Enhanced Alpha-Adrenoreceptor-Mediated Vasoconstriction in Essential Hypertension

FRANE W. AMANN, M.D., PETER BOLLI, M.D., WOLFGANG KIOWSKI, M.D., AND FRITZ R. BÜHLER, M.D.

SUMMARY Forearm blood flow (FAF) has been determined using venous occlusion plethysmography in 24 patients with essential hypertension (EHT) and in 16 age-matched normotensive subjects (NT) under basal resting conditions, following nonspecific vasodilatation with sodium nitroprusside and after intraarterial infusion of the postjunctional alpha-blocking drug, prazosin. Under basal conditions, FAF was significantly higher in EHT than in NT. Infusion of sodium nitroprusside produced a similar absolute increase in FAF in both groups, whereas postjunctional alpha-blockade with prazosin led to a significantly greater increase in FAF in EHT than in NT. A positive correlation was found between plasma epinephrine concentration and prazosin-induced FAF in EHT but not in NT. These results suggest an enhanced postjunctional alpha-adrenoreceptor-mediated vasoconstrictor component in established EHT. (Hypertension 3 (supp I): 1-119-1-123, 1981)

KEY WORDS • vasoconstriction • blood flow • prazosin • sodium nitroprusside • alpha-adrenoreceptors • peripheral resistance

ESTABLISHED essential hypertension (EHT) is characterized by an elevated total peripheral resistance, which has been mainly attributed to adaptive structural vascular changes while a possible contribution of neurogenic factors is still debated. Since sympathetic nervous system activity has been found to be increased in a fraction of patients with EHT, the question arises as to what extent increased adrenergic activity may participate in the elevated peripheral resistance through enhanced alpha-adrenoreceptor-mediated vasoconstriction. We therefore compared the effect of prazosin-induced postjunctional alpha-blockade on forearm blood flow (FAF) in patients with essential hypertension (EHT) and in normotensive (NT) subjects.

Methods and Subjects

Subjects

The study population consisted of 24 outpatients (14 men, 10 women) aged 31 to 70 (mean, 48) years with uncomplicated EHT, and of 16 NT (9 men, 7 women) aged 30 to 65 (mean, 48) years. Antihypertensive treatment was withdrawn at least 6 weeks prior to the study. Only those patients in whom sitting diastolic pressure (Korotkoff phase V) was repeatedly greater than 100 mm Hg were included. All normotensive subjects were selected on a basis of not being familiar with laboratory procedures and not taking any medication; their sitting diastolic blood pressure (BP) was less than 90 mm Hg. Informed consent was obtained from all participants.

Forearm Blood Flow Measurement

Forearm blood flow (FAF) was measured by venous occlusion plethysmography. A mercury within a Silastic strain gauge was placed at the proximal third of the left forearm, which rested on a supporting device slightly above the level of the heart. The strain gauge was coupled to an electronically calibrated plethysmograph (Hokanson EC3). Venous occlusion was achieved by means of a BP cuff inflated to 40 mm Hg by a rapid cuff inflator (Hokanson EC 10) and applied just proximal to the elbow. The hand was excluded from the circulation by placing a pediatric BP cuff around the wrist and inflating it to 50 mm Hg above systolic BP for 1 minute prior to and during the measurement of FAF. Determinations of FAF were made by analyzing five consecutive flow curve recordings, each lasting for 15 to 20 seconds, the mean value being taken for statistical evaluation.
Study Protocol

Investigations started at 8 am and lasted for 3½ hours. Subjects lay down in a quiet air-conditioned room with a constant temperature of 20° to 22° C. First, the forearm volume was measured by water displacement according to the Archimedes principle. Then, with the patient under local anesthesia, a canula was placed in a right brachial vein for blood sampling and another into the left brachial artery for monitoring of BP using a Statham P 23 Db pressure transducer, as well as for regional infusion of nitroprusside and prazosin. Following completion of the instrumentation, the patients were allowed to rest for 30 minutes. Thereafter, basal values for FAF, BP, and heart rate (derived from the pulse curve) were measured. Venous blood was withdrawn from 20 EHT and 16 NT for measurement of plasma epinephrine and norepinephrine concentrations using the radio enzymatic assay method as adapted in our laboratory.

Sodium nitroprusside, 0.6 μg/min/100 ml of forearm tissue, was infused into the left brachial artery with a constant rate infusion pump (Sage) for 3 minutes to assess nonspecific vasodilatation. The FAF was measured at the second and third minute of the infusion. After FAF had returned to basal values, prazosin, a selective postjunctional alpha-blocking agent, was infused at the constant rate of 0.5 μg/min/100 ml of forearm tissue for 10 minutes. The FAF was measured from the ninth to the tenth minute. In pilot studies, these doses of sodium nitroprusside and prazosin infused over 3 and 10 minutes were found to produce a maximal regional effect on FAF without causing systemic effects. These were checked in every individual in the dose finding studies as well as in all the later studies by monitoring BP and heart rate immediately after each infusion.

To investigate the nonspecific vasodilator effect of a dose of sodium nitroprusside producing similar increases in FAF as observed with prazosin, four EHT aged 39 to 59 (mean, 53) years and four NT aged 31 to 65 (mean, 51) years were studied once more using the same protocol as described above but with the exception that they were given an additional 3 minutes of sodium nitroprusside infusion, 0.06 μg/min/100 ml of forearm tissue, prior to infusions containing maximal doses of sodium nitroprusside and prazosin.

All measurements were recorded on a Hewlett Packard polygraph. Forearm peripheral vascular resistance was calculated as the ratio of mean BP and FAF and expressed as resistance units. Data were analyzed on an Apple II desk computer; statistical significance was assessed by the Students' t test for paired and unpaired data as well as by linear regression analysis. Data are shown as the mean ± standard error of the mean (SEM).

Results

As shown in table 1, under basal conditions FAF was significantly higher in EHT than in NT (p < 0.001). In the presence of the significantly higher BP in EHT, the calculated forearm resistance was similar in the two groups. Heart rate was higher in EHT than in NT (p < 0.005).

Infusion of sodium nitroprusside (0.6 μg/min/100 ml of forearm tissue) increased FAF about fourfold in EHT and fivefold in NT, hence resulting in almost the same absolute increase in FAF without causing systemic effects. These were checked in every individual in the dose finding studies as well as in all the later studies by monitoring BP and heart rate immediately after each infusion.

**TABLE 1. Blood Pressure, Heart Rate, Forearm Flow, and Forearm Resistance Under Basal Conditions and Following Sodium-Nitroprusside and Prazosin Infusions**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intraarterial Blood Pressure (mm Hg)</th>
<th>Heart Rate (bpm)</th>
<th>Forearm Flow (ml/min/100 ml)</th>
<th>Forearm Resistance (mm Hg/ml/min/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Basal:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHT</td>
<td>164 ± 4</td>
<td>97 ± 2</td>
<td>120 ± 2</td>
<td>73 ± 2</td>
</tr>
<tr>
<td>NT</td>
<td>115 ± 4</td>
<td>63 ± 2</td>
<td>80 ± 2</td>
<td>63 ± 2;†</td>
</tr>
<tr>
<td>Sodium-nitroprusside i.a. (0.6 μg/min/100 ml):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHT</td>
<td>159 ± 3</td>
<td>97 ± 2</td>
<td>118 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>NT</td>
<td>111 ± 3</td>
<td>64 ± 2</td>
<td>80 ± 2</td>
<td>63 ± 2</td>
</tr>
<tr>
<td>Prazosin i.a. (0.5 μg/min/100 ml):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EHT</td>
<td>163 ± 4</td>
<td>97 ± 2</td>
<td>119 ± 2</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>NT</td>
<td>115 ± 4</td>
<td>64 ± 2</td>
<td>81 ± 3</td>
<td>63 ± 2</td>
</tr>
</tbody>
</table>

EHT = 24 patients with essential hypertension; NT = 16 normotensive subjects. Measurements expressed as mean ± SEM.

* p < 0.05.
† p < 0.005.
‡ p < 0.001.
with the lowest and the four NT with the highest values. The degree of increase in FAF with prazosin was unrelated to age and BP level in EHT as well as in NT. Comparison of the sodium nitroprusside- and prazosin-induced increases in FAF showed that the increase in flow with prazosin amounted to 56% in EHT and to 20% in NT ($p < 0.001$, fig. 3). Since there was no attendant change in mean blood pressure (MAP) and heart rate, the increase in FAF can be attributed to a decrease in forearm resistance.

In the subgroup of four EHT and four NT who were reinvestigated, FAF (ml/min/100 ml of forearm tissue) under basal conditions was again significantly ($p < 0.02$) greater in EHT (4.7 ± 0.7) than in NT (2.3 ± 0.2). Infusion of prazosin, 0.5 µg/min/100 ml of forearm tissue, increased FAF to 11.0 ± 3.2 in EHT and to 4.3 ± 1.0 in NT, the difference in flow increase between EHT and NT being statistically significant ($p < 0.05$; fig. 4). Infusion of sodium nitroprusside in a smaller dose of 0.06 µg/min/100 ml of tissue increased FAF to 8.2 ± 1.1 in EHT and to 6.0 ± 1.7 in NT, resulting in almost the same absolute in-
A forearm blood flow ml/min/100 ml

NT n=4 EHT n=4 mean ± SEM

* p < 0.05

FIGURE 4. Change in forearm blood flow in four patients with essential hypertension (EHT) and four normotensive subjects (NT) during sodium nitroprusside infusion 0.06 μg/min/100 ml and 0.6 μg/min/100 ml of forearm tissue (open bars). The smaller dose produced flow changes similar to those observed with prazosin (hatched bars). While effects of sodium nitroprusside did not differ, the effect of prazosin was significantly greater in EHT.

TABLE 2. Plasma Epinephrine and Plasma Norepinephrine Concentrations Under Basal Conditions

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Plasma epinephrine (pg/ml)</th>
<th>Plasma norepinephrine (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHT (n = 20)</td>
<td>30 ± 5</td>
<td>296 ± 24</td>
</tr>
<tr>
<td>NT (n = 16)</td>
<td>19 ± 3</td>
<td>322 ± 28</td>
</tr>
<tr>
<td>p</td>
<td>0.06</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Plasma norepinephrine concentrations taken under basal conditions were similar in EHT and NT (table 2). Plasma epinephrine concentrations were higher in about half the patients with EHT compared with NT, but the difference between the two groups did not reach statistical significance (p = 0.06). In EHT, a significant positive correlation was found between basal plasma epinephrine concentration and prazosin-induced FAF (p < 0.001, fig. 5). No such correlation could be established in NT.

Discussion

Postjunctional alpha-blockade with prazosin resulted in a significantly greater increase in FAF in patients with EHT compared with age-matched NT subjects. In contrast, nonspecific vasodilatation with sodium nitroprusside given at the maximal dose of 0.6 μg/min/100 ml of forearm tissue resulted in a similar increase of FAF in EHT and NT. Since a smaller dose of sodium nitroprusside that produced increases in FAF comparable to those observed with prazosin resulted in almost the same absolute increase in FAF in EHT as well as in NT, these results suggest that the difference in the prazosin-induced increase in FAF is specific for blockade of alpha-adrenoreceptors. This may reflect an enhanced alpha-adrenoreceptor-mediated vasoconstriction in EHT, which together with the observed relationship to plasma epinephrine concentrations suggests a neurogenic contribution to peripheral vascular resistance in these patients. A pos-
The participation of an enhanced alpha-adrenoceptor-mediated vasoconstrictor component in the elevation of peripheral resistance in patients with EHT may thus help to explain the effectiveness of antihypertensive drugs that interfere with the sympathetic control of peripheral vascular resistance in the treatment of EHT.

Acknowledgments

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References

10. Da Prada M, ZOrcher G: Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. Life Sci 19: 1161, 1976
Enhanced alpha-adrenoreceptor-mediated vasoconstriction in essential hypertension.
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