SUMMARY Structural changes in resistance vessels have been considered an important factor in triggering and maintaining chronic hypertension in humans and in experimental animals. To determine whether the increased forearm vascular resistance observed following vasodilator maneuvers in hypertensive patients is predominantly due to structural or to functional changes, we examined the influence of different vasodilator stimuli on forearm blood flow and blood pressure in 22 male patients with established essential hypertension and in 22 age-matched normotensive men (age range, 28–52 years). Blood pressure was measured directly, and blood flow was measured by venous occlusion plethysmography. The maneuvers applied were 1) arterial occlusion combined with handgrip exercise and local heating, 2) intra-arterial infusion of the calcium entry blocker nifedipine, 3) intra-arterial infusion of the nonspecific vasodilator sodium nitroprusside, 4) arterial occlusion initiated after intra-arterial infusion of nifedipine. Vascular resistance during vasodilation induced by arterial occlusion or infusion of nifedipine or sodium nitroprusside remained significantly higher in the hypertensive than in the normotensive subjects. However, the maximal vasodilation achieved by the combination of arterial occlusion and nifedipine resulted in a similar resistance in both groups (1.6 ± 0.2 in the hypertensive vs 1.4 ± 0.2 mm Hg/ml/min/100 ml tissue in the normotensive subjects). These data suggest that there is an important functional component of the elevated resistance in patients with essential hypertension. (Hypertension 11: 320–325, 1988)

KEY WORDS • hypertension • forearm vascular resistance • arterial occlusion • sodium nitroprusside • nifedipine
vanderwaal was lower than that after arterial occlusion in hypertensive patients and was no longer significantly different from that in normotensive subjects. The results were attributed to a calcium influx-mediated functional vasoconstriction in hypertension.\textsuperscript{11, 12, 13}

The crucial question appears to be whether the vasoconstriction following arterial occlusion is maximal or whether it could be enforced by additional maneuvers such as local administration of a calcium entry blocker. We therefore combined the infusion of a calcium entry blocker with arterial occlusion and compared ensuing vasodilation with that produced by either procedure alone and that following administration of the non-specific vasodilator sodium nitroprusside. Our results show that the combination of local infusion of a calcium entry blocker with arterial occlusion leads to a pronounced vasodilation that is similar in hypertensive and normotensive subjects, thus pointing to an important functional abnormality of vascular smooth muscle in arterial hypertension.

Patients and Methods
Twenty-two male patients with uncomplicated essential hypertension and 22 carefully matched healthy male volunteers were studied after their informed consent had been obtained (Table 1). The study protocol was approved by the Ethical Committee of the Klinikum Steglitz. The patients either had not received any medication or had medication discontinued at least 4 weeks before the study. Eight of the patients had a family history of essential hypertension. Only those patients were included in whom sitting diastolic BP (Korotkoff phase V) was 110 mm Hg or above on four different occasions. Severe hypertension and secondary forms of hypertension were excluded by the usual routine evaluation in all patients. None of the patients had cardiac failure or any other major illnesses. None of the normotensive volunteers was taking any medication or had a family history of hypertension. Their sitting diastolic BP was below 90 mm Hg.

Measurement of Forearm Blood Flow
Blood flow was measured by venous occlusion plethysmography\textsuperscript{16, 17} in both forearms. Mercury-in-Silastic strain gauges were placed on both forearms approximately 5 cm below the antecubital crease. The forearms rested on a rigid support slightly above heart level. The gauges were coupled to an electronically calibrated plethysmograph (Periquant 3500, Gutmann LPM, Eurasburg, FRG). Venous occlusion was achieved by a collecting cuff pressure of 40 mm Hg during determination of forearm blood flow. Circulation to the hand was arrested by inflating a pediatric cuff around the wrist 50 mm Hg above systolic BP for 1 minute before and during blood flow measurement. Flows after drug infusion were recorded by five consecutive 6-second measurements. The average of the five flows recorded in the experimental arm was used for statistical evaluation. Blood flow was also measured in the control arm to exclude spontaneous changes in forearm circulation and to detect systemic drug effects. Heart rate was measured by electrocardiogram, and vascular resistance was calculated as mean BP/flow.

Measurement of Reactive Hyperemia
To produce maximal reactive vasodilation, blood flow to the forearm was occluded by inflating the upper arm cuff to a minimum of 220 mm Hg, or 50 mm Hg above systolic pressure, for 10 minutes. Blood flow was measured 1 second after the release of arterial occlusion and every 9 seconds thereafter. Peak flow after the release of arterial occlusion and simultaneous mean BP in the experimental arm were used to calculate resistance. To achieve minimal vascular resistance, arterial occlusion was combined with handgrip exercise and local heating.\textsuperscript{18} The subjects underwent intermittent handgrip exercise of the experimental arm at a rate of 40 to 60/min until exhaustion up to the 8th minute of arterial occlusion. Local heating was accomplished by placing the experimental forearm in a twinnelled Lucite tube, the outer compartment of which was perfused with water of a constant temperature of 70°C. These measures increased skin temperature to 40 to 42°C.

Study Protocol
On the day of the study, all subjects had only a light breakfast 2 hours before the investigation and refrained from using caffeine, alcohol, and smoking. Investigations started at 0900 to 1000 and lasted 3 to 3.5 hours. First, the forearm circumference was measured 5 cm below the antecubital wrist and forearm volume was measured by water displacement, subtracting the hand volume. The subjects were resting in the supine position, and laboratory temperature was kept constant at 22°C. A 22-gauge Teflon catheter (radial artery catheterization set, Arrow, Reading, PA, USA) was inserted with the subjects under local lignocaine hydrochloride (Lidocain 1%; Braun) anesthesia into the brachial artery of the nondominant (mostly left) arm for BP measurement with a Statham P23ID pressure transducer (Gould, Oxnard, CA, USA) as well as for local infusions. Intra-arterial BP was measured before and 1 minute after each experiment. Isotonic saline and drugs were infused by a constant rate pump (Perfusor secura, Braun, Melsungen, FRG). After a 30 minute rest, basal values of forearm blood flow, BP, and heart

| Table 1. Characteristics of the Male Study Subjects |
|-------------------|----------------|----------------|
| Variable           | HT (n = 22)   | NT (n = 22)   |
| Age (yr)           | 42 (28–50)    | 41 (30–52)    |
| Height (cm)        | 178 (170–186) | 179 (167–187) |
| Weight (kg)        | 83 (72–98)    | 82 (68–94)    |
| Forearm volume (ml)| 1180 (1000–1500) | 1150 (1000–1300) |
| Forearm circumference (cm) | 28 (26–33) | 28 (26–30) |

Range is shown in parentheses. HT = hypertensive; NT = normotensive.
rate were measured during saline infusion. Thereafter, the following experiments were performed in random order:

1. Nifedipine (Bayer), dissolved in light-protected solution containing 20% methyl alcohol and 20% polyethylene glycol 400, was infused in stepwise increasing doses of 10 to 40 
   \( \mu g/min/100 \) ml tissue, for 1 minute each.

2. Sodium nitroprusside (Nipride; Hoffmann-La Roche), dissolved in light-protected 5% glucose, was given in stepwise increasing doses of 0.3 to 1.2 \( \mu g/min/100 \) ml tissue, for 2 minutes each.

The doses of nifedipine or sodium nitroprusside were doubled until a maximal regional effect was attained without systemic effects being detected by heart rate and blood flow monitoring in the control arm. The drug doses had been determined in pilot experiments and corresponded to those used by others. A saline infusion period of approximately 15 minutes was intercalated between the drug infusions until basal flow rates were regained.

3. Arterial occlusion for 10 minutes was combined with handgrip exercise and local heating.

4. Arterial occlusion was combined with handgrip exercise and local heating immediately following the last nifedipine infusion.

Statistics
In all pairwise comparisons, statistical significance was assessed by the exact Wilcoxon signed rank test. The resultant nominal \( p \) values were analyzed by the multiple test procedure according to Bonferroni and Holm, whereby a \( p \) value of 0.05 or less was considered significant.

Results
Age, height, weight, forearm volume, and forearm circumference did not differ significantly between patients and matched healthy volunteers (Table 1).

Forearm Blood Flow
During all vasodilator maneuvers, forearm blood flow increased compared with the basal value in both groups (\( p < 0.001 \); Figure 1, Table 2). Arterial occlusion had a stronger vasodilator effect both in the hypertensive (\( p < 0.001 \)) and in the normotensive subjects (\( p < 0.003 \)) than did the drugs infused. The highest forearm blood flow (\( p < 0.001 \)) was achieved by the combination of nifedipine and reactive hyperemia.

One hypertensive patient reacted paradoxically with decreased blood flow and increased resistance after the combination of nifedipine and arterial occlusion; this reaction was probably due to an artifact (Figure 2). This patient and the matched normotensive control subject were therefore excluded from the statistical evaluation (see Table 2).

The blood flow following arterial occlusion was significantly higher in the hypertensive than in the normotensive subjects. However, the basal forearm blood flow, the blood flow during sodium nitroprusside and nifedipine infusion, and the maximum flow achieved by the combination of nifedipine plus arterial occlusion were comparable in both groups.

The solvent of nifedipine, when infused at an appropriate concentration, did not significantly alter either the blood flow or the mean BP in eight patients and eight healthy volunteers.

Forearm Mean BP
The mean BP in the experimental arm dropped during all experiments (\( p < 0.001 \)) in both groups compared with the initial value (see Table 2). The effect of arterial occlusion was stronger than that of sodium nitroprusside in the normotensive (\( p < 0.05 \)) and in the hypertensive subjects (\( p < 0.003 \)), but it was not stronger than that of nifedipine. The lowest (\( p < 0.001 \)) mean BP in our study was achieved by the combination of nifedipine and arterial occlusion. The mean BP decrease was greater in the hypertensive than in the normotensive subjects after administration of nifedipine (10 vs 7%; \( p < 0.02 \)) as well as after nifedipine plus arterial occlusion (17 vs 12%; \( p < 0.004 \)).

Forearm Vascular Resistance
The vascular resistance was reduced by all maneuvers applied (\( p < 0.001 \)) in both groups (see Figure 2 and Table 2). Arterial occlusion reduced the resistance in both groups more strongly than did sodium nitroprusside (\( p < 0.001 \)) or nifedipine in the normotensive (\( p < 0.006 \)) and in the hypertensive subjects (\( p < 0.001 \)). The lowest resistance (\( p < 0.001 \)) in our study, however, was achieved by the combination of nifedipine and arterial occlusion. Whereas forearm vascular resistance following sodium nitroprusside, nifedipine, or arterial occlusion remained significantly higher in the hypertensive than in the normotensive subjects, there was no longer any significant difference between groups after the combination of nifedipine plus arterial occlusion.
Hypertensive and Normotensive Subjects
Resistance Before and After Maximal Effects of Sodium Nitroprusside

Such structural changes (i.e., medial hypertrophy) have been demonstrated in arteries of hypertensive subjects. Obviously, however, arterial occlusion combined with handgrip exercise and local heating does not produce maximal vasodilation, since we were able to achieve a significant further increase in forearm blood flow by an additional intraarterial infusion of the calcium entry blocker nifedipine in doses that led to a maximal regional effect without lowering systemic BP. We attained maximal average flow values of 68.4 ml/min/100 ml tissue and a minimal vascular resistance of 1.6 mm Hg/ml/min/100 ml tissue in the hypertensive patients as compared with the maximal flow values of 28.5 to 60.0 ml/min/100 ml tissue and minimal resistance values of 2.2 to 4.2 mm Hg/ml/min/100 ml tissue reported in the literature. Under these conditions of a probable maximal flow and a minimal vascular resistance, there was no longer a significant difference between hypertensive and normotensive subjects, suggesting that the elevated resistance found following ischemia without infusion of the calcium entry blocker was predominantly due to functional rather than to structural changes. In contrast to some previous studies, however, patients with severe hypertension were not included in our study.

Under basal conditions, forearm blood flow and vascular resistance were comparable in both groups. Since resting blood flow values showed a wide variation (see Table 2), it is not surprising that the reports in the literature are conflicting. Forearm and skin blood flow rates in patients with established hypertension have been described to be increased, or comparable to those of normotensive subjects, and vascular resistance also has been reported to be increased, or normal. This wide variety of data is probably due to factors such as environmental conditions and emotional influences that are difficult to keep constant.

Forearm blood flow has been reported to be higher in patients with established hypertension than in normotensive subjects during infusion of the calcium entry blockers verapamil and nicardipine and to show a greater increase under verapamil infusion. These findings were interpreted as reflecting a functional disturbance with enhanced calcium influx-mediated vasoconstriction in the established phase of essential hypertension, as calcium entry blockers are believed to act by inhibiting the entry of calcium through poten-

### Table 2. Mean Forearm Blood Flow, Mean BP, and Vascular Resistance Before and After Maximal Effects of Sodium Nitroprusside, Nifedipine, Arterial Occlusion, and Combined Treatment in Hypertensive and Normotensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>HT (n = 21)</th>
<th>NT (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBF (ml/min/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>3.6 (1.5-5.9)</td>
<td>2.9 (2.0-4.8)</td>
</tr>
<tr>
<td>SNP</td>
<td>33.3 (15.0-57.0)</td>
<td>28.7 (17.0-40.0)</td>
</tr>
<tr>
<td>NIF</td>
<td>41.2 (24.0-60.0)</td>
<td>36.0 (18.0-50.0)</td>
</tr>
<tr>
<td>AO</td>
<td>54.9 (33.0-84.0)</td>
<td>44.5 (25.0-84.0)</td>
</tr>
<tr>
<td>NIF/AO</td>
<td>68.4 (51.0-90.0)</td>
<td>57.5 (29.0-96.0)</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>124 (92-142)</td>
<td>80 (65-88)</td>
</tr>
<tr>
<td>SNP</td>
<td>116 (85-133)</td>
<td>76 (62-88)</td>
</tr>
<tr>
<td>NIF</td>
<td>111 (84-132)</td>
<td>75 (60-88)</td>
</tr>
<tr>
<td>AO</td>
<td>110 (80-133)</td>
<td>73 (60-86)</td>
</tr>
<tr>
<td>NIF/AO</td>
<td>103 (72-124)</td>
<td>70 (56-84)</td>
</tr>
<tr>
<td>FVR (mm Hg/ml/min/100 ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>37.9 (19.0-61.3)</td>
<td>29.3 (14.6-40.0)</td>
</tr>
<tr>
<td>SNP</td>
<td>3.9 (2.1-7.2)</td>
<td>2.8 (1.7-4.9)</td>
</tr>
<tr>
<td>NIF</td>
<td>2.8 (1.6-5.0)</td>
<td>2.2 (1.6-4.6)</td>
</tr>
<tr>
<td>AO</td>
<td>2.1 (1.4-3.9)</td>
<td>1.8 (0.9-2.6)</td>
</tr>
<tr>
<td>NIF/AO</td>
<td>1.6 (1.0-2.4)</td>
<td>1.4 (0.8-2.6)</td>
</tr>
</tbody>
</table>

Range is shown in parentheses. HT = hypertensive; NT = normotensive; FBF = forearm blood flow; SNP = sodium nitroprusside; NIF = nifedipine; AO = arterial occlusion; NIF/AO = NIF and AO combined; FVR = forearm vascular resistance. *p<0.03, †p<0.001, ‡p<0.02, §p<0.05, compared with values for hypertensive men.

### Discussion

Arterial occlusion represents a highly effective metabolic stimulus that leads to marked vasodilation. When arterial occlusion is combined with handgrip exercise and local heating, an additional vasodilation that has been considered maximal, however, patients with severe hypertension were not included in our study.

In agreement with others, we observed a higher forearm vascular resistance in the hypertensive patients than in the normotensive subjects following arterial occlusion. The elevated resistance observed under these conditions in the patients with arterial hypertension has been attributed to structural changes. Such structural changes (i.e., medial hypertrophy) have been demonstrated in arteries of hypertensive subjects. Obviously, however, arterial occlusion combined with handgrip exercise and local heating does not produce maximal vasodilation, since we were able to achieve a significant further increase in forearm blood flow by an additional intraarterial infusion of the calcium entry blocker nifedipine in doses that led to a maximal regional effect without lowering systemic BP. We attained maximal average flow values of 68.4 ml/min/100 ml tissue and a minimal vascular resistance of 1.6 mm Hg/ml/min/100 ml tissue in the hypertensive patients as compared with the maximal flow values of 28.5 to 60.0 ml/min/100 ml tissue and minimal resistance values of 2.2 to 4.2 mm Hg/ml/min/100 ml tissue reported in the literature. Under these conditions of a probable maximal flow and a minimal vascular resistance, there was no longer a significant difference between hypertensive and normotensive subjects, suggesting that the elevated resistance found following ischemia without infusion of the calcium entry blocker was predominantly due to functional rather than to structural changes. In contrast to some previous studies, however, patients with severe hypertension were not included in our study.

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Forearm blood flow has been reported to be higher in patients with established hypertension than in normotensive subjects during infusion of the calcium entry blockers verapamil and nicardipine and to show a greater increase under verapamil infusion. These findings were interpreted as reflecting a functional disturbance with enhanced calcium influx-mediated vasoconstriction in the established phase of essential hypertension, as calcium entry blockers are believed to act by inhibiting the entry of calcium through poten-

![Figure 2. Forearm vascular resistance (R) during maximal effects of sodium nitroprusside (NIP), nifedipine (NIF), arterial occlusion (AO), and combined treatment NIF/AO in hypertensive (HT; n = 22) and normotensive (NT; n = 22) subjects.](image-url)
tial-operated channels. By contrast, we found comparable flow rates in both groups and an increased resistance in the hypertensive patients during administration of nifedipine.

In the study of Hulthén et al., verapamil and nifedipine had a greater vasodilator effect than did arterial occlusion, while in our study the effect of ischemia proved to be stronger. The more intensive action of the arterial occlusion as compared with nifedipine infusion that was observed in our study was probably due to an additional vasodilator effect of local heating and hand-grip exercise. Whereas both blood flow and vascular resistance during reactive hyperemia alone remained increased in the hypertensive patients, they were comparable in both groups following arterial occlusion combined with nifedipine.

In our study, the BP in the experimental arm showed a more pronounced decrease in the patients with essential hypertension both after administration of nifedipine alone and during combination with reactive hyperemia. This finding is in accordance with those of Hulthén et al., who also found a greater reduction of the intra-arterially measured BP in hypertensive than in normotensive subjects during regional calcium entry blockade. By contrast, Follokow et al., observed only a small, insignificant decrease of mean BP in the experimental arm following arterial occlusion, which was comparable in both groups. However, intra-arterial BP was measured only in a few subjects.

Although there is no doubt that medial hypertrophy of resistance arteries may occur early in the development but not in the beginning, of experimental and clinical hypertension the question arises to what extent this is relevant for chronic BP elevation. Against a predominant role of structural changes in the maintenance of elevated BP appears to speak the common clinical observation that there is usually an immediate normalization of BP following removal of a pheochromocytoma despite a preceding long-lasting elevation. Moreover, experimentally, a rapid normalization of BP has also been found after removal of the clip in one-kidney, one clip rats with hypertension was measured only in a few subjects.

In conclusion, our data show that the forearm vascular resistance of patients with essential hypertension can be reduced by appropriate vasodilator maneuvers to a similar extent as in age-matched normotensive subjects. This finding suggests that the elevated resistance found in the hypertensive patients during nonmaximal vasodilation is predominantly due to functional rather than to structural vessel changes. Whether this functional component of the elevated resistance consists in a hyperreactivity of the vascular smooth muscle, an increased sympathetic tone when related to the pressor responsiveness to norepinephrine, an increased intracellular sodium or calcium concentration, or a combination of these factors remains to be determined. However, since the addition of a calcium entry blocker increased the vasodilation induced by arterial occlusion, a calcium influx-mediated component appears to be of particular importance.

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