Correlation of Arterial Stiffness to Left Ventricular Function in Patients with Reduced Ejection Fraction

Sanae Noguchi,1 Hisashi Masugata,2 Shoichi Senda,2 Kaori Ishikawa,1 Hiromi Nakaishi,1 Ayu Tada,1 Toshihiro Inage,1 Tatsushi Kajikawa,1 Michio Inukai,2 Takashi Himoto,2 Naohisa Hosomi,3 Kazushi Murakami,4 Takahisa Noma,4 Masakazu Kohno,4 Hiroki Okada,5 Fuminori Goda2 and Koji Murao6

1Department of Clinical Laboratory, Kagawa University, Kagawa, Japan
2Department of Integrated Medicine, Kagawa University, Kagawa, Japan
3Department of Clinical Neuroscience and Therapeutics, Hiroshima University Graduate School of Biomedical Sciences, Hiroshima, Japan
4Department of Cardiorenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan
5Department of Medical Education, Kagawa University, Kagawa, Japan
6Department of Advanced Medicine and Laboratory Medicine, Kagawa University, Kagawa, Japan

Heart failure has been divided into heart failure with preserved left ventricular (LV) ejection fraction (EF) and heart failure with reduced EF, because the pathophysiologies of the two conditions are different. Cardio-ankle vascular index (CAVI) is a new indicator of arterial stiffness, and the most conspicuous feature of CAVI is its independence of blood pressure at the time of measurement. Arterial stiffness has been considered to increase LV afterload, which requires special care to avoid the onset of heart failure. We compared the correlation of arterial stiffness as assessed by CAVI to LV function in 44 hypertensive patients with preserved EF (EF: 71 ± 7%) and 31 patients with reduced EF (48 ± 8%). All of patients with reduced EF had history of both hypertension and myocardial infarction. Using Doppler echocardiography, LV diastolic and systolic function was evaluated by measuring peak early diastolic mitral annular velocity (e') and global LV peak systolic longitudinal strain (GPSLS), respectively. In patients with preserved EF, CAVI was correlated with e' (r = −0.313, p = 0.038), but not with GPSLS (r = 0.207). By contrast, CAVI was correlated with GPSLS (r = 0.604, p < 0.001) as well as e' (r = −0.393, p = 0.029) in patients with reduced EF. Thus, patients with reduced EF showed a closer correlation of arterial stiffness to LV function compared with patients with preserved EF. Therefore, hypertensive patients with reduced EF require a stricter regimen for treating arterial stiffness than their counterparts with preserved EF.

Keywords: arterial stiffness; echocardiography; hypertension; left ventricular function; left ventricular ejection fraction

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Correspondence: Hisashi Masugata, M.D., Ph.D., Department of Integrated Medicine, Kagawa University, 1750-1, Miki-cho, Kita-gun, Kagawa 761-0793, Japan.
e-mail: masugata@med.kagawa-u.ac.jp
LV function has been studied for heart failure with preserved EF to elucidate the contribution of arterial stiffness to onset of heart failure with preserved EF (Desai et al. 2009; Kang et al. 2010). Some previous studies demonstrated the relationship between arterial stiffness and LV function by measuring pulse wave velocity (Tsoufis et al. 2005; Wang et al. 2009). Other studies reported these relationships by assessing arterial stiffness based on aortic diameters measurement by echocardiography (Karamitsos et al. 2006, 2008). Although CAVI is based on pulse wave velocity measurement, CAVI is a new indicator of arterial stiffness. The most conspicuous feature of CAVI is its independence of blood pressure at the time of measurement. In this study, we investigated the relationship between arterial stiffness as assessed by CAVI and LV function and whether it differs in hypertensive patients with preserved and reduced EF.

**Methods**

**Subjects and protocol**

This study included 44 hypertensive patients (25 men, 19 female; mean age 66 ± 15 years, range 22-93 years) with preserved EF (EF ≥ 60%), and 31 patients (27 men, 4 female; mean age 68 ± 11 years, range 38-81 years) with reduced EF (EF < 60%). The 31 patients with reduced EF had history of both hypertension and myocardial infarction. Hypertension was diagnosed according to the guideline of the Japanese Society of Hypertension. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg. EF was measured using echocardiography. Patients with atrial fibrillation were excluded. Hypertensive patients with preserved EF had neither history of heart failure nor obvious heart disease. All patients with reduced EF were patients with old myocardial infarction, and the reduced EF was attributed to the myocardial infarction. Blood pressure was determined using the conventional cuff method at the time when the echocardiographic examination was performed. Echocardiographic examinations were performed to assess cardiac structural changes and cardiac function. Arterial stiffness was assessed by measuring the cardio-ankle vascular index (CAVI) (Shirai et al. 2006). CAVI measurement was performed for all participants. Before CAVI measurement, blood examination and echocardiography were performed. Relationships among clinical characteristics, including blood pressure and laboratory data, echocardiographic parameters, and CAVI were analyzed. This protocol was approved by the Ethics Committee of Kagawa University. Informed consent was obtained from all participants.

**Blood examinations**

Blood sampling was performed in the morning after a 12-hour overnight fast. Plasma total cholesterol, triglyceride, and high-density lipoprotein cholesterol (HDL-C) were measured by standard laboratory techniques.

**Measurement of CAVI**

CAVI was recorded using a VaseraVS-1000 vascular screening system (Fukuda Densi, Tokyo, Japan) with the patient resting in a supine position. The principal underlying CAVI has been described previously (Shirai et al. 2006). ECG electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the sternum, and cuffs were wrapped around both arms and both ankles. After automatic measurements, the obtained data were analyzed using VSS-10 software (Fukuda Densi), and the values of right and left CAVI were calculated. In each case the average of the right and left CAVIs was used for analysis. The average coefficient of variation of CAVI in our laboratory was 3.9%, which was sufficiently low for clinical usage and indicated that CAVI had good reproducibility.

**Echocardiographic examination**

Two-dimensional and M-mode echocardiographies were performed using the Vivid Seven System (GE; Horten, Norway). We first measured the following aortic and left ventricular structural parameters by M-mode echocardiography: ventricular septal thickness (VS), left ventricular end-diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), and left ventricular posterior wall (PW) thickness, all at the chordae tendineae level; the end-systolic dimension of the left atrium (LAD); and the aorta root diameter at the level of Valsalva’s sinuses (AO). The left ventricular mass was calculated according to the American Society of Echocardiography convention (Wallerson and Devereux 1987) using the following formula: left ventricular mass = 0.80 [(PW+VS+LVDd)3 − (LVDd)3] + 0.6. The left ventricular mass index was calculated as the left ventricular mass divided by the body surface area. The left ventricular ejection fraction (EF) was estimated by Teichholz’s method (Teichholz et al. 1976) and was used as the parameter of LV systolic function in the LV short-axis direction.

We next measured the parameters of LV diastolic function by recording the transmitral flow velocity using conventional Doppler echocardiography, which measures blood flow velocities in the cardiac cavity (Nishimura and Appleton 1996). The transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak velocity of early transmitral flow velocity (E velocity) and the peak velocity of late transmitral flow (A velocity) were recorded, and the ratio of E to A (E/A ratio) was calculated.

Furthermore, tissue Doppler echocardiography, which measures the velocities of the regional cardiac wall, was performed with activating the tissue Doppler echocardiographic function in the same machine. Mitral annular velocities were recorded from the apical window. Sample volumes were located at the septal site of the mitral annulus. Peak early diastolic mitral annular velocity (e') was measured over 3 cardiac cycles and the results were averaged (Ommen et al. 2000). Furthermore, the ratio of E velocity to e' velocity (E/e') was calculated and used as a parameter of LV preload (Nagueh et al. 1997). The parameters obtained from tissue Doppler echocardiography were also analyzed as parameters of LV diastolic function.

Offline analysis was performed using a special type of commercial software, automated function imaging (AFI) (EchoPAC, GE Healthcare, Japan) (Liu et al. 2009), in order to measure global LV peak systolic longitudinal strain (GPSLS), which was used as a parameter of LV systolic function in the LV longitudinal direction. The tracking algorithm follows the endocardium from this single frame throughout the cardiac cycle and for a further manual adjustment of the region of interest to ensure that the entire myocardium, from the endocardial to epicardial layers, are included. Values of peak systolic longitudinal strain from the apical long-axis, apical 4-chamber, and apical 2-chamber views were obtained automatically by AFI software (Fig. 1) The average of the 3 values obtained from 3 views was regarded as GPSLS. The average coefficient of variation
of $e'$ and GPSLS in our laboratory was 4.0% and 4.2%, respectively. These values were sufficiently low for clinical usage and indicated that $e'$ and GPSLS had good reproducibility.

Statistical analysis

Data are expressed as means ± s.d. Statistical analysis was performed using SPSS software (SPSS, Chicago, IL, USA). Dichotomous data are presented as frequencies for background variables. Categorical variables were compared by the chi-square test. For the comparison of mean values among the two groups, unpaired Student’s $t$-test was used. Linear regression analysis was performed to evaluate the association between CAVI and other variables. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Clinical and echocardiographic characteristics of subjects

Clinical and echocardiographic parameters in hypertensive patients with preserved and reduced EF are compared in Table 1. The mean age did not differ between the two groups. The body size, which was assessed by BMI, was significantly larger in patients with reduced EF than in those with preserved EF ($p = 0.011$). The prevalence of diabetes was higher in patients with reduced EF than in those with preserved EF ($p = 0.010$). The HDL-cholesterol level was significantly lower and the triglycerides level was significantly higher in patients with reduced EF than in those with preserved EF ($p = 0.019$ and $p = 0.017$, respectively).

The LVMI reflecting LV hypertrophy was significantly larger in patients with reduced EF than in those with preserved EF ($p = 0.006$). The E/A and $e'$ reflecting LV diastolic function were significantly lower (worse) in patients with reduced EF than in those with preserved EF ($p = 0.007$ and $p < 0.001$, respectively). The GPSLS reflecting LV systolic function in the LV longitudinal direction was significantly smaller (worse) in patients with reduced EF than in those with preserved EF ($p < 0.001$).

Association between CAVI and other variables

CAVI was correlated with age for hypertensive patients with both preserved and reduced EF. In patients with preserved EF, CAVI was correlated with $e'$ ($r = -0.313, p = 0.038$), but not with GPSLS ($r = 0.207, p = \text{NS}$). By contrast, CAVI was correlated with GPSLS ($r = 0.604, p < 0.001$) as well as $e'$ ($r = -0.393, p = 0.029$) in patients with reduced EF.

Discussion

The present study presents data on the relationship between arterial stiffness and LV function in hypertensive patients with preserved EF and reduced EF. The data led us to the following conclusions: (1) although arterial stiffness was correlated only with LV diastolic function in patients with preserved EF, arterial stiffness was correlated with LV systolic function in the LV longitudinal direction as well as LV diastolic function in patients with reduced EF; (2) in the present study, hypertensive patients with reduced EF had a higher prevalence of diabetes and worse blood examination data of dyslipidemia compared with those with preserved EF; and (3) hypertensive patients with reduced EF showed worse LV systolic function in the LV longitudinal direction.
The most striking result in our analysis was that hypertensive patients with reduced EF showed a closer relationship between arterial stiffness and LV function than hypertensive patients with preserved EF. Previous studies (Miyoshi et al. 2011; Xu et al. 2011) have demonstrated an association between arterial stiffness and LV diastolic dysfunction in patients with preserved EF, and suggested that increased arterial stiffness may be a causative factor of heart failure produced by LV diastolic dysfunction. Our data is in agreement with the association between arterial stiffness and LV diastolic dysfunction in hypertensives with preserved EF. However, our data provide new information about the relationship of arterial stiffness to LV function in hypertensive patients with reduced EF. The close relationship of arterial stiffness to LV systolic function in the LV longitudinal direction in patients with reduced EF suggests that, in order to prevent heart failure, these patients may require a stricter regimen to treat arterial stiffness than those with preserved EF.

High blood pressure and increased arterial stiffness are closely associated (Kruger et al. 2011). High blood pressure and increased arterial stiffness lead to increased LV afterload, which is a causative factor of the onset of heart failure in patients with subclinical LV dysfunction. Indeed,
blood pressure control by antihypertensive agents is essential for preventing heart failure in patients with prior myocardial infarction (Seki et al. 1996). In the present study, hypertensive patients with reduced EF had a higher prevalence of diabetes and worse blood examination data of dyslipidemia compared with those with preserved EF (Table 1). Therefore, arteriosclerosis with increased arterial stiffness may have been more apparent in patients with reduced EF than those in preserved EF even if the CAVI did not differ between the two groups. Differences in the degree of arteriosclerosis between the two groups may have led to the differences in the association between arterial stiffness and LV function.

In the present study, e' reflecting LV diastolic function in early diastolic phase was correlated with CAVI. However, E/A ratio and E/e' as parameters of LV diastolic function were not associated with CAVI. E/A ratio and E/e' are influenced by LV loading condition, which is namely left atrial pressure (Nagueh et al. 1997; Ommen et al. 2000). Therefore, e', which is less influenced by LV loading condition, may be a best indicator of arterial stiffness in all parameters of LV diastolic function. Several studies (Donal et al. 2011; Park et al. 2011) have suggested that peak late diastolic mitral annular velocity (a') and e'/a' are also useful parameters of LV function. Further studies including a' and e'/a' may be needed for assessing association between arterial stiffness and LV diastolic function.

The present study has several limitations. First, we did not use modified Simpson’s method by 2-dimensional echocardiography for measuring EF. Modified Simpson’s method is more adequate than Teichholz’s method for measuring EF especially in patients with myocardial infarction. Second, we did not measure global LV peak early diastolic longitudinal strain rate as a parameter of LV diastolic function. Global LV peak early diastolic longitudinal strain rate may have provided more accurate assessment of LV diastolic function. Third, it has been reported that LV systolic function in the longitudinal direction is impaired in hypertensive patients with not only reduced EF but also preserved EF (Mizuguchi et al. 2010). Therefore, data from age-matched normal control group may be needed to clarify association between arterial stiffness and LV function. Finally, LV systolic function should be evaluated by the sum of longitudinal, circumferential, and radial deformation (Mizuguchi et al. 2010). Further studies including data of LV longitudinal, circumferential, and radial directions may be needed to clarify association between CAVI and LV function.

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<th></th>
<th>Preserved EF</th>
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<th>Reduced EF</th>
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<td></td>
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<td>p value</td>
<td>r</td>
<td>p value</td>
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<tr>
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<td>NS</td>
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<td>NS</td>
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<td>NS</td>
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</tr>
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<tr>
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</tr>
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<td>Diastolic BP (mmHg)</td>
<td>0.269</td>
<td>NS</td>
<td>−0.195</td>
<td>NS</td>
</tr>
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HDL, high-density lipoprotein; BP, blood pressure; CAVI, cardio-ankle vascular index; LV, left ventricular; LVMI, left ventricular mass index; LAD, left atrial dimension; AO, aorta root diameter at the level of Valsalva’s sinuses; EF, left ventricular ejection fraction; GPSLS, global LV peak systolic longitudinal strain; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; e', peak early diastolic annular velocity; E/e', the ratio of E to e'.

Table 2. Correlation coefficients of linear regression analysis between CAVI and other parameters.
In conclusion, hypertensive patients with reduced EF showed a closer relationship of arterial stiffness to LV function than hypertensive patients with preserved EF. Therefore, to prevent heart failure, hypertensive patients with reduced EF may require a stricter regimen to treat arterial stiffness than those with preserved EF.

Conflict of Interest
The authors have no conflict of interest to declare in relation to this article.

References


