Elevation of brachial arterial blood velocity and volumic flow mediated by peripheral \(\beta\)-adrenoreceptors in patients with borderline hypertension


ABSTRACT Simultaneous determinations of cardiac output and brachial arterial blood flow were performed in patients with hypertension and high cardiac output in comparison with normal subjects of the same age. Brachial arterial blood flow was measured with a previously described pulsed Doppler apparatus that permitted the noninvasive determination of arterial diameter and blood flow velocity. In patients with borderline hypertension, brachial blood flow was significantly increased (136 ± 11 vs 72 ± 8 ml/min; \(p < .001\)). After short-term administration of indomethacin, cardiac output decreased while brachial blood flow remained constant. After short-term administration of a selective \(\beta_1\)-receptor antagonist (primidol) and nonselective blocker (propranolol), cardiac output decreased significantly in both cases but the decrease in brachial blood flow was significant only after the administration of the nonselective \(\beta\)-blocking agent. The study strongly suggested that in patients with borderline hypertension, the increased cardiac output is related to a prostaglandin and \(\beta_1\)-adrenergic mechanisms whereas the increased brachial blood flow depends mainly on \(\beta_2\)-adrenergic mechanisms.


HIGH CARDIAC OUTPUT is a well-established finding in patients with borderline hypertension.\(^1\),\(^2\) However, the distribution of cardiac output in the systemic circulation has been poorly investigated.\(^4\),\(^7\) Several reports\(^5\),\(^6\) indicated an increase in limb blood flow, while hepatic and renal blood flows remained within the normal range.\(^5\)

In this study, forearm blood flow was investigated in borderline hypertensive patients by means of a new noninvasive pulsed Doppler system. With this apparatus it was possible to determine quantitatively both the velocity of red cells and the arterial diameter, thus permitting an adequate evaluation of peripheral blood flow.\(^8\),\(^9\) In addition, the respective roles of cardiac and peripheral factors on the control of the brachial arterial blood flow were analyzed in patients with borderline hypertension by two methods: (1) simultaneous determinations of cardiac output and brachial blood flow and (2) short-term inhibition of the prostaglandin and the adrenergic systems, which have been shown to be implicated in the pathophysiology of blood pressure regulation.\(^10\),\(^12\)

**Materials and methods**

Patients. Fifty-three male subjects were included in the study: 24 normotensive subjects and 29 patients with borderline hypertension. The ages of the two populations were similar and the two groups did not show any significant differences in weight and body surface area (table 1). All patients were untreated or had discontinued their therapy at least 4 weeks before the study. They were admitted to the hospital for 6 days and placed on a diet including 100 mmol sodium/day. The subjects were considered normal when the reason for their admission was not cardiovascular disease and when results of clinical and extensive laboratory investigations were strictly normal. Patients were considered to have borderline hypertension when, in the previous 12 months, at least two of the five casual pressure recordings showed a diastolic pressure of 90 mm Hg or more and at least two showed a diastolic pressure of less than 90 mm Hg. The patients underwent extensive investigations, including blood and urinary electrolytes, urinary catecholamines, and time pynelography. The 29 patients were classified as having essential hypertension. None had cardiac and neurologic involvement. In all cases creatinine clearance was above 100 ml/min. Consent for investigations was obtained from all sub-

From the Diagnostic Center and the Hemodynamic Laboratory of the Hypertension Research Center, Broussais Hospital, Paris.

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Address for correspondence: Jaime Levenson, M.D., Centre de Diagnostic, Hopital Broussais, 98 rue Didot, 75674 Paris, Cedex 14, France.

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TABLE 1
Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n = 24)</th>
<th>Borderline hypertensives (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>30 ± 2</td>
<td>29 ± 2</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>69 ± 2</td>
<td>74 ± 2</td>
</tr>
<tr>
<td><strong>Body surface area (m²)</strong></td>
<td>1.82 ± 0.03</td>
<td>1.88 ± 0.03</td>
</tr>
</tbody>
</table>

Data expressed as mean ± 1 SEM.

No significant difference was observed between the two groups.

jects after a detailed description of the procedure. The protocol was approved by the Institut National de laSanté et de la Recherche Médicale.

Methods. Central hemodynamic studies were performed with patients in the recumbent position, after an overnight fast, on the third day of hospitalization, and without premedication. The room temperature varied between 20° and 22°C. A transcutaneous catheter was inserted via an antecubital vein of the left arm for injections of dye and drugs. An 18-gauge thin-walled needle was inserted into the right brachial artery for the measurement of intra-arterial pressure (with a Statham P 23 ID balanced resistive strain gauge) and for withdrawal of blood for indication dilution curves. Cardiac output (ml/min/m²) was determined at least twice with the use of a Waters cuvette and densitometer and was corrected for body surface area. Total peripheral resistance (dyne-sec-cm⁻²-m²) was calculated as the ratio between electronically integrated mean arterial pressure (Electronic for Medicine apparatus) and cardiac index.

Forearm hemodynamic values were obtained with a bidimensional pulsed Doppler system whose probe was fixed with a stereotaxis device over the course of the right brachial artery. This apparatus enabled the diameter and the blood velocity of the artery to be measured by two fundamental characteristics: a bidimensional recording of the Doppler signals and a range-gated time system of reception. The former was obtained with a probe containing two transducers, forming between them an angle of 120 degrees, so that when Doppler signals recorded by each transducer were equal in absolute value, the incidence angle of each transducer with the vessel axis was 60 degrees. With the latter, it was possible to select the time delay from the emission and the duration of the reception and to convert these times echographically into the depth and the width of the Doppler measurement volume. A pedal incorporated with the apparatus enabled the investigator to vary automatically the depth and the width of the measurement volume by incremental or decremental steps of 0.4 mm. To determine the arterial diameter, the width of the measurement volume was reduced to the smallest convenient value with sufficient reflected energy (about 0.4 mm), and its depth from the transducer was progressively increased step by step. This was continued across the lumen of the artery with a small measurement volume and permitted the recording of velocities of the different stream lines involved in the arterial flow; thus the first and the last Doppler signals recorded when crossing the vessel corresponded to the vessel walls and the difference in depth between these two signals represented the internal arterial diameter. To take into account the ultrasonic incidence angle, a correction was made by multiplying this difference by sine 60 degrees, 60 degrees being the adequate angle used in the measurements. Arterial diameter was expressed in centimeters with an error of less than 8% and a reproducibility of 5 ± 3%. Once the arterial diameter was determined, the velocity of the whole arterial blood column was measured. For this, the width of the measurement volume was increased to the value of arterial diameter; its depth from the transducer was adjusted to superimpose the measurement volume and the lumen of the artery. The arterial blood velocity was expressed in centimeters per second and mean arterial blood velocity was electronically integrated. Brachial arterial flow was calculated as the product of blood velocity and arterial section (S) deduced from diameter (D) by using a cylindrical representation of the artery (S = πD²/4). Forearm volume was estimated by measuring the water displacement obtained after immersion of the forearm in a water-filled basin and was similar in control and in borderline hypertensive patients (1225 ± 86 vs 1190 ± 66 ml) (± 1 SEM). Brachial blood flow was expressed in milliliters per minute. Forearm vascular resistance (mm Hg/ml/sec) was calculated as the ratio between simultaneous mean pressure and mean blood flow in the brachial artery.

Design of the procedure. The hemodynamic measurements were made in the basal state and after short-term administration of drugs in different subgroups of subjects. The characteristics of each subgroup were not statistically different from those of the overall population.

Basal study: Both central and forearm hemodynamics were determined in nine normotensive control subjects and 24 borderline hypertensive patients.

Special forearm measurements as a function of time (0, 1, 2, 3 hr) were made in five normotensive control subjects and five borderline hypertensive subjects for testing the time response of the brachial arterial blood flow to the experimental procedure.

Pharmacologic study. The 24 borderline hypertensive patients who underwent central and forearm hemodynamic measurements were divided into three randomized subgroups of eight subjects each to repeat the study after short-term drug administration. The first subgroup received an intramuscular injection of the potent prostaglandin synthetase inhibitor indomethacin at a dose of 1 mg/kg. The second group of patients received an intravenous infusion of a selective β₁-receptor blocker pridimolol, which has been used experimentally in normal man. This drug has a β-blocker effect equipotent to that of propranolol in experiments with cat and guinea pig atria in vitro, but with much weaker β-blocker effects with guinea pig trachea and negligible α-blocker activity (one-fiftieth that of phentolamine) in the artery of the rabbit ear. The ratio between the activity in cardiac tissue and trachea smooth muscle was analogous to that of the cardioselective β-blockers tolamolol and practolol. Qualitatively similar indications of cardioselectivity were found in the intact animal. The last group of patients received an intravenous infusion of the well-known nonselective β-blocker propranolol. The β₁-adrenergic blockade was produced by intravenous injection of 10 mg of pridimolol and 15 mg of propranolol over 10 to 15 min, and the effectiveness of inhibition was shown by failure of heart rate to increase with a submaximal dose of isoproterenol. Hemodynamic studies were then repeated.

Forearm measurements were made in 10 normotensive subjects, including six receiving propranolol and four receiving pridimolol at the same doses and routes of administration as borderline hypertensive patients.

Statistical analysis. Means ± SEM and correlation coefficients were calculated by standard statistical methods. Regression analysis was performed by the least squares method. Differences in values between different groups of patients were assessed by Student’s t test and variance analysis (F test). For the pharmacologic study, the different parameters of the three subgroups of patients were compared. According to the F test, age, weight, body surface area, blood pressure, heart rate, and cardiac output measured in basal conditions were similar in the three subgroups. Differences in means before and after drug
TABLE 2
Central hemodynamics at rest

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n = 9)</th>
<th>Borderline hypertensives (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>126 ± 4</td>
<td>147 ± 3²</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>68 ± 2</td>
<td>75 ± 1¹</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88 ± 3</td>
<td>102 ± 2¹</td>
</tr>
<tr>
<td>Cardiac index (ml/min/m²)</td>
<td>3559 ± 239</td>
<td>4846 ± 224²</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>70 ± 3</td>
<td>81 ± 3</td>
</tr>
<tr>
<td>Total peripheral resistance (dyne-sec-cm⁻³-m²)</td>
<td>2046 ± 164</td>
<td>1884 ± 77</td>
</tr>
</tbody>
</table>

Data expressed as mean ± 1 SEM.

¹p < .01; ²p < .001.

administration were made by comparing the percent change of variation to zero by means of the paired t test.

Results

Basal study. Central and forearm hemodynamics (nine control subjects and 24 patients) were determined as described above. Systemic hemodynamics are listed in table 2. Fourteen borderline hypertensive patients had a cardiac index above normal (mean ± 1 SD) (<4276 ml/min/m²). Mean blood pressure was elevated in borderline hypertensive patients (p < .01). Although heart rate appeared to differ between the groups, this trend was not significantly different. Total peripheral resistance did not differ from control values.

Forearm hemodynamics are shown in table 3. Brachial arterial blood velocity and flow were both increased significantly in patients (p < .01, p < .001) while arterial diameter was within the normal range. Forearm vascular resistance was significantly decreased in borderline hypertensive patients (p < .05).

TABLE 3
Forearm hemodynamics at rest

<table>
<thead>
<tr>
<th></th>
<th>Normal subjects (n = 9)</th>
<th>Borderline hypertensives (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial artery diameter (cm)</td>
<td>0.433 ± 0.026</td>
<td>0.446 ± 0.010</td>
</tr>
<tr>
<td>Brachial artery blood velocity (cm/sec)</td>
<td>8.7 ± 1</td>
<td>14.4 ± 1²</td>
</tr>
<tr>
<td>Brachial artery blood flow (ml/min)</td>
<td>72 ± 8</td>
<td>136 ± 1¹</td>
</tr>
<tr>
<td>Forearm vascular resistance (mm Hg/ml/sec)</td>
<td>87 ± 9</td>
<td>52 ± 5¹</td>
</tr>
</tbody>
</table>

Data expressed as mean ± 1 SEM.

¹p < .05; ²p < .01; ³p < .001.

Special forearm measurement was done in five control subjects and five patients. In the normotensive control subjects and borderline hypertensive patients (submitted to the time-response forearm measurement), brachial arterial blood flow did not change significantly with time in any group and remained significantly higher at each time in patients than in control subjects (figure 1).

Pharmacologic study. Central and forearm hemodynamics were obtained in 24 patients. Figure 2 shows the percent changes in hemodynamic parameters after drug administration in the three subgroups.

After indomethacin, mean arterial pressure increased significantly (5 ± 2%; p < .02) and heart rate decreased (-13 ± 4%; p < .01); cardiac output significantly decreased (p < .001) while brachial arterial flow remained unchanged. Total peripheral resistance increased (32 ± 7%; p < .001) while forearm vascular resistance was unchanged.

After primidolol, heart rate was reduced significantly (-22 ± 3%; p < .001) while pressure did not change significantly. Cardiac output decreased strikingly (-28 ± 3%; p < .001) and brachial arterial flow decreased insignificantly. Total peripheral resistance increased (58 ± 8%; p < .001). Forearm vascular resistance increased slightly but insignificantly, even when the result was expressed in absolute values (figure 3).

After propranolol, heart rate was reduced significantly (-24 ± 3%; p < .001) but pressure did not change significantly. Cardiac output and brachial arterial flow decreased simultaneously (-29 ± 4% and
Discussion

Elevated limb blood flow was previously reported in patients with borderline hypertension.5-7 The present study demonstrated that increased forearm blood flow is a characteristic of the basal hemodynamic status of the borderline hypertensive patients, since it was not dependent on time or on the experimental procedure.18 The goal of the present investigation was to determine the relative contribution of prostaglandin and β-adrenoceptor mechanisms to the forearm vasodilation observed in patients with borderline hypertension.

In previous reports19,20 plasma prostaglandin E2 was found to be significantly increased in patients with borderline hypertension and positively correlated with the level of cardiac output. From these findings it has been suggested that the central hemodynamic abnormalities in patients with borderline hypertension could
be prostaglandin mediated. Further endogenous PGE$_2$ has also been shown to act as a local regulator of forearm flow in man in conditions of reactive and functional hyperemia.\(^{21}\) In this investigation, the short-term administration of indomethacin induced several central hemodynamic effects, such as an increase in pressure and peripheral resistance and a decrease in heart rate and cardiac output, as previously reported.\(^{20}\) However, no peripheral consequence was observed: brachial arterial flow remained increased to the same extent as in the basal state. Thus the prostaglandin system did not seem to participate dominantly in the maintenance of the elevated brachial arterial flow in these patients.

Several reports have emphasized the role of the $\beta$-adrenergic system in the mechanism of the elevated cardiac output in patients with borderline hypertension.\(^{10,11}\) However, no study has been performed to investigate the role of the $\beta$-adrenergic system in the mechanism of the elevation of forearm blood flow in these patients. This lack of data is surprising because, in normal man, the elevation of forearm blood flow induced by isoprenaline is abolished by a nonselective but not by a selective $\beta_1$-blocking agent\(^ {22}\) and forearm blood flow in young subjects is positively correlated with plasma epinephrine.\(^ {23}\) Accepting these observations, we investigated the effect of selective and nonselective acute $\beta$-blockade in young patients with borderline hypertension. The similar heart rate and decrease in cardiac output obtained with both propranolol and primidolol could be related to the $\beta_1$-adrenergic blockade effect of the drug. Identical increases in total peripheral resistance occurring in response to each drug demonstrated that both compounds lack intrinsic agonist or $\alpha$-blocking activity in our patients. In contrast, only the nonselective $\beta$-blocking agent propranolol decreased brachial arterial blood flow and increased forearm vascular resistance in borderline hypertensive patients. Since baseline forearm vascular resistance was lower in patients than in normotensive subjects, the magnitude of the propranolol vasomotor response could be conditioned by such a difference according to the law of initial values.\(^ {24}\) Based on previous reports, baseline resistance must be considered in interpreting response to vasomotor stimuli. In general vasoconstriction is inversely related to initial resistance.\(^ {25}\) In the present study, the response to propranolol did not depend on the initial resistance. The lack of such a correlation in borderline hypertensive patients seems to indicate that propranolol acts directly on the responsiveness, perhaps by a true blockade of a $\beta_2$-receptor-mediated effect. Indeed, the increases in forearm vascular resistance produced by propranolol were not greater in hypertensive subjects with low baseline than with high baseline values of resistance, so that augmented vasconstrictor responses to propranolol in patients with borderline hypertension could represent a specific alteration of $\beta_2$-receptor function rather than a nonspecific or generalized effect of decreased basal resistance on the response to any superimposed vasconstrictor stimulus. The enhanced $\beta_2$-receptor activity with a vasodilator influence might be the result of an epinephrine-mediated mechanism, in agreement with three findings: (1) administration of epinephrine induces a hemodynamic pattern including elevated systolic pressure, increased cardiac output and forearm blood flow, with normal splanchnic and renal blood flow, as in borderline hypertension\(^ {26}\); (2) plasma epinephrine has been shown to be elevated in patients with borderline hypertension both at rest\(^ {27}\) and during stress\(^ {28}\); and (3) in essential benign hypertension, the elevation of forearm blood flow consecutive to prazosin-induced vasodilatation has been found to be directly correlated to plasma epinephrine concentration.\(^ {29}\) The precise epinephrine-mediated mechanisms might be related to an augmented uptake of circulating epinephrine in the peripheral adrenergic nerve terminals, which is then released as a cotransmitter as proposed experimentally.\(^ {30}\) Therefore further investigation in patients with borderline hypertension is necessary to obtain data on plasma epinephrine levels.

Another result of this investigation concerns the ability to determine large vs small arterial responses
with the Echovar Doppler Pulse method in studies of the peripheral circulation. This apparatus provides information about the caliber of the large arteries that are directly measured and of the small arteries that are indirectly calculated by the forearm vascular resistance. In borderline hypertensive patients the brachial arterial diameter was normal in contrast with the increased arterial diameter observed in patients with sustained essential hypertension. The decrease in forearm vascular resistance observed in borderline hypertensive patients in the face of the elevated pressure indicates an increase in the total cross-sectional area or caliber of forearm vessels. Thus borderline hypertensive patients have increased small-vessel caliber but normal large-vessel caliber. The fact that large arterial caliber was normal despite a higher arterial distending pressure indicates higher vasomotor tone or lesser distensibility of large arteries.

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References
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