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 in the course of the hypertensive process is related 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. Thus, arterioles restructure their geometry with a consequent reduced vasodilator capacity during reactive hyperemia, the heart remolds and hypertrophies, and the kidney undergoes structural and functional modifications leading to reduced glomerular filtration rate and increased urinary albumin excretion (UAE). However, if indisputable evidence links reduced forearm blood flow (FBF) reserve, cardiac hypertrophy, and reduced renal function to high blood pressure (BP), the 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, left ventricular mass (LVM) values and postischemic minimal forearm vascular resistances (Rmin) did not show any correlation in a previous series of hypertensive patients, and altogether, contradictory and few data regarding the association of LVM and maximal forearm flow capacity are available. Abnormal Rmin was also found in normotensive patients with hypertrophic cardiomyopathy and in others with microvascular angina, 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. 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, macroproteinuria, con- gestive 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 urinocolture. 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

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Echocardiographic Studies

was substituted for intra-arterial BP recording. We have
views, using a standard transducer position. End-diastolic and
parasternal long- and short-axis, apical four- and two-chamber
formed with 2.5- and 3.5-MHz transducers. During the regis-
tation of the study and gave informed consent.

Experimental Procedures

Ananthropometric measurements were made after each par-
ticipant had removed his shoes and upper garments.

Basal BP

Systolic and diastolic BP (Korotkoff phase V by mercury
phymomanometer), BP, and heart rate (HR, palpatory
method) were measured in the morning with patients in the
supine position and several times over a 30-minute period.

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-
artic cuff inflated at suprasystolic levels, as already de-
scribed. 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 enge-
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 postisch-
emic hyperemia.12 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 re-
lease. The technique strictly follows the procedure already
described, with the exception that, to simplify patient con-
sent, indirect BP measurement at the contralateral forearm
was substituted for intra-arterial BP recording. We have
previously validated the short-term reproducibility of postisch-
emic FBF determinations.13 To evaluate the long-term repro-
ducibility 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 determina-
tions, respectively. Peak FBF was 38±5.6 versus 40±4.3
mL/dL tissue per minute; RBFn values were 3.15±0.6 versus
2.95±0.3 U, a 6.8% replicate difference.

Echocardiographic Studies

Monodimensional and bidimensional echocardiograms with
Doppler analysis (Hewlett-Packard Sonos 1000) were per-
formed with 2.5- and 3.5-MHz transducers. During the regis-
tration, subjects were in a semuposition, 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 echocardi-
ography 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' for-
mula. Interventricular septum thickness (IVST) and posterior
wall thickness (PWT) in diastole and LVM were measured
according to the Penn convention14 by averaging at least five
consecutive cardiac cycles from the two-dimensional guided
M-mode echocardiographic tracings. No patient showed areas
of hypokinesia, akiniesia, dyskinesia, or wall thinning such as to
invalidate the theoretical assumptions behind the echocardi-
ographic calculations. All tracings were read by a single ob-
server (L.T.) unaware of the overall clinical status of the
patients. Previous validation studies of the echocardiographic
technique had shown a within-observer variabilities (average
variation coefficient of six replications in six normotensive
subjects) for LVM determination of 8.9%.

Urine Collections

To minimize the confounding influence of daily physical
activity and to facilitate the urine collection procedure, we
asked our outpatients to collect urine from 8 PM to 8 AM
during 3 consecutive days. Within-patient variability of urinary creat-
ine 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 mea-
surements.15 UAE variability was 35% (average variation coefficient of 40 triplicate samples), a value in agreement with the
known biologic variability of this parameter.16,17 Urinary albumin was measured by nephelometry with Behring antise-
rum and reagents (Istituto Behring Spa) with a detection limit
of 6 g/L and an interassay variation of 3.5%.18 Urinary
creatinine was measured by standard colorimetric

Data Analysis

Basal BP was the average of multiple indirect recordings.
FBF values represented the average of several recordings in
the preschismic period. RBFn values were derived as a ratio of
preschismic mean BP (diastolic BP+1/3 pulse pressure) and
maximal postschismic 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.19 Cardiac output (end-diastolic
volume=end-systolic volume x HR), total peripheral resis-
tance (TPR, mean BP×80/cardiac output), and forearm vas-
ular resistance (FVR, mean BP/FFB) were derived according
to standard formulas. UAE (micrograms per minute) and
creatinine clearance (milliliters per second, normalized for
body surface area) values were the mean of three determina-
tions. The skewed data distribution and strict relation between
the SD of the triplicate urine collections and mean values
(r=.90, 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 prob-
ability value of less than .05 was chosen as statistically
significant.

Results

RBFn 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).
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CONTROLS

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, Table 1). Individual mean BP values were related positively with Rmin (r=.65, P<.0001; Fig 2, left), IVST (r=.46, P<.001; Fig 2, right), and PWT (r=.37, P<.01). 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

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.

Fig 3. Scatterplots show minimal forearm vascular resistances (Rmin, top) and left ventricular mass index (LVMI, bottom) vs mean blood pressure (MBP). n=40; data pooled for hypertensive and normotensive individuals.
we used indirect BP recordings, the present Rmn values were overestimated by approximately 10% when compared with those obtained through direct BP measurement (compare with values of Reference 9), but this detail is irrelevant as hypertensive and normotensive individuals were studied according to identical procedures. Furthermore, it was by indirect recording that an abnormal FBF reserve was first identified in hypertensive patients, even when evaluated in the long term (see "Methods"). Therefore, great vessels might resemble more closely the heart than arterioles. Thus, taking into account the relatively low methodological variability of Rmn, 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 LVMI 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 Rmn as well might harbor raised wall-to-lumen ratios because exaggerated vascular reactivity to agonists persisted in spontaneously hypertensive rats, even when raised Rmn 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-

| TABLE 2. Age, Blood Pressure, Body Mass Index, and Echocardiographic, Renal, and Plethysmographic Data in Hypertensive Patients With (<2.6 U) and Without (<2.6 U) Abnormal Minimal Vascular Resistances (Rmin) |
|-----------------|----------------|
| Variable        | Increased Rmn (n=17) | Normal Rmn (n=12) |
| SBP, mm Hg      | 162±15           | 152±18            |
| DBP, mm Hg      | 100.0±8          | 94.0±7*           |
| Age, y          | 58.5±9.9         | 52.0±11           |
| BMI, kg/m²      | 25.7±3.0         | 26.2±3            |
| LVMI, g/m²      | 129.0±28         | 114.0±19          |
| IVST, mm        | 12±1.3           | 11.6±1.3          |
| PWT, mm Hg      | 11.7±1.1         | 10.8±0.9*         |
| MBP, mm Hg      | 121±8            | 114.0±9*          |
| CO, mL/min      | 5.7±1.3          | 5.8±0.8           |
| TPR, dyne·s·cm⁻⁵ | 1776±371         | 1625±259          |
| FBF, mL/dL/min  | 3.1±0.7          | 4.2±1.9t          |
| FVR, U          | 41.0±11.0        | 33.0±12†          |
| Peak FBF, mL/dL/min | 39±5           | 49±5†             |
| Rmn, U          | 3.1±0.5          | 2.3±0.2           |
| UAE, µg/min     | 17 (8-171)       | 10 (6-41)*        |
| CrCl/1.73 m², mL/s | 1.53±0.53     | 2.03±0.57*        |
| ml/min          | 92±32            | 122±34*           |

Definitions are as in Table 1. Values are means±SD, except for UAE, which is median and range. *P<.05, †P<.001.
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,28 salt intake,29 and other factors possibly unrelated to hypertension, at least according to the reduced abnormal FBF reserve found in normotensive subjects with hypertrophic cardiomyopathy.9,19 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.36 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 arterioles11 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 permselectivity 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 capillaries37 seemed to play a major role in our male hypertensive patients, a finding possibly helpful to the understanding of why microalbuminuria may predict cardiovascular events38 in male nondiabetic subjects. Different results could be obtained in females, in whom gender-related differences in UAE may be of importance.39 At variance with data obtained in patients with advanced atherosclerosis and a wide prevalence of essential hypertension,17 UAE was unrelated to LVMI in the present series. The tendency of UAE to reach pretreatment levels shortly after drug withdrawal10,23 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 previous17 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,40 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,41 but their importance in this context is debated.17

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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