Evidence of Early Degenerative Changes in Large Arteries in Human Essential Hypertension

ALAIN C. SIMON, JAIME LEVENSON, JEAN BOUTHIER, MICHEL E. SAFAR, AND ALBERTO P. AVOLIO

SUMMARY Noninvasive evaluation of brachial artery diameter (pulsed Doppler velocimetry) and pulse wave velocity (strain gauge mechanography) was performed in 23 normal subjects and 49 patients with uncomplicated essential hypertension. Pulsatile arterial function was described in terms of derived characteristic impedance and arterial compliance. Compared with normal controls, hypertensive patients had greater arterial diameter ($p < 0.01$) and pulse wave velocity ($p < 0.001$). Two nomograms obtained from normal subjects relating the product of age and diastolic pressure to diameter and pulse wave velocity were used for analysis of the hypertensive group; 35 patients were inside the 95% confidence limits of the diameter and pulse wave velocity nomograms (Group 1), while 14 patients were outside the pulse wave velocity nomogram (Group 2). Age and mean pressure were similar, but pulse wave velocity was higher ($p < 0.001$), arterial compliance lower ($p < 0.001$), and characteristic impedance higher ($p < 0.001$) in Group 2 than in Group 1. The amplitude of pulse pressure was higher in Group 2 than in Group 1 ($p < 0.001$), and a negative correlation was found between pulse pressure and arterial compliance in Group 2, but not in Group 1. Thus, in the majority of hypertensive patients, arterial modifications could be related to the normal influence of age and pressure. In contrast, other patients exhibited features suggesting excessive arterial stiffness, manifested by abnormally high pulse wave velocity, decreased arterial compliance, and increased characteristic impedance. (Hypertension 7: 675-680, 1985)

KEY WORDS • large arteries • essential hypertension • pulsed Doppler • brachial artery diameter • pulse wave velocity • arterial compliance

DAMAGE of large arteries is a major contributing factor to the high cardiovascular morbidity and mortality observed in hypertension. Moreover, it has been established recently that even in treated hypertensive patients, ischemic lesions continue to develop as a consequence of the injury to the large arteries. Such arterial damage is nonuniform. Arteriosclerotic lesions represent the direct effect of increased intraluminal pressure on the arterial wall. However, this effect is not specific to hypertension but appears as a consequence of arterial aging caused by the amplitude of pressure oscillation as well as time. Arterial damage caused by the process of atherosclerosis can also occur in hypertension. Although not directly caused by hypertension per se, it is accelerated by high arterial pressure and not always reduced by antihypertensive treatment.

Recent progress in noninvasive techniques for the assessment of arterial function allows early screening for detection of damage in large arteries in hypertension. In this study, the forearm arteries were chosen for investigation because they are the site of clinical and epidemiological blood pressure measurements. Quantitative information on the state and function of these large arteries was obtained by means of concomitant determinations of pulse wave velocity by mechanography and brachial artery caliber by pulsed Doppler velocimetry. Arterial compliance and characteristic impedance, which express the pulsatile behavior of large arteries, were derived from measurements of arterial wave velocity and diameter. To analyze the effects of the natural aging processes and those of other possible degenerative factors on the large arteries in...
hypertension, the concomitant role of age and arterial pressure on the forearm artery properties were analyzed in normal subjects and patients with uncomplicated mild to moderate hypertension.

**Patients and Methods**

Twenty-three normal men, from 17 to 62 years of age, and 49 ambulatory male patients, 24 to 63 years of age, with mild to moderate hypertension (supine diastolic pressure of 95-114 mm Hg, average of 3 outpatient visits) entered the hemodynamic study (Table 1). All patients had not been treated for at least 1 month and had essential hypertension documented by classical laboratory tests and timed intravenous pyelography. In all subjects the hypertension was uncomplicated, and none had cardiac, neurological, or renal involvement or arteriopathy of the legs. After giving informed consent, the patients were referred in the course of one morning to the hemodynamic laboratory to carry out the noninvasive arterial investigations.

After evaluation of forearm volume by measuring the volume of water displacement caused by the immersion of the forearm inside a measuring glass filled with water (see Table 1), the subjects were placed in the recumbent position with the right arm supported at the midthoracic level and the hand relaxed and opened in a controlled environment of 20 ± 1 °C. After 10 minutes of rest, systemic blood pressure was determined as the mean of at least three measurements by standard sphygmomanometric procedures (see Table 1).

Pulse wave velocity along the brachial and radial artery was measured using two transcutaneous strain gauge transducers (VR 12 Simultrace Recorder, Electronics for Medicine, Pleasantville, NY, USA) fixed to the skin over the most prominent part of the brachial and radial arteries. The foot-to-foot arterial wave velocity was calculated as the ratio between the distance separating the two transducers and the time interval separating the feet of the brachial and radial waves. The brachial and radial pulses were recorded simultaneously with a paper speed of 150 mm/sec, and the time delay and the duration of reception and determination of the distance from the transducer of the first and the last Doppler signals corresponding respectively to the proximal and distal arterial walls. The arterial diameter was deduced from the difference between the respective distances of the proximal and distal wall of the artery from the transducer and expressed in centimeters. The method has a reproducibility of 7 ± 2% and was reported to correlate in vitro measurements; in humans in vivo, the arterial flow of superficial arteries deduced from concomitant pulsed Doppler measurements of diameter and blood velocity was found to be strongly correlated 1) for the brachial artery to the forearm arterial flow measured by strain gauge plethysmography (unpublished data) and 2) for the common carotid artery to the cerebral blood flow measured by the xenon intra-arterial method.

Measurements of arterial pulse wave velocity and internal diameter were used to calculate characteristic impedance and compliance of the brachial artery. The characteristic impedance ($Z_C$) of a large artery can be calculated as $Z_C = 4\pi C \rho D^2$, where $C$ is pulse wave velocity, $\rho$ is the blood density considered as a constant and equal to 1.06, and $D$ is the internal diameter of the artery.

Characteristic impedance and the compliance per unit length were determined from measurements of pulse wave velocity and diameter in brachial artery expressed in dyn/second-cm$^{-3}$ and in cm$^2$-dyn$^{-1}$, respectively, according to the centimeter-gram-second [CGS] system of units.

**Statistical Analysis**

Group data were expressed as mean ± SEM. Comparisons of arterial parameters between the different groups of subjects were made by using Student’s $t$ test, and differences were considered significant if the $p$
value was less than 0.05. Correlations between parameters were made according to the least-squares method and expressed in linear regression ± 95% confidence limits.11

Results
Comparison of Normal Subjects and Hypertensive Patients
Compared with normal subjects, hypertensive patients showed higher pulse wave velocity (11.5 ± 0.3 vs 8.8 ± 0.3 m/sec; \( p < 0.001 \)) and larger arterial diameter (0.500 ± 0.008 vs 0.463 ± 0.013 cm; \( p < 0.01 \)). In normal subjects pulse wave velocity was correlated to age (\( p < 0.001 \)) and diastolic pressure (\( p < 0.01 \)) and to the product of age and pressure (\( p < 0.01 \); Table 2). Such correlations were not found in hypertensive patients except for that between pulse wave velocity and systolic pressure (\( p < 0.01 \); Figure 1). Arterial diameter was correlated in both normal and hypertensive subjects to age (\( p < 0.001 \), \( p < 0.05 \) respectively), diastolic pressure (\( p < 0.01 \)), and the product between age and pressure (\( p < 0.001 \)), but correlation coefficients were higher in the former than in the latter group (see Table 2).

Nomograms of Pulse Wave Velocity and Arterial Diameter According to Age and Pressure
Pulse wave velocity and arterial diameter were strongly correlated in normal subjects to the product between age and blood pressure (\( p < 0.001 \); see Table 2), and the highest correlation coefficients were obtained with the product of age and diastolic pressure (\( p < 0.001 \); see Table 2). The regression equations for pulse wave velocity and arterial diameter are as follows. Pulse wave velocity = (1.00 ± 0.13)\( 10^3 \) [age × diastolic pressure] + (5.58 ± 0.37). Arterial diameter = (0.042 ± 0.006)\( 10^3 \) [age × diastolic pressure] + (0.329 ± 0.020).

The 95% confidence limits of these relationships allowed a definition of a statistical range for pulse wave velocity and systolic pressure (\( p < 0.01 \); see Table 2). The regression equations for pulse wave velocity and arterial diameter data from normal subjects that was used to construct the nomograms (in Figure 1).

Division of Hypertensive Patients
Of the 49 hypertensive patients, 14 had a pulse wave velocity higher than the upper 95% confidence limits of the normal data while the 35 remaining patients were inside the pulse wave velocity nomogram (Figure 1). In contrast, all the hypertensive patients had arterial diameters that were under the upper 95% confidence limits of the normal data (see Figure 1). Thus, patients were divided according to their location on the nomogram of pulse wave velocity into two groups: Group 1 included patients inside (mean age, 44 ± 1 yr) while Group 2 included patients outside the nomogram (mean age, 41 ± 3 yr). No statistically significant difference in age was found between the two groups nor between each group and normal subjects. In addition, systemic blood pressure was not statistically different between the first (166 ± 3/100 ± 2 mm Hg) and second (174 ± 4/94 ± 3 mm Hg) group of patients, but systolic and diastolic pressure were slightly higher and lower, respectively, in Group 2 than in Group 1.

Compared with normal subjects, Group 1 showed higher pulse wave velocity (\( p < 0.001 \)), greater arterial diameter (\( p < 0.01 \)), lower arterial compliance (\( p < 0.001 \)), higher pulse pressure (\( p < 0.001 \)), and similar levels of characteristic impedance (Figure 2). Group 2 exhibited higher pulse wave velocity (\( p < 0.001 \)), lower arterial compliance (\( p < 0.001 \)), higher pulse pressure (\( p < 0.001 \)), and higher characteristic impedance (\( p < 0.001 \)) than did normal subjects, but the increase in arterial diameter was not statistically significant (see Figure 2).

Figure 2 shows also that despite the same level of mean arterial pressure in the two groups, pulse wave velocity was higher (\( p < 0.001 \)), arterial compliance lower (\( p < 0.001 \)), and characteristic impedance higher (\( p < 0.001 \)) in Group 2 than in Group 1; arterial diameter was not significantly different between the two groups. In addition, pulse pressure was higher in Group 2 than in Group 1 (\( p < 0.001 \)), and a strong negative relationship was found in Group 2 between pulse pressure and arterial compliance of the brachial artery (\( r = -0.67, p < 0.01 \); Figure 3). No such correlation was observed in Group 1.

Discussion
Elevated pulse wave velocity in large arteries is known to be associated with hypertension in humans.12-15 Reports have also indicated that an increase in the diameter of large arteries occurs in hypertension.16-19 By means of concomitant measurements of

Table 2. Correlation Coefficients of Pulse Wave Velocity and Arterial Diameter to Age, Blood Pressure, and the Product of Age and Blood Pressure in Normal Subjects and Hypertensive Patients

<table>
<thead>
<tr>
<th>Arterial parameters</th>
<th>Age</th>
<th>Blood pressure</th>
<th>Age × blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Mean</td>
</tr>
<tr>
<td>Pulse wave velocity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>0.82*</td>
<td>0.40†</td>
<td>0.56‡</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>0.20</td>
<td>0.39‡</td>
<td>0.20</td>
</tr>
<tr>
<td>Arterial diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>0.83*</td>
<td>0.43†</td>
<td>0.69*</td>
</tr>
<tr>
<td>Hypertensive subjects</td>
<td>0.31†</td>
<td>0.41‡</td>
<td>0.55*</td>
</tr>
</tbody>
</table>

*\( p < 0.001 \), †\( p < 0.05 \), ‡\( p < 0.01 \).
arterial pulse wave velocity and diameter, the present study demonstrates that increased pulse wave velocity is associated with increased diameter in the same vessel in hypertension, namely, the brachial artery, the artery in which clinical and epidemiological measurements of blood pressure are made. Age and the level of arterial pressure are among the mechanisms that may contribute to increased pulse wave velocity and caliber of the brachial artery in hypertension, because these two variables are capable of changing the properties of large arteries.

In normal subjects the influence of age and pressure on the brachial artery was observed in terms of the relationship between pulse wave velocity and diameter and between age and blood pressure. The higher the age, the higher the pulse wave velocity and the larger the diameter of the brachial artery. Such correlations agree with anatomical reports showing that the caliber and collagen to elastin ratio of large arteries increase with aging. Likewise, the higher the pressure, the higher the arterial pulse wave velocity and the larger the diameter, partly because distensibility and caliber of large arteries depend on the extent to which they are stretched by intraluminal pressure. In hypertensive patients the relationships between age and pressure and pulse wave velocity were not observed except for systolic pressure; in contrast, arterial diameter remained dependent on age and pressure, although to a lesser extent than was seen in normal subjects. These lesser effects of age and pressure on arteries, and especially on pulse wave velocity, in hypertensive subjects suggested that hypertension might affect arterial properties by mechanisms other than age and pressure.

To elucidate these mechanisms, hypertensive patients were compared in terms of the continuous gradations that appear in normal subjects between arterial diameter, pulse wave velocity, and the product of age and arterial pressure. Such relations express the effect of natural aging processes on arterial properties, and the product of age and pressure represents a quantita-
tive expression of the accelerating effect of pressure on this aging phenomenon. Accordingly, the increased diameter of the brachial artery in hypertension can be considered to be a consequence of aging, simply accelerated by pressure elevation. Indeed, all arterial diameters in hypertensive subjects were found to be inside the limits representing the normal effect of the product of age and pressure on brachial artery diameter. In contrast, in some hypertensive patients pulse wave velocity was observed to be higher than the value corresponding to the normal aging and pressure effect. This observation permitted the classification of hypertensive patients according to whether their pulse wave velocity was inside (Group 1) or outside (Group 2) the 95% confidence bands of normal regression of pulse velocity with the product of age and pressure. These two groups of patients had similar values of age and pressure but showed marked differences with respect to the state and function of large arteries.

In Group 1, the observation that pulse wave velocity and arterial diameter concomitantly increased inside the limits of the normal regression of these parameters with the product of age and pressure indicates that 1) the aging factor is related to these arterial modifica-
tions by the same relationship as in normal subjects and 2) pressure elevation acts in concurrence with the normal evolution of aging as an accelerating factor of this aging process. In addition, these patients showed little decrease in arterial compliance, notwithstanding pressure elevation, and they had normal characteristic impedance because their pulse wave velocity elevation was counterbalanced by a proportional increase in arterial diameter, which appears to be a means of maintaining the pulsatile function of the forearm arteries.

In addition to exhibiting the same aging process as that seen in Group 1, patients of Group 2 exhibited marked arterial changes. Their pulse wave velocity was more elevated than expected from their level of age and pressure. Their brachial artery diameter failed to increase significantly above the normal value, in contrast to Group 1 and despite having the same pressure and age levels as the latter; this point constitutes an additional indication of abnormal stiffness of their arterial walls. Moreover, this lesser arterial dilatation could not compensate for the marked elevation of pulse wave velocity, which would explain the profound decrease in arterial compliance and abnormal elevation in characteristic impedance of these patients. One consequence of the alteration of their arterial function was an increased amplitude of pulse pressure inversely related to the level of arterial compliance. The mechanisms responsible for the arterial modifications of Group 2 are unclear. In addition to the effects of aging and pressure, they include other degenerative factors perhaps related in part to subclinical atherosclerosis, as suggested by pulse wave velocity studies in animals.

Results from this investigation suggest that early modifications of large arteries of the forearm occur in essential hypertension. These changes, however, may be attributed to different mechanisms. The first change, which affected most of the hypertensive patients in this study, could be considered to be an accelerated aging process: in this instance, the function of large arteries expressed in terms of arterial compliance and characteristic impedance was little impaired. The second form of arterial disease concerned a minority of patients and was associated with the natural aging process and the effects of other degenerative factors, perhaps atherosclerotic in nature; this change caused profound impairment of the arterial buffering function in these patients and led to increased amplitude of the arterial pulse pressure.

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References
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