Abnormalities of the resistance vasculature in hypertension: correction by vasodilator therapy

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Abstract
The structure of the resistance vessels in patients with essential hypertension is altered, with reduction of the lumen diameter and increase in wall-to-lumen ratio without change in wall mass, known as eutrophic remodelling. The alteration appears to cause a reduction in the vascular reserve, in particular the coronary reserve (the ability to increase blood flow during hyperaemia). Successful treatment of hypertension should therefore seek not only to reduce blood pressure but also to normalize the structure of the resistance vessels. The available evidence shows that the effect of antihypertensive treatment on resistance vessel structure is variable and not related to the reduction in blood pressure. Instead it appears that the key feature allowing normalization of vascular structure is the ability of the treatment to cause a reduction in total peripheral resistance. Thus beta-blocker treatment is apparently unable to correct the abnormal vascular structure, although vasodilator treatment – for example with angiotensin converting enzyme (ACE)-inhibitors – is able to do this. In vivo studies in rats, and in vitro organ culture experiments have suggested that the remodelling is related to the activation of the vascular smooth muscle. The process seems to be mediated at least in part by tissue transglutaminase, an enzyme which specifically controls the interaction of smooth muscle with the extracellular matrix. Taken together the data support the desirability of vasodilator therapy in the treatment of essential hypertension.

Key words: small artery, structure, antihypertensive therapy, beta-blocker, ACE-inhibitor, tissue transglutaminase

Introduction
The placebo-controlled trials of the 1970s and 1980s demonstrated the benefits of treating mild to moderate hypertension [10]. However, the data also showed that the treatments (primarily with diuretics and beta blockers) did not provide as much benefit as might have been expected from the epidemiological evidence. More recent evidence comparing the newer drugs with diuretics and beta blockers have had conflicting results [11, 16, 30], suggesting that even modern antihypertensive therapy is still not optimal in reducing risk. Thus it appears that blood pressure reduction is not the only factor of importance, and that other factors may also be relevant in the successful management of the disease [17, 20].

Investigations of the cause of hypertension are complicated by the general finding that most parameters are on average normal, e.g. sympathetic activity and plasma renin activity. There is, however, one parameter which is consistently abnormal: an increased peripheral resistance. The peripheral resistance is determined mainly by the distal part of the arterial vasculature (the resistance vessels), consisting of the small arteries (arteries with diameter < ca. 300 µm) and the arterioles (the arteries just prior to the capillaries) [8]. Current evidence [20] indicates that the in-