Opposite Effects of Remodeling and Hypertrophy on Arterial Compliance in Hypertension

Jean-Jacques Mourad, Xavier Girerd, Pierre Boutouyrie, Michel Safar, Stéphane Laurent

Abstract—Sustained hypertension is associated with a reduction in large artery compliance. However, we previously showed that, at the site of the radial artery, a distal muscular artery, the compliance of hypertensive patients was not significantly different from those of normotensive controls when the two groups were studied at their respective mean arterial pressures, despite increased wall thickness in hypertensives. To determine whether this paradoxical finding could be related to a specific pattern of geometrical changes, we studied arterial compliance in never-treated hypertensive patients characterized either by radial artery hypertrophy or remodeling, and compared them to normotensive controls. By analogy with Devereux's classification for left ventricular hypertrophy, we defined remodeling as an increased thickness to radius ratio (h/r) and a normal vascular mass (VM), and arterial hypertrophy as an increased VM irrespective of the values of h/r. Internal diameter and wall thickness were measured at the site of the radial artery using a high resolution echo-tracking system. The lumen cross-section pressure curve was determined from the two simultaneous and continuous recordings of arterial diameter and blood pressure. Then, the cross-sectional compliance (CC)-pressure curve was calculated. Isobaric compliance was calculated at 100 mmHg. Thresholds for h/r and VM were determined according to gender as the 95th percentile of a group of 100 normotensive subjects. The group of hypertensive patients included 58 patients with hypertrophy (h/r 0.25±0.04; VM 31±6 mg/cm², mean±SD) and 25 patients with remodeling (h/r 0.29±0.06, VM 20±4 mg/cm²) and was compared to a group of 50 age- and gender-matched normotensives (h/r 0.16±0.02, VM 17±4 mg/cm²). Compared to normotensives, isobaric compliance of the radial artery was increased in hypertensive patients with hypertrophy (HH) whereas it was not different in hypertensive patients with remodeling (RH). These results indicate that compliance is dependent on hypertrophy or remodeling pattern and suggest that in the face of hypertension, only arterial hypertrophy is an adaptive process leading to normal operating compliance through an increased isobaric compliance. (Hypertension. 1998;31[part 2]:529-533.)

Key Words: medium-sized artery ■ essential hypertension ■ vascular hypertrophy ■ remodeling ■ arterial compliance
Eighty-three never-treated hypertensive patients were included in the present study. The first group was characterized by arterial remodeling (increased intima-media thickness to radius ratio (h/r)) and normotensive control subjects free of clinical evidence of coronary artery or cerebrovascular disease, valvular heart disease, and renal disease were included. The study was approved by the Ethics Committee of Broussais Hospital, and all patients gave their written consent.

Methods

Eighty-three never-treated hypertensive patients were included in the study. The diagnosis of essential hypertension was established by the presence of a sustained increase in blood pressure (>140 mm Hg systolic pressure and/or >90 mm Hg diastolic pressure on the basis of sphygmomanometer measurements) and the absence of clinical or laboratory evidence suggesting secondary forms of hypertension. Fifty normotensive control subjects free of clinical evidence of coronary artery or cerebrovascular disease, valvular heart disease, and renal disease were included. The study was approved by the Ethics Committee of Broussais Hospital, and all patients gave their written consent.

Measurements of Radial Artery Parameters

The investigation was performed in a controlled environment kept at 22±1°C. Measurements of radial artery internal diameter and wall thickness were obtained on the right arm, after the forearm was extended and secured comfortably on a splint. The ultrasound system used in the present study (NIUS 02 marketed by Capital Medical Services) has been previously described and validated for the measurement of radial artery internal diameter and intima-media thickness in humans. Briefly, a high-resolution pulse-echo tracking device was used to acquire backscattered radiofrequency (RF) data from the radial artery at the wrist. The probe consisted of a 10 MHz strongly focused piezoelectric transducer (6 mm diameter, 11 mm focal length) operated in the pulse-echo mode. A stereotactic arm permits motion of the transducer in x, y, and z coordinates with micrometric steps in order to place the probe perpendicular to the arterial axis, in its largest cross-sectional dimension. The transducer is positioned so that its focal zone is located in the center of the artery and the reflected echoes from both the anterior and posterior walls could be visualized. A typical radiofrequency (RF) signal is then displayed on a computer monitor interfaced to the transducer system, and the signal over several cardiac cycles is digitized and temporarily stored in a large memory. Arterial diameter and posterior wall thickness are measured when a “double peak” RF ultrasound signal of the anterior and the posterior wall are obtained. These signals are only visible as the ultrasound beam crosses the axis (center) of the vessel. There are characterized by a first high-amplitude signal followed by a relatively silent acoustic zone and then a second high-amplitude signal. To measure internal diameter and intima-media wall thickness of the posterior wall, electronic trackers are positioned as previously described. The outer RF line of the second peak of the anterior wall and on the inner RF lines of the first and second peaks of the posterior wall. The analysis of the RF line allows the detection, from surface to depth, of the proximal wall, the lumen (empty of any echo), then the distal wall. At this level, the first small and narrow echo encountered corresponds to the intima-media interface, the second wide and ample echo corresponds to the media-intima interface.

The vessel walls are continuously tracked by sample volume according to phase. Then, the displacement of the arterial walls is obtained by autocorrelation processing of the Doppler signal originating from the sample volumes. The accuracy of the system is 30 µm for diastolic diameter (Dd) and wall thickness (h) measurements and less than 1 µm for the stroke change in diameter (Ds-Dd) and wall thickness. Mean internal diameter and wall thickness were calculated by integrating the time-course of their systolic-diastolic variations over at least 6 consecutive cardiac cycles. Very small changes in wall thickness can be detected throughout the cardiac cycle with this methodology. In addition, the pulsatile changes in wall thickness mirror the changes in internal diameter.

Thickness/radius ratio (%) was calculated as

\[ \text{Thickness/radius ratio} = \frac{h}{r} \]

where \( h \) is mean wall thickness and \( r \) is mean internal diameter.

Mean circumferential wall stress (kPa) was calculated according to Lamé's equation as

\[ \text{Wall stress} = \frac{2h}{D_1} \]

where \( MBP \) is mean blood pressure.

Since wall thickness is influenced by instantaneous variations in blood pressure level, radial artery mass is a more appropriate parameter because of the incompressibility of the VM. VM was calculated, as previously reported, as

\[ \text{VM} = \rho L \left( \frac{\pi R_2^2 - \pi R_1^2}{\pi R_1^2} \right) \]

where \( \rho \) is the arterial wall density, \( L \) is the length of the arterial segment, and \( R_2 \) and \( R_1 \) are the values of mean internal and external radius, respectively. VM was normalized to the length of the arterial segment and expressed as mg/cm length. The calculation of the radial artery mass has been previously described and validated.

Arterial function evaluation was derived from the analysis of the pressure-volume relationship. Cross-sectional compliance (CC), a marker of the exchange capacities of the vessel (Windkessel effect), was defined as \( CC = \frac{AV}{AP} \), where \( V \) is arterial volume, \( \Delta V \) is the change in volume, and \( AP \) is the change in pressure. It is assumed that the increase in volume of an artery segment is almost exclusively caused by an increase in radius because elongation is negligible in vivo at this site. Thus, arterial compliance can be estimated through the variations in arterial cross-sectional area \( \Delta A \) and blood pressure \( \Delta P \) during systolic. The above relation could be rewritten as follows:

Cross-sectional compliance \( CC = \frac{\Delta V}{\Delta P} \)

Finally, CC was calculated under two different conditions. First, under operational conditions, CC was determined at the operational MAP of each group. Secondly, under isobaric condition, CC was calculated at a reference pressure of 100 mm Hg, thus allowing comparisons of groups at the same level of pressure. The echo-tracking system described above was coupled to a commercially available plethysmograph (Finapres system, Ohmeda, BOC Group Inc.) to allow simultaneous blood pressure measurement. From the two simultaneous and continuous recordings of arterial diameter and blood pressure, the computerized acquisition system derived the cross-section-pressure curve, fitted it using an arctangent model with three independent parameters and then calculated the CC-pressure curve, according to previous studies.

Classification of Geometric Changes of the Radial Artery

Thresholds for \( h/r \) and VM were determined according to gender as the 95th percentile of a group of 100 normotensive subjects. They
TABLE 1. Clinical Characteristics of Hypertensive Patients According to the Pattern of Radial Artery, Hypertrophy or Remodeling (see text for definition), and Normotensive Controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertrophy</th>
<th>Remodeling</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>58</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±10</td>
<td>49±12</td>
<td>48±11</td>
</tr>
<tr>
<td>Gender (M/ F)</td>
<td>40/18</td>
<td>18/7</td>
<td>29/21</td>
</tr>
<tr>
<td>Height (m * 10^-2)</td>
<td>170±8</td>
<td>167±10</td>
<td>168±10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75±15</td>
<td>70±12</td>
<td>71±14</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>163±14</td>
<td>166±21</td>
<td>121±9*</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mm Hg)</td>
<td>99±5</td>
<td>99±8</td>
<td>73±7*</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>120±7</td>
<td>122±11</td>
<td>89±6*</td>
</tr>
</tbody>
</table>

Mean±1 SD
*P< 0.001 vs hypertrophy and remodeling
were 0.20 m men and women for h/r and 27 mg/cm (kg m^-1 10^-4) in men and 21 mg/cm in women for VM.
A hypertrophic pattern was defined by a VM >27 mg/cm in men and by a VM >21 mg/cm in women, whatever h/r value was. The remodeling pattern was determined by the presence of a h/r > 0.20 along with a normal VM.

Statistical Analysis
The statistical analyses were performed using the Statview SE 1.03 software on a Macintosh computer. A one-factor analysis of variance (ANOVA), followed by the Fisher test, was used to compare the three groups. Results are presented as means±1 SD. A P< 0.05 was considered significant.

Results
Among the hypertensive population, 58 subjects demonstrated a hypertrophic pattern of radial artery geometrical changes and 25 patients presented a remodeling. Clinical characteristics of hypertensive patients with hypertrophy (HH) or remodeling (RH) and control normotensives are summarized in Table 1. Age, sex ratio, height, and weight were comparable in the 3 groups. By definition, arterial pressure parameters were different between hypertensive patients and controls but were similar in patients with hypertrophy or remodeling.

Table 2 summarizes the radial artery structural and functional parameters in each group. Radial artery internal diameter was significantly lower in RH than in HH, whereas it was not significantly different between HH and controls. The radial artery wall was significantly thicker in hypertensive patients than in controls, and significantly thicker in HH than in RH. By definition, VM was higher in HH than in RH and controls, and was not significantly different between the two latter groups. The wall on lumen ratio (h/r) was significantly higher in RH than in HH and controls. Circumferential wall stress was significantly lower in RH than in HH and controls.

Operational CC was not significantly different between HH and controls, whereas it was significantly lower in RH. Isobaric (100 mm Hg) radial artery compliance was significantly higher in HH than in RH and controls, whereas the latter 2 groups were comparable.

Discussion
The main finding of the present study is that radial artery remodeling and hypertrophy have opposite effects on arterial compliance. RH have a lower operational compliance than normotensives subjects whereas no significant difference was observed between HH and normotensives. HH have a higher isobaric compliance than normotensives subjects whereas no significant difference was observed between RH and normotensives.

The present finding is consistent with the working hypothesis that the hypertrophic pattern would be associated with an increased isobaric compliance whereas the remodeling pattern would not. This hypothesis was raised because we observed in previous studies different pat-

TABLE 2. Structural and Functional Parameters of the Radial Artery in Hypertensive Patients, According to the Pattern of Vascular Hypertrophy or Remodeling (see text for definition) and in Controls

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hypertrophy</th>
<th>Remodeling</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean internal diameter (m * 10^-6)</td>
<td>2567±339</td>
<td>1900±330*</td>
<td>2442±399</td>
</tr>
<tr>
<td>Intima-media thickness (m * 10^-6)</td>
<td>317±42†</td>
<td>289±40*</td>
<td>196±25</td>
</tr>
<tr>
<td>Vascular mass (kg * m^-1 * 10^-4)</td>
<td>30.6±6.0‡</td>
<td>19.6±4.5</td>
<td>17.4±4.4</td>
</tr>
<tr>
<td>Intima-media thickness/ internal radius ratio</td>
<td>0.25±0.04‡</td>
<td>0.29±0.06*</td>
<td>0.16±0.02</td>
</tr>
<tr>
<td>Circumferential wall stress (kPa)</td>
<td>65.6±11.3‡</td>
<td>58±13.4*</td>
<td>73.9±10.5</td>
</tr>
<tr>
<td>Operational cross-sectional compliance (m² * kPa^-1 * 10^-6)</td>
<td>1.82±0.84</td>
<td>1.03±0.52*</td>
<td>1.81±0.87</td>
</tr>
<tr>
<td>Cross-sectional compliance at 100 mm HG (m² * kPa^-1 * 10^-6)</td>
<td>2.62±1.16‡</td>
<td>1.52±0.81</td>
<td>1.32±0.62</td>
</tr>
</tbody>
</table>

Mean±1 SD
*P< 0.01 remodeling vs hypertrophy and controls, †P< 0.01 hypertrophy vs remodeling and controls.
patterns of radial artery geometrical changes despite similar blood pressure levels, ranging from no change to a large increase in wall cross-sectional area, and from no change to a reduction in internal diameter. In addition, we previously observed that radial artery isobaric compliance was positively and significantly related to wall cross-sectional area but not to wall thickness.

The mechanism explaining the increase in isobaric compliance in patients having radial artery hypertrophic pattern remains purely speculative, although such an association between arterial wall hypertrophy and decreased stiffness has already been reported. For instance, in animals, Baumbach et al and Mulvany showed that the elastic modulus of the wall material for a given wall stress was decreased in the small arteries from spontaneously hypertensive rats (SHR) compared with normotensive controls, despite increased wall thickness. These authors suggested that this could be an alteration either in the characteristics of the individual wall components or in the relative proportions of these components in the wall. For instance, according to Baumbach, the hypertension-induced hypertrophy of the arterial wall may lead to an increase in the amount of extensible tissue like smooth muscle and to a decrease in the relative amount of the less extensible connective tissue in the vessel wall, like collagen fibers, thus favoring a "structural" increase in distensibility. Hayoz et al determined the CC of the carotid artery in Wistar Kyoto rats (WKY) and SHR according to the methodology used in the present study, and reported that the compliance-pressure curve of SHR, although shifted toward higher blood pressure levels, was not significantly different from that of WKY. Similar results were found in our laboratory.

That isobaric compliance was not higher in patients having a remodeling pattern of their radial artery than in control normotensive controls suggests that the rearrangement of wall components around a smaller lumen without increase in VM, was unable to modify the isobaric elastic properties of the radial artery, thus leading to a reduction in arterial compliance at mean blood pressure. The mechanisms leading to the remodeling pattern rather than to the hypertrophic pattern are unknown. Gender is unlikely, since sex ratio was not different between both patterns. In the present study, because we did not measure blood flow at the site of the radial artery, we could not determine whether the reduced lumen in RH was associated with a decrease in local blood flow, likely through a flow-dependent remodeling. The various mechanisms relating the geometry of the artery to its elastic properties through the changes in local blood flow thus remain to be determined.

Thus, the adaptive structural changes that we previously reported at the site of the radial artery could only occur in patients having a hypertrophic pattern and not in patients having a remodeling pattern. In the former, the elastic properties of the radial artery could be maintained despite hypertrophy of the arterial wall, and an advantage of arterial wall hypertrophy would be the maintenance of a "normal" compliance despite the increased intravascular pressure. The functional behavior of the radial artery is thus different from that of proximal large arteries, the compliance of which is decreased during hypertension.

The compliance gradient resulting from the higher proximal compliance than distal compliance, has been reported to generate wave reflections, which increase pulse pressure and cardiac afterload. During hypertension, proximal compliance is reduced, but not distal compliance. Thus, the compliance gradient between proximal and distal arteries is lower in hypertensives than in normotensives. We suggest that this decrease in compliance gradient would be a means by which the vasculature could attenuate wave reflections and pulse pressure at central arterial sites. Whether different patterns of pressure wave exist between RH and HH remains to be determined.

Hypertrophy and remodeling may be two separate responses of the radial artery to hypertension or part of a continuum. That the duration of hypertension was not significantly different between RH and HH suggests that a continuum is unlikely. However, because of the cross-sectional feature of the study, it is not possible to conclude, and a longitudinal survey is necessary.

In conclusion, these results indicate that compliance is dependent on hypertrophy or remodeling pattern and suggest that in the face of hypertension, only arterial hypertrophy is an adaptive process leading to normal operating compliance through an increased isobaric compliance.

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