res* 2001, **38:**1–12.
This very interesting paper deals with the definition of structural alterations of small resistance arteries in relation to systemic hemodynamics.

5.•• Mulvany MJ: **Small artery remodeling and significance in the development of hypertension.** *News Physiol Sci* 2002, **17:**105–109.
A comprehensive review, taking into account methodologic approaches, functional consequences, and the clinical meaning of structural and functional alterations of small resistance arteries.

6. Aalkjaer C, Haegerty AM, Petersen KK, et al.: **Evidence for increased media thickness, increased neural amine uptake, and depressed excitation-contraction coupling in isolated resistance vessels from essential hypertensives.** *Circ Res* 1987, **61:**181–186.
7. Schiffrin EL, Deng LY, Larochelle P: **Morphology of resistance arteries and comparison of effects of vasoconstrictors in mild essential hypertensive patients.** *Clin Invest Med* 1993 **16:**177–186.
8. Agabiti-Rosei E, Rizzoni D, Castellano M, et al.: **Media: lumen ratio in human small resistance arteries is related to forearm minimal vascular resistance.** *J Hypertens* 1995, **13:**341–347.
9. Baumbach GL, Heistad DD: **Remodeling of cerebral arterioles in chronic hypertension.** *Hypertension* 1989, **13:**968–972.
10. Heagerty AM, Aalkjaaer C, Bund SJ, et al.: **Small artery structure in hypertension: dual process of remodeling and growth.** *Hypertension* 1993, **21:**391–397.
11. Mulvany MJ, Baumbach GL, Aalkjaer C, et al.: **Vascular remodeling.** *Hypertension* 1996, **28:**505–506.
12. Bund SJ, Lee RMKW: **Arterial structural changes in hypertension: a consideration of methodology, terminology and functional conseqences.** *J Vasc Res* 2003, **40:**547–557.
13. Rizzoni D, Porteri E, Castellano M, et al.: **Vascular hypertrophy and remodeling in secondary hypertension.** *Hypertension* 1996, **28:**785–790.
14. Rizzoni D, Porteri E, Guelfi D, et al.: **Cellular hypertrophy in subcutaneous small arteries of patients with renovascular hypertension.** *Hypertension* 2000, **35:**931–935.
15. McNally PG, Watt PAC, Rimmer T, et al.: **Impaired contraction and endothelium-dependent relaxation in isolated resistance vessels from patients with insulin-dependent diabetes mellitus.** *Clin Sci* 1994, **87:**31–36.
16.• Rizzoni D, Porteri E, Guelfi D, et al.: **Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin dependent diabetes mellitus.** *Circulation* 2001, **103:**1238–1244.
A paper addressing in detail the structural and functional alterations in small resistance arteries taken from hypertensive and normotensive diabetic patients.

17.• Schofield I, Malik R, Izzard A, et al.: **Vascular structural and functional changes in type 2 diabetes mellitus: evidence for the role of abnormal myogenic responsiveness and dyslipidemia.** *Circulation* 2002, **106:**3037–3043.
In this manuscript, the authors propose an interesting hypothesis about the relation between the lack of myogenic response and the development of hypertrophic remodeling of subcutaneous small arteries in diabetic patients.

18. Lever AF: **Slow pressor mechanisms in hypertension: A role for hypertrophy of resistance vessels?** *J Hypertens* 1986, **4:**515–524.
19. Korner PI, Bobik A, Jennings GL, et al.: **Significance of cardiovascular hypertrophy in the development and maintenance of hypertension.** *J Cardiovasc Pharmacol* 1991, **17(Suppl2):**S25–S32.

20. Folkow B: **Physiological aspects of primary hypertension.** *Physiol Rev* 1982, **62:**347–504.
21. Sivertsson R: **The hemodynamic importance of structural vascular changes in essential hypertension.** *Acta Physiol Scand* 1970, **343:**14–19.
22. Rizzoni D, Palombo C, Porteri E, et al.: **Relationships between coronary vasodilator capacity and small artery remodeling in hypertensive patients.** *J Hypertens* 2003, **21:**625–632.
23.• Park JB, Schiffrin EL: **Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension.** *J Hypertens* 2001, **19:**921–930.
Remodeling of small arteries is supposed to occur very early in the clinical history of hypertension. This may have important clinical consequences in terms of development of target organ damage.
24. Muiesan ML, Rizzoni D, Salvetti M, et al.: **Structural changes in small resistance arteries and left ventricular geometry in patients with primary and secondary hypertension.** *J Hypertens* 2002, **20:**1439–1444.
25.•• Rizzoni D, Porteri E, Boari GEM, et al.: **Prognostic significance of small artery structure in hypertension.** *Circulation* 2003, **108:**2230–2235.
The first demonstration of a relevant prognostic role of structural alterations of subcutaneous small resistance arteries in a high-risk population.
26.• Izzard AS, Rizzoni D, Agabiti-Rosei E, Heagerty AM: **Small artery structure and hypertension: adaptive changes and target organ damage.** *J Hypertens* 2005, **23:**247–250.
An interesting editorial focused on the pathophysiologic and clinical significance of small artery remodeling.
27. Sihm I, Schroeder AP, Aalkjaer C, et al.: **Normalization of resistance artery structure and left ventricular morphology with a perindopril-based regimen.** *Can J Cardiol* 1994, **10(SupplD):**30D–32D.
28. Thybo NK, Stephens N, Cooper A, et al.: **Effect of antihypertensive treatment on small arteries of patients with previously untreated essential hypertension.** *Hypertension* 1995, **25(Pt 1):**474–481.
29. Schiffrin EL, Deng LY, Larochelle P: **Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension.** *Hypertension* 1994, **23:**83–91.
30. Schiffrin EL, Deng LY, Larochelle P: **Progressive improvement in the structure of resistance arteries of hypertensive patients after 2 years of treatment with an angiotensin I-converting enzyme inhibitor. Comparison with effects of a beta-blocker.** *Am J Hypertens* 1995, **8:**229–236.
31. Rizzoni D, Muiesan ML, Porteri E, et al.: **Effect of long-term antihypertensive treatment with lisinopril on resistance arteries in hypertensive patients with left ventricular hypertrophy.** *J Hypertens* 1997, **15:**197–204.
32. Schiffrin EL, Deng LY: **Structure and function of resistance arteries of hypertensive patients treated with a beta blocker or a calcium channel antagonist.** *J Hypertens* 1996, **14:**1237–1244.
33. Sihm I, Schroeder AP, Aalkjaer C, et al.: **Effect of antihypertensive treatment on cardiac and subcutaneous artery structure: a comparison between calcium channel blocker and thiazide-based regimens.** *Am J Hypertens* 1998, **11:**263–271.
34. Schiffrin EL, Park JB, Integan HD, Toyuz RM: **Correction of arterial structure and endothelial dysfunction in human essential hypertension by the angiotensin receptor antagonists losartan.** *Circulation* 2000, **101:**1653–1659.
35. Schiffrin EL, Park JB, Pu Q: **Effect of crossing over hypertensive patients from a beta-blocker to an angiotensin receptor antagonist on resistance artery structure and on endothelial function.** *J Hypertens* 2002, **20:**71–78.
36. Guidelines Committee: **2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension.** *J Hypertens* 2003, **21:**1011–1053.
37. Endemann DH, Pu Q, De Ciuceis C, et al.: **Persistent remodeling of resistance arteries in type 2 diabetic patients on antihypertensive treatment.** *Hypertension* 2004, **43:**399–404.
38. Rizzoni D, Porteri E, De Ciuceis C, et al.: **Effect of treatment with candesartan or enalapril on subcutaneous small artery structure in hypertensive patients with non insulin-dependent diabetes mellitus.** *Hypertension* 2005, **45:**659–665.