Vasodilatory effect of nicardipine and verapamil in the forearm of hypertensive as compared with normotensive man

U. L. HULTHÉN*, P. BOLLI & F. R. BÜHLER

Department of Medicine and Research, University Hospital, Basel, Switzerland

1 The intent of this study was to determine whether or not increased calcium-influx-mediated vasoconstriction is a primary pathogenetic disturbance in essential hypertension.

2 Ten normotensive subjects (NT) (aged 45 ± 12 years) and 23 patients with essential hypertension (EH) were studied. Twelve of the patients (aged 42 ± 12 years) were classified as having mild EH and 11 patients (aged 49 ± 11 years) as having moderate EH.

3 Forearm blood flow and intra-arterial blood pressure were measured. Forearm vascular resistance (FVR) was calculated under basal conditions, during reperfusion following 10 min arterial occlusion, and after infusion into the brachial artery of sodium nitroprusside (0.15 and $0.6 \mu\text{g min}^{-1} 100 \text{ ml}^{-1}$ tissue for 2 min each) and the calcium-influx inhibitors nicardipine (5 and $40 \mu\text{g min}^{-1} 100 \text{ ml}^{-1}$ tissue for 1 min each) and verapamil ($80 \mu\text{g min}^{-1} 100 \text{ ml}^{-1}$ tissue for 1 min).

4 FVR after 10 min arterial occlusion was lower in mild EH than in moderate EH and still lower in NT. FVR was comparable in the three groups following infusion of maximal doses of sodium nitroprusside, nicardipine, and verapamil.

5 To allow for the vasodilator response to arterial occlusion, the decrease in FVR measured after each drug was divided by that obtained after arterial occlusion in each individual. The adjusted vasodilator response to nicardipine and verapamil, but not to sodium nitroprusside, was greater in moderate EH than in NT and mild EH. In the latter two groups the adjusted vasodilator responses were comparable.

6 Calcium-influx mediated vasoconstriction is thus enhanced in moderate (established) EH but not in mild EH and, therefore, is unlikely as a primary pathogenetic disturbance in essential hypertension.

Keywords hypertension nicardipine vasodilatation verapamil

Introduction

Mikkelsen and colleagues (1978, 1979) have shown that calcium entry blockers inhibit contractions induced by potassium and noradrenaline in preparations of human arteries. Furthermore, these drugs produced a marked vasodilator effect in the human forearm (Robinson *et al.*, 1979, 1980).

Studies with verapamil have shown a selective enhancement of forearm vasodilatation in pat-

ients with established essential hypertension as compared with normotensive subjects (Hulthén *et al.*, 1982; Robinson *et al.*, 1982).

The possible pathogenetic importance of enhanced calcium-influx-dependent vasoconstriction in essential hypertension was explored in the present study. The vasodilatation induced by verapamil and nicardipine, two calcium entry blockers with different chemical structures, was

* Present address: Department of Endocrinology, Lund University Clinics, General Hospital, S-214 01 Malmö, Sweden.

compared with the vasodilator response to sodium nitroprusside and to reperfusion following arterial occlusion for 10 min in normotensive subjects and in patients with mild and moderate essential hypertension. Some of the findings from this study have been presented elsewhere (Hulthén *et al.*, 1983).

Methods

Subjects

Ten subjects aged 30–66 (mean 45) years, who were not taking any medication and had a casual sitting diastolic blood pressure of less than 85 mm Hg (Korotkoff phase V) and no family history of hypertension, were classified as normotensive (NT). Twenty-three patients aged 19–64 (mean 45) years, who had a casual sitting diastolic blood pressure equal to or greater than 95 mm Hg on at least two occasions and normal renal function, were classified as having essential hypertension (EH). All EH patients were in WHO disease stage I or II, and use of any antihypertensive medication was prohibited at least 3 weeks prior to the study. The EH group of patients was further subdivided before the plethysmographic study into 12 patients aged 19–60 (mean 42) years with mild EH (intra-arterial diastolic blood pressure < 85 mm Hg) and 11 patients aged 28–64 (mean 49) years with moderate EH (intra-arterial diastolic blood pressure $\geq$ 85 mm Hg).

Methodology

With the subjects resting in the supine position, a catheter was placed in the left brachial artery for measurement of blood pressure with a Statham 23 Db pressure transducer and for infusion of drugs. After 30 min rest, arterial blood was sampled for analysis of plasma renin activity (Sealey *et al.*, 1972) and plasma noradrenaline and adrenaline concentrations (Da Prada & Zürcher, 1976).

Basal forearm blood flow (FAF) was measured with venous occlusion plethysmography (Hulthén *et al.*, 1982) as the mean of seven readings, and forearm vascular resistance (FVR) was calculated as mean intra-arterial blood pressure (MBP)/FAF. Forearm ischaemia was then maintained for at least 10 min by inflating a cuff on the upper arm above 200 mm Hg. When the cuff was released, FAF was measured repeatedly during 1 min. The peak value was taken for

analysis, and MBP was calculated as the mean value during the initial 15 s.

Fifteen minutes later sodium nitroprusside was infused into the left brachial artery at rates of 0.15 and 0.6 $\mu\text{g min}^{-1}$ 100 ml $^{-1}$ forearm tissue for 2 min each with a 10 min interval inbetween. Forearm blood flow was measured repeatedly for 1 min after stopping the infusions. The mean of the three highest values was taken for analysis and MBP was calculated as the mean value during the initial 30 s.

Fifteen minutes later nicardipine was infused into the brachial artery in doses of 5 and 40 $\mu\text{g min}^{-1}$ 100 ml $^{-1}$ tissue for 1 min each, with 10 min between infusions. One hour later, verapamil was infused for 1 min in a dose of 80 $\mu\text{g min}^{-1}$ 100 ml $^{-1}$ tissue. For nicardipine as and calculated as for sodium nitroprusside. The highest dose given for sodium nitroprusside and nicardipine, as well as the verapamil dose, induces a maximal vasodilator response in the forearm (Hulthén *et al.*, 1982, 1983).

Statistical analysis

Statistical analysis of data was performed with nonparametric methods using the Kruskal–Wallis test for evaluation of differences between the three groups. When the null hypothesis was rejected, pairs of groups were compared by use of the Mann–Whitney test. Paired observations were analysed by the Wilcoxon signed rank test, and correlations were calculated by Spearman's Rho. The values are given as mean $\pm$ s.d., and the level of significance is taken as $P < 0.05$.

Results

Plasma renin activity was higher in mild EH than in moderate EH; 2.4 ± 1.4 and 1.3 ± 1.0 ng ml $^{-1}$ 3 h $^{-1}$, respectively ($P < 0.01$). In NT plasma renin activity was 2.8 ± 1.3 ng ml $^{-1}$ 3 h $^{-1}$ and did not differ significantly from any of the EH groups. Arterial catecholamine levels were comparable in the three groups: noradrenaline 222 ± 64 pg ml $^{-1}$ in NT, 192 ± 74 pg/ml in mild EH, and 195 ± 90 pg ml $^{-1}$ in moderate EH; and adrenaline 52 ± 25 pg ml $^{-1}$ in NT, 55 ± 27 pg/ml in mild EH, and 43 ± 18 pg ml $^{-1}$ in moderate EH.

During basal conditions, intra-arterial MBP was 74 ± 5 mm Hg in NT, 90 ± 7 mm Hg in mild EH, and 119 ± 13 mm Hg in moderate EH. During reperfusion after arterial occlusion, as

Figure 1 Decrease (mean $\pm$ s.d.) in intra-arterial mean blood pressure (Δ MBP) during reperfusion after 10 min arterial occlusion (AO) and after intra-arterial infusion of sodium nitroprusside (NIP: 0.3 and 1.2 μ g 100 ml⁻¹ tissue), nicardipine (NIC: 5 and 40 μ g 100 ml⁻¹ tissue) and verapamil (VER: 80 μ g 100 ml⁻¹ tissue) in 10 normotensive subjects (open bars), 12 patients with mild essential hypertension (hatched bars), and 11 patients with moderate essential hypertension (cross-hatched bars). * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$.

well as directly following all intra-arterial infusions, MBP in the experimental arm was significantly decreased in NT as well as in mild EH and moderate EH ($P < 0.05$ – $P < 0.001$). Only after nicardipine 40 μ g and verapamil 80 μ g 100 ml⁻¹ tissue did the reduction of MBP differ between the groups, being greater in moderate EH than in NT and mild EH (Figure 1).

Basal forearm blood flow did not differ between the groups (Table 1). Forearm flow was

comparable in the three groups following infusion of each dose of sodium nitroprusside and during reperfusion after ischaemia. After infusion of each dose of nicardipine, as well as of verapamil, forearm blood flow was greater in moderate EH than in NT.

Basal forearm vascular resistance was similar in NT and mild EH and tended to be greater in moderate EH (Table 1). After the low dose of sodium nitroprusside, forearm vascular resistance was higher in mild EH than in NT, and still higher

Table 1 Forearm blood flow (FAF) and forearm vascular resistance (FVR) during basal conditions and reperfusion after 10 min arterial occlusion (AO) and after intra-arterial infusion of sodium nitroprusside (NIP: 0.3 and 1.2 mg tissue), nicardipine (NIC: 5 and 40 μ g 100 ml⁻¹ tissue), and verapamil (VER: 80 μ g 100 ml⁻¹ tissue) in 10 normotensive subjects (NT), 12 patients with mild essential hypertension (MiEH), and 11 patients with moderate essential hypertension (MoEH)

	FAF (ml min ⁻¹ 100 ml ⁻¹ tissue)			FVR (mm Hg ml ⁻¹ min ⁻¹ 100 ml ⁻¹)		
	NT	MiEH	MoEH	NT	MiEH	MoEH
Basal	2.5 $\pm$ 1.2	2.9 $\pm$ 0.8	2.9 $\pm$ 1.4	34.4 $\pm$ 12.6	32.8 $\pm$ 7.3	51.3 $\pm$ 24.9
NIP 0.3	5.8 $\pm$ 1.9	6.0 $\pm$ 2.0	5.8 $\pm$ 1.8	12.9 $\pm$ 3.6	15.4 $\pm$ 4.7*	20.6 $\pm$ 7.3***§
NIP 1.2	9.4 $\pm$ 4.2	12.8 $\pm$ 6.5	11.9 $\pm$ 3.0	8.0 $\pm$ 3.0	8.1 $\pm$ 4.5	9.3 $\pm$ 2.6
AO	37.6 $\pm$ 6.1	36.6 $\pm$ 8.3	35.9 $\pm$ 8.1	1.6 $\pm$ 0.4	2.1 $\pm$ 0.5**	2.9 $\pm$ 0.8***§§
NIC 5	12.5 $\pm$ 7.3	17.3 $\pm$ 8.0	22.8 $\pm$ 5.9***	7.2 $\pm$ 4.8	6.0 $\pm$ 4.0	4.8 $\pm$ 1.2
NIC 40	28.9 $\pm$ 9.4	34.9 $\pm$ 7.9	40.1 $\pm$ 5.9**	2.2 $\pm$ 0.9	2.2 $\pm$ 0.5	2.3 $\pm$ 0.5
VER 80	33.0 $\pm$ 8.9	36.2 $\pm$ 8.9	43.5 $\pm$ 4.8**§	1.9 $\pm$ 0.6	2.2 $\pm$ 0.5	2.2 $\pm$ 0.5

Mean $\pm$ s.d.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ NT compared with MiEH or MoEH.

§ $P < 0.05$; §§ $P < 0.01$ MiEH compared with MoEH.

Table 2 Decrease in forearm vascular resistance (Δ FVR) after intra-arterial infusion of sodium nitroprusside (NIP: 0.3 and 1.2 μg 100 ml⁻¹ tissue), nicardipine (NIC: 5 and 40 μg 100 ml⁻¹ tissue), and verapamil (VER: 80 μg 100 ml⁻¹ tissue) adjusted for Δ FVR during reperfusion after 10 min arterial occlusion (AO) in 10 normotensive subjects (NT), 12 patients with mild essential hypertension (MiEH), and 11 patients with moderate hypertension (MoEH)

	NT	MiEH	MoEH
Δ FVR NIP 0.3/ Δ FVR AO	0.64 $\pm$ 0.08	0.56 $\pm$ 0.15	0.60 $\pm$ 0.14
Δ FVR NIP 1.2/ Δ FVR AO	0.79 $\pm$ 0.08	0.81 $\pm$ 0.13	0.84 $\pm$ 0.11
Δ FVR NIC 5/ Δ FVR AO	0.82 $\pm$ 0.15	0.87 $\pm$ 0.13	0.95 $\pm$ 0.03**§
Δ FVR NIC 40/ Δ FVR AO	0.98 $\pm$ 0.02	1.00 $\pm$ 0.02	1.02 $\pm$ 0.02**§
Δ FVR VER 80/ Δ FVR AO	0.99 $\pm$ 0.02	1.00 $\pm$ 0.02	1.02 $\pm$ 0.02*§

Mean $\pm$ s.d.

* $P < 0.01$; ** $P < 0.001$ NT compared with MoEH.

§ $P < 0.01$ MiEH compared to MoEH.

in moderate EH, whereas after the high dose of sodium nitroprusside forearm vascular resistance was comparable in the three groups. During reperfusion after ischaemia, the minimal forearm vascular resistance achieved was higher in mild EH than in NT and highest in moderate EH. Following nicardipine and verapamil, forearm vascular resistance did not differ between the groups. In moderate EH, FVR after infusion of nicardipine 40 μg and verapamil 80 μg 100 ml⁻¹ tissue was lower than that during reperfusion after arterial occlusion ($P < 0.001$ and $P < 0.05$, respectively). The decrease in FVR during reperfusion after arterial occlusion and following intra-arterial infusion of sodium nitroprusside, nicardipine or verapamil did not correlate significantly with basal plasma renin activity or plasma concentration of noradrenaline or adrenaline in any of the groups.

In order to adjust for the vasodilator response during reperfusion after arterial occlusion, the decrease in FVR after sodium nitroprusside, nicardipine, or verapamil was divided by that achieved during reperfusion after arterial occlusion in each individual. The adjusted vasodilator response to sodium nitroprusside was comparable in the three groups (Table 2). The adjusted vasodilator response to both doses of nicardipine and to verapamil was greater in moderate EH than in NT or mild EH and did not differ between the latter two groups.

Discussion

The decrease in intra-arterial BP in the experimental arm during early reperfusion after arterial

occlusion (Figure 1) accords with the report of Patterson & Whelan (1955) and reflects the reduction of regional vascular resistance. As previously observed by Folkow *et al.* (1958), the fall in intra-arterial MBP during reactive hyperaemia was similar in NT and EH. Likewise, comparable decreases in MBP were found in NT and EH after sodium nitroprusside. However, the reduction of intra-arterial MBP in the experimental arm after maximal regional doses of the calcium entry blockers nicardipine and verapamil was greater in moderate EH than in NT and mild EH.

These findings support the concept of a selective enhancement of a vasodilator response to the calcium entry blockers in moderate EH (Hulthén *et al.*, 1982; Robinson *et al.*, 1982). Forearm blood flow also reached higher levels in moderate EH than in NT with both doses of nicardipine and verapamil, but not with sodium nitroprusside and not during reperfusion following arterial occlusion (Table 1).

The findings of higher minimal forearm vascular resistance in moderate EH and mild EH than in NT during reactive hyperaemia after arterial occlusion for 10 min (Table 1) is in accordance with the studies of Folkow *et al.* (1958), Conway (1963), and Takeshita & Mark (1980). The former two groups of investigators used vasodilator stimuli such as handgrip exercise and local heating, in addition to ischaemia; this combined procedure has been taken to represent the maximal vasodilatation obtainable in the forearm.

The finding of lower forearm vascular resistance in moderate EH after maximal regional doses of nicardipine or verapamil than during reperfusion after 10 min arterial occlusion (Table 1) tallies

with the theory of an increased calcium-influx-dependent vasoconstriction in essential hypertension. Accordingly, the decrease in forearm vascular resistance in response to nicardipine and verapamil, adjusted for the response during reactive hyperaemia (as an index of 'nonspecific vasodilatation'), was greater in moderate EH than in NT and mild EH (Table 2).

In contrast to the selective enhancement of the forearm vasodilator response to calcium entry blockers in moderate EH, in patients with mild EH the decrease in intra-arterial MBP and FAF following the infusions of either nicardipine or verapamil was similar to those seen in NT (Figure 1, Table 1). Furthermore, in mild EH the

decrease in FVR to nicardipine and verapamil, as adjusted for the response during reactive hyperaemia, was not different from that in NT (Table 2). These findings indicate that the vasodilator response to calcium entry blockers is not accentuated in the early phase of essential hypertension.

The results from the present study support the concept of an enhanced calcium-influx-mediated vasoconstriction in the established phase of essential hypertension, but they do not indicate that this is a primary pathogenetic disturbance in essential hypertension.

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