Large arteries in hypertension: heterogenous haemodynamic response to β -adrenoceptor antagonists with and without intrinsic sympathomimetic activity

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1 Hypertension is associated with a distension of the large arteries and consequently a marked reduction in arterial compliance, which does not result merely from the mechanical effects of elevated arterial pressure but also from early functional and/or structural changes in the arterial walls. This suggests that one of the aims of antihypertensive therapy should be to reverse these arterial abnormalities in the hope of protecting the patient from the atherosclerotic complications of hypertension.

2 Studies have been carried out to compare the effects of equieffective antihypertensive doses of pindolol and propranolol on the arterial circulation in patients suffering from essential hypertension. After 3 months therapy pindolol produced a dilatation of the brachial artery with an increase in arterial compliance and blood flow. In contrast, propranolol, despite comparable antihypertensive effects, did not influence brachial artery circulation.

3 These different effects on the arterial circulation presumably reflect the differing pharmacological properties of the two β -adrenoceptor antagonists and suggest that the intrinsic sympathomimetic activity of pindolol may be responsible for the qualitative differences in the arterial responses to the two drugs.

4 The results reviewed here reveal that even when two drugs of the same class are used to treat patients with essential hypertension the effects of these agents on arterial haemodynamics can vary greatly and are unrelated to the degree of blood pressure lowering. Thus, pindolol, in contrast to propranolol, not only lowers blood pressure but also reverses some of the changes in arterial haemodynamics which are characteristic of hypertensive disease. Since the arterial system is one of the main targets of the disease process in hypertension these differences between the effects of antihypertensive agents on arterial function may be of importance in the choice of drugs for the long term therapy of the disease.

Introduction

Until recently the large arteries have received little attention in investigations of the pathophysiology and therapy of hypertension. Such neglect was due largely to the lack of suitable

methods for the quantitative analysis of the physiological and physical properties of these vessels. This failure to study the large arteries in hypertension is paradoxical since the arterial

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system is the site of the raised blood pressure and one of the targets of the hypertensive disease process (Freis, 1982). The arteries are not only responsible for the transport of blood from the heart to the periphery but also, by virtue of the elasticity of their walls, they act as a secondary pump system which dampens the pulsatility of the intermittently active cardiac pump (Simon *et al.*, 1983) and thereby supplies the capillaries with a smooth flow of blood with little variation in pressure. In view of their important physiological role the large arteries clearly deserve close study not only in investigations into the pathophysiology of hypertension but also in studies of the haemodynamic responses to anti-hypertensive therapy.

Method

The study of blood flow in the brachial artery represents a convenient model for the investigation of arterial haemodynamics in man (Simon *et al.*, 1983) and the use of a pulsed Doppler velocimeter permits non-invasive studies to be carried out. Using this technique the diameter of the brachial artery and the velocity of blood flow within the vessel can be measured transcutaneously. The technique employs two devices (Levenson *et al.*, 1981), a double transducer probe which permits bidimensional Doppler signal recording and an electronic range-gated time system. The latter allows the Doppler signal to be focused so that it crosses the lumen of the artery thus generating a succession of velocity peaks the width of which corresponds to the diameter of the artery (Levenson *et al.*, 1981). In addition to measuring the diameter of the arterial lumen and the velocity of the blood flowing within it the pulsed Doppler permits the evaluation of arterial compliance (Simon *et al.*, 1983).

Arterial haemodynamics in essential hypertension

Using the techniques described above it has been shown that, compared with normotensive subjects of the same age, hypertensive subjects have an increased brachial artery diameter with blood flow velocity and blood flow within normal limits (Table 1). Furthermore, forearm arterial compliance was found to be significantly lower in hypertensives than in age-matched normotensive individuals (Simon *et al.*, 1983; Figure 1). The aetiology of these changes in arterial diameter and compliance is imperfectly understood; the mechanical effect of the elevated arterial

Table 1 Brachial artery parameters in normal subjects and sustained essential hypertension patients

	Normal subjects (n = 7)	Hypertensive patients (n = 22)
Brachial artery diameter (cm)	0.438 ± 0.018	0.515 ± 0.013**
Brachial artery blood velocity (cm s ⁻¹)	11 ± 2	10 ± 1
Brachial artery blood flow (ml min ⁻¹)	98 ± 17	122 ± 7

Values are mean ± s.e. mean, n = number of patients
***P* < 0.01.

Modified from Simon *et al.* (1983).

Figure 1 Individual values of forearm arterial compliance in mild and moderate essential hypertensive patients. (Modified from Simon *et al.* (1983))

pressure on the arterial wall itself is probably an important factor (Hallock & Benson, 1937) but the influence of neurohumoral factors on the vessel wall and structural changes in the walls themselves induced by chronically elevated pressure (Dobrin, 1983) may also play a role. However, the finding that the decrease in arterial compliance is similar in patients with mild hypertension to those with established severe hypertension (Simon *et al.*, 1983) suggests that arterial wall distention resulting from elevated pressure is not the only mechanism involved in the reduced arterial compliance in hypertension and that early functional and structural changes in the arterial wall may also be involved.

Effects of antihypertensive therapy with β -adrenoceptor antagonists on arterial circulation

Since hypertension is associated with an increase in the calibre and a decrease in the compliance

of the large arteries, when treating the disease it would appear logical not only to lower the elevated pressure but also to reverse the changes in arterial function in the hope of preventing the atherosclerotic complications of the disease (O'Rourke, 1976). The differing effects of antihypertensive drugs of the same therapeutic class on the arterial circulation is illustrated by results which we have obtained recently in investigations in which patients with mild to moderate hypertension were treated with pindolol (Maarek *et al.*, 1986) or propranolol (Simon *et al.*, 1984, 1985) given as monotherapy for a period of 12 weeks.

Table 2 summarises the results of these investigations and shows the effects of 3 months treatment with pindolol ($n = 13$) or propranolol

($n = 14$) on arterial circulation. Despite the fact that both β -adrenoceptor antagonists produced similar antihypertensive effects the haemodynamic effects of the two drugs were characteristically different. Pindolol treatment led to an increase in arterial flow measured directly in the brachial artery with a pulsed Doppler system or indirectly using a strain gauge plethysmograph positioned around the forearm (Maarek *et al.*, 1986). The increase in blood flow was associated with an increase in diameter of the brachial artery and an increase in the velocity of the blood within the vessel. There was a significant positive correlation between the increase in blood flow and the increase in blood velocity (Figure 2) but not between the increase in blood flow and the increase in arterial diameter. This observation

Table 2 Effects of pindolol and propranolol after 3 months of treatment on brachial artery circulation

	Propranolol group ($n = 14$)		Pindolol group ($n = 13$)	
	P	A	P	A
Mean arterial pressure (mm Hg)	123 ± 3	$101 \pm 4^{***}$	121 ± 3	$105 \pm 3^{***}$
Brachial artery diameter (cm)	0.446 ± 0.024	0.439 ± 0.018	0.456 ± 0.011	$0.480 \pm 0.010^{**}$
Brachial artery blood velocity (cm s^{-1})	8 ± 1	10 ± 1	7 ± 1	$10 \pm 1^{***}$
Brachial artery blood flow (ml min^{-1})	79 ± 13	91 ± 12	67 ± 7	$105 \pm 10^{***}$
Forearm arterial compliance ($10^{-4} \text{ ml mm Hg}^{-1}$)	105 ± 15	116 ± 12	114 ± 9	$174 \pm 14^{***}$

Values are means $\pm$ s.e. mean, $^{**}P < 0.01$, $^{***}P < 0.001$.

Figure 2 Relationship between percent increase in brachial artery velocity and percent increase in forearm arterial flow after 3 months of pindolol treatment, ($r = 0.67$, $P < 0.01$), (from Maarek *et al.* (1986)).

suggests that pindolol increases blood flow by dilating the arterioles rather than the large arteries. In contrast, propranolol treatment although producing a similar fall in mean arterial pressure did not produce any significant changes in blood flow or velocity or the diameter of the brachial artery. Plethysmographic measurements have revealed that forearm blood flow is reduced during short-term treatment with propranolol (Ireland & Littler, 1981) but returns to pretreatment levels during long term treatment (Bolli *et al.*, 1982). Since cardiac output remains depressed during long term treatment with propranolol (Tarazi & Dustan, 1972) these observations indicate that the effects of a drug on regional circulation cannot be predicted on the basis of its cardiac effects.

Pindolol and propranolol also differ from each other in terms of their effects on arterial compliance. As shown in Table 2, after 3 months therapy with pindolol a statistically significant increase in forearm arterial compliance was recorded. Since arterial compliance (or distensibility) is dependent on the volume of the arterial lumen and the intrinsic distensibility of the arterial wall (Hallock & Benson, 1937) the increase in compliance may result from a dilatation of the artery or from an increased distensibility of the arterial wall. The finding that chronic treatment with pindolol results in a dilatation of the brachial artery (Maarck *et al.*, 1986) despite the fact that arterial pressure fell (which would be expected to result in a passive reduction of the calibre of the artery) suggests that pindolol increases arterial compliance by the former mechanism.

In contrast, although propranolol treatment produced a comparable degree of blood pressure

reduction to that seen in the pindolol treated patients (Table 2), the drug exerted no significant effect on arterial compliance (Maarek *et al.*, 1986). As arterial compliance is one of the major determinants of the degree of dampening of pulsatility of pressure within the arterial system (McDonald, 1974) the increase in arterial compliance would be expected to result in a reduction in arterial pulsatility and in fact pindolol, but not propranolol treatment, results in a significant reduction in the amplitude of the arterial pulse pressure (Maarek *et al.*, 1986). Since chronic excessive arterial pulsatility may result in degenerative changes in the bioelastomers of the arterial walls (Gent, 1972), the reduction in pulsatility seen after pindolol treatment may constitute an additional protective factor in the therapy of hypertension.

Although the precise mechanism whereby these two β -adrenoceptor antagonists at equipotent antihypertensive doses exert qualitatively different effects on arterial haemodynamics remains unknown, it is tempting to speculate that the partial agonist effects exerted by pindolol but not by propranolol are ultimately involved. Indeed it has been reported that following acute intraarterial administration of pindolol in man a β -adrenoceptor mediated vasodilator effect is seen (Chang *et al.*, 1985) and that during the long term treatment of hypertension with β -adrenoceptor antagonists, compounds with partial agonist activity tend to reduce calculated systemic vascular resistance whereas those lacking the property do not (Man in't Veld & Schalekamp, 1982). However, further investigations are necessary to elucidate the precise mechanisms of actions involved.

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