Forearm Blood Flow Reserve and Cardiac and Renal Indexes of Pressure Load in Normotensive and Hypertensive Individuals

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Abstract In response to hypertension, arterioles remodel their structure, the heart develops myocardial hypertrophy, and the kidney reduces creatinine clearance and increases albuminuria. To better understand the interrelations among the target organs involved in hypertension, we evaluated minimal forearm vascular resistances—a hemodynamic index of arteriolar structure derived from mean blood pressure and maximal postischemic forearm blood flow—the echocardiographic indexes of cardiac structure, and urinary albumin excretion and creatinine clearance in 29 male mild to moderate non-macroalbuminuric essential hypertensive patients on no drugs and 11 age- and sex-matched normotensive control subjects. Minimal forearm resistances were elevated in hypertensive patients and correlated with left ventricular mass, wall thickness, and mean arterial pressure. Patients with abnormal minimal forearm resistances (2 SD above normal) were characterized by higher pressure, greater wall thickness, lower creatinine clearance, and higher albumin excretion, suggesting that maximal forearm flow capacity does relate to the hemodynamic load exerted on both the kidney and heart. However, the correlation with cardiac structure and mean arterial pressure explained only part of the variability of minimal forearm resistances. Furthermore, no correlation among these parameters was found when hypertensive patients were evaluated separately from normotensive subjects, possibly because of heterogeneous factors active on arteriolar structure and unrelated to the pressor load. Overall, the data suggest that the development of abnormal minimal forearm resistances indices of hypertension relates to the pressor load, but its details need further understanding. (Hypertension. 1994;24:24-29.)

Key Words • hypertension, essential • forearm vascular resistance • albuminuria

Arterial hypertension induces adaptive changes in the organs exposed to the pressure load.1-3 Thus, arterioles restructure their geometry with a consequent reduced vasodilator capacity during reactive hyperemia, the heart remodels and hypertrophies, and the kidney undergoes structural and functional modifica-
tions leading to reduced glomerular filtration rate and increased urinary albumin excretion (UAE). However, if indisputable evidence links reduced forearm blood flow (FFB) reserve, cardiac hypertrophy, and interrelation among arteriolar restructuring and other indexes of hypertensive end-organ damage in humans is less clear. As regards arterioles and the heart, although it is usually assumed that the two processes evolve in parallel,1 left ventricular mass (LVM) values and postischemic minimal forearm vascular resistances (Rmin) did not show any correlation in a previous series of hypertensive patients,4 and altogether, contradictory and few data regarding the association of LVM and maximal forearm flow capacity are available.5-7 Abnormal Rmin was also found in normotensive patients with hypertrophic cardiomyopathy6,9 and in others with microvascular angina,10 possibly implying that the process of structural remodeling of the arteriolar bed is driven by factors unrelated to hypertension. Furthermore, inconsistent evidence exists regarding the effect of therapy on the abnormal structure in hypertension, suggesting that unspecified factors override the vasoconstrictor structural arteriolar amplifier during the course of the hypertensive process.11 As regards systemic arterioles and kidney function in hypertension, little if anything is known about their relation. Therefore, a clarification of the relation of the indexes of end-organ involvement in hypertension may contribute to a better understanding of the nature of the physiological adaptive mechanisms to high BP in humans and may possibly improve our way to evaluate the progression of the hypertensive target organ disease. For this reason, we measured and related Rmin, the echocardiographic indexes of cardiac structure, creatinine clearance, and UAE in normotensive and essential hypertensive individuals.

Methods

Subjects

Preliminary selection criteria were male sex; absence of malignant or accelerated hypertension, macroproteinaemia, congestive heart failure, cardiomyopathy, obesity (body mass index <30 kg/m²), and diabetes (fasting blood glucose <6.6 mmol/L [120 mg/dL]); no previous myocardial infarction; negative history for renal and connective tissue disease; serum creatinine less than 106 µmol/L (1.2 mg/dL); and normal sediment and urinoculture. Once identified, subjects underwent echocardiography for LVM determination, reserving study eligibility to those with a good acoustic window and absence at Doppler examination of valvular lesions that might contribute to hypertrophy. Urinary, cardiac, and forearm
Echocardiographic Studies

End-diastolic and end-systolic diameters were measured by M-mode echocardiography in the left ventricular parasternal long-axis view under views, using a standard transducer position. End-diastolic and end-systolic volumes were derived from Teicholz's formulas, minimal forearm vascular resistances, and monodimensional and bidimensional echocardiograms with Doppler analysis (Hewlett-Packard Sonos 1000) were performed with 2.5- and 3.5-MHz transducers. During the registration, subjects were in a semisupine position, slightly rotated to the left. Two-dimensional images were obtained in the parasternal long- and short-axis, apical four- and two-chamber views, using a standard transducer position. End-diastolic and end-systolic diameters were measured by M-mode echocardiography in the left ventricular parasternal long-axis view under the mitral leaflet at the chordae tendineae level; end-diastolic and end-systolic volumes were derived from Teicholz's formulas.

Minimal Forearm Vascular Resistances

Subjects were studied while lying comfortably in a bed in a quiet, climatized room (22° to 24°C). FBF was measured by strain-gauge venous plethysmography (DE Hokanson EC 5R plethysmograph), excluding hand circulation through a pedi- atric cuff inflated at suprasystolic pressures, as already described. All experiments were performed on the left forearm, run, and read by a single investigator (G.C.). Forearms were suspended well above the heart level to avoid venous engorge- ment at the moment of the massive inflow of blood after occlusion release, thus allowing accurate plethysmographic FBF measurements even at very high flow rates. Forearm arterial occlusion was obtained by inflating the plethysmo- graphic cuff at 300 mm Hg for 13 minutes; dynamic exercise (20 to 30 hand contractions) was added during the last minute of ischemia. In our experience, this procedure causes minimal discomfort to the patients while allowing maximal postischemic hyperemia. FBF (milliliters per deciliter of tissue per minute) was measured frequently in basal conditions and at 15-second intervals during the 3 minutes after ischemic release. The technique strictly follows the procedure already described, with the exception that, to simplify patient consent, indirect BP measurement at the contralateral forearm was substituted for intra-arterial BP recording. We have previously validated the short-term reproducibility of postischemic FBF determinations. To evaluate the long-term reproducibility of this parameter, we restudied four patients (one never treated, three on no drugs for 2 weeks) after an average of 296 days (range, 273 to 312 days). Mean BP was 117.5±2.6 versus 117.3±6.2 mm Hg at the first and second determinations, respectively. Peak FBF was 38±5.6 versus 40±4.3 mL/dl tissue per minute; $R_n$ values were 3.15±0.6 versus 3.25±0.3 U, a 6.8% replicate difference.

Echocardiographic Studies

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Urine Collections

To minimize the confounding influence of daily physical activity and to facilitate the urine collection procedure, we asked our patients to collect urine from 8 AM to 8 AM during 3 consecutive days. Within-patient variability of urinary creatine excretion was 12.3% (average variation coefficient of 40 triplicate samples), a value that shows the reliability of our procedure to be well below that expected from routine measurements. UAE variability was 35% (average variation coefficient of 40 triplicate samples), a value in agreement with the known biologic variability of this parameter.1617 Urinary albumin was measured by nephelometry with Behring antisem- rum and reagents (Istituto Behring SpA) with a detection limit of 6 g/L and an interassay variation of 3.5%. Urinary creatinine was measured by standard colorimetric methods.

Data Analysis

Basal BP was the average of multiple indirect recordings. FBF values represented the average of several recordings in the preischemic period. $R_n$ values were derived as a ratio of preischemic mean BP (diastolic BP+1/3 pulse pressure) and maximal postischemic FBF. Values 2 SD above normotensive mean were considered abnormal. LVM index (LVMI) was expressed in grams per meter of height to take into account the effects of body weight. Cardiac output (end-diastolic volume=end-systolic volume×HR), total peripheral resistance (TPR, mean BP×80/cardiac output), and forearm vascular resistance (FVR, mean BP/FBF) were derived according to standard formulas. UAE (micrograms per minute) and creatinine clearance (milliliters per second, normalized for body surface area) were the mean of three determinations. The skewed data distribution and strict relation between the SD of the triplicate urine collections and mean values $(r=.60, P<.001, n=40)$ required natural log transformation to stabilize variances and to apply parametric tests under the assumption of equal variances.

Statistics

Descriptive statistics are arithmetic mean±SD. Because of its skewed distribution, median and the range as a dispersion measure were used for UAE. Correlation coefficients were calculated according to standard methods. An unpaired t test was used to assess differences between mean values. A probability value of less than .05 was chosen as statistically significant.

Results

$R_n$ values were 2.8±0.6 U in hypertensive patients and 2.1±0.4 U ($P<.001$ in normotensive subjects (Fig 1), a 25% difference. LVMI, IVST, and PWT were greater in hypertensive patients (Table 1), who also showed higher UAE, TPR, and FVR values while resting, and peak FBF was lower (Table 1). HR, age, body mass index, creatinine clearance, and cardiac output were comparable (Table 1).
Fig 1. Bar graph shows minimal forearm vascular resistance (Rmin) in essential hypertensive (EH) patients (n=29) and control subjects (n=11). Mean±SEM is shown.

Pooling both normotensive subjects and hypertensive patients in the analysis, a statistically significant correlation was found between Rmin and LVMI (r=.39, P<0.05).

TABLE 1. Age, Blood Pressure, Heart Rate, Body Mass Index, and Echocardiographic, Renal, and Plethysmographic Data in Essential Hypertensive Patients and Normotensive Control Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive Patients (n=29)</th>
<th>Normotensive Subjects (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>158±17</td>
<td>135±8†</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>98±8</td>
<td>80±7†</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>76.0±11</td>
<td>74.1±12.4</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.8±10</td>
<td>56.8±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±3</td>
<td>24.8±2.5</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>120±25</td>
<td>100±12†</td>
</tr>
<tr>
<td>IVST, mm</td>
<td>11.8±1.3</td>
<td>10.8±1.9*</td>
</tr>
<tr>
<td>PWT, mm Hg</td>
<td>11.3±1.0</td>
<td>10.4±0.5†</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>118±9</td>
<td>99±7†</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>5.7±1.1</td>
<td>5.4±0.8</td>
</tr>
<tr>
<td>TPR, dyne · s · cm⁻⁸</td>
<td>1705±335</td>
<td>1499±313*</td>
</tr>
<tr>
<td>FBF, mL/dL/min</td>
<td>3.4±1.4</td>
<td>4.9±1.6†</td>
</tr>
<tr>
<td>FVR, U</td>
<td>38.6±12.5</td>
<td>22±6‡</td>
</tr>
<tr>
<td>Peak FBF, mL/dL/min</td>
<td>42.5±7.8</td>
<td>48.4±9*</td>
</tr>
<tr>
<td>Rmin, U</td>
<td>2.8±0.6</td>
<td>2.1±0.4†</td>
</tr>
<tr>
<td>UAE, µg/min</td>
<td>16 (6-171)</td>
<td>10 (4-211)</td>
</tr>
<tr>
<td>CrCl/1.73 m², mL/s</td>
<td>1.75±0.58</td>
<td>1.98±0.46</td>
</tr>
<tr>
<td>mL/min</td>
<td>105±35</td>
<td>119±28</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute; BMI, body mass index; LVMI, left ventricular mass index; IVST, Interventricular wall thickness; PWT, posterior wall thickness; MBP, mean blood pressure; CO, cardiac output; TPR, total peripheral resistance; FBF, basal forearm blood flow; FVR, basal forearm vascular resistance; peak FBF, postischemic FBF; Rmin, postischemic minimal forearm vascular resistance; UAE, urinary albumin excretion; and CrCl, creatinine clearance. Values are mean±SD, except UAE, which is median and range.

*P<0.05, †P<0.01, ‡P<0.001.

Fig 2. Scatterplots show left ventricular mass index (LVMI, left) and interventricular septum thickness (IVST, right) vs minimal forearm vascular resistances (Rmin). n=40; data pooled for hypertensive and normotensive individuals.

P<0.01, n=40; Fig 2 (left), IVST (r=.46, P<.003; Fig 2, right), and PWT (r=.37, P<.01). Individual mean BP values were related positively with Rmin (r=.65, P<.0001; Fig 3, top), LVMI (r=.46, P<.001; Fig 3, bottom), and UAE (r=.48, P<.001). No correlation was found between UAE and LVMI (r=.19). No correlation among these variables was found when hypertensive patients were analyzed separately from normotensive subjects.

Seventeen patients had Rmin values 2 SD above normal. In them, cardiac wall thickness, FVR, and UAE were higher, and creatinine clearance and resting and peak FBF were lower than in those 12 with normal Rmin (Table 2). Age and body mass index did not differ.

Discussion

One of the research questions of this study concerned the mutual behavior in normotensive and hypertensive
vascular rarefaction, because both may increase the extent of an increased wall-to-lumen ratio versus permissive patients. Possibly, the use of an indirect preischodynamic regimen, we cannot provide any answer as regards the relative contributions to the abnormal maximal forearm flow capacity of an increased wall-to-lumen ratio versus vascular rarefaction, because both may increase R\text{min}, which is a function of the regional vascular cross-sectional area. Steeper agonist-mediated resistance increases for given smooth muscle contractions may help to identify an altered wall-to-lumen ratio, as other researchers have reported in both well-established and fairly early essential hypertension, but we did not address this issue. Neither can we speculate about hypertrophic or nonhypertrophic remodeling, which R\text{min} cannot discriminate. The significant correlation between R\text{min} and LVM\text{I} complements and integrates our previous data collected in a hypertensive sample, in which the absence of appropriate normotensive control subjects probably hid the association between these variables, which our present combined series disclosed. We also found a correlation between measured mean arterial pressure and LVM\text{I}, UAE, and R\text{min}, which supports the contention that these parameters reflect, as postulated, the prevailing pressor load. Further evidence existed that a reduced forearm vasodilator capacity did indeed reflect exposure to a different pressor load acting on the heart, arterioles, and kidney. In fact, hypertensive patients with abnormal R\text{min} had greater PWT and reduced creatinine clearance, totally unrelated parameters but sensitive to the long-term hemodynamic regimen. In addition, those patients also showed evidence of greater forearm vasconstriction at rest combined with increased diastolic BP and UAE, which is more sensitive to short-term changes in afterload. Thus, FBF reserve tended to vary in parallel with other unrelated indexes of pressure load. Whether this index of arteriolar structure might possibly be used to stage hypertensive patients and to forecast their prognosis is unknown at this point. It has to be noted, however, that even the highest correlation of R\text{min} with the indexes of afterload left a large amount of variance unexplained. For example, 58% of R\text{min} variability was not explained by mean arterial pressure ($r^2=0.42$), and one might contend that the correlation coefficient was overestimated by the mathematically built-in interrelation of the two variables. We also found no correlation among these indexes when hypertensive patients were analyzed separately from normotensive subjects; in this sense, great vessels might resemble more closely the heart than arterioles. Thus, taking into account the relatively low methodological variability of R\text{min}, even when evaluated in the long term (see “Methods”), it seems likely that several potential mechanisms unrelated to the hemodynamic load per se could have been active on the arteriolar bed. One might think that peripheral and cardiac readaptation evolved with different time rates in response to high BP. Because increased LVM\text{I} and BP coexisted with normal FBF reserve in several patients, it might also be inferred that arteriolar restructuring was not necessary to sustain hypertension, possibly because, in humans as in experimental animals, mechanisms unrelated to arteriolar structure override the structural amplifier in the control of BP. However, hypertensive patients with normal R\text{min} as well might harbor raised wall-to-lumen ratios because exaggerated vascular reactivity to agonists persisted in spontaneously hypertensive rats, even when raised R\text{min} values were reduced by physical training. It might also be speculated that the type of previous antihypertensive medication and the length of previous treatment affected heart and vessels in a different manner. We cannot deny or support these possibilities because our age-matched subjects were recruited cross-
sectionally, at unknown but most likely variable points of the individual clinical course. The interpretation of data regarding maximal flow capacity must also take into account the effect of hereditary components, salt intake, and other factors possibly unrelated to hypertension, at least according to the reduced abnormal FBF reserve found in normotensive subjects with hypertrophic cardiomyopathy. Because the constituent tissues of the forearm likely differ as regards maximal flow capacity, different proportions of skeletal muscle and skin, fat, and bone might also contribute independently to the overall spread of R_{\text{min}} values. Finally, although our sample was composed of sedentary subjects, a role of subtle differences in the level of physical conditioning as a codeterminant of R_{\text{min}} cannot be excluded. Thus, multiple concurring factors as well as the heterogeneous (hypertrophy, nonhypertrophic remodeling, and/or vascular rarefaction) spectrum of structural abnormalities of the hypertensive small arteries and arterioles might independently affect FBF reserve.

The behavior of UAE deserves further comment. Several factors have been proposed to explain the pathogenesis of an increased UAE in essential hypertension, including structural modifications of arterioles and glomeruli, hemodynamic and permeselectivity changes of the glomerular filter, and increased intrarenal angiotensin II levels, which we did not investigate in this study. However, increments in systemic BP transmitted to still undamaged glomerular capillaries seemed to play a major role in our male hypertensive patients, a finding possibly helpful to the understanding of why microalbuminuria may predict cardiovascular events in male nondiabetic subjects. Different results could be obtained in females, in whom gender-related differences in UAE may be of importance. At variance with data obtained in patients with advanced atherosclerosis and a wide prevalence of essential hypertension, UAE was unrelated to LVMI in the present series. The tendency of UAE to reach pretreatment levels shortly after drug withdrawal might possibly explain the lack of association of albuminuria with cardiac mass, a structural index of cardiovascular injury that takes a long time to modify. The high biologic variability of UAE confirmed in this and previous patient series must also be taken into account. Even the existing vascular status may influence UAE: Microalbuminuria and macroalbuminuria were related to a systemic dysfunction of vascular endothelium and future atherosclerotic events in diabetics, and the same may happen in nondiabetic essential hypertensive patients. Hyperinsulinemia and altered lipid levels were also associated with an increased UAE in nondiabetic hypertensive patients, but their importance in this context is debated.

In conclusion, R_{\text{min}} values were elevated in the present group of hypertensive patients, and an abnormal forearm vasodilator capacity was associated with evidence of a greater pressor load, reduced creatinine clearance, and increased UAE. R_{\text{min}} values were also related to LVMI, a parameter that undergoes a well-recognized structural adaptation in response to hypertension, suggesting that arteriolar and cardiac structure to some extent evolve in parallel during the clinical course of hypertension. However, more studies are needed to understand fully the determinants of the adaptive mechanisms of cardiac structure to hypertension in humans.

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References


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