Effects of Angiotensin-Converting Enzyme Inhibition on Vascular Remodeling of Resistance Vessels in Hypertensive Patients

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Essential hypertension is known to be associated with a decrease in the lumen diameter and an increase in the wall thickness to lumen diameter ratio of the resistance vessels. Recently, it has been clarified that this alteration does not necessarily involve vascular growth, but could be due to a rearrangement of the same amount of material, a phenomenon now termed "eutrophic remodeling." These changes are found both in human essential hypertension and in animal models of genetic hypertension. Antihypertensive treatment with angiotensin-converting enzyme (ACE) inhibitors causes a dose-dependent regression of the media to lumen ratio in rats. Clinical studies have now confirmed these findings, showing that when previously untreated essential hypertensive patients are treated with the ACE inhibitor perindopril (PE), the abnormal structure of resistance vessels regresses toward normal values; in contrast, treatment with a β-blocker does not affect the abnormal vascular structure. The available evidence thus indicates that ACE inhibitors are able to normalize the abnormal resistance vessel structure in essential hypertension, and suggest that this effect may not only be dependent on their ability to reduce blood pressure. This review summarizes these findings, and discusses the extent to which this is desirable.

IN ESSENTIAL HYPERTENSION, the peripheral resistance is increased, as is the ratio of the wall (or media) thickness to the lumen diameter of the vasculature.[1] There is a positive correlation between increased blood pressure and increased minimum vascular resistance, and there is also a quantitative relationship between increased blood pressure and increased pressor response to infusion of agonists.[2-4] This led Folkow[1,5] to propose that the increased media to lumen ratio was functionally equivalent to an increased neurohumoral drive, such that the increased peripheral resistance observed in hypertension could be maintained with a normal level of activation. Thus, resistance vessel structure is an important factor in the pathogenesis of hypertension, and this basic hypothesis has been amply confirmed since (for review, see Mulvany and Aalkjaer[6]).

Not only does altered resistance vessel structure appear to be an adaptive response to blood pressure, but neurohumoral growth factors are also able to alter resistance vessel structure (see Lever[7] for review), as suggested previously.[3] Thus, this has led to the concept that what was originally a secondary adaptation of resistance vessel structure later becomes a primary mechanism for maintaining increased blood pressure.

A corollary of these arguments is that interventions specifically inhibiting resistance vessel growth will, for this reason alone, also reduce blood pressure. Although this proposal is attractive, the evidence for altered structure playing a primary role in the development of hypertension is not strong. Nevertheless, normalization of vascular structure is likely important not so much to reduce the pressure but to increase the vascular reserve.[8] This article summarizes some of the evidence on resistance vessels. It is based on reviews previously published elsewhere.[9-11]

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0026-0495/98/4712-1006$3.00/0

ABNORMALITIES OF RESISTANCE VESSEL STRUCTURE IN HYPERTENSION

Previous histological studies[12,13] demonstrated increased wall to lumen ratios in the resistance vasculature of essential hypertensive patients, and this has been confirmed by in vitro experiments[14-18] (Fig 1, left). Importantly, however, the in vitro experiments (eg, Short,[19] using a histological technique) indicate that the cross-sectional area of the tunica media is unchanged[20] (Fig 1), and is thus due to eutrophic remodeling.[21,22] Furthermore, the size of individual smooth muscle cells within the media is also normal,[16] while the functional responses of the smooth muscle are not altered.[14] These findings support the concept that the altered hemodynamic characteristics of resistance vasculature in essential hypertension are mainly due to alterations in the structure of the vessels. It should be noted that the finding of eutrophic remodeling is in contrast to the hypertrophic remodeling found in conduit arteries in essential hypertension.[23]

It may therefore be concluded that changes in the structure of the resistance vasculature found in hypertension can indeed account for the altered hemodynamic characteristics.

IS RESISTANCE VESSEL STRUCTURE A DETERMINANT OF BLOOD PRESSURE?

Angiotensin II (AII) is able to cause proliferation of vascular smooth muscle cells in vitro.[24-26] Furthermore, infusion of AII into rats at subpressor doses using osmotic minipumps[27] causes an increase in both the media to lumen ratio and the media cross-sectional area of mesenteric small arteries, even if rats are treated with hydralazine to prevent the increase in blood pressure. Moreover, as discussed later, in human essential hypertension (Fig 1 and Table 1) treatment with an angiotensin-converting enzyme (ACE) inhibitor causes a greater reduction in the media to lumen ratio than treatment with a β-blocker, even though both treatments have the same hypotensive effect.[18,28] It therefore appears that the altered resistance vessel structure observed in hypertension is not purely a secondary response to the increased blood pressure. Thus, resistance vessel structure could play a direct role in determining blood pressure.

The possibility that resistance vessel structure has a direct

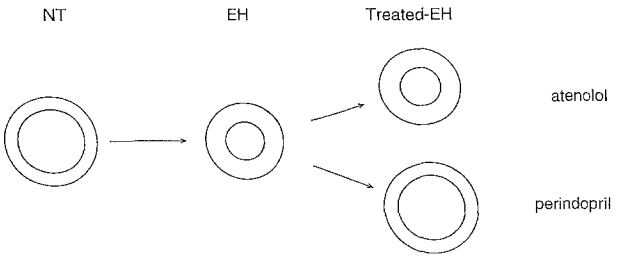

Fig 1. Difference between the structure of resistance vessels in normotensive patients (NT) and essential hypertensive patients (EH) and the effect of treatment of EH on resistance vessel structure with either PE (ACE inhibitor) or atenolol (β-blocker) for 12 months. The decreased lumen diameter and increased media to lumen ratio in EH is achieved without a change in the media cross-sectional area, a phenomenon known as remodeling. Treatment of EH with PE normalizes the vascular structure, again without changing the media cross-sectional area, thus also a remodeling process. Treatment with atenolol did not alter the structure of resistance vessels. Actual measurements are shown in Table 1; see Thybo et al.[18]

influence on blood pressure can be tested by first using an intervention that changes the blood pressure and alters the resistance vessel structure; thereafter, one can determine whether the rate of blood pressure normalization when the intervention is removed is related to the resistance vessel structure before removal of the intervention. Initial investigation by Pickering[29] suggested that this was the case, but studies since then have in general failed to provide much support for such a clear-cut relation, as discussed previously.[9] Some examples of this are as follows.

First, in the AII infusion model, as soon as AII infusion is stopped, blood pressure returns to normal[30] despite the changes in resistance vessel structure.[27] Similarly, in the one-kidney, one-clip Goldblatt hypertension model, the increase in blood pressure that occurs over a few weeks and causes changes in resistance vessel structure[31] is halted as soon as the clip is removed.[32] The decrease in blood pressure is due to massive release of "medullipin," but once again, the altered resistance vessel structure is not able to sustain the hypertension. Yet another example is in human essential hypertension, where Korner et al[33] have shown that when antihypertensive therapy is withdrawn from patients being treated for essential hypertension, blood pressure returns to hypertensive levels most rapidly in patients in whom total peripheral resistance is lowest. Again, this suggests a dissociation between the vascular structure and ability to maintain blood pressure.

Therefore, in none of these examples is there any indication that resistance vessel structure has a direct effect on blood pressure. In each case, it appears that other factors have the dominant effect.

RESISTANCE VESSEL STRUCTURE AND BLOOD PRESSURE

These considerations suggest that although resistance vessel structure and blood pressure are closely connected, changes in one are not automatically associated with changes in the other. Instead, the available data suggest that resistance vessels should be considered the effector organ of neurohumoral drive, with the altered structure merely having an amplifier effect (Fig 2). As suggested by Julius,[35] the cardiovascular system apparently seeks to maintain blood pressure at a "required blood pressure," which is a compromise between the requirements of a number of factors, eg, renal function. Then if, for example, the pressure is too low, a signal is sent to increase the neurohumoral drive. The effect of this signal is dependent both on its strength and the actual resistance vessel structure (eg, media to lumen ratio). The resulting increase in peripheral resistance then increases the pressure, the process continuing until the pressure equals the required pressure. This is a fast process, a negative-feedback mechanism, inherently stable, and mediated through a variety of systems, not only the baroreceptors.

However, there are also slow processes, since the resistance vessel media to lumen ratio is not static but in the long-term can be altered by (1) neurohumoral influences (as discussed already), and (2) the pressure (eg, as shown in experiments where a clip is placed on one femoral artery[36]). Thus, if for some reason the required pressure increases, there will initially be an increase in the neurohumoral drive, and the fast process will result in increased pressure. But then the slow process will ensue, with an increase in the resistance vessel media to lumen ratio, due to both the increased neurohumoral drive and the increased pressure. With the increase in the resistance vessel media to lumen ratio, the neurohumoral drive necessary to maintain increased blood pressure will be reduced. Thus, in the long-term, the increased pressure will be maintained by a

Table 1. Structural Characteristics of Subcutaneous Small Arteries From Patients With Essential Hypertension Before and After Treatment With PE or Atenolol

Variable	Patients				
	Before Treatment		After Treatment		
	PE	Atenolol	PE	Atenolol	Controls
No. of subjects	13	12	13	12	25
Lumen (μm)	208 ± 12	222 ± 13	247 ± 12*	208 ± 12†	237 ± 11
Media (μm)	15.7 ± 0.9	15.1 ± 2.5	13.9 ± 0.7	13.6 ± 0.6	10.9 ± 0.8‡
Media to lumen ratio (%)	7.94 ± 0.65	7.14 ± 0.47	5.96 ± 0.42*	6.79 ± 0.45†	5.82 ± 0.34‡
Media cross-sectional area ($\mu m^2 \times 10^3$)	12.1 ± 1.2	12.1 ± 0.9	11.6 ± 0.8	9.8 ± 0.8*	10.9 ± 0.8

NOTE. Values are the mean ± SEM. Data are from Thybo et al.[18]

*$P < .05$, before *v* after by paired *t* test.

†$P < .05$, effect of treatment, PE *v* atenolol, by grouped *t* test.

‡Control *v* pooled data for patients before treatment by grouped *t* test.

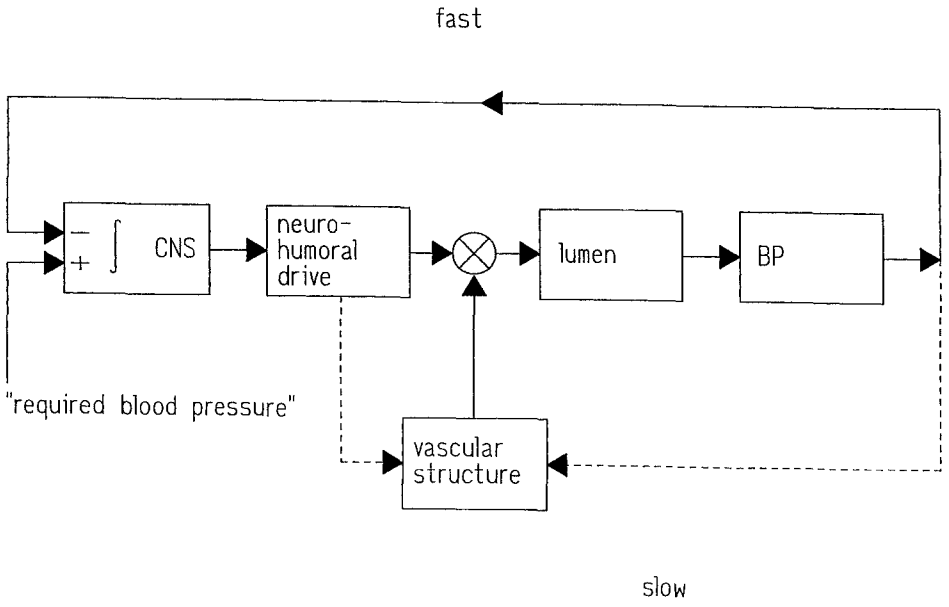

Fig 2. The proposed role for resistance vessel structure in the control of blood pressure. The schematic embodies ideas proposed principally by Folkow[1] but also by Lever,[7] Korner,[34] and Julius.[35] I, integrator; ×, multiplier. (Reproduced from Mulvany.[9])

normal neurohumoral drive but with an increased media to lumen ratio—precisely the situation normally found in essential hypertension.

The implication of these arguments is that the resistance vessels should not be considered prime determinants of blood pressure. Rather, they should be considered effector organs of the cardiovascular control system.

ACE INHIBITOR TREATMENT AND RESISTANCE VESSEL STRUCTURE

These arguments can account for the finding (Fig 1) that blood pressure can be reduced without normalizing the structure of resistance vessels, and one can therefore ask whether normalization of the structure is necessary for successful antihypertensive treatment. As regards blood pressure itself, evidently not, but it must be remembered that a reduction in blood pressure without a normalization of resistance vessel structure will reduce the vascular reserve. Thus, the decreased coronary vascular reserve in essential hypertension will be exacerbated rather than relieved.[8] Therefore, normalization of the vascular structure must nevertheless be seen as an important goal of antihypertensive treatment.

To achieve normalization of the abnormalities in the structure of resistance vessels in essential hypertension (decreased lumen, increased media to lumen ratio, and no change in media cross-sectional area), I have shown (Fig 1) that this should be obtained not so much by inhibition of growth but by facilitation of remodeling, ie, a rearrangement of the wall material around a larger lumen. Animal experiments have suggested[37] that this indeed occurs with certain drugs (eg, ACE inhibitors and calcium antagonists) but not with β-blockers. Figure 1 and Table 1 indicate that this is also the case in man,[18,28] where, for example, the ACE inhibitor perindopril (PE) was found to cause normalization of the vasculature through a remodeling process, whereas treatment with the β-blocker atenolol did not (Fig 1). However, it should be pointed out that both in spontaneously hypertensive rats[37] and in essential hypertension,[38] treatment with calcium antagonists also causes regression of vascular structure.

We may conclude that abnormal resistance vessel structure is a major characteristic of hypertensive disease, and this is likely the fundamental cause of the observed reduced vascular reserve. It is therefore reasonable that treatment should aim to normalize the vascular structure, but investigations are now required to determine whether, in fact, improvement of vascular reserve is dependent on normalization of resistance vessel structure. Importantly, it needs to be determined whether such correction of the vascular reserve also improves the prognosis of essential hypertensive patients.

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