Arterial Stiffening as a Possible Risk Factor for Both Atherosclerosis and Diastolic Heart Failure

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While arterial stiffness is known to be related to atherosclerosis, the association between arterial stiffness and cardiac systolic and diastolic function in hypertension has not been fully evaluated. The present study was conducted to simultaneously evaluate the relationship of brachial-ankle pulse wave velocity (PWV) to parameters reflecting atherosclerosis and to those reflecting the risk of congestive heart failure in patients with hypertension. In 147 patients with hypertension, the left ventricular ejection fraction, the ratio of the peak velocity of early rapid filling and the peak velocity of atrial filling (E/A ratio), and left ventricular mass index were obtained from echocardiographs, the intima-media thickness of the common carotid artery was obtained by ultrasonography, the plasma B-type natriuretic peptide (BNP) level was measured by radioimmunoassay, and the brachial-ankle PWV was measured by the volume rendering method. Brachial-ankle PWV correlated positively with the intima-media thickness of the carotid artery, E/A ratio and BNP. Multiple linear regression analysis demonstrated that the relationship between the brachial-ankle PWV and the E/A ratio was significantly independent from other clinical variables. The receiver operator characteristic curve demonstrated that a brachial-ankle PWV of 1,600 cm/s was useful to discriminate mild cardiac diastolic dysfunction (E/A ratio of 0.75) (sensitivity = 78% and specificity = 58%). The present study demonstrated that increased brachial-ankle PWV relates not only to the parameters reflecting atherosclerosis but also to those reflecting cardiac diastolic dysfunction. Therefore, increased arterial stiffness is a possible simultaneous risk for atherosclerotic cardiovascular disease and diastolic heart failure in patients with hypertension. (Hypertens Res 2004; 27: 625–631)

Key Words: arterial stiffness, diastolic dysfunction, atherosclerosis

Introduction

Increased pulse wave velocity (PWV), which reflects arterial stiffness, is an independent predictor of the prognosis in hypertension, including in subjects under anti-hypertensive medication (1). Atherosclerotic cardiovascular events and heart failure are major determinants of the prognosis of hypertension (2). Several studies have demonstrated that PWV relates to ultrasonographically detected atherosclerotic change in the carotid artery, which is an established marker of atherosclerosis (3, 4). On the other hand, it has been reported that increased arterial stiffness increases cardiac overload and impairs coronary blood supply through a falling diastolic blood pressure (5, 6). These pathophysiological changes are harmful in the case of congestive heart failure (7). While the arterial stiffness is elevated in congestive heart failure (8), the association between increased PWV and preclinical heart failure has not been fully evaluated. Recent studies have demonstrated that not only systolic heart failure but also diastolic heart failure is frequently accompanied with hypertension (9). Increased cardiac ventricular stiffness is thought to be one of the pathogenic mechanisms of diastolic heart failure (10). Cardiac diastolic dysfunction as as-
sessed by Doppler ultrasound examination is thought to relate to diastolic heart failure (11). While arterial stiffness relates to ventricular stiffening (12), it has not been clarified whether an increased PWV relates to the impairment of cardiovascular function in hypertension. Furthermore, the association between PWV and the plasma level of B-type natriuretic peptide (BNP), which is an established marker of congestive heart failure (13), has not been clarified. Therefore, it should be evaluated whether increased arterial stiffness in hypertension is a simultaneous risk for atherosclerotic cardiovascular disease and heart failure.

The present study was conducted to simultaneously evaluate the association of PWV with parameters of atherosclerosis and with the risk of congestive heart failure, with parameters of atherosclerosis and with parameters reflecting the risk of congestive heart failure, such as decreased cardiac systolic and diastolic function, increased left ventricular mass index, and increased plasma level of BNP in patients with hypertension.

Methods

Subjects and Protocol

One hundred and forty-seven consecutive patients who were diagnosed as having essential hypertension at Tokyo Medical University Hospital were entered in the present study from September 2001 to the end of July 2003. Informed consent was obtained from all of the participants. None of the subjects had a history of any atherosclerotic cardiovascular diseases, including arrhythmia, symptoms related to ischemic heart disease, or electrocardiographic evidence of ischemic heart disease. Patients with serious medical problems requiring specific medical treatment were excluded. Blood pressure was determined in the outpatients clinic using the conventional cuff method. Brachial-ankle PWV, echocardiography, ultrasonography of the carotid artery, and blood sampling were performed in the morning after a 12-h overnight fast. This protocol was approved by the Ethical Committee of Tokyo Medical University.

PWV

Brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI; Colin Co., Ltd., Komaki, Aichi, Japan). Details of the methodology have been described elsewhere (14). The subjects were examined while resting in the supine position. Electrocardiographic electrodes were placed on both wrists, and cuffs were wrapped on the bilateral brachia and ankles. Pulse volume waveforms at the brachium and ankle were recorded using a semiconductor pressure sensor after a rest of at least 5 min. The validation of this method has been reported previously (14).

Ultrasonographic Examination of the Heart and Carotid Arteries

M-mode echocardiograms were obtained by guided by two-dimensional guided echocardiography using an echocardiographic instrument (Acuson Sequoia 512; SIEMEMS, Munich, Germany) equipped with a transducer having a frequency range of 3–5 MHz. The mean of two M-mode measurements obtained by two different investigators was used. The left ventricular mass was calculated by Devereux’s method (15). The left ventricular mass index was calculated as the left ventricular mass divided by the body surface area. Relative wall thickness at diastole (RWTd) was calculated by the following formula: RWTd = (2 × thickness of left ventricular posterior wall/left ventricular diameter at diastole). The left ventricular systolic and diastolic volumes and ejection fraction were derived from M-mode images according to standard criteria (16). Pulsed Doppler measurements of left ventricular diastolic inflow were obtained by two-dimensional echo-guide. Briefly, the left ventricular diastolic filling pattern was recorded from the apical transducer position in patients in the partial left lateral decubitus position during inspiratory apnea, with the sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity) were recorded, and the E/A ratio and deceleration time was the interval from the E-wave peak to the decline of the velocity to baseline values were obtained from 3 consecutive cardiac cycles. An E/A ratio of ≤0.75 was considered to indicate mild cardiac diastolic dysfunction (17). All the subjects in the present study had a normal systolic cardiac function and no subject had a pseudonormal cardiac diastolic function (E/A ratio of 1.0 to 1.5 and deceleration time >240 ms) (18).

After the echocardiographic examination, both carotid arteries were imaged using an ultrasonographic system (Aspen Advanced; SIEMEMS) equipped with a 10.0-MHz transducer. Using guided two-dimensional ultrasonography, longitudinal M-mode tracings, approximately 1 cm proximal to the carotid sinus, were obtained with simultaneous electrocardiogram recordings. The intima-media thickness (IMT) was measured at a site free of any discrete plaques along a 10-mm-long segment of the far wall of the common carotid artery and measured as the distance between the lumen-intima interface and the media-adventitia interface. The mean of the right and left measurements was used in the analysis. The presence of an atherosclerotic plaque was defined as 50% wall thickening compared to the adjacent arterial wall. Plaque was measured in B-mode images, and the plaque score was determined (19).

The reproducibility of the echocardiographic and ultrasonographic measurements of the carotid arteries has been reported elsewhere (20).
Laboratory Measurements

Plasma high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and blood sugar were measured enzymatically. BNP (Shionoria BNP Kit; Shionogi, Osaka, Japan) was determined by radioimmunoassay. All blood samples were obtained after 30 min rest in the morning after an overnight fast.

Statistics

Data are expressed as the mean ± SD. Statistical analysis was performed using an SPSS software package (SPSS, Chicago, USA). Linear regression analysis was performed to evaluate the association between brachial-ankle PWV and other clinical variables.

Multiple linear regression analysis was applied to evaluate whether the relationship between brachial-ankle PWV and E/A ratio is independent from other related factors. A receiver operating characteristic (ROC) curve was used to discriminate patients with mild cardiac diastolic dysfunction (E/A ratio ≤ 0.75) by brachial-ankle PWV. Then, the value with the highest sum of sensitivity and specificity was identified as the cutoff value.

Results

Clinical characteristics and the ultrasonographic results for the heart and carotid artery are shown in Tables 1 and 2. Brachial-ankle PWV was correlated significantly with E/A ratio and BNP (Fig. 1). While IMT and plaque score also correlated with brachial-ankle PWV, LVMI did not correlate with brachial-ankle PWV (Table 3). Multiple linear regression analysis demonstrated that the relationship between brachial-ankle PWV and E/A ratio is independent from other related factors (Table 4). Table 5 shows the clinical characteristic in subjects with or without diastolic dysfunction. As for the ROC curve for discriminating patients with mild cardiac diastolic dysfunction by brachial-ankle PWV of 1,600 cm/s, the area under the curve was 0.71, and the highest discriminating sensitivity and specificity were 78% and 58% (likelihood ratio = 1.34) (Fig. 2).

Discussion

We simultaneously evaluated the relationship of PWV with parameters of atherosclerosis and parameters of risk for congestive heart failure, and showed that PWV was significantly related to cardiac diastolic function, plasma BNP level, and atherosclerotic changes in the carotid artery of patients with hypertension.

Several studies have demonstrated that arterial stiffness
Table 3. Correlation Coefficients of Linear Regression Analysis between Brachial-Ankle Pulse Wave Velocity and Other Clinical Parameters Except Plasma Level of BNP and E/A Ratio

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$r$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.54</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP</td>
<td>0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DBP</td>
<td>0.18</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVMI</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>RWTd</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVEF</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>DcT</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>IMT</td>
<td>0.32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PLQ</td>
<td>0.24</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; RWTd, relative wall thickness at diastole; LVEF, left ventricular ejection fraction; DcT, deceleration time of mitral inflow; IMT, intima-media thickness; PLQ, plaque score.

Table 4. Results of Multiple Linear Regression Analysis to Evaluate the Independency of the Relationship between Brachial-Ankle PWV and E/A ratio

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\beta$</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.392</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVMI</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>RWTd</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVEF</td>
<td>—</td>
<td>n.s.</td>
</tr>
<tr>
<td>PWV</td>
<td>-0.21</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

$r^2 = 0.25$. SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LVMI, left ventricular mass index; RWTd, relative wall thickness at diastole; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity.

Table 5. The Clinical Characteristic in Subjects with or without Diastolic Dysfunction (E/A Ratio ≤ 0.75)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>E/A ≤ 0.75 ($n = 44$)</th>
<th>E/A &gt; 0.75 ($n = 103$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>64 ± 8</td>
<td>57 ± 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>138 ± 14</td>
<td>134 ± 15</td>
<td>n.s.</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 ± 10</td>
<td>84 ± 10</td>
<td>n.s.</td>
</tr>
<tr>
<td>baPWV (cm/s)</td>
<td>1,804 ± 334</td>
<td>1,573 ± 304</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IMT (mm)</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>125 ± 29</td>
<td>121 ± 31</td>
<td>n.s.</td>
</tr>
<tr>
<td>RWTd (mm)</td>
<td>0.42 ± 0.07</td>
<td>0.42 ± 0.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>67 ± 6</td>
<td>67 ± 5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

E/A, E/A ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; baPWV, brachial-anke pulse wave velocity; IMT, intima-media thickness; LVMI, left ventricular mass index; RWTd, relative wall thickness at diastole; LVEF, left ventricular ejection fraction.
arterial stiffness compared with pulse pressure (1, 5, 6). We demonstrated that increased PWV relates to the impairment of cardiac diastolic function. Furthermore, PWV correlated with the plasma level of BNP in this study. BNP has been shown to be elevated in patients with diastolic dysfunction (13, 29, 30), and a recent study demonstrated that even a mild elevation of plasma BNP level presents a risk of cardiovascular events and death (31). Therefore, to our knowledge, this is the first study to propose that increased PWV is a possible risk factor for diastolic heart failure.

The prevalence of diastolic heart failure is high both in elderly subjects and in patients with hypertension, left ventricular hypertrophy, or ischemic heart disease (9, 10). Chen et al. demonstrated that arterial stiffening associated with age is matched by ventricular stiffening independent of hypertrophy (32). In the present study, the relationship between PWV and cardiac diastolic function was independent of age. Although some studies have reported that arterial stiffness correlates with left ventricular hypertrophy, which is one of the major determinants of cardiac diastolic dysfunction (33), the present study did not confirm this relationship. The subjects in the present study had been hypertensive for different periods, and they were under treatment with various kinds of antihypertensive drugs. It is noted that different anti-hypertensive medications have different effects on the regression of left ventricular hypertrophy and the improvement of arterial stiffness, and the reversal of structural changes in arteries is thought to require a longer treatment period than the regression of ventricular hypertrophy (34, 35). The patients’ background factors (the duration of the treatment and/or the kinds of antihypertensive drugs) might be responsible, at least in part, for the lack of a significant relationship between PWV and left ventricular hypertrophy in this study. In addition, none of the subjects in the present study presented abnormal electrocardiographic findings or symptoms related to ischemic heart disease. Therefore, our results suggest that increased PWV is a possible risk factor for diastolic heart failure, along with aging, left ventricular hypertrophy and/or ischemic heart disease.

A recent epidemiological study demonstrated that cardiac diastolic dysfunction as assessed by the Doppler technique was associated with marked increases in all-cause mortality (17). The relationship among cardiac diastolic dysfunction, PWV, and atherosclerotic changes in the carotid artery was revealed by ultrasonography are predictors for future atherosclerotic cardiovascular events (1, 21–24). The significant relationship of PWV with both IMT and plaque score in the present study agrees with the concept that increased PWV is an indicator of atherosclerotic cardiovascular risk in hypertension. The results of a recent study strongly suggest that plaque morphology is an additional indicator of atherosclerotic risk (25). Zureik et al. reported the relationship between carotid plaque morphology and PWV (3), but we did not assess plaque morphology in this study.

Chae et al. reported that elevation of pulse pressure increased the incidence of congestive heart failure, and they suggested that arterial stiffening was a risk factor of congestive heart failure (26). However, they did not examine the details of congestive heart failure (systolic heart failure or diastolic heart failure). In other recent reports, 30–50% of patients hospitalized for congestive heart failure were diagnosed as having diastolic heart failure, and, therefore, diastolic heart failure has drawn much attention (9, 10). Prolonged relaxation and increased passive myocardial stiffness cause diastolic heart failure (10). It has been shown that pulse pressure reflects arterial stiffness (1, 5, 6). Increased arterial stiffness influences those abnormalities via the impairment of coronary blood supply as a consequence of a decreased diastolic blood pressure, induction of cardiac hypertrophy, or increased cardiac stiffening (5, 6). E/A ratio and deceleration of mitral inflow are established markers of cardiac diastolic function (11). E/A ratio is a more sensitive parameter for estimating the left ventricular filling pressure than the deceleration time of mitral inflow (27, 28), and the changes in E/A ratio seem to precede the changes in the deceleration time of mitral inflow in the early stage of cardiac diastolic dysfunction (17). PWV is a more valid marker of arterial stiffness compared with pulse pressure (1, 5, 6).
Redfield et al. proposed the criteria of mild cardiac diastolic dysfunction by Doppler ultrasound examination in the general population (17). According to their criteria, the ROC curve demonstrated that a brachial-ankle PWV over 1,600 cm/s is a marker of abnormal cardiac diastolic function. It is noted that carotid-femoral PWV is an established and standard method (1, 5, 6, 21), and a large body of evidence supports its clinical usefulness as a marker of atherosclerotic cardiovascular risk. Compared with this method, brachial-ankle PWV includes a much more peripheral component which shows less atherosclerotic changes, and this fact should be taken into account in its clinical use (14, 38). However, some studies have demonstrated a good correlation between brachial-ankle PWV and aortic PWV (14), and that brachial-ankle PWV correlates strongly with conventional atherosclerotic risk factors (38). Therefore, while no prospective study has demonstrated that brachial-ankle PWV is a predictor of future cardiovascular events, it seems to potentially reflect atherosclerotic cardiovascular risk, similar to carotid-femoral PWV. Brachial-ankle PWV is a simple method and quite applicable to a population study. Thus, we propose a prospective study to examine the prevalence of diastolic heart failure in hypertensive subjects with increased brachial-ankle PWV.

In conclusion, the present study demonstrated that brachial-ankle PWV correlates both with parameters reflecting atherosclerosis and parameters of cardiac diastolic dysfunction. Therefore, increased arterial stiffness may be a simultaneous risk factor for atherosclerotic cardiovascular disease and diastolic heart failure in patients with hypertension.

**References**


2402–2407.


