Clinical Research

Elevated radial arterial augmentation index in hypertensive patients with diastolic dysfunction

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Objective To investigate the correlation between augmentation index (AI) of the radial artery and diastolic heart function in patients with hypertension. Method Echocardiographs were obtained for 305 patients with hypertension. AI, pulse wave velocity (PWV) of peripheral arteries and serum pro-brain natriuretic peptide (proBNP) levels were determined. Correlations and receiver operating characteristic (ROC) curves were drawn between AI values and impaired diastolic function. Results AI levels were significantly increased in patients with impaired diastolic function diagnosed by ultrasound. Assessment of diastolic heart function based on proBNP levels revealed that AI and aortic pulse wave velocity were significantly elevated in patients with impaired diastolic function. The operating curve indicated that AI may be a more accurate and efficient index for the evaluation of impaired diastolic function compared to PWV. Correlation analysis also showed that proBNP levels had altered in parallel with changes in AI and PWV. After adjusting for various factors including age, gender, blood pressure and blood lipid, a positive correlation was observed between proBNP and AI with a correlation coefficient of 0.3697 (P=0.003). However, no correlation between proBNP and aortic PWV was seen after adjustment. Conclusion Changes in radial AI levels may reflect parallel changes in diastolic cardiac function in patients with hypertension, suggesting that AI may be utilized as a non-invasive clinical indicator of diastolic heart function. (J Geriatr Cardiol 2008; 5: )

Key Words augment index; diastolic heart failure; hypertension; pro BNP; pulse wave velocity

Introduction

Various cardiac diseases often result in heart failure. The mortality rate from acute cardiovascular events such as myocardial infarction has been greatly reduced, and the survival period of patients has effectively been prolonged with rapid advances in medical technology and cardiovascular disease therapeutics. Nonetheless, the overall number of patients with heart failure continues to grow at an alarming rate. A survey conducted in 2003 revealed that nearly 5 million patients were afflicted with chronic heart failure in the United States, with another 500,000 newly diagnosed each year 1. At present, diastolic heart dysfunction is commonly thought to trigger diastolic heart failure (DHF), and thus remains an active area of research in cardiology 2,4. Medical economic data show that DHF accounts for more than one forth of heart failure patient costs in the US, equivalent to approximately $15-40 billion. DHF is also prevalent in other areas of the world including at least 4 million afflicted in China 1,6.

Hypertension commonly contributes to the pathogenesis of DHF due to severely increased heart afterload 7,8. An epidemiologic survey in Europe suggested that DHF patients with a history of hypertension account for 42.1% of the entire DHF population 9. Additionally, Bonow 10 found that 53-60% of left ventricular DHF cases were due to hypertensive heart disease, and Vasodilator Heart Failure Trial (V-HeFT) reported that hypertension induces 53.0% and 39.4% of DHF and systolic heart failure (SHF), respectively. Thus, hypertension is closely correlated with DHF. Current treatments for DHF have combined prevention and management of risk factors rather than the application of simple therapies. Screening patients with impaired diastolic function early, quickly and conveniently in high-risk populations (such as patients with hypertension) is of great significance for the prevention and treatment of DHF.

Determination of the augmentation index (AI) of the reflected wave is a measurement of arterial pressure waves at various sites by using applanation tonometry. Segers et al. 11, 12 reported a significant correlation between AI values determined by this technique and those from the direct invasive method with a coefficient of 0.66 (P<0.001). Therefore, AI values determined using the non-invasive method can accurately reflect the arterial wave and serve as a reliable indicator of arterial function.

The amplitude of the reflected wave is determined by the functional state and anatomic structure of the artery, including thickening of the arterial wall, increased rigidity, lumen stenosis, changes in blood flow rate and epithelial function. Augmented amplitudes of the reflected wave leads
to changes in AI levels. Therefore, AI values may more accurately and comprehensively reflect the state of the artery compared to PWV values. Vasoactive substances such as nitrates were also found to possibly lower AI but not PWV levels\(^{15}\), indicating that changes in AI are more sensitive to arterial pressure changes and contractile state.

Further studies suggested that changes in AI levels provide more information than changes in artery compliance alone. Nurnberger \(^{14}\) examined individuals with cardiovascular disease risk factors and found that AI levels were positively correlated with blood pressure, heart rate, gender, age and stature. AI may thus be used as a unique indicator to evaluate the risk of cardiovascular disease. Several clinical studies have demonstrated that hyperlipidemia prompts the development of arteriosclerosis, which may also affect AI levels\(^{13}\). The presence of cardiovascular disease can influence AI, as patients with coronary heart disease displayed increased AI levels and a further significant change was observed when hypertension was added to the analysis\(^{16}\). Comparing coronary angiographic images with AI levels showed noted increases in both AI values and narrowed branches. AI values were positively correlated with scores of coronary stenosis. When AI $\geq 45\%$ was considered positive, the accuracy and specificity of diagnosis were 91.5% and 92.6%, respectively\(^{13}\). AI levels in patients receiving percutaneous coronary intervention (PCI) operations may therefore reliably predict the incidence of serious cardiovascular disease\(^{18}\).

A previous diabetic study revealed that aortic AI values were correlated with BNP levels, and a simultaneous increase of both usually indicated the presence of impaired diastolic function\(^{19}\). Additionally, a Japanese study comparing aortic AI values and echocardiography results found that AI levels may be correlated with systolic function in patients with hypertension\(^{18}\). Nevertheless, there is little evidence supporting the correlation between AI levels and diastolic function, especially in hypertensive patients. Thus, the aim of our present study was to examine the correlation between AI values and diastolic heart function in hypertensive patients. Besides the evaluation of peripheral AI values and echocardiograms, levels of pro-BNP were also used for further diagnostic analysis.

**Materials and Methods**

**Subjects**

Patients preliminarily diagnosed with hypertension between October 2006 and January 2007 were examined with cardiac ultrasound and tested for serum pro-BNP at the Health Center of Chinese PLA General Hospital. Patients with a history of coronary disease, myocardial infarction, myocardial disease, valvular disease, chronic renal disease, renal failure, mitral regurgitation and low ejection fraction (<50%) were excluded. The study design was approved by the Ethics Committee of Chinese PLA General Hospital.

**Diagnosis of hypertension**

Blood pressure was determined under resting conditions with a calibrated mercury sphygmomanometer. According to standards issued by WHO/ISH in 1999, hypertension was diagnosed when blood pressure $\geq 140/90$ mmHg on at least two occasions on different days. The mean of three independent measurements was reported.

**Collection and analysis of blood samples**

Fasting blood samples were collected and analyzed at the Biochemistry Department of the Chinese PLA General Hospital to determine pro-BNP levels. MODULAR ANALYTICS E170 was used to perform automated analysis using a kit (Cobas Company) according to the manufacturer’s instruction\(^{17}\) with variations of 5% and 10% within and between groups, respectively. A value of pro-BNP $> 125$ ng/mL was used as the diagnostic standard for heart failure\(^{20,21}\).

**Evaluation of cardiac diastolic functions by ultrasound**

Cardiac ultrasonography (Model HP 5500) was performed by a specialized physician in the Ultrasound Diagnosis Department of the Chinese PLA General Hospital. The following parameters were determined: (1) left ventricular diastolic filling, i.e. the blood flow rate into left ventricle, early filling wave (wave E) and atrial systolic wave (wave A), E/A value, decay time of wave E (DcT) and duration of wave A (Ad); (2) wave of pulmonary venous blood flow, comprised of systolic wave (wave S), diastolic wave (wave D), back flow produced by atrial contraction (wave PVA) and peak flow rate; PVA duration (PAad) and decay time of wave D (PA2DT); (3) Doppler graph formulated by the mitral ring. Blood flow wave of the mitral ring included systolic wave (Sw), early diastolic wave (Ew) and atrial systolic wave (Aw). Patients abnormal for these three indicators were diagnosed with impaired diastolic function.

**Determination of arterial compliance**

Pulse wave velocity (PWV) was determined to evaluate the arterial compliance of each subject. A PP1100-Pulse Wave Meter (Hanbyul Meditech Co.) was used to assess PWV of brachial and femoral arteries. An attached software was applied to calculate the aortic PWV.

**Determination of AI**

Radial AI values were determined by trained professionals using an Omron Augmentation Index Monitor (HEM-9000AI, Omron Company) with the following standard procedure: The patient assumed a sitting rather than a supine position with the right arm laid flat and a bracelet probe placed perpendicular to the site of the radial artery with the most obvious pulse. The probe pressure and site were gradually adjusted until a stable level was reached,
and an ideal radial arterial pressure wave was obtained. All subjects were tested twice with each recording lasting for at least 10 seconds to calculate the mean value.

**Statistical analysis**

Continuous variables were expressed as mean ±SD, and discontinuous variables were expressed as frequencies. Statistical analysis was conducted using the SPSS 10.0 software (SPSS Inc.) with \( P<0.05 \) considered significant. Tests for homogeneity of variance was conducted prior to comparison between groups and followed by \( t \)-tests. Rates were compared using \( \chi^2 \) analysis, and correlations were determined for proBNP, AI values and diastolic function. ROC curves of AI values were constructed to evaluate any effects on impaired diastolic function.

**Results**

**Characteristics of subjects**

Patients preliminarily diagnosed as hypertensive (179 males and 126 females) were examined and had an average age of 48.97±11.54. The left ventricular ejection fraction was >50% in all individuals, excluding the presence of systolic heart dysfunction. The serum creatinine clearance rate was normal in each of the enrolled patients.

**Evaluation of diastolic heart function by ultrasound**

Among 305 cases enrolled in this study, 171 had abnormal diastolic filling profiles for the left ventricle. Further examination of pulmonary venous blood flow and Doppler graphs of the mitral ring confirmed impaired diastolic function in 157 cases. All subjects were grouped and compared according to examination results. The average age of patients with impaired diastolic function was 53.11±13.1 years, which was significantly higher than that of the normal group (\( P<0.001 \)). The average systolic pressure and AI level of the radial artery were higher in the impaired diastolic function group than in the normal group (\( P<0.01 \)). Comparison of the average proBNP levels between the two groups was intriguing. Although the proBNP level of the impaired diastolic function group was markedly increased as expected, 33.3% of these patients still displayed levels below the diagnostic threshold (Table 1).

**Evaluation of diastolic function according to proBNP levels in patients with hypertension**

Serum proBNP is presently used as the gold standard for diagnosis of impaired diastolic function. Patients diagnosed with impaired diastolic function according to proBNP levels were older than those from the normal group (\( P<0.01 \), with marked increases in AI levels (92.19±18.71 vs. 68.68±16.31, \( P<0.01 \)). A significant difference in the ratio of blood flow in the mitral orifice was observed, and patients with greater levels of proBNP had inverted blood flow ratios. In four patients with abnormal proBNP levels, no changes in diastolic function were identified upon ultrasonic examination. In addition, pulse rate was greatly increased in the abnormal diastolic function group, suggesting the presence of altered aortic compliance in these patients (Table 2).

**Receiver operating characteristic (ROC) curves of AI values in hypertensive subjects with impaired diastolic function**

ROC curves of hypertensive patients with impaired diastolic function diagnosed using AI values were constructed (Figure 1). The area under the curve (AUC) was calculated as 0.911 (\( P<0.01 \)). These results suggest that AI is a valid and accurate parameter to assess hypertension.

Several cut off values were determined according to the sensitivity and specificity of the possible tangential point in statistical results. Youden’s index was calculated and the largest tangential point was adopted as the borderline point. The optimal borderline of each AI value used for diagnosis of impaired diastolic function was 85.5, with a sensitivity of 0.909 and a specificity of 0.889.

PWV was another common indicator reflecting arte-

### Table 1 Comparison of diastolic heart function indicators by ultrasound

<table>
<thead>
<tr>
<th></th>
<th>Normal diastolic function group</th>
<th>Impaired diastolic function group</th>
<th>( P )</th>
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<tbody>
<tr>
<td>Number of cases</td>
<td>148</td>
<td>157</td>
<td>0.000</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.37±6.74</td>
<td>51.31±12.9</td>
<td>0.000</td>
</tr>
<tr>
<td>proBNP (ng/mL)</td>
<td>48.79±36.53</td>
<td>106.48±17.62</td>
<td>0.000</td>
</tr>
<tr>
<td>AI</td>
<td>60.28±17.36</td>
<td>81.06±16.97</td>
<td>0.002</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>131.57±9.24</td>
<td>116.25±13.81</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92.25±5.26</td>
<td>95.06±10.15</td>
<td>0.409</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>58.02±13.17</td>
<td>59.98±16.34</td>
<td>0.449</td>
</tr>
<tr>
<td>Aortic PWV (cm/ms)</td>
<td>7.25±0.78</td>
<td>8.73±0.76</td>
<td>0.102</td>
</tr>
<tr>
<td>PWV of upper limb artery (cm/ms)</td>
<td>9.21±1.20</td>
<td>9.07±0.43</td>
<td>0.640</td>
</tr>
<tr>
<td>PWV of lower limb artery (cm/ms)</td>
<td>9.480±0.75</td>
<td>9.72±1.04</td>
<td>0.349</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SEM.
Correlation analysis of ultrasonic results, blood pressure and arterial function

Correlation analyses were performed between AI levels and diastolic function determined by ultrasound, blood pressure and arterial function. Results indicated that diastolic function determined by ultrasound was highly correlated with AI levels. Reduced E/A ratios were inversely correlated with increases in AI levels (correlation coefficient = -0.382). Decreased arterial compliance and increased PWV levels were accompanied by a large increase in AI. In addition, an inverse correlation was observed between AI levels and systolic pressure.

Results of partial correlation analysis

Age, gender, blood pressure and blood lipid content may influence levels of AI and proBNP. A partial correlation analysis was performed between AI and proBNP following adjustment of the aforementioned factors, and changes in AI levels were found to positively correlate with changes in proBNP levels (correlation coefficient = 0.3697, P=0.003). However, correlations were no longer detected between proBNP and aortic PWV (r=0.0991, P>0.05) or between AI and PWV (r=0.0798, P>0.05).

Discussion

We analyzed radial AI levels and diastolic function in
patients with hypertension, and our data revealed significantly elevated AI levels in hypertensive patients with impaired diastolic function. More importantly, changes in AI levels were closely correlated with systolic pressure, levels of proBNP, E/A of mitral blood flow and aortic PWV. After adjusting for age, gender and blood pressure, AI continued to exhibit a positive correlation with changes in proBNP concentration. The ROC curve of impaired diastolic function in hypertension patients indicated an AUC of 0.911, suggesting a diagnostic significance of AI levels in assessment of diastolic function in hypertensive patients.

The artery reflected wave is an essential parameter commonly used for diastolic function, coronary perfusion and overall cardiovascular risk. The reflected wave normally depicts an increase in blood pressure during end systole (afterload) in hypertensive patients. This increased afterload contributes to myocardial damage, leading to compromised diastolic function. As a result, AI level is an index of arterial reflected wave and plays a key role in the evaluation and management of hypertensive heart failure.

Ejection fraction and left ventricular ejection time are non-invasive indicators for left ventricular systolic function. Sakurai examined 41 cases receiving cardiac catheterization and found a correlation between left ventricular ejection time and AI value. For patients with confirmed chronic cardiac insufficiency, AI levels were closely correlated with left ventricular ejection fraction and ejection time, even after adjusting for other factors including age. Therefore, AI levels are believed to be an indicator for the assessment of cardiac systolic function. In this study, we found that changes in AI also reflected changes in left ventricular diastolic function in patients preliminarily diagnosed with hypertension.

Increasing attention has been paid to the management of diastolic heart function, as its impairment triggers symptoms characteristic of heart failure such as chest tightness and labored breathing. The AI value of the descending aorta is suggested to be linearly associated with the left ventricular AI value. In Adamantiades-Behcet patients, there is a correlation between the radial AI level and left ventricular diastolic function. Thus, AI values may provide additional information for patients with hypertension. Hashimoto evaluated 77 hypertensive cases and found a high correlation between radial AI level and occurrence of left ventricular hypertrophy. The risk of left ventricular hypertrophy was increased 1.99 times with every 10% increase in AI level. Changes in mitral blood flow E/A ratios tended to correlate with AI levels, though not statistically significance. Although Iketa and coworkers confirmed the correlation between left ventricular hypertrophy and AI level, these investigators did not probe the relationship between diastolic function and AI level. Data from our study revealed greatly elevated AI values in hypertensive patients with impaired diastolic function and a negative correlation between the radial AI value and ratio of mitral blood flow (an index for left ventricular filling). The diagnostic AI value of impaired diastolic function was also evaluated using ROC curves, confirming the role of AI values in the evaluation of cardiac function in patients with hypertension and confounding diastolic function.

Compared with conventional ultrasonic evaluation to diagnose heart failure, the use of proBNP levels eliminates subjective influences to achieve higher sensitivity and specificity. In addition, the diagnostic specificity of proBNP is greater than that of BNP, which is particularly important for early diagnosis of diastolic heart failure patients lacking early clinical symptoms. To further confirm the use of radial AI levels in the evaluation of diastolic function, the correlation between AI and proBNP levels was determined. AI was found to closely correlate with both cardiac sonography results and proBNP levels, with a stronger correlation with proBNP. In addition, our study revealed that the positive correlation between proBNP and aortic PWV (another arterial functional indicator) disappeared after adjusting for age, gender, blood pressure and circulating lipids. The ROC curves also validated the superior diagnostic value of AI over PWV. Therefore, AI values better evaluate diastolic function in patients with hypertension, compared with the common PWV indicator previously used to rank arterial function.

AI values vary depending on the artery of interest, providing disparate clinical information based on the nature of the vessel. Previous studies have indicated that aortic and carotid AI values have a closer correlation with risk factors, mortality rate and prognosis of cardiovascular disease. Nevertheless, clinical applications for AI values are somewhat limited due to difficulties during the determination process. Sugawara recently reported a correlation between aortic and carotid AI with a correlation coefficient of 0.86, despite a seemingly higher AI value calculated from the radial wave than carotid AI value (by approximately 66%). These data support that AI levels may be used to evaluate progression of cardiovascular disease, as radial AI levels closely correlated with cardiac (particularly diastolic) function.

In summary, in this study we provided evidence that radial AI can serve as a noninvasive and reliable indicator of diastolic function in hypertensive patients based on the analysis of untreated patients with hypertension. However, more studies are needed to further address how AI values are correlated with systolic heart function in more advanced hypertension and whether or to what extent pharmaceutical intervention of ventricular hypertrophy aimed at improving ventricular compliance can affect the radial AI levels.

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References


