Response of forearm resistance vessels to verapamil and sodium nitroprusside in normotensive and hypertensive men: evidence for a functional abnormality of vascular smooth muscle in primary hypertension

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Summary

1. The response of the forearm resistance vessels to local intra-arterial infusion of verapamil and sodium nitroprusside has been assessed by a plethysmographic method in 23 men with normal arterial pressure and 35 men with primary hypertension.

2. In the 20 patients with hypertension for whom full dose-response curves were determined, the dilator response to verapamil was significantly greater than that in the normal controls, whereas the response to sodium nitroprusside was reduced.

3. Comparison of responses to the two dilators in individual subjects enabled the scattering effect of variables common to both drugs to be reduced. Analysis of the results in this way showed a highly significant difference between the hypertensive men as a whole and the normotensive controls ($P < 0.00001$); 24 out of the 35 hypertensive men showed responses that were outside the normal range.

4. The abnormal pattern of response observed in the hypertensive group cannot be accounted for by structural changes in the vessels and strongly suggests a functional abnormality of the vascular smooth muscle.

Key words: arterioles, forearm, hypertension, iproveratril, nitroprusside, phentolamine, smooth muscle.

Introduction

Abnormalities of sodium transport have been demonstrated in both erythrocytes and leucocytes from patients with primary (or essential) hypertension [1–3], and it has been suggested that related abnormalities of ion transport affect the vascular smooth muscle with consequent changes in the functional properties of the blood vessels. An augmented response to noradrenaline has been observed in the resistance vessels of the forearm [4], finger [5] and hand [6] of patients with hypertension and this has been taken by some authors as evidence of the postulated functional abnormality in the smooth muscle. Folkow [7], however, has challenged this interpretation and has pointed out that increased responsiveness to noradrenaline could result from structural changes in the resistance vessels and need not necessarily imply any change in the functional properties of the smooth muscle: vessels that are chronically exposed to a raised distending pressure develop medial hypertrophy with an increase in the wall/lumen ratio [6, 8] and this could result in an exaggerated response to both constrictor and dilator agents as a direct consequence of the altered vascular geometry. It therefore remains uncertain whether or not there is a functional abnormality of the vascular smooth muscle in primary hypertension.

It seemed possible that this problem might be resolved by examining the response of the resistance vessels to dilator agents. An impaired response to certain dilators has been observed in vessels taken from hypertensive rats [9, 10], and if a similar abnormality could be shown in man it
could not be accounted for by the structural hypothesis. We have therefore examined the response of the forearm resistance vessels to two dilator agents, verapamil and sodium nitroprusside, which are known to induce relaxation by a direct effect on the vascular smooth muscle, but which act in different ways.

**Subjects and methods**

**Subjects**

Studies were carried out in 23 volunteers with normal arterial pressure and 35 patients with hypertension for which no underlying cause could be demonstrated; all the subjects were male. The normotensive group consisted of 20 whites, two blacks and one Asian; their ages ranged from 25 to 64 years (mean 41 years).

The hypertensive subjects formed two series: series 1 (20 patients) were studied with exactly the same protocol as that used for the normotensive group; series 2 (15 patients) were studied subsequently with an abbreviated protocol. The patients in the first series included 12 whites and eight blacks; their ages ranged from 36 to 63 years (mean 49 years). The patients in the second series included 10 whites, one black and four Asians; their ages ranged from 29 to 63 years (mean 48 years).

In addition to routine clinical examination, all patients were investigated by urinalysis, estimation of plasma electrolytes, urea and creatinine, chest X-ray and electrocardiography; 12 in series 1 and seven in series 2 had also been investigated by intravenous urography. No patient was receiving treatment at the time of the study. Of the patients in series 1, four had never been treated and two had had no drugs for more than 2.5 months; 11 had received diuretics, which had been discontinued for at least 12 days, with the exception of one patient in whom hydrochlorothiazide, 50 mg daily, was withdrawn 4 days before the study; 13 patients had received other drugs (\(\beta\)-adrenoceptor antagonists in 11, \(\alpha\)-methyldopa in two and betanidrine in one); these had been withdrawn for at least 1 week in eight patients and, in the other five, atenolol had been withdrawn for 5 and 6 days respectively, \(\alpha\)-methyldopa for 5 days, betanidrine for 4 days and propranolol (40 mg three times daily) for 2 days. Of the patients in series 2, six had never been treated and three had no treatment for more than 5 weeks; two had received diuretics, which had been discontinued for a minimum of 13 days before the study; six had received \(\beta\)-adrenoceptor antagonists, which had been discontinued for a minimum of 6 days. The study was approved by the Ethical Committee of St George's Hospital and all subjects gave informed consent.

The subjects were studied while resting on a bed; the laboratory temperature varied between 19.8 and 26.7°C on different occasions. Arterial pressure was recorded by the same observer at the beginning and end of each study; a standard sphygmomanometer was used and phase 4 of the Korotkoff sounds was taken as the diastolic pressure. Mean arterial pressure was calculated by adding one-third of the pulse pressure to the diastolic and the average of the two readings was taken as the pressure at the time of the study. Heart rate was counted from the pulsations on the plethysmographic record; it was determined over a 30 s period at the same stage in each study.

Blood flow was recorded in both forearms by venous occlusion plethysmography with mercury-in-silastic gauges [11]. A collecting cuff pressure of approximately 40 mmHg was used and the wrist cuffs were inflated to at least 30 mmHg above systolic pressure to exclude the hands from the circulation. Flows were recorded for 8–12 s in every 15 s. A 26 SWG needle was introduced into the brachial artery on one side under local anaesthesia with lignocaine and attached by a connecting catheter to a syringe driven by a Harvard infusion pump. Saline (sodium chloride solution, 150 mmol/l) or drugs dissolved in saline were infused at rates varying from 0.25 to 1.0 ml/min.

**Protocol**

**Normotensive and hypertensive subjects (series I).** After introduction of the arterial needle, forearm flow was recorded for 2–3 min. After a short pause, flows were again recorded for 2–3 min during infusion of saline, and verapamil was then infused at 1.25, 2.5 and 5.0 \(\mu\)g/min for 3 min at each dose. After a 10 min pause, a second dose–response curve was recorded with infusion of verapamil at 5.0, 10.0 and 20.0 \(\mu\)g/min. After a 30 min rest period, the response to sodium nitroprusside was determined in the same way by infusion of 200 ng/min, 800 ng/min and 3.2 \(\mu\)g/min for 3 min each in a continuous run. In some subjects, after a further 15 min rest period, phentolamine was infused at 100 \(\mu\)g/min for 10 min, after which sodium nitroprusside was infused at 3.2 \(\mu\)g/min for 5 min together with the phentolamine.

The control forearm flow for each dose–response curve was obtained by averaging the six
to eight flows recorded immediately preceding infusion of the drug; the response at each dose was taken as the average of the last five flows. The results were expressed as the increment in blood flow (ml min\(^{-1}\) 100 ml\(^{-1}\) of forearm) compared with the immediately preceding control flow.

**Hypertensive subjects (series 2).** These patients were studied by an abbreviated protocol: in the first verapamil infusion, the 1·25 and 2·5 µg/min dose rates were omitted and an infusion at 5 µg/min was maintained for 4 min; the second verapamil infusion was unchanged; the lowest dose rate in the nitroprusside infusion was omitted.

**Drugs**

Drugs used were lignocaine hydrochloride (Lidothesin, Pharmaceutical Manufacturing Co.), sodium nitroprusside (Nipride, Roche), phentolamine (Rogitine, Ciba) and verapamil (Cordilox, Abbot). Dilutions of drugs in saline were made up immediately before use on each occasion.

**Statistics**

Non-parametric methods were used in all tests of significance of differences. The Mann–Whitney U-test was used for unpaired data and the Wilcoxon signed rank test for paired data.

**Results**

**Basal circulatory measurements in the normotensive and hypertensive subjects**

Mean values for arterial pressure, heart rate and control forearm blood flow are shown for the normotensive subjects and the two series of hypertensive subjects (Table 1). Heart rate was slightly higher on average in the hypertensive than in the normotensive group, but the difference did not achieve statistical significance. Forearm blood flow was slightly higher in the hypertensive subjects and tended to rise in the course of the study; this contrasted with the normotensive subjects, in whom flow remained essentially constant throughout.

**Dose–response curves to verapamil and sodium nitroprusside in the normotensive and hypertensive subjects (series 1)**

**Verapamil.** All of the normotensive men showed a dose-dependent increase in forearm blood flow in response to infusion of verapamil over the dose range 1·25–20 µg/min (Fig. 1). The response at 5 µg/min was on average smaller in the second dose–response curve than in the first (P < 0·01). The slope of the dose–response curve increased with increasing dose and in every subject the increase in flow at 20 µg/min was more than 2½ times the increase at 5 µg/min in the same run.

The hypertensive patients showed a response to verapamil that was significantly greater than that of the control subjects at all doses (Fig. 1). The response at 5 µg/min was again smaller in the second dose–response curve than in the first (P < 0·01). In five out of the 20 patients, the shape of the dose–response curve was abnormal in that the slope became less at the higher doses and the increase in flow at 20 µg/min was less than twice the increase at 5 µg/min in the second run; the response thus appeared to be approaching a maximum.

**Sodium nitroprusside.** The normotensive subjects showed a dose-dependent increase in

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<th>Table 1. Basal circulatory measurements in the normotensive controls and the hypertensive patients</th>
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<td><strong>Mean arterial pressure (mmHg)</strong></td>
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<td><strong>Control</strong></td>
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<td><strong>Normotensive (n = 23)</strong></td>
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* n = 19.
forearm blood flow in response to sodium nitroprusside over the dose range 200 ng/min–3.2 μg/min (Fig. 2). The patients with hypertension showed a response to sodium nitroprusside at 200 ng/min that was not significantly different from that of the normal subjects, but, in contrast to the findings with verapamil, the response at 800 ng/min and 3.2 μg/min was smaller than that of the normal subjects. The differences between the groups did not achieve a high level of significance when analysed in terms of the absolute increase in forearm flow. When differences in control flow were taken into account, however, by expressing the results in terms of the percentage increase in flow, there was a highly significant difference between the responses at 3.2 μg/min (normotensive, +285 ± 24% and hypertensive, +173 ± 26%; mean ± SEM, P < 0.001). The response to ischaemia was studied in six patients in order to exclude the possibility that the impaired response to nitroprusside resulted from an intrinsic limitation of the capacity of the vessels to dilate. In every case the increase in flow after 2 min of ischaemia was greater than that to the highest dose of nitroprusside and the response to ischaemia exceeded the response to nitroprusside by a large margin in the four patients in whom response to the drug was clearly subnormal (Table 2).

The effect on the response to nitroprusside of inhibition of sympathetic constrictor tone was investigated in six normotensive and six hypertensive subjects by repeating the infusion of sodium nitroprusside at 3.2 μg/min during infusion of phentolamine at 100 μg/min. The increase in blood flow induced by nitroprusside was not significantly affected by simultaneous α-adrenoceptor blockade. In normotensive subjects, flow was 8.30 ± 1.59 ml min⁻¹ 100 ml⁻¹ before phentolamine and 8.67 ± 0.88 after; in hypertensive subjects, 6.15 ± 1.04 ml min⁻¹ 100 ml⁻¹ before and 6.76 ± 1.51 after.
Response of resistance vessels in hypertension

Comparison of response to verapamil and sodium nitroprusside

Normotensive and hypertensive subjects (series I). Despite the significant difference between the groups in their response to verapamil and nitroprusside, results from most individual patients fell within the normal range when responses to the two drugs were considered separately; this reflected the large variance of the responses in both normal subjects and patients.

When an index of responsiveness to verapamil (sum of the responses to the two 5 μg doses) was plotted against the response to sodium nitroprusside (3.2 μg/min), however, a strongly positive correlation was apparent for the normal subjects (Fig. 3; \( r = 0.85; P < 0.001 \)). The hypertensive men show greater variability (\( r = 0.54; P < 0.05 \)), but most are above the range of the normotensive group; the regression line (not shown) has the equation \( y = 0.29x + 3.78 \).

The relative responsiveness of individual subjects to the two drugs can be characterized in several ways. The most generally useful index of responsiveness, however, appears to be the amount by which the sum of the responses to verapamil (5 μg/min on two occasions) exceeds that predicted from the regression line for normal subjects for the observed response to nitroprusside (3.2 μg/min). The ‘excess verapamil response’ had, in accordance with its definition, a mean value of 0.0 ± 0.2 in the normal subjects, whereas it was 2.7 ± 0.4 ml min\(^{-1}\) 100 ml\(^{-1}\) of forearm in the hypertensive subjects of series 1 (Fig. 4); the difference was highly significant (\( P < 0.00001 \)). The increase in the excess verapamil response in the patients with hypertension was largely accounted for by an increase in the sum of the responses to the two infusions of verapamil at 5 μg/min (5.7 ± 0.4 in the patients compared with 3.8 ± 0.3 ml min\(^{-1}\) 100 ml\(^{-1}\) of forearm in the normal subjects), but it was also due in part to a reduction in the response to sodium nitroprusside at 3.2 μg/min (6.7 ± 0.8 in the patients compared with 8.6 ± 0.7 ml min\(^{-1}\) 100 ml\(^{-1}\) of forearm in the normal subjects).

Since the patients and normal controls were not well matched for age and race, the excess verapamil response in the subgroup of 12 hypertensive subjects who were white was compared with that in the 13 normotensive men who were both white and of the same age range as the...
hypertensive men (36 years or more); the difference between the subgroups was similar to that for the groups as a whole, the mean excess verapamil response in the normotensive group being 0-0 ± 0-2 and that for the hypertensive group 2-8 ± 0-4 ml min⁻¹ 100 ml⁻¹ of forearm.

Limited information is available concerning the reproducibility of estimations of the excess verapamil response. Assuming that normal subjects show some biological variability, the variance of repeated measurements in a single subject must necessarily be less than that shown by the group as a whole. Three studies were performed in one normotensive subject and yielded values of 0-3, -0-1 and 0-1 ml min⁻¹ 100 ml⁻¹ of forearm despite variations of up to twofold in control forearm blood flow and in the absolute responses to the drugs.

**Hypertensive subjects (series 2).** The hypertensive subjects in the second series had a mean excess verapamil response of 2-1 ± 0-5 ml min⁻¹ 100 ml⁻¹ of forearm, which was less than that of the first series but significantly greater than that of the normal subjects (P < 0-001); nine out of the 15 patients showed a pattern of response that was outside the normal range (Fig. 4).

**Relation between excess verapamil response and other variables**

There was no significant relationship between the excess verapamil response and age either for the normotensive group (r = -0-04) or for the two series of hypertensive subjects taken together (r = 0-04). Within the combined hypertensive group there was no significant relationship between excess verapamil response and mean arterial pressure at the time of the study (r = 0-10). There was no evidence to suggest that previous treatment had any significant effect upon the result: mean excess verapamil response in the 10 patients who had never received any treatment for their hypertension was 2-3 ± 0-5 ml min⁻¹ 100 ml⁻¹ of forearm whereas in the 25 patients who had received treatment it was 2-5 ± 0-4 ml min⁻¹ 100 ml⁻¹ of forearm.

Examination of the results for the two series of hypertensive patients reveals that relative responsiveness to the two drugs was within the normal range in about one-third of the group. It therefore appears probable that the functional abnormality that underlies the altered responsiveness to verapamil and sodium nitroprusside is not present in all patients with hypertension, or if present is not expressed to the same degree. Patients whose results fell outside the normal range did not, however, differ in any major feature from those whose results were normal: in particular, the 24 patients with abnormal responses did not differ in age, mean arterial pressure or heart rate from the 11 whose results fell within the normal range (48 ± 2 years, 132 ± 3 mmHg and 73 ± 2 beats/min compared with 49 ± 3 years, 128 ± 5 mmHg and 74 ± 4 beats/min respectively).

**Discussion**

Assessment of the response to dilator agents provides a convenient tool for the investigation of function in vascular smooth muscle, and this approach has been applied to a variety of vascular preparations from animals with experimental hypertension of different types. Overbeck [12] examined the effect of intra-arterial potassium in dogs with renal hypertension; he reported a reduction in the dilator response and suggested this might reflect impaired activity of the electrogenic sodium pump. Cohen & Berkowitz [9] worked with aortic strips from spontaneously hypertensive and renal hypertensive rats and observed impaired relaxation to several agents including isoprenaline and glyceryl trinitrate. Shibata & Cheng [10], who also worked with spontaneously hypertensive rats, reported that the response to isoprenaline and acetylcholine was reduced in the thoracic, but not in the abdominal, aorta; they were unable to confirm the impaired response to glyceryl trinitrate. Castro-Tavares [13], on the other hand, observed an increased response to isoprenaline and sodium nitroprusside in mesenteric vessels from dogs with renal hypertension. These varied and in some cases conflicting results are difficult to interpret: some of the discrepancies may reflect differences in methodology and others may reflect differences in the mechanisms that underly the raised arterial pressure.

There have been few reports on the response to dilator agents in human hypertension. Infusion of magnesium sulphate into the brachial artery caused an increase in blood flow in hypertensive subjects that was not significantly different from that in normal controls [14]. Infusion of potassium resulted in an impaired dilator response in four out of 20 patients with primary hypertension [15]. Inhibition of sympathetic tone by infusion of phenolamine into the brachial artery caused an increase in forearm blood flow in patients with hypertension that was not significantly different from that in the control group [16]. In a later study from the same laboratory, however, infusion of a maximally effective dose of the α-adrenoceptor antagonist, prazosin, led to a significantly greater increase in
forearm blood flow in patients with hypertension than occurred in normal subjects; the increase in blood flow in response to a maximally effective dose of sodium nitroprusside was similar in the two groups [17]. In a study of cerebral blood flow there was, on average, no response to hypercapnia in a group of 10 patients with hypertension, whereas the expected increase in flow could be clearly demonstrated in a matched group of normal volunteers [18]. With the exception of the increased response to prazosin and the remarkable inhibition of the response of the cerebral resistance vessels to raised partial pressure of carbon dioxide, the results of previous studies of dilator agents in man have thus been negative or inconclusive.

In the present study, arterial pressure was not recorded continuously and it has been assumed that it remained essentially constant throughout each drug infusion so that changes in forearm blood flow can be taken as an indication of changes in tone of the vascular smooth muscle. This assumption appears justified since the plethysmographic techniques used in this laboratory do not themselves affect directly recorded arterial pressure in either normal subjects or patients (B. F. Robinson, R. J. Dobbs, C. R. Kelsey & S. Saverymuttu, unpublished work) and the doses of dilator substances used were lower by at least one order of magnitude than the threshold for systemic circulatory effects. The assumption of essentially constant arterial pressure is strongly supported by the results of studies with phentolamine [16] and maximally effective doses of prazosin and sodium nitroprusside [17] in which intra-arterial pressure was recorded before and immediately after infusion of the drug: no changes in pressure were observed and changes in blood flow closely paralleled changes in calculated forearm resistance.

The response of the forearm resistance vessels to dilator agents can be assessed in several ways. Results may be expressed as the absolute change in forearm flow (assuming constant pressure) or the change in calculated vascular resistance; alternatively, percentage changes in one or other of these variables may be used. No method of presentation is entirely satisfactory, particularly in the comparison of groups with differing mean arterial pressures where initial values for forearm flow and calculated resistance cannot both be matched. In the present study, the absolute increase in forearm blood flow has been used as the index of response to dilator drugs because this measure appeared less affected than others by variations in the initial blood flow. Calculated forearm vascular resistance offers no advantage over measurements of flow in the assessment of changes in the vascular smooth muscle since the unknown contribution of structural changes to the resistance of hypertensive vessels [7] implies a different relationship between resistance and smooth muscle tone in normal subjects and hypertensive patients. The comparison of responses to two dilator drugs, which is central to the present study, should be little influenced by the method of analysis since differences in initial conditions should affect responses to both drugs similarly if the relative sensitivity to each remains unchanged.

The results of the present study indicate that the forearm resistance vessels of patients with primary hypertension respond abnormally to both verapamil and sodium nitroprusside: the dilator response to verapamil is, on average, greater than normal whereas that to sodium nitroprusside is less. The findings with nitroprusside are, at first sight, in conflict with the only other report on response to this drug [17]. The previous study differed, however, in that a maximally effective dose of nitroprusside was infused and the response in the hypertensive patients would, in fact, have appeared to be diminished if expressed as a percentage increase in flow rather than in absolute terms. The augmented response to verapamil in the patients with hypertension can be interpreted in two ways. Firstly, it might reflect a specific functional change in the vascular smooth muscle. Secondly, it might result from a non-specific enhancement of dilator responses resulting from structural modification of the vessels as suggested by Folkow [7]. There is insufficient evidence to distinguish with confidence between these possibilities and they are not mutually exclusive; it should be noted, however, that an augmented response has not been observed with any of the other dilator agents that have been studied in man apart from prazosin [17]. The relative impairment of the response that was observed at higher doses of verapamil in certain hypertensive subjects from the two groups could be accounted for by postulating the presence of an additional resistance in series that was relatively insensitive to verapamil. Such a resistance might develop in the smaller arteries, which are known to be relatively insensitive to nifedipine, a dilator with actions very similar to those of verapamil [19], and have also been shown to develop disproportionately severe medial hypertrophy in primary hypertension [8].

The reduced response to nitroprusside cannot be accounted for by the structural mechanism put forward by Folkow [7] and it is therefore...
probable that it reflects a functional abnormality of the resistance vessels. Examination of the relative responsiveness to verapamil and nitroprusside revealed a larger difference between the normotensive and the hypertensive subjects than had been seen when the response to each drug was considered separately, and this provides even stronger evidence of a functional abnormality in the vascular smooth muscle. Comparison of the response to verapamil and nitroprusside in individual subjects reduces or eliminates the effect of several sources of variance including the level of brachial blood flow before infusion of the dilator, the distribution of the drug within the forearm and any errors that may arise in the calibration of the plethysmographic system. Furthermore, any effect on the response of structural changes in the vessels will be automatically compensated since the response to both drugs should be affected in the same way. The major alteration in the relative responsiveness to the two drugs that was observed in the hypertensive subjects can therefore be interpreted in only one way: it must result from a functional abnormality of the vascular smooth muscle.

The difference between the groups could be related only to the difference in arterial pressure and it was not accounted for by differences in age or race. The lack of any relation between the 'excess verapamil response' and arterial pressure within the hypertensive group makes it unlikely that the functional abnormality is a consequence of the raised pressure and we think it more likely that it is related to its cause. It appears, however, that the functional abnormality is not demonstrable in all patients with hypertension. The results of the present study apply only to men, but it is to be expected that women with primary hypertension will show similar changes in the response of their forearm resistance vessels; they were excluded from this initial study, however, in view of the possibility that the resistance vessels may undergo functional changes in the course of the menstrual cycle analogous to those occurring in the hand veins [20].

Attempts to deduce the nature of the functional alteration that underlies the altered responsiveness to verapamil and sodium nitroprusside are limited by incomplete knowledge of their mechanism of action. Over the range of concentrations used, verapamil is a relatively specific inhibitor of intrinsic or phasic myogenic activity in vascular smooth muscle, whether spontaneous or agonist induced [21, 22]; it is believed to act by inhibiting the entry of calcium through potential-operated channels [23]. Nitroprusside, on the other hand, is particularly effective in relaxing sustained contractions such as those induced by noradrenaline in the veins [21, 22]; it should be noted, however, that the estimated blood concentration at the highest intra-arterial dose is about ten times that required to achieve complete relaxation of venous smooth muscle and it is therefore possible that the effect in the resistance vessels is mediated in a different way from that in the veins. Less is known about the mechanism of action of sodium nitroprusside than is known about verapamil. Possible mechanisms include inhibition of the entry of calcium through receptor-operated channels, inhibition of the release of calcium from stores within the cell and hyperpolarization of the cell membrane as a result of the inhibition of chloride efflux [24].

The change in relative responsiveness to nitroprusside and verapamil in patients with hypertension could be interpreted in several ways. It might be assumed by analogy with their action in the veins that nitroprusside and verapamil induce relaxation of resistance vessels by the inhibition of differing activation systems. The altered responsiveness in the hypertensive subjects might then reflect a greater contribution to resistance vessel tone by the verapamil-sensitive, intrinsic myogenic mechanism relative to that of an independent, nitroprusside-sensitive mechanism. This view would be in accord with reports of increased spontaneous phasic activity in both arterial and portal venous preparations from hypertensive rats [25, 26]. An independent nitroprusside-sensitive mechanism might be expected to be agonist controlled, and the experiments with phentolamine were undertaken to investigate the possibility that the effect of nitroprusside in the resistance vessels reflected the inhibition of a noradrenaline-dependent component of the contraction. The dose of phentolamine used is believed to cause a high degree of blockade of sympathetic activity [16], but the results gave no indication of a relation between sympathetic stimulation and the response to nitroprusside. Despite this negative result, it remains probable that nitroprusside acts, at least in part, by inhibiting an activation mechanism that is independent of the verapamil-sensitive mechanism.

Whatever the functional significance of the altered response to verapamil and nitroprusside, it is likely that it reflects some disturbance of ion transport in the vascular smooth muscle. Studies of vascular smooth muscle from animals with hypertension of different types have revealed a number of abnormalities in the handling of sodium and other inorganic ions [27]. It is, as yet, uncertain if similar abnormalities affect the
vascular smooth muscle in primary hypertension in man. Studies of leucocytes from patients with hypertension, however, have revealed a reduction of sodium pump activity which is thought to result from a circulating inhibitor [3], and erythrocytes exhibit additional disturbances of sodium transport that may be genetically determined [1, 2].

We believe that the present investigation provides strong evidence that there is a functional abnormality of the vascular smooth muscle in a majority of patients with primary hypertension. We suggest that the abnormality reflects an underlying disorder of ion handling in the myocytes which is probably related to the defects that have been demonstrated by others in erythrocytes and leucocytes. We also think it likely that the abnormality of function contributes to the development of hypertension in some patients, but the way in which it might do so is as yet unclear. It is a reasonable assumption, however, that the underlying defect that gives rise to the change in responsiveness to verapamil and nitroprusside will also give rise to other changes in the functional properties of the resistance vessels and two abnormalities that might be relevant can be considered. The increased response to noradrenaline observed in certain resistance vessels [4, 5, 6] could be, at least in part, another reflection of the same underlying defect and a functional alteration of this sort would clearly favour the development of increased peripheral resistance. Another possibility that lacks experimental evidence in man but is suggested by the relative augmentation of the response to verapamil is an increase in myogenic activity with enhanced contraction in response to stretch; a functional alteration of this type might be expected to raise peripheral resistance directly and might also facilitate the process of 'whole body autoregulation' in response to increased cardiac output that has been proposed as a major mechanism in the genesis of hypertension.

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References


