Original Article

A New Index of “Cardiac Age” Derived from Echocardiography: Influence of Hypertension and Comparison with Pulse Wave Velocity

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Although pulse wave velocity is the primary indicator of arteriosclerosis and is widely used as an index of vascular age in anti-aging medicine, no index is available to quantify cardiac age. We proposed a “cardiac age” index and sought to clarify its clinical significance. The study subjects were 234 patients with atherosclerosis-related diseases. These patients were divided into 127 normotensive (mean age: 64 ± 12 years) and 107 hypertensive (mean age: 65 ± 11 years) patients. Echocardiography was performed, and brachial-ankle pulse wave velocity (baPWV) was measured using an automatic waveform analyzer. The index of cardiac age was determined as $1,000 \times VS_{ot}/BSA/(VS-AO)$, where VS_{ot} (mm) was the ventricular septal thickness at the left ventricular outflow tract, BSA (m^2) was the body surface area, and VS-AO (degree) was the angle between the basal ventricular septum and the ascending aorta. The index of cardiac aging correlated significantly with age in both the normotensive ($r=0.63$, $p<0.001$) and hypertensive ($r=0.58$, $p<0.001$) patients, and these correlations were closer than those between transmitral E/A (early to atrial velocity) ratio and age in normotensive ($r=0.54$, $p<0.001$) and hypertensive ($r=0.44$, $p<0.001$) patients. The slope between age (x -axis) and the index of cardiac age (y -axis) was greater in hypertensive (1.50) than normotensive (1.32) patients. Stepwise regression analysis showed that age (β coefficient=0.35, $p<0.001$), the presence of hypertension (β coefficient=0.26, $p<0.001$), the left ventricular mass index (β coefficient=0.34, $p<0.001$), the left ventricular end-diastolic dimension (β coefficient=-0.35, $p<0.001$), the dimension of the left atrium (β coefficient=0.14, $p=0.014$), and the ratio of E to A (E/A) (β coefficient=-0.12, $p=0.046$) were independently associated with the index of cardiac age. The index was also significantly correlated with baPWV ($r=0.53$, $p<0.001$). The proposed index of cardiac age can quantitatively assess cardiac morphological changes due to aging and/or hypertension and may be a useful marker of peripheral arterial stiffening. (*Hypertens Res* 2008; 31: 1573–1581)

Key Words: aging, hypertension, echocardiography

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Introduction

Both carotid ultrasonography and pulse wave velocity are established means of diagnosing arteriosclerosis (1–5). In particular, because pulse wave velocity can reflect arterial stiffening due to arteriosclerosis, it is a useful index of vascular age in clinical settings of anti-aging medicine (3–5). In contrast, no indexes of cardiac age have been derived from echocardiography. This may be attributable to the fact that echocardiography has mainly been used for diagnosing cardiac disease and assessing cardiac function.

However, with the advent of echocardiography, numerous reports have revealed that the sigmoid septum is the result of a cardiac morphological change that occurs due to aging (6, 7). This cardiac malformation is a structural change, characteristic of a diminished angle between the basal ventricular septum and the ascending aorta (8, 9). The sigmoid septum has been considered the result of aging and has not been thought to have any pathophysiologic or clinical significance (6–9) in most elderly people; however, several reports have demonstrated that a sigmoid septum sometimes causes a significant narrowing of the left ventricular outflow tract (10, 11). We propose a new cardiac age index for the quantitative assessment of age-related changes in the heart and ascending aorta by measuring the sigmoidity of the left ventricular septum. We hypothesize that this index, which quantifies age-related cardiac structural changes assessed by echocardiography, correlates with the real cardiac age of patients.

The purpose of the present study was to propose a new index of cardiac age that is easily measured using echocardiography and to clarify the clinical significance of the index.

Methods

Subjects and Protocol

The study subjects were 234 patients aged 40–80 years (mean age: 65 ± 12 years) who were diagnosed as having atherosclerosis-related diseases at Sakaide Municipal Hospital between April 2004 and the end of March 2007. Atherosclerosis-related diseases included hypertension, diabetes mellitus, and dyslipidemia, which were diagnosed according to the guidelines of the Japanese Society of Hypertension (12), the Japan Diabetes Society (13), and the Japan Atherosclerosis Society (14). Informed consent was obtained from all of the participants. None of the subjects had a history of any atherosclerotic cardiovascular diseases or stroke. Blood pressure was determined using the conventional cuff method at the time when the echocardiographic examination was performed. An echocardiograph was performed to assess cardiac structural changes and cardiac function. The patients were divided into normotensive and hypertensive groups, based on the criteria proposed by the Japanese Society of Hypertension in 2004 (12). Hypertension was defined as systolic blood

$$\text{Index of cardiac age} = 1,000 \times \text{VS}_{\text{ot}} / \text{BSA} / (\text{VS-AO})$$

Fig. 1. Schematic of the measurement of the index of cardiac age. VS_{ot} , ventricular septal thickness at the left ventricular outflow tract; VS-AO, angle between the ventricular septum and the ascending aorta; BSA, body surface area; VS, ventricular septal thickness at the chordae tendineae level; LVDd, left ventricular end-diastolic dimension at the chordae tendineae level; PW, left ventricular posterior wall thickness at the chordae tendineae level; LAD, end-systolic dimension of the left atrium.

pressure ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg. Normotension was defined as systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg. From our diagnosis 107 patients (mean age: 65 ± 11 years) had hypertension (hypertensive group) and 127 patients (mean age: 64 ± 12 years) did not have hypertension (normotensive group). Clinical characteristics, including blood pressure and echocardiographic findings, were compared between the groups. This protocol was approved by the Ethics Committee of Sakaide Municipal Hospital.

Echocardiographic Examination

Two-dimensional and M-mode echocardiography were performed using an echocardiographic instrument (Vivid Seven System; GE Vingmed, Horten, Norway). We first measured the following left ventricular structural parameters: the ventricular septal thickness at the left ventricular outflow tract (VS_{ot}), the angle between the ventricular septum and the ascending aorta (VS-AO), the ventricular septal thickness at the chordae tendineae level (VS), the left ventricular end-diastolic dimension at the chordae tendineae level (LVDd), the left ventricular posterior wall thickness at the chordae tendineae level (PW), and the end-systolic dimension of the left atrium (LAD). In all subjects, the echocardiographic examination was carried out by the same sonographer. Measurement of the above-mentioned parameters was performed by two physicians who had no medical information about the subjects. The VS_{ot} and VS-AO were measured at the end-

Fig. 2. Representative measurement of the proposed index of cardiac age. The index equals $1,000 \times VS_{ot}/BSA/(VS-AO)$, where VS_{ot} (mm) is the ventricular septal thickness at the left ventricular outflow tract, BSA (m^2) is the body surface area, and $VS-AO$ (degree) is the angle between the basal ventricular septum and the ascending aorta. The index of cardiac age is 51 in a normotensive patient whose real age is 56 years (left). In contrast, the index of cardiac age is 87 in a hypertensive patient whose real age is 48 years (right).

diastolic phase by two-dimensional echocardiography (Fig. 1). We drew a straight line on the internal edge of the ascending aorta wall and another straight line on the right ventricular edge of the ventricular septum in order to measure the VS-AO. The VS-AO was measured as the angle between the two lines. When it was difficult to draw a straight line on the right ventricular edge of the ventricular septum in a subject with a severe sigmoid septum, we drew another straight line on the left ventricular edge of the ventricular septum. Thus, we determined the straight line on the right ventricular edge of the ventricular septum by trying to make the two lines parallel. The VS, LVDD, PW, and LAD were measured by M-mode echocardiography. The left ventricular ejection fraction (LVEF) was estimated by Teichholz's method (15).

We determined the index of cardiac age by the following equation:

$$\text{Index of cardiac age} = 1,000 \times VS_{ot}/BSA/(VS-AO),$$

where VS_{ot} (mm) is the ventricular septal thickness at the left ventricular outflow tract, BSA (m^2) is the body surface area, and $VS-AO$ (degree) is the angle between the basal ventricular septum and the ascending aorta (Fig. 1). We selected VS_{ot} and $VS-AO$ as factors of the equation mentioned above because it is well known that left ventricular wall thickness increases with advancing age in normotensive patients even if the left ventricular mass index (LVMI) does not change (16). In addition, the $VS-AO$ was expected to decrease with advancing age because of the sigmoid septum. Therefore, we believed it was likely that the index of cardiac age described above would increase with advancing age. The value of $VS_{ot}/BSA/(VS-AO)$ reflects both age-related thickening of the basal ventricular septum normalized by body surface area and the extent of the sigmoid septum. In the present study, we

Table 1. Comparison of Clinical and Ultrasonographic Variables between Normotensive and Hypertensive Patients

	Normotensive	Hypertensive	<i>p</i> value
Number (male/female)	127 (70/57)	107 (63/44)	n.s.
Diabetes mellitus (No. of subjects)	40% (51)	36% (39)	n.s.
Dyslipidemia (No. of subjects)	36% (46)	34% (36)	n.s.
Age (years)	64±12	65±11	n.s.
BMI (kg/m ²)	22.0±3.1	23.3±3.5	n.s.
BSA (m ²)	1.55±0.19	1.59±0.19	n.s.
Heart rate (beats/min)	69±13	70±12	n.s.
Systolic BP (mmHg)	124±16	140±19	<0.001
Diastolic BP (mmHg)	77±11	84±12	<0.001
baPWV (m/s)	14.7±2.8	15.8±2.4	<0.05
No medication (No. of subjects)		32% (34)	
Medication (No. of subjects)		68% (73)	
ACEI/ARB (No. of subjects)		42% (45)	
CCB (No. of subjects)		33% (35)	
β-Blockers (No. of subjects)		10% (11)	
α-Blockers (No. of subjects)		4% (4)	
Echocardiographic parameters			
VS _{ot} (mm)	11.7±2.8	14.5±2.7	<0.001
VS-AO (degree)	113±13	104±14	<0.001
Index of cardiac age	70±26	92±30	<0.001
VS (mm)	9.7±2.0	10.8±2.3	<0.001
PW (mm)	9.1±1.5	9.9±1.5	<0.001
LVDd (mm)	45±6	45±6	n.s.
LVMI (g/m ²)	94±26	104±36	<0.05
LVEF (%)	71±8	71±8	n.s.
LAD	34±6	36±5	<0.001
<i>E</i> (m/s)	0.61±0.15	0.55±0.17	<0.01
<i>A</i> (m/s)	0.71±0.20	0.77±0.19	<0.01
<i>E/A</i>	0.92±0.32	0.73±0.24	<0.001
DcT (ms)	215±74	231±64	n.s.

BMI, body mass index; BSA, body surface area; BP, blood pressure; baPWV, brachial-ankle pulse wave velocity; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-II receptor blockers; CCB, calcium channel blockers; VS_{ot}, ventricular septal thickness at left ventricular outflow tract; VS-AO, angle between the ventricular septum and the ascending aorta; VS, ventricular septal thickness at the chordae tendineae level; PW, posterior wall thickness at the chordae tendineae level; LVDd, left ventricular end-diastolic dimension at the chordae tendineae level; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; *E*, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; *E/A*, the ratio of *E* to *A*; DcT, deceleration time of early diastolic transmitral flow; n.s., not significant.

multiplied VS_{ot}/BSA/(VS-AO) by 1,000 to show the index of cardiac age as a number in double or triple figures. Thus, this index may be useful because we can compare its value with the real age of a patient. For example, the index of cardiac age was 51 in a normotensive patient whose real age was 56 years (Fig. 2, left). In contrast, the index of cardiac age was 87 in a hypertensive patient whose real age was 48 years (Fig. 2, right). The index of cardiac age was lower than the real age of the normotensive patient but higher than that of the hypertensive patient.

The left ventricular mass was calculated according to the American Society of Echocardiography convention (17) using the following formula:

$$\text{Left ventricular mass} = 0.80[1.04 \times (\text{PW} + \text{VS} + \text{LVDd})^3 - (\text{LVDd})^3] + 0.6.$$

The LVMI was calculated as the left ventricular mass divided by the BSA. We next measured the parameters of left ventricular diastolic function by recording the left ventricular diastolic inflow using pulsed Doppler echocardiography (18). The left ventricular diastolic filling pattern was recorded from the apical transducer position 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 ratio of *E* to *A* (*E/A* ratio) was calculated. The deceleration time of the *E* velocity (DcT)

was measured as the time interval from the E-wave peak to the return of the velocity to baseline values.

Assessment of Pulse Wave Velocity

Brachial-ankle pulse wave velocity (baPWV) was measured using an automatic waveform analyzer (Form/ABI, Omron-Colin Co. Ltd., Komaki, Japan). This measurement was not performed on all patients, but was performed on 101 normotensive patients and 42 hypertensive patients. Details of the methodology have been described elsewhere (3–5). Measurements were taken with subjects lying in a supine position after resting for at least 5 min. 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.

Statistical Analysis

Data are expressed as means $\pm$ SD. Statistical analysis was performed using the SPSS software package (SPSS, Chicago, USA). An unpaired Student *t*-test was performed to compare the variables between the normotensive and hypertensive groups. Linear regression analysis was performed to evaluate the association between the index and other variables. Stepwise multiple regression analysis was performed to determine the correlation between the index and each independent variable. Values of $p < 0.05$ were considered to indicate statistical significance.

Results

Comparison of Clinical and Ultrasonographic Characteristics between Normotensive and Hypertensive Patients

The clinical and echocardiographic results for the patients in the present study are summarized in Table 1. The age and body surface area were similar between normotensive and hypertensive patients. Blood pressure and baPWV were significantly higher in hypertensive patients than in normotensive patients ($p < 0.001$ and $p < 0.05$, respectively). VS_{ot} was significantly higher and $VS-AO$ significantly lower in hypertensive patients than in normotensive patients ($p < 0.001$). Thus, the index of cardiac age was significantly higher in hypertensive patients than in normotensive patients ($p < 0.001$). The LVMI was significantly higher and the E/A significantly lower in hypertensive patients than in normotensive patients ($p < 0.05$ and $p < 0.001$, respectively).

Association between Index of Cardiac Age and Other Variables

Linear regression analysis was performed to examine the rela-

Table 2. Correlation Coefficients of Linear Regression Analysis between Index of Cardiac Age and Other Parameters

	<i>r</i>	<i>p</i> value
Age	0.57	<0.001
Hypertension	0.37	<0.001
Diabetes mellitus	−0.03	n.s.
Dyslipidemia	−0.08	n.s.
Heart rate	0.04	n.s.
Systolic BP	0.12	n.s.
Diastolic BP	−0.10	n.s.
baPWV	0.53	<0.001
Echocardiographic parameters		
VS	0.31	<0.001
PW	0.22	0.001
LVDd	−0.18	0.009
LVMI	0.28	<0.001
LVEF	0.11	n.s.
LAD	0.31	<0.001
<i>E</i>	−0.30	<0.001
<i>A</i>	0.45	<0.001
<i>E/A</i>	−0.52	<0.001
DcT	0.36	<0.001

BP, blood pressure; baPWV, brachial-ankle pulse wave velocity; VS, ventricular septal thickness at the chordae tendineae level; PW, left ventricular posterior wall thickness at the chordae tendineae level; LVDd, left ventricular end-diastolic dimension at the chordae tendineae level; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; *E*, peak early diastolic transmitral flow; *A*, peak late diastolic transmitral flow; *E/A*, the ratio of *E* to *A*; DcT, deceleration time of early diastolic transmitral flow; n.s., not significant.

tionship between the index of cardiac age and other variables in all subjects (normotensive and hypertensive patients combined). The significant associated parameters are shown in Table 2. The index correlated with age ($r = 0.57$, $p < 0.001$), the presence of hypertension ($r = 0.37$, $p < 0.001$), baPWV ($r = 0.53$, $p < 0.001$), and E/A ($r = -0.52$, $p < 0.001$).

We analyzed the relationship between the index and age in normotensive and hypertensive patients (Fig. 3, left). The index tended to be higher in hypertensive patients than in normotensive patients in all age strata. The slope between age (*x*-axis) and the index of cardiac age (*y*-axis) was greater in hypertensive (1.50) than normotensive (1.32) patients. In addition, we analyzed the relationship between E/A and age in each group (Fig. 3, right). The E/A in hypertensive patients tended to be lower than that in normotensive patients in all age strata. The correlation between the index and age (normotensive: $r = 0.63$, $p < 0.001$; hypertensive: $r = 0.58$, $p < 0.001$) was closer than that between E/A and age (normotensive: $r = 0.54$, $p < 0.001$; hypertensive: $r = 0.44$, $p < 0.001$) in both normotensive and hypertensive patients.

Fig. 3. Relationships between the index of cardiac age, E/A , and age. E , peak early diastolic transmitral flow; A , peak late diastolic transmitral flow; E/A , the ratio of E to A .

Table 3. Multiple Regression Analysis for Index of Cardiac Age and Related Parameters

Independent variables	β coefficient	t value	p value
Age	0.35	6.03	<0.001
Hypertension	0.26	4.84	<0.001
LVMi	0.34	5.44	<0.001
LVDd	-0.35	-5.42	<0.001
LAD	0.14	2.48	0.014
E/A	-0.12	-2.01	0.046
F ratio=34.75		$r^2=0.55$	
$(p<0.001)$			

LVMi, left ventricular mass index; LVDd, left ventricular end-diastolic dimension at the chordae tendineae level; LAD, end-systolic dimension of the left atrium; A , peak late diastolic transmitral flow; E , peak early diastolic transmitral flow; E/A , the ratio of E to A .

Assessment of the Factors Related to Index of Cardiac Age

Stepwise multiple regression analysis was performed to identify which of the parameters were independently associated with the index of cardiac age. The present study included the patients who did not undergo baPWV. For all patients, the stepwise multiple regression analysis (model 1) was performed for age, hypertension, diabetes mellitus, dyslipidemia, heart rate, systolic blood pressure, diastolic blood pressure, LVDd, LVMi, LVEF, LAD, E/A , and DcT; see Table 2. This analysis indicated that age (β coefficient=0.35, $p<0.001$), the presence of hypertension (β coefficient=0.26, $p<0.001$), LVMi (β coefficient=0.34, $p<0.001$), LVDd (β coefficient=-0.35, $p<0.001$), LAD (β coefficient=0.14, $p=0.014$), and the ratio of E to A (E/A) (β coefficient=-0.12, $p=0.046$) were independently associated with the index

Table 4. Multiple Regression Analysis for Index of Cardiac Age and Related Parameters in Patients Who Underwent baPWV

Independent variables	β coefficient	t value	p value
Age	0.42	5.20	<0.001
Hypertension	0.25	3.81	<0.001
baPWV	0.22	2.71	0.008
F ratio=35.94		$r^2=0.44$	
$(p<0.001)$			

baPWV, brachial-ankle pulse wave velocity.

(Table 3). For patients who underwent baPWV, the stepwise multiple regression analysis (model 2) was performed for the same parameters above plus baPWV. This analysis indicated that age (β coefficient=0.42, $p<0.001$), the presence of hypertension (β coefficient=0.25, $p<0.001$), and the baPWV (β coefficient=0.22, $p=0.008$) were independently associated with the index (Table 4). Thus, among the clinical factors, only age and the presence of hypertension were independently associated with the index in both model 1 and model 2.

Relationship between Index of Cardiac Age and baPWV

Figure 4 shows the relationship between the index and baPWV in 143 patients whose baPWV could be measured in the present study. The correlation between the index and baPWV ($r=0.53$, $p<0.001$) was closer than that between LVMi and baPWV ($r=0.27$, $p=0.001$).

Discussion

The present study proposed a new index of cardiac age. The

Fig. 4. Relationships between the index of cardiac age, LVMI, and pulse wave velocity. LVMI, left ventricular mass index.

data led us to the following conclusions: 1) The proposed index demonstrates a good correlation with age, and this correlation is as close as that between E/A and age in both normotensive and hypertensive patients; 2) the index is higher in hypertensive patients than in normotensive patients, and the index increases more with advancing age in hypertensive patients than in normotensive patients; 3) the index demonstrates a good correlation with baPWV, and the correlation is closer than that between LVMI and baPWV.

It is well known that the value of E/A is influenced by aging and demonstrates a good correlation with age (19, 20). In addition, several previous studies (21, 22) reported that E/A was lower in hypertensive patients than in normotensive patients. In the present study, the data regarding the relationship between E/A and age agreed with those of previous studies (19, 20). The data in the present study demonstrated that the correlation of the proposed index with age was as close as that of E/A with age in both normotensive and hypertensive patients (Fig. 3). Thus, the proposed index may be a useful marker in the assessment of cardiac age in both normotensive and hypertensive patients.

Systolic arterial pressure increases with aging due, in part, to arterial stiffening (23, 24). The heart and vasculature of normotensive elderly subjects take on the appearance of “muted” hypertension (25). Younger hypertensive patients exhibit many of the same characteristics as older normotensives, such as cardiac hypertrophy (26), increased vascular stiffness (25, 27), and increased aortic impedance (28). Thus, aging has sometimes been referred to as blunted hypertension, and hypertension has been described as accelerated aging (23, 24). Therefore, the increase in the index of cardiac age in the present study may represent cardiac and aortic adaptation to arterial stiffening in aging or hypertension. This increase in arterial stiffening in aging or hypertension is likely to be a reason why both age and the presence of hypertension were independently associated with the index (Table 3).

Clinical Implications

The linear regression analysis showed that the proposed index correlated significantly with the pulse wave velocity. Furthermore, stepwise regression analysis showed that the baPWV was independently associated with the proposed index for the patients who underwent baPWV. This suggests that the proposed index may reflect arteriosclerosis as well as the pulse wave velocity.

In addition, the present study showed that the proposed index has the advantage of independence from blood pressure at the time the index is measured (Table 2). It is well known that pulse wave velocity is influenced by blood pressure at the time the velocity is measured (29). In clinical settings, some patients have not paid attention to their own blood pressure and, thus, have unclear histories of hypertension. The proposed index may be useful for presuming the existence of hypertension in these patients.

Moreover, the present study demonstrated considerably high Pearson's correlation coefficients of interobserver ($r=0.96$, $p<0.001$) and intraobserver ($r=0.99$, $p<0.001$) reproducibility by analyzing the data for all subjects. The reproducibility of the proposed index measurement is acceptable in clinical practice.

Study Limitations

First, we have no data for assessing the prognostic value of the increase in the proposed index in hypertensive patients. It is well known that left ventricular hypertrophy detected *via* an increase in left ventricular mass predicts an increased risk for cardiovascular disease in patients with essential hypertension (30). Schillaci *et al.* demonstrated an independent relationship between E/A and the risk of cardiovascular events in untreated hypertensive patients by analyzing the results of a prospective follow-up study of Caucasian adult patients with

essential hypertension (31). LVMI is slightly increased with normal aging. In addition, coronary flow reserve remarkably decreases and cardiac diastolic function deteriorates with normal aging. The decrease in E/A with normal aging reflects age-related changes in cardiac diastolic function. In contrast, the proposed index reflects cardiac morphological changes with aging. The present study demonstrated that E/A is an independent determinant for the proposed index (Table 3). However, the clinical significance of the proposed index may be different from that of E/A . Therefore, a prospective follow-up study is needed in order to validate the usefulness of the proposed index.

Second, we have no data regarding whether or not anti-hypertensive therapy leads to a decrease in the proposed index. Further study is needed in order to assess the effect of treatment on the proposed index in hypertensive patients.

Third, we have no data regarding new indexes of diastolic dysfunction such as tissue Doppler imaging-derived mitral E/e' or brain natriuretic peptide. In addition, we have no data on subjects with diastolic dysfunction. Moreover, exercise capacity is also affected by cardiac aging. Therefore, further study is needed to validate the proposed index by comparing it to other indexes (e.g., exercise capacity) for which age-related changes have been established.

Fourth, we obtained no data from normal volunteers with no atherosclerosis-related diseases in the present study. Although the proposed index potentially estimates the individual cardiac aging process, data obtained from normal volunteers are needed in order to assure this possibility. A prospective follow-up study in normal volunteers is also needed so that the results can be compared with those obtained from patients with atherosclerosis-related diseases. In addition, the subjects in the present study might include patients who showed a pseudonormal left ventricular filling pattern due to their atherosclerosis-related diseases such as hypertension.

Fifth, the proposed index is influenced by the left ventricular wall thickness, which is increased in hypertensive patients. However, other risk factors were not selected as independent variables for the proposed index in the present study. Further investigation is needed to elucidate effects of other risk factors on cardiac age.

Finally, we only analyzed the relationships of the proposed index to age, blood pressure, pulse wave velocity, and risk factors of atherosclerosis in the present study. Although the proposed index showed a close correlation with age, we cannot definitively say that the proposed index itself can represent cardiac age. Further study is needed to develop a new equation that can determine cardiac age.

Conclusions

In conclusion, the proposed index of cardiac age can quantitatively assess the cardiac morphological changes that occur due to aging and/or hypertension. It may, therefore, be a clin-

ically useful indicator of cardiac aging, which is produced by vascular aging and/or hypertension. In addition, it may be a useful marker of peripheral arterial stiffening because of the close correlation with brachial-ankle pulse wave velocity.

References

1. Hoshida S, Ishikawa J, Eguchi K, Ojima T, Shimada K, Kario K: Masked nocturnal hypertension and target organ damage in hypertensives with well-controlled self-measured home blood pressure. *Hypertens Res* 2007; **30**: 143–149.
2. Okura T, Watanabe S, Kurata M, *et al*: Relationship between cardio-ankle vascular index (CAVI) and carotid atherosclerosis in patients with essential hypertension. *Hypertens Res* 2007; **30**: 335–340.
3. Tomiyama H, Hirayama Y, Hashimoto H, *et al*: The effects of changes in the metabolic syndrome detection status on arterial stiffening: a prospective study. *Hypertens Res* 2006; **29**: 673–678.
4. Shiina K, Tomiyama H, Takata Y, *et al*: Concurrent presence of metabolic syndrome in obstructive sleep apnea syndrome exacerbates the cardiovascular risk: a sleep clinic cohort study. *Hypertens Res* 2006; **29**: 433–441.
5. Koji Y, Tomiyama H, Yamada J, *et al*: Relationship between arterial stiffness and the risk of coronary artery disease in subjects with and without metabolic syndrome. *Hypertens Res* 2007; **30**: 243–247.
6. Bernstein RF, Tei C, Child JS, Shah PM: Angled interventricular septum on echocardiography: anatomic anomaly or technical artifact? *J Am Coll Cardiol* 1983; **2**: 297–304.
7. Fowles RE, Martin RP, Popp RL: Apparent asymmetric septal hypertrophy due to angled interventricular septum. *Am J Cardiol* 1980; **46**: 386–392.
8. Goor D, Lillehei CW, Edwards JE: The “sigmoid septum.” Variation in the contour of the left ventricular outlet. *Am J Roentgenol* 1969; **107**: 366–376.
9. Toth AB, Engel JA, McManus AM, McManus BM: Sigmoidity of the ventricular septum revisited: progression in early adulthood, predominance in men, and independence from cardiac mass. *Am J Cardiovasc Pathol* 1988; **2**: 211–223.
10. Dalldorf FG, Willis PW IV: Angled aorta (“sigmoid septum”) as a cause of hypertrophic subaortic stenosis. *Hum Pathol* 1985; **16**: 457–462.
11. Konishi C, Shiraishi J, Muraguchi N, *et al*: Beneficial effect of cibenzoline on left ventricular pressure gradient with sigmoid septum. *Circ J* 2004; **68**: 968–971.
12. Japanese Society of Hypertension: Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006; **29** (Suppl): S1–S105.
13. Japan Diabetes Society: Guidelines for diagnosis of diabetes mellitus. *J Jpn Diabetes Soc* 1999; **42**: 385–404.
14. Hata Y, Mabuchi H, Saito Y, *et al*: Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. *J Atheroscler Thromb* 2002; **9**: 1–27.
15. Teichholz LE, Kreulen T, Herman MV, Gorlin R: Problems

- in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol* 1976; **37**: 7–11.
16. Pearson AC, Gudipati CV, Labovitz AJ: Effects of aging on left ventricular structure and function. *Am Heart J* 1991; **121**: 871–875.
 17. Devereux RB, Wallerson DC: Reproducibility of echocardiographic left ventricular measurements. *Hypertension* 1987; **9** (Suppl II): II-6–II-18.
 18. Appleton CP, Firstenberg MS, Garcia MJ, Thomas JD: The echo-Doppler evaluation of left ventricular diastolic function. A current perspective. *Cardiol Clin* 2000; **18**: 513–546.
 19. Spirito P, Maron BJ: Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function. *Br Heart J* 1988; **59**: 672–679.
 20. Prasad A, Popovic ZB, Arbab-Zadeh A, et al: The effects of aging and physical activity on Doppler measures of diastolic function. *Am J Cardiol* 2007; **99**: 1629–1636.
 21. Aeschbacher BC, Hutter D, Fuhrer J, Weidmann P, Delacretaz E, Allemann Y: Diastolic dysfunction precedes myocardial hypertrophy in the development of hypertension. *Am J Hypertens* 2001; **14**: 106–113.
 22. Chang NC, Lai ZY, Wang TC: Enalapril does not improve left ventricular diastolic dysfunction in young and mild hypertensives without concomitant hypertrophy. *Am J Hypertens* 1996; **14**: 909–914.
 23. Lakatta EG: Arterial pressure and aging. *Int J Cardiol* 1989; **25** (Suppl 1): S81–S89.
 24. Lakatta EG: Similar myocardial effects of aging and hypertension. *Eur Heart J* 1990; **11** (Suppl G): 29–38.
 25. Wolinsky H: Long-term effects of hypertension on the rat aortic wall and their relation to concurrent aging changes. Morphological and chemical studies. *Circ Res* 1972; **30**: 301–309.
 26. Devereux RB, Savage DD, Drayer JI, Laragh JH: Left ventricular hypertrophy and function in high, normal, and low-renin forms of essential hypertension. *Hypertension* 1982; **4**: 524–531.
 27. Learoyd BM, Taylor MG: Alterations with age in the viscoelastic properties of human arterial walls. *Circ Res* 1966; **18**: 278–292.
 28. Ting CT, Brin KP, Lin SJ, et al: Arterial hemodynamics in human hypertension. *J Clin Invest* 1986; **78**: 1462–1471.
 29. Tomiyama H, Yamashina A, Arai T, et al: Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement—a survey of 12517 subjects. *Atherosclerosis* 2003; **166**: 303–309.
 30. Verdecchia P, Schillaci G, Borgioni C, et al: Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation* 1998; **97**: 48–54.
 31. Schillaci G, Pasqualini L, Verdecchia P, et al: Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. *J Am Coll Cardiol* 2002; **39**: 2005–2011.