Independent Determinants of the Tei Index in Hypertensive Patients With Preserved Left Ventricular Systolic Function

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SUMMARY

The clinical usefulness of the Tei index, which reflects left ventricular (LV) systolic and diastolic function, is known to have prognostic value in patients with overt heart disease such as ischemic heart disease or congestive heart failure. Additionally, LV diastolic functional parameters such as the transmitral E/A (early to atrial velocity) ratio have been shown to have prognostic value in hypertensive patients. However, the clinical usefulness of the Tei index for hypertensive patients without overt heart disease has not yet been fully studied. We compared the Tei index between hypertensive and normotensive patients and examined independent determinants of the Tei index in hypertensive patients with preserved LV systolic function. Our subjects were 319 patients with cardiovascular risk factors including hypertension and diabetes, all of whom had preserved LV systolic function (LV ejection fraction ≥ 55%). They were divided into two groups: 100 normotensives (67 ± 11 years) and 219 hypertensives (69 ± 13 years). LV structural and functional parameters including transmitral E/A ratio and the Tei index were measured with Doppler echocardiography. The correlations of the transmitral E velocity to the Tei index (r = -0.311, $P < 0.001$) were the closest in all echocardiographic parameters in hypertensives. Stepwise regression analysis showed that E velocity (β coefficient = -0.315, $P < 0.001$) and relative wall thickness (β coefficient = 0.262, $P < 0.001$) were independently associated with the Tei index. The Tei index in hypertensives with preserved LV systolic function may be determined primarily by LV diastolic dysfunction during early diastole with LV concentric remodeling and may, together with the E/A ratio, have prognostic value in hypertensive patients. (Int Heart J 2009; 50: 331-340)

Key words: Echocardiography, Tei index, Left ventricular diastolic function

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It is well known that the Tei index, which reflects left ventricular (LV) systolic and diastolic function, provides prognostic information in a variety of heart diseases, including myocardial infarction,[1,2] cardiac amyloidosis,[3] and heart failure.[4] Several previous studies have demonstrated that the Tei index is abnormal even in hypertensive patients without overt heart disease.[5-7] However, there have been few studies[8] regarding the influences of hypertension on the Tei index in lifestyle-related diseases such as hypertension. The Tei index is not affected by LV loading conditions such as LV preload[9] or blood pressure[10] in patients who show impaired LV systolic function due to myocardial infarction or heart failure. However, the parameters influencing the Tei index in hypertensive patients without overt heart disease have not yet been fully examined.

Therefore, we examined the relationships between the Tei index and clinical parameters including LV loading conditions in hypertensive patients without overt heart disease who had preserved LV systolic function. We also examined the relationships between the Tei index and other echocardiographic parameters in order to identify independent determinants of the Tei index in these patients.

Methods

Subjects and protocol: The study subjects were 319 patients (153 males, 166 females; mean age, 69 ± 12 years; range, 21-98 years) who were diagnosed as having cardiovascular risk factors at Kagawa University Hospital from April, 2007 through September, 2008. The cardiovascular risk factors included in the present study were hypertension and diabetes mellitus, which were diagnosed according to the guidelines of the Japanese Society of Hypertension[11] and the Japan Diabetes Society,[12] respectively. Patients with a history of heart failure or obvious heart disease were excluded. None of the subjects had a history of any atherosclerotic cardiovascular diseases or stroke. In addition, all patients had preserved LV systolic function because patients whose echocardiographic LV ejection fraction was < 55% were excluded. Blood pressure was determined using the conventional cuff method upon echocardiographic examination. Hypertension was defined as a systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg. Echocardiographic examinations were performed to assess cardiac structural changes and cardiac function. Blood sampling was performed in the morning after a 12-hour overnight fast. Plasma total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), and HbA1c were measured by standard laboratory techniques. The estimated glomerular filtration rate (eGFR) was estimated using the equation for Japanese patients that was recently proposed by a working group of the Japanese Chronic Kidney Disease Initiative:[13]

$eGFR = 194 \times age^{-0.287} \times (serum\ creatinine)^{-1.094}$ (× 0.739 if female).

The subjects were divided into 2 groups: 100 normotensive patients (67 ± 11 years) and 219 hypertensive patients (69 ± 13 years). The hypertensive patients had been previously diagnosed with hypertension at Kagawa University Hospital, and were being treated with medication. The medications are summarized in Table I. Clinical and echocardiographic parameters were compared between the 2 groups. The blood pressure for analysis (Table I) was measured immediately before echocardiographic examination in all patients. Relationships among the Tei index, clinical characteristics including blood pressure and laboratory data, and other echocardiographic parameters were analyzed in the 219 hypertensive patients. This protocol was approved by the Ethics Committee of Kagawa University. Informed consent was obtained from all participants.

Echocardiographic examination: Two-dimensional and M-mode echocardiography were performed using the Vivid 7 System (GE, Horten, Norway). We first measured the following LV structural parameters by M-mode echocardiography: ventricular septal thickness (VS) at the chordae tendineae level, LV end-diastolic dimension (LVDd) and LV end-systolic dimension (LVDs) at the chordae tendineae level, LV posterior wall (PW) thickness at the chordae tendineae level, and

Table I. Clinical Characteristics in the Study Groups

	Normotensives (n = 100)	Hypertensives (n = 219)	P value
Sex (male (%))	49 (49%)	104 (47%)	NS
Age (years)	67 ± 11	69 ± 13	NS
Diabetes (number (%))	27 (27%)	60 (27%)	NS
BMI	20.8 ± 3.1	22.9 ± 4.0	$P < 0.001$
Heart rate (beats/min)	71 ± 13	70 ± 11	NS
Systolic BP (mmHg)	113 ± 11	138 ± 16	$P < 0.001$
Diastolic BP (mmHg)	66 ± 9	76 ± 13	$P < 0.001$
Uric acid (mg/dL)	4.8 ± 1.4	5.6 ± 1.8	$P < 0.001$
eGFR (mL/min/1.73m^2)	82 ± 22	64 ± 30	$P < 0.001$
Haematocrit (%)	36 ± 6	37 ± 6	NS
Serum albumin (g/L)	3.7 ± 0.6	3.8 ± 0.6	NS
Total cholesterol (mg/dL)	177 ± 38	192 ± 41	$P < 0.01$
HDL cholesterol (mg/dL)	47 ± 15	48 ± 12	NS
Triglycerides (mg/dL)	103 ± 49	126 ± 74	$P < 0.01$
Hemoglobin A1c (%)	5.6 ± 1.3	5.8 ± 1.3	NS
Hypertensive treatment			
ACEI/ARB	-	65%	-
CCB	-	45%	-
β-blockers	-	20%	-
α-blockers	-	5%	-

NS indicates not significant; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HT, hypertension; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-II receptor blockers; and CCB, calcium channel blockers.

the end-systolic dimension of the left atrium (LAD). LV mass was calculated following the conventions of the American Society of Echocardiography[14] and using the formula, LV mass = 0.80 [1.04 × (PW + VS + LVDd)^3 - (LVDd)^3] + 0.6. The LV mass index (LVMI) was calculated as the LV mass divided by the body surface area. Relative wall thickness (RWT), which increases with concentric remodeling and concentric hypertrophy, was calculated as (VS + PW)/LVDd. The LV ejection fraction (LVEF) was estimated by Teichholz's method[15] and was used as a parameter of LV systolic function.

We next measured the parameters of LV diastolic function by recording the transmitral flow velocity using conventional Doppler echocardiography.[16] The transmitral flow velocity was recorded from the apical transducer position with the sample volume situated between the mitral leaflet tips. The peak velocities of the early (E velocity) and late (A velocity) transmitral flow velocities were recorded, and the ratio of E to A (E/A ratio) was calculated. The deceleration time of E velocity (DcT) was measured as the time interval from the E-wave peak to the decline of the velocity to baseline values.

Additionally, we measured the Tei index, which reflects both left systolic and diastolic function.[17] Details of the method for measuring the Tei index have been previously published by Tei, *et al.*[3] The Tei index, defined as the sum of the isovolumic contraction time and isovolumic relaxation time divided by ejection time, was obtained from Doppler recordings of LV inflow and outflow. The Tei index is derived as (a-b)/b, where 'a' is the interval between the cessation and onset of mitral inflow, and 'b' is the ejection time of LV outflow. In measuring 'a' and 'b', we confirmed that the preceding RR intervals were the same in each patient.

Finally, pulsed-wave tissue Doppler echocardiography was performed by 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 (E') and late (A') diastolic mitral annular velocities and the E'/A' ratio were measured over 3 cardiac cycles and the results were averaged.[18,19] The data obtained from tissue Doppler echocardiography were also analyzed as parameters of LV diastolic function. Furthermore, the E/E' ratio was calculated and used as a parameter of LV preload.[20]

Statistical analysis: Data are expressed as the mean ± SD. Statistical analysis was performed using an SPSS software package (SPSS, Chicago, IL, USA). Differences between normotensive and hypertensive patients were assessed using Student's *t* test. Linear regression analysis was performed to evaluate the association between the Tei index and other variables. Stepwise multiple regression analysis was performed to determine the correlation between the Tei index

and each independent variable. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

Comparison of clinical characteristics between hypertensive and normotensive patients: The clinical parameters of the subjects are summarized in Table I. There was no difference in the mean age between the normotensive and hypertensive subjects. The body mass index, systolic and diastolic blood pressures, uric acid, total cholesterol, and triglycerides were all significantly higher in hypertensives than in normotensives ($P < 0.01$), and eGFR was significantly lower ($P < 0.001$).
Comparison of echocardiographic parameters between hypertensive and normotensive patients: The echocardiographic parameters of the subjects are summarized in Table II. LVMI was significantly larger in hypertensives than in normotensives ($P < 0.001$), indicating LV hypertrophy in hypertensives. Although LVEF showed no significant difference between the two groups, E/A and E' were significantly lower in hypertensives than in normotensives ($P < 0.05$ and

Table II. Echocardiographic Parameters in the Study Groups

	Normotensives (n = 100)	Hypertensives (n = 219)	P value
LAD (mm)	34 ± 6	37 ± 7	$P < 0.01$
VS (mm)	9.6 ± 1.8	11.8 ± 2.9	$P < 0.001$
PW (mm)	9.5 ± 1.7	10.6 ± 2.2	$P < 0.001$
LVDs	27 ± 4	27 ± 5	NS
LVDd	45 ± 5	46 ± 6	NS
RWT	0.43 ± 0.09	0.50 ± 0.13	$P < 0.001$
LVMI (g/m^2)	98 ± 24	123 ± 35	$P < 0.001$
LVEF (%)	71 ± 6	70 ± 7	NS
E (cm/s)	57 ± 17	58 ± 20	NS
A (cm/s)	72 ± 17	82 ± 23	$P < 0.001$
E/A	0.81 ± 0.28	0.74 ± 0.34	$P < 0.05$
DcT	204 ± 71	234 ± 77	$P < 0.01$
E'	6.6 ± 2.0	4.9 ± 1.4	$P < 0.001$
A'	9.0 ± 1.9	8.8 ± 1.9	NS
E'/A'	0.77 ± 0.30	0.58 ± 0.19	$P < 0.001$
E/E'	8.9 ± 2.7	12.4 ± 4.9	$P < 0.001$
Tei index	0.51 ± 0.16	0.56 ± 0.16	$P < 0.01$

LAD indicates left atrial dimension; VS, ventricular septal thickness; PW, posterior wall thickness; LVDs, left ventricular end-systolic dimension; NS, not significant; LVDd, left ventricular end-diastolic dimension; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; DcT, deceleration time of E velocity; E', peak early diastolic mitral annular velocity; A', peak late diastolic mitral annular velocity; E'/A', the ratio of E' to A'; and E/E', the ratio of E to E'.

$P < 0.001$, respectively), indicating LV diastolic dysfunction with preserved LV systolic function in hypertensives. In addition, the significantly increased E/E' in hypertensives compared to normotensives ($P < 0.001$) indicates an increased LV preload. The Tei index was significantly higher in hypertensives than in normotensives ($P < 0.01$).

Association between the Tei index and other parameters in hypertensive patients: Linear regression analysis was performed to examine the relationship between

Table III. Correlation Coefficients of Linear Regression Analysis Between the Tei Index and Other Parameters in Hypertensive Patients

	r	*P* value
Clinical parameters		
Age (years)	-0.062	NS
BMI	-0.005	NS
Heart rate (beats/min)	0.164	$P < 0.05$
Systolic BP (mmHg)	0.019	NS
Diastolic BP (mmHg)	0.120	NS
Uric acid (mg/dL)	0.089	NS
eGFR (mL/min/1.73m^2)	-0.101	NS
Haematocrit (%)	0.029	NS
Serum albumin (g/L)	-0.056	NS
Total-cholesterol (mg/dL)	0.113	NS
HDL-cholesterol (mg/dL)	0.005	NS
Triglycerides (mg/dL)	0.055	NS
Hemoglobin A1c (%)	-0.043	NS
Echocardiographic parameters		
LAD (mm)	-0.120	NS
VS (mm)	0.155	$P < 0.05$
PW (mm)	0.170	$P < 0.05$
LVDs	-0.064	NS
LVDd	-0.203	$P < 0.01$
RWT	0.258	$P < 0.001$
LVMI (g/m^2)	0.060	NS
LVEF (%)	-0.129	NS
E (cm/s)	-0.311	$P < 0.001$
A (cm/s)	-0.075	NS
E/A	-0.190	$P < 0.01$
DcT	0.087	NS
E'	-0.259	$P < 0.001$
A'	0.007	NS
E'/A'	-0.202	$P < 0.01$
E/E'	-0.040	NS

NS indicates not significant; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LAD, left atrial dimension; VS, ventricular septal thickness; PW, posterior wall thickness; LVDs, left ventricular end-systolic dimension; LVDd, left ventricular end-diastolic dimension; RWT, relative wall thickness; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; E, peak early diastolic transmitral flow; A, peak late diastolic transmitral flow; E/A, the ratio of E to A; DcT, deceleration time of E velocity; E', peak early diastolic mitral annular velocity; A', peak late diastolic mitral annular velocity; E'/A', the ratio of E' to A'; and E/E', the ratio of E to E'.

Table IV. Multiple Regression Analysis for the Tei Index and Related Echocardiographic and Clinical Parameters in Hypertensive Patients

Independent variable	β coefficient	t value	P value
E velocity (cm/s)	-0.315	-4.679	< 0.001
RWT	0.262	3.884	< 0.001
	F ratio = 19.462		r^2 = 0.176
	(P < 0.001)		

E indicates peak early diastolic transmitral flow and RWT, relative wall thickness.

the Tei index and other variables in the present 219 hypertensive patients (Table III). With respect to the clinical parameters, only heart rate showed a weak correlation with the Tei index ($r = 0.164$, $P < 0.05$), while of the echocardiographic parameters, LV wall thickness (VS: $r = 0.155$, $P < 0.05$; and PW: $r = 0.170$, $P < 0.05$) and RWT ($r = 0.258$, $P < 0.001$) showed significant correlations. LVMI did not correlate with the Tei index, however, LV diastolic functional parameters from both conventional and tissue Doppler echocardiography did show correlations. Among the LV diastolic functional parameters, E velocity showed the closest correlation with the Tei index ($r = -0.311$, $P < 0.001$). E/E', which reflects LV preload, did not correlate with the Tei index.

Independent determinants of the Tei index in hypertensive patients: Stepwise multiple regression analysis was performed for all parameters shown in Tables I and II to identify which clinical and echocardiographic parameters were independently associated with the Tei index in the present 219 hypertensive patients. This analysis indicated that E velocity (β coefficient = -0.315, $P < 0.001$) and RWT (β coefficient = 0.262, $P < 0.001$) were independently associated with the Tei index (Table IV).

Discussion

The present study presents data regarding the relationships between the Tei index and other echocardiographic parameters in hypertensive patients without overt heart disease who have preserved LV systolic function. The data led us to the following conclusions: (1) although the Tei index is slightly related to heart rate, it is influenced by neither blood pressure nor E/E', which reflects LV preload, in hypertensive patients; (2) although the Tei index is not related to LVMI, it correlates with RWT reflecting LV concentric remodeling due to hypertension; (3) of the echocardiographic parameters, E velocity, which reflects LV relaxation during early diastole, correlates best with the Tei index in hypertensive patients; and (4) E velocity and RWT are the independent determinants of the Tei index in hypertensive patients.

The present data demonstrate that the merit of the Tei index with respect to the independence of LV loading conditions can be observed in hypertensive patients without overt heart disease, as well as in those with heart disease such as myocardial infarction and heart failure. Furthermore, our data also demonstrate that the Tei index is not affected by increasing age. These results suggest the potential clinical usefulness of the Tei index in assessing LV dysfunction in hypertensive patients in various age strata.

The most striking result of the present analysis was that the Tei index correlated with RWT rather than LVMI in hypertensive patients with preserved LV systolic function. Indeed, LV end-diastolic dimension correlated inversely with the Tei index (Table III). These results indicate that LV concentric remodeling with decreased LV dimension can worsen the Tei index in hypertensive patients even if the LVMI does not increase. LV concentric remodeling due to hypertension may lead to impaired LV relaxation, which then decreases E velocity during early diastole. This may explain why E velocity and RWT were found to be the independent determinants of the Tei index in the present study. Tei, *et al*[21] previously reported that the Tei index correlates with simultaneously recorded diastolic peak -dP/dt (r = 0.833, P < 0.001) and tau (r = 0.680, P < 0.0001) in patients with heart failure; the present study was consistent with Tei's report in that the Tei index was found to correlate with early diastolic parameters such as E (r = -0.311, P < 0.001) and E' (r = -0.259, P < 0.001), but did not correlate with mid or late diastolic parameters such as DcT and A (Table III).

In the present study, E' from tissue Doppler echocardiography was inferior to E velocity from conventional Doppler echocardiography in its correlation with the Tei index. Recently, tissue Doppler echocardiography has been used in patients with subclinical LV dysfunction because the parameters derived from it are sensitive and independent of LV preload.[22,23] However, E' from tissue Doppler echocardiography is an LV diastolic functional parameter that reflects regional LV function measured at the mitral annulus. Therefore, E' may be different from global LV functional parameters such as the Tei index. This may be why E' was not selected as an independent determinant of the Tei index in the present study.

A previous study by Mishra, *et al*[8] demonstrates that the Tei index has a weak association with E velocity (r = -0.093, P < 0.001) in a population-based sample of adults with a high prevalence of diabetes, hypertension, and obesity without overt cardiovascular disease. Moreover, the Tei index did not provide prognostic information for cardiovascular events in the study population of Mishra, *et al*. They concluded that the Tei index has limited utility in a high-risk population without clinical cardiovascular disease. However, the prevalence of hypertension in the population they studied was only 44%, and the population

consisted entirely of American Indians. Thus, the low prevalence of hypertension and/or racial differences may have contributed to the differences between the results of Mishra and those of the present study.

The present study had several limitations. First, we have no data regarding prognostic information for cardiovascular events in these hypertensive patients. Therefore, a prospective follow-up study is needed in order to validate the usefulness of the Tei index in hypertensive patients without overt heart disease in a Japanese population. Second, we have no data regarding whether or not antihypertensive therapy leads to an improvement of the Tei index. It has been reported that the Tei index can detect carvedilol-induced improved LV function in patients with heart failure.[24] In addition, the Tei index has been reported to be useful in evaluating improvement in cardiac function under exercise training in patients with myocardial infarction.[25] Further study is needed to assess the effect of treatment on the Tei index in hypertensive patients.

Recently, LV diastolic functional parameters such as the transmitral E/A ratio have been shown to have prognostic value in hypertensive patients.[26,27] These studies demonstrate that hypertensive patients with LV diastolic dysfunction, as assessed by the E/A ratio and other parameters, have a poor prognosis for cardiovascular events. The present data indicate that although the Tei index reflects both LV systolic and diastolic function, abnormal Tei index values in hypertensive patients with preserved LV systolic function reflect LV diastolic dysfunction during early diastole. Therefore, not only the E/A ratio but also the Tei index may have prognostic value in hypertensive patients.

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