ACE inhibition and brachial artery haemodynamics in hypertension

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1 Brachial artery haemodynamics, including arterial diameter, blood flow velocity, blood flow and compliance of the brachial artery may be evaluated non-invasively in man, using pulsed Doppler methods.

2 In patients with sustained untreated essential hypertension, brachial artery diameter is increased, blood flow is normal and arterial compliance is reduced independently of the level of blood pressure.

3 Converting enzyme inhibition may reverse the large artery abnormalities, causing an increase in arterial diameter, blood flow and arterial compliance both in acute and long-term investigations.

4 These changes in large arteries may contribute towards improved cardiovascular morbidity and less mortality in treated hypertensive patients.

Keywords essential hypertension arterial compliance converting enzyme inhibition large arteries

Introduction

The renin-angiotensin system has for a long time been considered a causal factor in the mechanism of hypertension, and hyperactivity of the system has been related to the changes in resistance vessels. In contrast, little is known about the possible effects of the system on the visco-elastic properties of large arterial vessels. However, the question may be relevant since cardiovascular morbidity and mortality in hypertension are usually linked with atherosclerotic changes in large arteries.

Methods have recently been developed to investigate large arteries in man. In the present study, these methods have been applied to the particular effect of converting enzyme inhibition on the brachial arteries of subjects with sustained essential hypertension.

Large arteries in hypertension

Epidemiological studies have shown that anti-hypertensive treatment may have heterogeneous effects on cardiovascular morbidity and mortality (Freis, 1982). These include reduced incidence of cerebrovascular haemorrhages, congestive heart failure and rupture of abdominal aneurysms, which are directly linked to the level of blood pressure. However, improvement in atherosclerotic disease, such as ischaemic heart disease, remains less obvious.

Such dissociation of the effects of antihypertensive treatment is observed both in severe and in mild to moderate hypertension, particularly in older subjects.

On the basis of animal and clinical investigations, it has been established that a redesign of vascular geometry occurs during the develop-

ment of hypertension. Small arteries are narrowed, causing an increase in arterial resistance, partly due to medial hypertrophy with a decrease in the arterial wall to lumen ratio (Sivertsson, 1970; Folkow, 1982).

However, arterial disease in hypertension is not restricted to arterioles but also involves large arteries. The arterial calibre is normal or increased (Safar *et al.*, 1981). In animal hypertension, an increased thickness of the arterial wall has been observed (Wolinski, 1972). Both in animal and human hypertension, arterial compliance is decreased (Wolinski, 1972; Safar *et al.*, 1981; Simon *et al.*, 1983a). The decrease is not exclusively related to the level of blood pressure and involves structural and/or functional abnormalities of the vessel wall (Simon *et al.*, 1983b).

Alterations in large arteries may have important consequences for the severity of hypertension. Firstly, a disproportionate increase in systolic pressure results from the decrease in arterial compliance (Safar *et al.*, 1984). Systolic pressure is a greater cardiovascular risk factor than diastolic pressure over 50 years (Kannel & Gordon, 1971). Secondly, mean systolic pressure is the major determinant of cardiac oxygen need and thus of myocardial blood flow requirement, cardiac hypertrophy and congestive heart failure (O'Rourke, 1982). Indeed, the two latter conditions are more related to systolic rather than diastolic pressure (Tarazi, 1982). Thirdly, vascular damage may be attributed also to the increase in pulsative work due to decreased arterial compliance. Indeed increased pulse pressure may play a role in the early intimal and subintimal changes of atherosclerosis often observed in hypertension (O'Rourke, 1982).

The renin-angiotensin system and large arteries in hypertension

The role of the renin-angiotensin system in renovascular and essential hypertension is still debated. Although other non-specific mechanisms can maintain blood pressure which had been initially raised by renin hypersecretion, it is possible that the renin-angiotensin system might be active in strategic tissues, such as the central nervous system (Ganten & Schelling, 1976) or the arterial wall (Swales, 1979), independently of plasma renin. Indeed it has been shown that the other essential components of the renin-angiotensin system, such as substrate (Desjardins-Giasson & Gutwoska, 1981) and converting enzyme activity (Aiken & Vane, 1972; Collier & Robinson, 1974) are present in the aortic wall of several animal models of hypertension. Further,

it has been suggested that vascular renin has an important role to play in blood pressure maintenance by the local arterial generation of angiotensin II (Thurston & Hurst, 1981).

In animal experiments, the changes in aortic wall renin have been related to changes in blood pressure and hence to modifications in the small artery resistance vessels. However, it would be more relevant to relate aortic renin to modifications in the visco-elastic properties of large arteries and therefore to the distensibility of the aortic wall. Investigations of this are difficult to perform in small animals but may be carried out in man, using new non-invasive haemodynamic techniques.

Non-invasive investigations of large arteries in man

Most of the previous studies of arterial haemodynamics in hypertension were based on invasive recordings of pressure and flow in the aorta, thus enabling the impedance spectrum of large arteries to be estimated in man (O'Rourke, 1982). With these current methods, it is possible to investigate simultaneously the resistance, the capacitance and the inertial components of the arterial system. In more simple models, only the elastic component of the systemic circulation can be taken into consideration (Simon *et al.*, 1979). However, determination of impedance in hypertensive man, although possible, still offers many practical and ethical difficulties.

In recent years, pulsed Doppler methods have become available to investigate, transcutaneously, intact superficial large arteries in hypertensive man (Levenson *et al.*, 1981). For this purpose two important pieces of apparatus are necessary: a range-gated system and a double transducer probe. Thus, adequate measurements can be made on straight superficial arteries, such as the brachial artery. It is possible to measure simultaneously the arterial diameter and the cross-sectional velocity of the blood. Assuming the artery to be a cylindrical model, the cross-section is calculated from the measured diameter and blood flow is then the product of arterial cross-section and blood flow velocity. Adequate validations of this method have been performed *in vitro* and *in vivo* after surgery.

Although the large arteries make a negligible contribution to flow resistance, they instantaneously accommodate the volume of blood ejected from the heart during each cardiac contraction, storing part of the stroke volume during each systole and draining this volume during diastole. Thus, the periodic flow of the

heart is changed into a continuous flow at the capillary level (O'Rourke, 1982). This damping effect is due to the visco-elastic properties of large arteries. A quantitative evaluation of the elasticity of large arteries may be obtained from the determination of arterial compliance, that is the ratio between the change in volume and the change in pressure within the artery. In clinical investigation, compliance of the brachial artery can be evaluated either from the Bramwell and Hill equation (Levenson *et al.*, 1984) or from a simple Windkessel first-order model of the circulation (Simon *et al.*, 1983a). For this purpose, both invasive (Simon *et al.*, 1983a) and non-invasive methods (Levenson *et al.*, 1984; Simon *et al.*, in preparation) incorporating the Doppler system have been developed and validated recently in man.

Converting enzyme inhibition and large arteries in essential hypertension

The first demonstration of the dilator effect of converting enzyme inhibition on large arteries was performed with captopril (Simon *et al.*, 1983b). In acute investigations in patients with sustained essential hypertension, it was shown that, with a slight decrease in blood pressure, brachial artery diameter increased markedly. According to the classical Hallock and Benson experiments (Hallock & Benson, 1937), a decrease in diameter should be expected, since the distending pressure decreased. Such an obser-

vation proved the direct dilating effect of converting enzyme inhibition on intact large arteries, in addition to the more classical dilating effect on small arteries.

A longer-term effect of converting enzyme inhibition on large arteries was demonstrated with enalapril (Simon *et al.*, 1984). In a double-blind study, the changes in forearm arterial haemodynamics after enalapril and propranolol were compared over a 6-month period. For the same decrease in blood pressure, propranolol did not change the brachial haemodynamic indices while enalapril improved them. Arterial diameter and blood flow velocity increased, causing a significant elevation in brachial blood flow. Furthermore, arterial compliance increased (Simon *et al.*, in preparation). The increase in arterial compliance was more pronounced with enalapril than with propranolol, which caused the same decrease in blood pressure. Thus, the weight of evidence suggested that converting enzyme inhibition was directly responsible for the improvement in the visco-elasticity properties of large arteries in treated hypertensive patients.

In conclusion, converting enzyme inhibition may reverse the functional alterations (reduced arterial compliance) of large arteries in patients with essential hypertension. Whether this effect may modify the thickness of the arterial wall and improve cardiovascular morbidity and mortality in the long term remains unknown and requires further investigation.

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