The Influence of the Peripheral Reflection Wave on Left Ventricular Hypertrophy in Patients with Essential Hypertension

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The objective of this study was to clarify the relationship between afterload, which consists mainly of the vascular reflection wave, and left ventricular hypertrophy in patients with untreated essential hypertension using the fingertip photoplethysmogram (PTG) and second derivative wave (SDPTG) methods, the simplest and most convenient tools for pulse wave analysis. The augmentation index (AI) is defined as the ratio of the height of the late systolic peak, augmented by the peripheral reflection wave, to that of the early systolic peak caused mainly by left ventricular ejection in the pulse. Increased AI of the PTG and negative d/a, obtained by multiplying the ratio of the late re-decreasing wave (d wave) to the initial positive wave (a wave) of the SDPTG by −1, have the same meaning as increased ascending aortic AI. The left brachial artery blood pressure was measured in 60 patients. The PTG and SDPTG of the right second finger were recorded by a digital photoplethysmograph. The left ventricular mass index (LVMI) was investigated by ultrasonography. Subjects were assigned to one of two groups: a low AI (AI of PTG<1.6; group 1) or a high AI (AI of PTG≥1.6; group 2) group. LVMI was significantly higher in group 2 than in group 1. In the study group as a whole, the LVMI was positively correlated with both the AI of PTG (r=0.60, p<0.0001) and negative d/a (r=0.63, p<0.0001). An increase in the LVMI was seen in subjects with an augmented late systolic component in the waveform. It was concluded that an increase in the peripheral reflection wave on the left ventricle is one of the important factors causing cardiac hypertrophy in patients with hypertension. (Hypertens Res 2000; 23: 451-458)

Key Words: cardiac hypertrophy, hypertension, augmentation index, photoplethysmography, second derivative wave

Introduction

Left ventricular hypertrophy is an important marker of cardiovascular events in patients with hypertension (1, 2). The severity of hypertrophy is not closely correlated with blood pressure of the brachial artery (3, 4). This is probably because brachial arterial blood pressure measured by the cuff method is not a sufficient index for evaluating cardiac afterload. Common afterload indices such as systolic blood pressure, diastolic blood pressure, and mean blood pressure do not indicate the afterload, i.e., the aortic wall distensibility and peripheral reflection waves, following rhythmical contraction of the left ventricle. Aortic input impedance is a left ventricular afterload index that comprehensively indicates the total peripheral resistance and that is derived from steady flow, aortic properties obtained from pulsatile flow, and peripheral reflection waves (5-7). This impedance is obtained by dividing pulsatile pressure by pulsatile flow and is expressed as the...
modulus and phase in individual harmonics as a function of frequency. For this calculation, ascending aortic pressure and flow velocity waveforms should be recorded invasively and simultaneously. Pressure wave analysis of the ascending aorta, the carotid artery, and the radial artery has been used to evaluate hemodynamics more easily. The augmentation index, defined as the ratio of the late systolic component (mainly consisting of the reflection pressure wave) to the early systolic component (mainly consisting of the driving pressure wave) in the pulse, has been reported to be closely related to the aortic input impedance (5-9). The augmentation index (AI) obtained from the fingertip photoplethysmogram (PTG) and the negative \( \frac{d}{a} \) ratio obtained by multiplying \( d/a \) [the ratio of the late re-decreasing wave (d wave) to the initial positive wave (a wave) of the second derivative of the PTG (SDPTG)] by \(-1\) could be used as indices for pulsatile vascular load, with aortic input impedance (10, 11).

In previous studies, the noninvasively determined carotid augmentation index has been used to show that left ventricular structure is related to the reflection pressure wave in nonhypertensive subjects (12, 13). The objective of the present study was to clarify the relationship between afterload, which consists mainly of the vascular reflection wave, and left ventricular hypertrophy in patients with untreated essential hypertension using PTG and SDPTG, the simplest and most convenient noninvasive tools for pulse wave analysis.

**Methods**

**Subjects**

Subjects consisted of 60 patients (30 men and 30 women; age range, 35 to 68 years; mean age, 54±8) with untreated essential hypertension. Blood pressure was measured at baseline and after one month. Systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more was diagnosed as hypertension, based on the JNC-VI criteria (14). All patients had had hypertension for 3 to 18 years (mean duration, 6±4 years). Patients with diseases that may directly affect the left ventricular mass, such as metabolic diseases, cardiomyopathy, myocardial infarction, or valvular diseases, or diseases characterized by obstruction of the peripheral vessels and therefore precluding the transmission of the pulse wave were excluded. All patients provided informed written consent to participate in this study.

**Blood Pressure, PTG and SDPTG**

After blood pressure of the left brachial artery was measured by the cuff method with patients seated, the PTG and SDPTG of the right second finger were recorded by a digital photoplethysmograph (FCP-4731, Fukuda Denshi, Tokyo, Japan). The FCP-4731 automatically analyzed each SDPTG wave. The accuracy of the FCP-4731 has been described previously (15). The mean brachial arterial blood pressure was calculated as follows: Diastolic blood pressure + (pulse pressure/3).

**The AI of PTG and Negative \( \frac{d}{a} \) of SDPTG**

The ascending aortic AI correlates positively with arterial impedance and indicates vascular afterload in the left ventricle (5, 6, 8, 9). In previous studies, the AI of PTG has been shown to be about 35% lower than that of the ascending aorta, but both showed parallel changes with increased or decreased blood pressure (9-11). The SDPTG consists of systolic a, b, c, and d waves and a diastolic e wave. The state of the late component of the PTG is well expressed by the d wave portion of the SDPTG: as AI or the late component at the ascending aorta increases, AI or the late component of PTG also increases and the \( \frac{d}{a} \), or ratio of the height of the d wave to that of the a wave of the SDPTG, greatly decreases. Accordingly, the increase in negative \( \frac{d}{a} \) obtained by multiplying the \( d/a \) of the SDPTG by \(-1\) has the same meaning as the increase in AI (10, 11). The negative \( d/a \) was used to adjust the polarity for comparison with the AI. The AI of the PTG and the negative \( d/a \) represent the late systolic component of the pressure wave at the ascending aorta, and are indices of the reflection wave. Figure 1 shows the analysis of each wave. Figure 2 shows sample tracings with administration of vasoactive agents. On the basis of the configuration of the pressure waveform, subjects were assigned to one of two groups: a low AI (AI of PTG<1.6; group 1) or a high AI (AI of PTG ≥1.6; group 2) group.

**Echocardiography**

An experienced cardiologist performed standard M-mode and two-dimensional echocardiograms in all subjects using an echocardiograph (SONOS 500, Hewlett Packard, Andover, MA, USA) with a 2.5 MHz single-element transducer. Left ventricular dimensions were obtained by averaging the measurements made from two-dimensionally guided M-mode tracings according to the recommendations of the American Society of Echocardiography (16). The left ventricular mass was calculated using the corrected American Society of Echocardiography measurements and adjusted for body surface area (17). Left ventricular geometry was further characterized by the relative wall thickness, calculated as follows: \((2\times\text{Left ventricular posterior wall thickness})/\text{Left ventricular end-diastolic dimension}\) (18). Left ventricular end-systolic and end-diastolic volumes were calculated according to the Teichholz formula to determine stroke volume. Total peripheral resistance and left ventricular fractional shortening...
Fig. 1. Pulse wave measurement. The ascending aortic pressure (AoP) augmentation index (AI) was defined as \( P_2 - P_0 / P_1 - P_0 \), where \( P_2 \) is the ascending aortic late peak systolic pressure, \( P_0 \) is the ascending aortic diastolic pressure, and \( P_1 \) is the ascending aortic early peak systolic pressure. The AI of fingertip photoplethysmogram (PTG) was defined as \( PT_2 / PT_1 \), where \( PT_2 \) is the amplitude of the late systolic component, and \( PT_1 \) is the amplitude of the early systolic component. The second derivative wave of PTG (SDPTG) consists of the initial positive wave (a wave), early negative wave (b wave), re-increasing wave (c wave), late re-decreasing wave (d wave), and diastolic positive wave (e wave), and the shift from the baseline to the top of each wave is taken as the value for each wave. The ratios of the height of the d wave to that of the a wave were measured as dia. The negative dia (-dia) was derived by multiplying the dia by -1. EGG, electrocardiogram. After Takazawa et al. (10).

Fig. 2. The sample tracings show results of vasoactive agents. An increase in the late systolic component of aortic pressure (AoP) and PTG after intravenous injection of 2.5 \( \mu \)g angiotensin (AGT) and a deepened d wave in relation to the height of the a wave (decreased dia) are seen in the SDPTG. On the other hand, nitroglycerin (NTG) produces marked reduction in late systolic components of aortic pressure and PTG, with the d wave becoming shallower in relation to the height of the a wave (increased dia). ECG, electrocardiogram; AoF, ascending aortic flow velocity. After Takazawa et al. (10).
were calculated using standard formulas. Peak velocity of the early diastolic filling flow (E) and peak velocity of the late systolic filling flow associated with atrial systole (A) were measured using two-dimensional Doppler echocardiography in the center of the mitral orifice in diastole, and the E/A ratio was calculated as an index of left ventricular diastolic function (19).

**Statistical Analysis**

All measurements were expressed as means±SD. The correlation was analyzed using single-regression analysis. Comparisons between subjects with an augmentation index of less than 1.6 (group 1) and subjects with an augmentation index of 1.6 or more (group 2) were performed using Student’s t test. P values less than 0.05 were considered to indicate statistical significance.

**Results**

**Cases 1 and 2**

The age, gender, duration of hypertension, and blood pressure were similar in Cases 1 and 2, except for the AI of the PTG and the negative d/a. The AI of the PTG was 1.3 in Case 1 and 1.8 in Case 2, and the negative d/a was 0.31 in Case 1 and 0.64 in Case 2. Case 2 myocardial wall thickness and left ventricular mass index were larger than those in Case 1. BP, brachial blood pressure; HR, heart rate; AI, augmentation index; PTG, fingertip photoplethysmogram; SDPTG, second derivative wave of PTG; IVSTd, interventricular septal diastolic thickness; PWTd, left ventricular diastolic posterior wall thickness; LVIDd, left ventricular diastolic internal diameter; LVIDs, left ventricular systolic internal diameter; FS, fractional shortening; DT, deceleration time of the velocity of the early diastolic filling flow; E, peak velocity of the early diastolic filling flow; A, peak velocity of the late systolic filling flow associated with atrial systole.

**AI and Demographic Variables**

The 30 type L subjects (group 1) and the 30 type H subjects (group 2) were similar with regard to gender, age, duration of hypertension, height, body mass index, body surface area, brachial artery blood pressure and pulse pressure. The AI and negative d/a were higher in group 2.
than in group 1 (Table 1).

**AI and Left Ventricular Structure and Function**

Left ventricular wall thickness was greater in subjects with a high late systolic component (group 2) than in those with a lower late systolic component (group 1) (Table 2). The left ventricular mass, left ventricular mass index, and relative wall thickness were higher in group 2 than in group 1 (191±39 vs. 156±29 g, p<0.0005; 118±22 vs. 96±15 g/m², p<0.0001; 0.48±0.1 vs. 0.44±0.07, p<0.05, respectively). Total peripheral resistance was increased in group 2 subjects, and the E/A ratio was lower in group 2 than in group 1 subjects.

**Relation of Negative d/a, Blood Pressure, Duration of Hypertension and Total Peripheral Resistance to AI**

In the study group as a whole, the AI was most closely related to negative d/a (r=0.73, p<0.0001), as previously reported (10) (Fig. 4). The AI was also correlated with brachial artery mean blood pressure (r=0.31, p<0.05), duration of hypertension (r=0.30, p<0.05) and total peripheral resistance (r=0.23, p<0.05). However, the AI was not related to age, brachial systolic blood pressure, brachial diastolic blood pressure, pulse pressure, body mass index, body surface area or height.

**Table 1. Demographic Features and Arterial Pressures in Subjects with a High or Low AI of Fingertip Photoplethysmographic Waveform**

<table>
<thead>
<tr>
<th>n</th>
<th>Group 1 (type L beats, AI&lt;1.6)</th>
<th>Group 2 (type H beats, AI≥1.6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AI</td>
<td>1.32±0.17</td>
<td>1.97±0.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Negative d/a</td>
<td>0.37±0.12</td>
<td>0.52±0.08</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52±9</td>
<td>55±6</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/15</td>
<td>15/15</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of Hypertension (yr)</td>
<td>6±3</td>
<td>7±4</td>
<td>NS</td>
</tr>
<tr>
<td>Height (m)</td>
<td>160±10</td>
<td>160±9</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (Kg/m²)</td>
<td>23.3±2.7</td>
<td>23.8±2.8</td>
<td>NS</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.62±0.18</td>
<td>1.62±0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial SBP (mmHg)</td>
<td>149±9</td>
<td>154±7</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial DBP (mmHg)</td>
<td>94±6</td>
<td>96±8</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial PP (mmHg)</td>
<td>55±10</td>
<td>58±11</td>
<td>NS</td>
</tr>
<tr>
<td>Brachial MBP (mmHg)</td>
<td>113±6</td>
<td>115±6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values presented are mean values±SD or number of subjects. AI, augmentation index; SBP, systolic blood pressure; DBP, diastolic blood pressure; F, female; M, male; PP, pulse pressure; MBP, mean blood pressure.

**Table 2. Relation of Augmentation Index to Left Ventricular Structure and Function**

<table>
<thead>
<tr>
<th>n</th>
<th>Group 1 (type L beats, AI&lt;1.6)</th>
<th>Group 2 (type H beats, AI≥1.6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV diastolic posterior wall thickness (cm)</td>
<td>0.98±0.11</td>
<td>1.09±0.17</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>IV septal diastolic thickness (cm)</td>
<td>1.05±0.11</td>
<td>1.21±0.16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV diastolic internal diameter (cm)</td>
<td>4.5±0.4</td>
<td>4.6±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>LV mass (g)</td>
<td>156±29</td>
<td>191±39</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>96±15</td>
<td>118±22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.44±0.07</td>
<td>0.48±0.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes-cm/s⁻⁵)</td>
<td>2,331±634</td>
<td>2,651±609</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>62±15</td>
<td>60±15</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>4.2±1.1</td>
<td>3.7±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>39±9</td>
<td>36±8</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.0±0.2</td>
<td>0.9±0.2</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean values±SD. AI, augmentation index; IV, interventricular; LV, left ventricular; E, peak velocity of the early diastolic filling flow; A, peak velocity of the late systolic filling flow associated with atrial systole.
Relation of AI and Negative d/a to Left Ventricular Mass Index

In the study group as a whole, the left ventricular mass index was positively correlated with the AI ($r=0.60$, $p<0.0001$) and negative d/a ($r=0.63$, $p<0.0001$) (Fig. 5). Age ($r=0.37$, $p<0.005$), brachial artery systolic blood pressure ($r=0.34$, $p<0.01$), brachial artery diastolic blood pressure ($r=0.32$, $p<0.05$), brachial artery mean blood pressure ($r=0.42$, $p<0.001$) and duration of hypertension ($r=0.38$, $p<0.005$) were correlated with the left ventricular mass index. Neither brachial artery pulse pressure nor total peripheral resistance was related to the left ventricular mass index.

Discussion

Blood Pressure and Left Ventricular Hypertrophy

Left ventricular hypertrophy is associated with pressure load and enhancement of the sympathetic nervous and renin-angiotensin systems (20). It has been shown that mechanical loads, such as hemodynamic load, activate kinases in cardiac muscle cells and induce enhanced specific gene expression and protein synthesis (21), making pressure load the most important factor in cardiac hypertrophy. However, in this study, as in previous reports (3, 4), the low level of correlation was found between the brachial arterial blood pressure and the degree of left ventricular hypertrophy. One possible reason for the low level of correlation between the brachial blood pressure and left ventricular hypertrophy is that this blood pressure reading may not be a sufficient index to indicate afterload, and specifically pulsatile vascular load, following rhythmical contraction of the left ventricle. Another possible reason is that brachial arterial systolic blood pressure may not correspond with systolic blood pressure of the ascending aorta and thus may not indicate the maximum load on the left ventricle. In fact, blood pressure measurement of the brachial artery is suspected to underestimate the changes in systolic blood pressure in the ascending aorta (9). The most important point is that systolic pressure has two components. The ascending aortic pressure wave can be divided into two components at an early systolic inflection point that coincides with the ascending aortic flow peak (8). The early systolic component is mainly caused by ejection from the left ventricle and the late systolic component by the reflection wave from the periphery. These two components are transmit-
Cardiac Hypertrophy

Relation between the Vascular Reflected Wave and Cardiac Hypertrophy

Left ventricular hypertrophy may be influenced by gender, age, blood pressure, and history of hypertension (12, 13, 22, 23). In the present study, however, the relationship between an increase in the late systolic component and each of several measurements of cardiac structure and functions was confirmed by comparing two groups with no significant differences in gender, age, blood pressure, or history of hypertension. Most notably, higher left ventricular mass index was detected in subjects with late systolic augmentation of the PTG waveform and high negative d/a ratios. In addition, the left ventricular mass index was positively correlated to both the AI of PTG and negative d/a. These findings indicate that an increase in the ascending aortic AI caused by a reflected wave may be involved in the formation of left ventricular hypertrophy.

In the present study, a decrease in the transmitral E/A ratio was seen in subjects with an augmented late systolic component in the waveform. Decrease in the rate of left ventricular relaxation is known to be closely associated with left ventricular hypertrophy (24). However, the change in left ventricular relaxation due to afterload varies with the magnitude of the change in load and the time point during contraction at which the load is changed (25-28). Thus, biochemical changes in cardiac muscle cells may vary with the time point during contraction at which the mechanical load is changed. The increase in the late systolic component that consists mainly of the reflection wave, i.e., the increase in the AI, prolongs the time constant (Tau) of the isovolumic left ventricular pressure decline and disturbs the left ventricular relaxation (29), suggesting that the reflection pressure wave may be important in the formation of left ventricular hypertrophy.

As arteriosclerosis progresses with age, AI also elevates (8). However, the present cohort included subjects whose AI was higher than that of normal individuals of the same generation due to rapid progress of arteriosclerosis that was due, in turn, to various risk factors, including hypertension. Thus, the correlation between age and AI that would normally be present was not detected in this study.

Conclusions

The AI of PTG and negative d/a of SDPTG are peripheral reflection wave indices that can be measured easily and noninvasively. Those methods are useful for determining left ventricular afterload, which cannot be evaluated merely by brachial artery blood pressure. In this study, the left ventricular mass index was positively correlated with both the AI of PTG and negative d/a of SDPTG. It is therefore possible that a late systolic load that mainly consists of a peripheral reflection wave is involved in the formation of left ventricular hypertrophy in patients with hypertension. In medical consultations on hypertension, measurement of the AI of PTG and negative d/a of SDPTG should enable easy prediction of left ventricular hypertrophy.

Limitations

The formation of cardiac hypertrophy is associated with a complex interaction among various factors that include increased pressure load and enhancement of the sympathetic nervous and renin-angiotensin systems. Given this complexity, there is a limit to which the risk of cardiac hypertrophy can be effectively evaluated based on pressure load alone.

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References


