Value of Ventricular Stiffness Index and Ventriculoarterial Interaction in Patients With Nonischemic Dilated Cardiomyopathy

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***Background*:** Whether echo-Doppler-derived index of ventricular elastance or ventriculoarterial interaction can reliably reflect circulatory efficiency in various conditions was investigated in the present study and whether they can be helpful in predicting exercise capacity in patients with dilated cardiomyopathy (DCM).

***Methods and Results*:** The 25 patients with DCM, 25 age- and gender-matched hypertensive patients, and 25 marathon runners underwent symptom-limited graded supine bicycle exercise echocardiography after resting echo-Doppler evaluation. Echo-Doppler-derived left ventricular (LV) diastolic elastance index (Ed), ventricular–vascular coupling index ($10 \times Ea/Ees$), based on arterial elastance index (Ea) to LV end-systolic elastance index (Ees), and hemodynamic parameters were measured during rest and exercise. DCM patients had lower Ees, higher Ed and Ea/Ees with blunted exercise responses of Ees than the other groups, and the hypertensive patients had lower Ees and ΔEes compared with the marathon runners. Resting Ed, Ea/Ees, and total stiffness index ($10 \times Ed \times Ea/Ees$) correlated with exercise duration independent of age and gender. A stiffness index of 0.8 could reliably predict impaired exercise capacity.

***Conclusions*:** Echo-derived elastance is predictive of exercise capacity in patients with DCM.   (*Circ J* 2009; **73**: 1683–1690)

Key Words: Dilated cardiomyopathy; Ventricular elastance; Ventriculoarterial interaction

Patients with congestive heart failure have exercise intolerance,[1] and exercise capacity, as measured by oxygen consumption and total exercise duration, has been shown to be an important determinant of prognosis and has been used for the identification of optimal cardiac transplantation candidates.[2,3] In patients with markedly decreased left ventricular (LV) systolic function, increased vascular resistance,[4] restricted ventricular filling[5] or dyssynchronous contraction,[6] rather than the LV ejection fraction (LVEF) itself, has been shown to be associated with a poor prognosis. Actually, in patients with the same systolic function, the prognosis can vary depending on their vulnerability to a loading change, such as an increased preload or afterload. The vulnerability to an acute loading change is determined by ventricular stiffness and the end-systolic ventriculoarterial interaction.[7,8] These parameters can be measured in an invasive manner using a pressure–volume curve, but in the clinical practice and in the monitoring of treatment effectiveness, the invasive approach to measuring this parameter is impossible. Recent studies have introduced the concepts of single beat-derived ventricular diastolic elastance (Ed), ventricular end-systolic elastance (Ees) and effective arterial elastance (Ea).[9–11] In this study, we sought

to investigate whether these echo-Doppler derived indices can be used reliably in various groups of subjects, and whether there is any difference in the ventricular stiffness or ventriculoarterial interaction between dilated cardiomyopathy (DCM) patients, hypertensive patients, and healthy controls at rest and during exercise. In addition, we sought to investigate whether these parameters can provide important information regarding exercise capacity.

Methods

Study Population
We prospectively enrolled 25 patients diagnosed with long-standing (>6 months) nonischemic DCM with advanced systolic dysfunction (LVEF <40%). All the patients were enrolled after controlling for acute loading changes, such as pulmonary edema or termination of dobutamine infusion. As the positive control, age- and gender-matched, uncomplicated hypertensive patients were enrolled, and for healthy controls, we enrolled marathon runners who had completed a full marathon course. We excluded patients who were ≥75 years old to exclude the effects of age-related aortic stiffening or those who had a previous history of ischemic

Table 1. Schematic Presentation of Hemodynamic Indexes Used in This Study

Parameter	Conceptual framework	Conceptual formula
Ed	LVEDP/SV	(E/E')/SV
Ees	Pulsed-wave Doppler of LVOT flow	Peak velocity/acceleration time
ESP		$(2 \times SBP + DBP)/3$
Total systemic afterload	Pulsatile component+nonpulsatile component	
Ea	Pulsatile+nonpulsatile component at end-systole	ESP/SV
Pulsatile component	Total arterial compliance	SV/pulse pressure
Nonpulsatile component	Systemic vascular resistance	$80 \times (MAP - RAP)/CO$
VVI	Ratio of effective arterial elastance to LV end-systolic elastance	$10 \times (Ea/Ees)$
Total stiffness index	Product of preload and afterload indices	$Ed \times VVI$

Ed, left ventricular (LV) diastolic elastance; LVEDP, LV end-systolic pressure; SV, stroke volume; Ees, LV end-systolic elastance; LVOT, LV outflow tract; ESP, end-systolic blood pressure; Ea, effective arterial elastance; MAP, mean arterial pressure; RAP, right atrial pressure; CO, cardiac output; VVI, ventricular-vascular coupling index.

heart disease, valvular heart disease, other than functional mitral or tricuspid regurgitation, or atrial fibrillation. We also excluded patients who could not perform the exercise, had coronary artery stenosis >70% on conventional or magnetic resonance coronary angiography, or who had suspected infiltrative heart disease. All enrolled patients provided informed consent, and the institutional review board approved this study.

Conventional Echocardiography

All of the enrolled subjects underwent comprehensive echo-Doppler evaluation. Standard 2-dimensional echo measurements were obtained with M-mode quantification. The LVEF was measured by modified Quinone's method. The left atrial volume index (LAVI) was measured by a prolated ellipsoidal method, and the LV outflow tract diameter was measured in the parasternal long-axis view. From the apical window, a 1–2-mm pulsed Doppler sample volume was placed at the mitral valve tip, and mitral flow velocities through 5–10 cardiac cycles were recorded. Of them, 3 consecutive beats were measured and the average value was used for further calculations. The mitral inflow velocities were traced, and the following variables were obtained: peak velocity of early (E) and late (A) filling and deceleration time of the E wave velocity. The tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure using continuous-wave Doppler, if measurable. Mitral annular velocity was measured by Doppler tissue imaging. Early diastolic (E') and systolic (S') velocities of the mitral annulus were measured from the apical 4-chamber view with a 5-mm sample volume placed at the septal corner of the mitral annulus.

Echo-Doppler-Derived Hemodynamic Parameters

To provide a continuous variable that might estimate Ed (LV end-diastolic pressure/SV, Ed), E/E' was divided by the volume of filling during diastole (stroke volume: SV), as used in a previous study.[9,12] Right atrial pressure was measured using the inferior vena cava diameter and the presence of its respiratory variation in the subcostal view.[13] Blood pressure (BP) was measured on the left arm using an oscillometric monitoring device (Solar 8000 patient monitoring device, GE Medical Systems). End-systolic pressure was estimated as (2×systolic pressure+diastolic pressure)/3.[9,11] SV was calculated as 0.785×(LV outflow tract diameter)[2]×(time velocity integral at LV outflow tract), and this value was used to calculate cardiac output (SV×heart rate). As a pulsatile component of arterial afterload, total arterial compliance was calculated as SV/pulse pressure.

In addition, as a nonpulsatile component of afterload, the systemic vascular resistance index was calculated as 80× (mean arterial pressure–right atrial pressure)/cardiac index.[14] The effective Ea was estimated as the end-systolic pressure/SV.[9,11] LV Ees index (m/s²), was calculated using a trans-LV outflow tract pulsed wave Doppler as peak velocity (cm/s)/accelerating time (ms) as validated in a previous study.[10] To see the interaction between peripheral resistance and LV systolic stiffness, the ventricular–vascular coupling index (VVI, 10×Ea/Ees) was calculated (**Table 1**).

Exercise Echocardiography

After obtaining the rest images from the standard parasternal and apical views, multistage supine bicycle exercise testing was performed with a variable load bicycle ergometer (Medical Positioning, Inc, Kansas City, MO, USA). Patients pedaled at a constant speed beginning at a workload of 25 W, and then the workload increased 25 W every 3 min. Echocardiography was performed using a GE Vivid 7 ultrasound system with a 2.5-MHz transducer during rest, each stage of exercise, and recovery. During the exercise and recovery periods BP was measured at the end of each stage on the left arm using an oscillometric monitoring device. Mitral inflow velocities and mitral annular velocities were measured during exercise stages and recovery phases. At each exercise stage and recovery phase, an LV outflow pulsed Doppler image was obtained, and this image was used for the measurement of Ees and SV. To improve the accuracy of the measurements at peak exercise, the LV outflow acceleration time was measured immediately after peak exercise, and it was used for further calculations. The filter was set to exclude high-frequency signals, and the Nyquist limit was adjusted to a range of 15–20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. At each stage, Ed, Ees, Ea, total arterial compliance, and the systemic vascular resistance index were measured in the same way as in the resting stage. All data were stored digitally, and measurements were made at the completion of each study. To improve the accuracy of each parameter, parameters obtained from 3 consecutive beats were averaged and used for further calculations. To improve the accuracy of the acceleration time of the LV outflow tract Doppler, the sweep speed was increased to 200 mm/s in the post-processing analysis. To assess the interobserver variability, 2 independent investigators measured resting and immediate peak exercise values. To assess the intra-observer variability, an investigator measured each echo-Doppler value twice. As a measure of exercise capacity, the total exercise duration was used.

Table 2. Baseline Clinical Characteristics and Echo-Doppler Indices

	Marathon runners (n=25)	Hypertension (n=25)	DCM (n=25)	P value
Age (years)	43.9±8.3	58.0±10.1**	58.2±11.2**	<0.001
Female (%)	1 (4)	12 (48)**	12 (48)**	0.001
Body mass index (kg/cm^2)	23.7±1.8	25.0±2.8	24.4±3.1	0.234
Hypertension (%)	0	25(100)**	11 (41)**,†	<0.001
Diabetes (%)	0	0	4 (16)**,††	0.015
End-systolic pressure (mmHg)	111.2±14.2	115.3±14.8	102.0±17.8	0.006
Heart rate (beats/min)	61.4±6.9	62.0±9.9	70.3±13.8**	0.006
Pulse pressure (mmHg)	46.4±8.0	52.5±14.0	45.5±14.9	0.112
Systemic vascular resistance index (dyne·s^{-1}·m^{-2}·cm^{-5})	2,910.9±572.9	3,053.3±695.3	3,083.7±872.9	0.668
Total arterial compliance (ml/mmHg)	1.56±0.26	1.36±0.41	1.20±0.35**	0.002
Ea (mmHg/ml)	1.60±0.32	1.77±0.34	2.08±0.49**,†	<0.001
LV end-diastolic dimensional index (mm/m^2)	28.5±2.4	27.8±3.5	37.3±4.6**,††	<0.001
LV end-systolic dimensional index (mm/m^2)	19.0±2.1	18.1±2.2	32.2±5.2**,††	<0.001
LV mass index (g/m^2)	100.4±20.4	90.1±14.1	131.9±27.1**,††	<0.001
LV ejection fraction (%)	65.4±4.8	67.1±5.9	26.0±7.8**,††	<0.001
Stroke volume (ml)	71.4±12.4	67.3±11.5	51.5±12.9**,††	<0.001
Left atrial volume index (ml/m^2)	20.3±4.9	24.2±5.2	43.7±50.8*,†	0.014
Early mitral inflow velocity (cm/s)	72.3±13.9	64.6±17.1	61.4±21.3	0.090
Late mitral inflow velocity (cm/s)	52.2±9.7	65.7±14.9*	72.4±23.8**	<0.001
Early diastolic mitral annular velocity (cm/s)	9.4±1.6	7.3±1.7**	4.4±1.5**,††	<0.001
Late diastolic mitral annular velocity (cm/s)	8.1±1.5	8.5±2.0	6.2±1.4**,††	<0.001
Ed (1/ml)	00.11±0.03	0.13±0.06	0.30±0.15**,††	<0.001
Ees (m/s^2)	13.2±3.4	10.5±3.1*	7.3±2.6**	<0.001
Systolic mitral annular velocity (cm/s)	7.7±1.6	6.6±1.6*	4.3±1.0**,††	<0.001

Data are presented as mean±standard deviation, *P<0.05, **P<0.001 vs marathon runner, †P<0.05, ††P<0.001 vs hypertension. DCM, dilated cardiomyopathy. Other abbreviations see in Table 1.
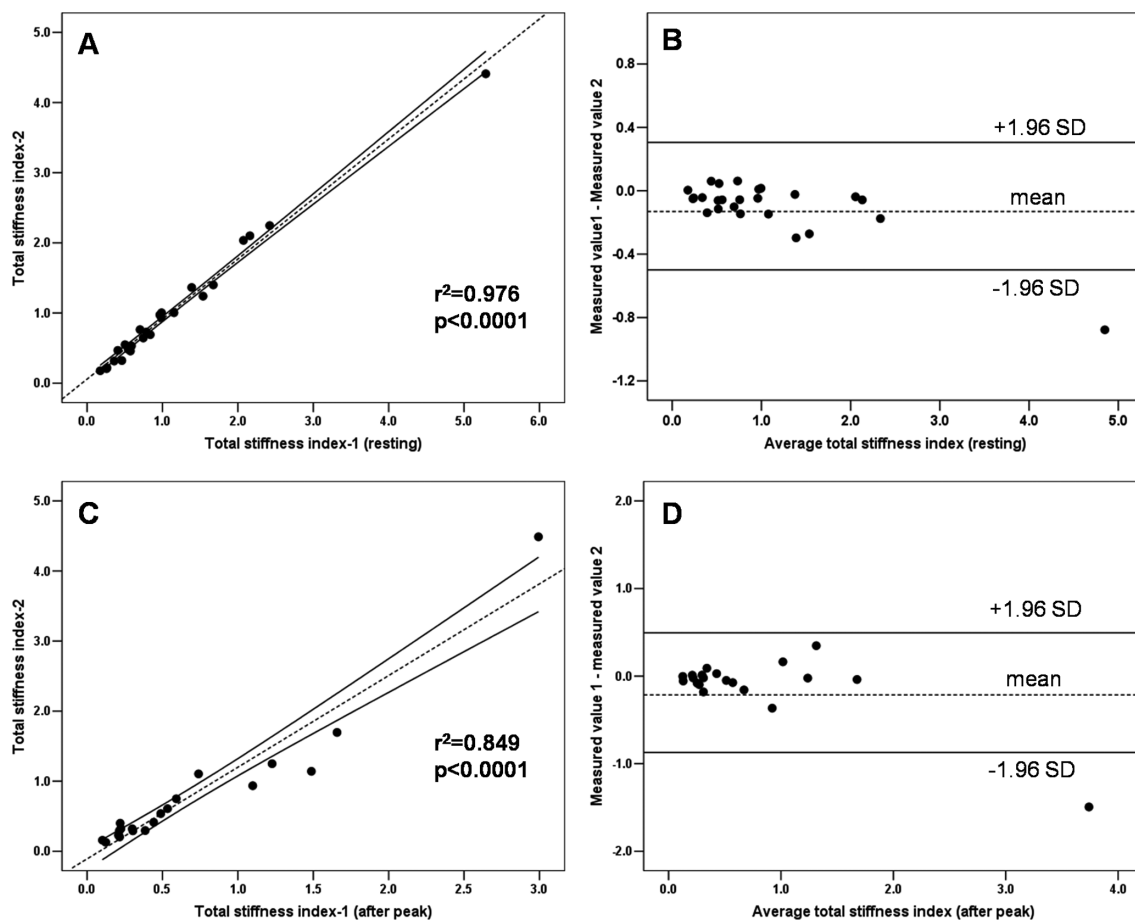

Figure 1. Inter-observer variability of echo-Doppler indices in patients with dilated cardiomyopathy. Correlation and Bland-Altman analysis of total stiffness indices measured by 2 independent investigators at rest (**A**,**B**) and after peak exercise (**C**,**D**).
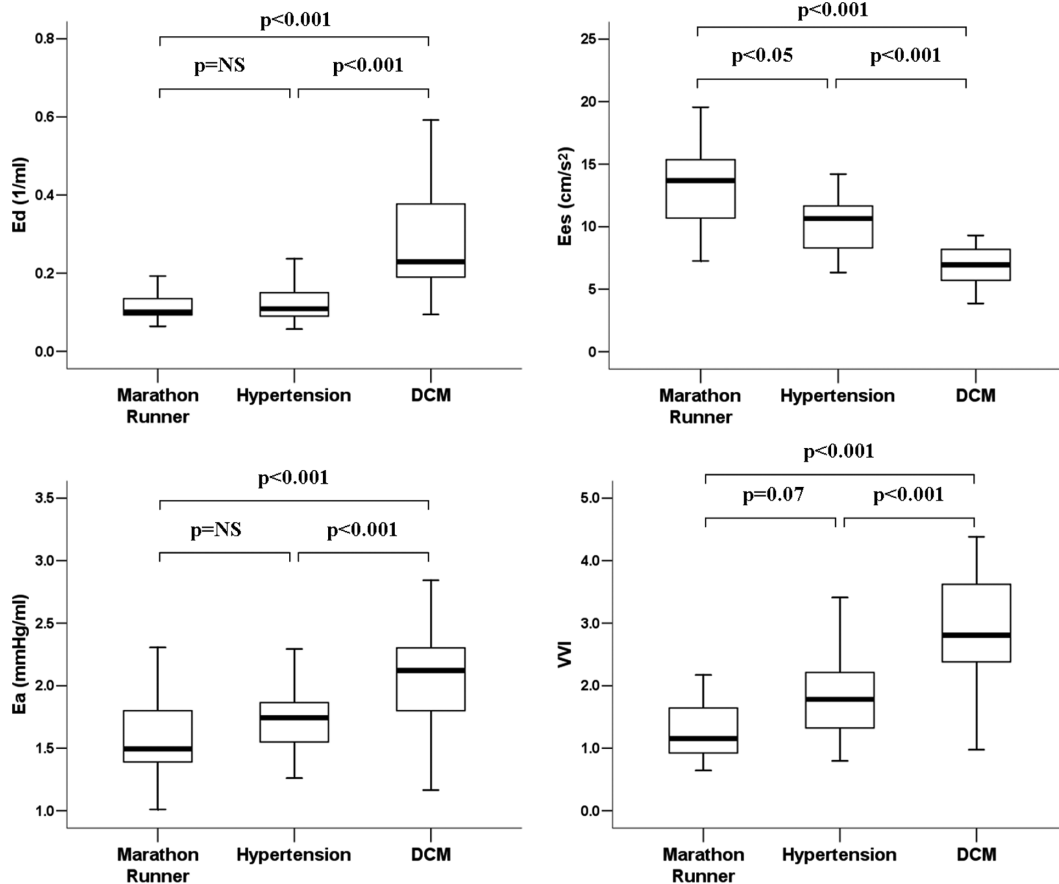
Figure 2. Comparison of resting Ed, Ees, Ea and ventriculoarterial coupling index between the 3 groups. Solid bar in the box represents median value. See text for explanation of abbreviations.

Statistical Analysis

Continuous variables are summarized as mean±standard deviation. Categorical variables are summarized as a percentage of the group total. To compare continuous and categorical variables, we used the ANOVA test with Tukey *post hoc* analysis and chi-square analysis, respectively. To assess the inter- and intra-observer variability of echo-Doppler indices, Pearson's correlation and Bland-Altman analysis were performed with each measured value. Differences in hemodynamic variables and Doppler indices between rest and each exercise stage were compared with repeated-measures ANOVA. The degree of correlation between hemodynamic parameters and exercise duration was analyzed by Pearson's correlation method. Multiple linear regression analysis was performed for exercise duration with covariates of age and gender to exclude their effects. Statistical significance was defined as P<0.05.

Results

Baseline Clinical Characteristics

The mean age of the DCM patients was 58 years, and 13 of them were male. The mean LVEF for the DCM patients was 26%; 18 patients had functional class II symptoms and 7 had class III symptoms with right ventricular systolic pressures of 27.8±14.0 mmHg. Other baseline clinical and hemodynamic parameters of the DCM patients, hypertensive patients, and healthy controls are described in **Table 2**.

Inter- and Intra-Observer Variability

In patients with DCM, the interobserver correlation coefficient was 0.998 for resting Ed, 0.916 for resting Ea/Ees, 0.935 for Ed after peak exercise and 0.876 for Ea/Ees after peak exercise. The correlation coefficient of the total stiffness indices measured by 2 independent investigator was 0.988 in the resting stage and 0.917 after peak exercise (**Figure 1**). The intra-observer correlation coefficient of total stiffness index was 0.975 in the resting stage and 0.942 after peak exercise. In 5 DCM patients, Ed at peak exercise could not be measured because of summation of the E and A waves as a result of tachycardia.

Ventricular Mechanics and Ventriculoarterial Interaction

The resting echo-Doppler indices of each group are described in **Table 2**. DCM patients had significantly higher Ed (0.30±0.15 vs 0.13±0.06 vs 0.11±0.03 ml, P<0.001) and lower Ees (7.3±2.6 vs 10.5±3.1 vs 13.2±3.4 m/s², P<0.001) compared with age- and gender-matched hypertensive patients and marathon runners. The Ees of hypertensive patients was lower than that of the healthy controls (P<0.05), despite no significant differences in LVEF. Regarding afterload, DCM was associated with a higher Ea (2.08±0.49 vs 1.77±0.34 vs 1.60±0.32 mmHg/ml, P<0.001) and lower total arterial compliance (1.20±0.35 vs 1.36±0.41 vs 1.56± 0.26 ml/mm, respectively, P<0.001). However, the systemic vascular resistance index did not differ between the groups. The VVI of DCM patients was significantly higher than
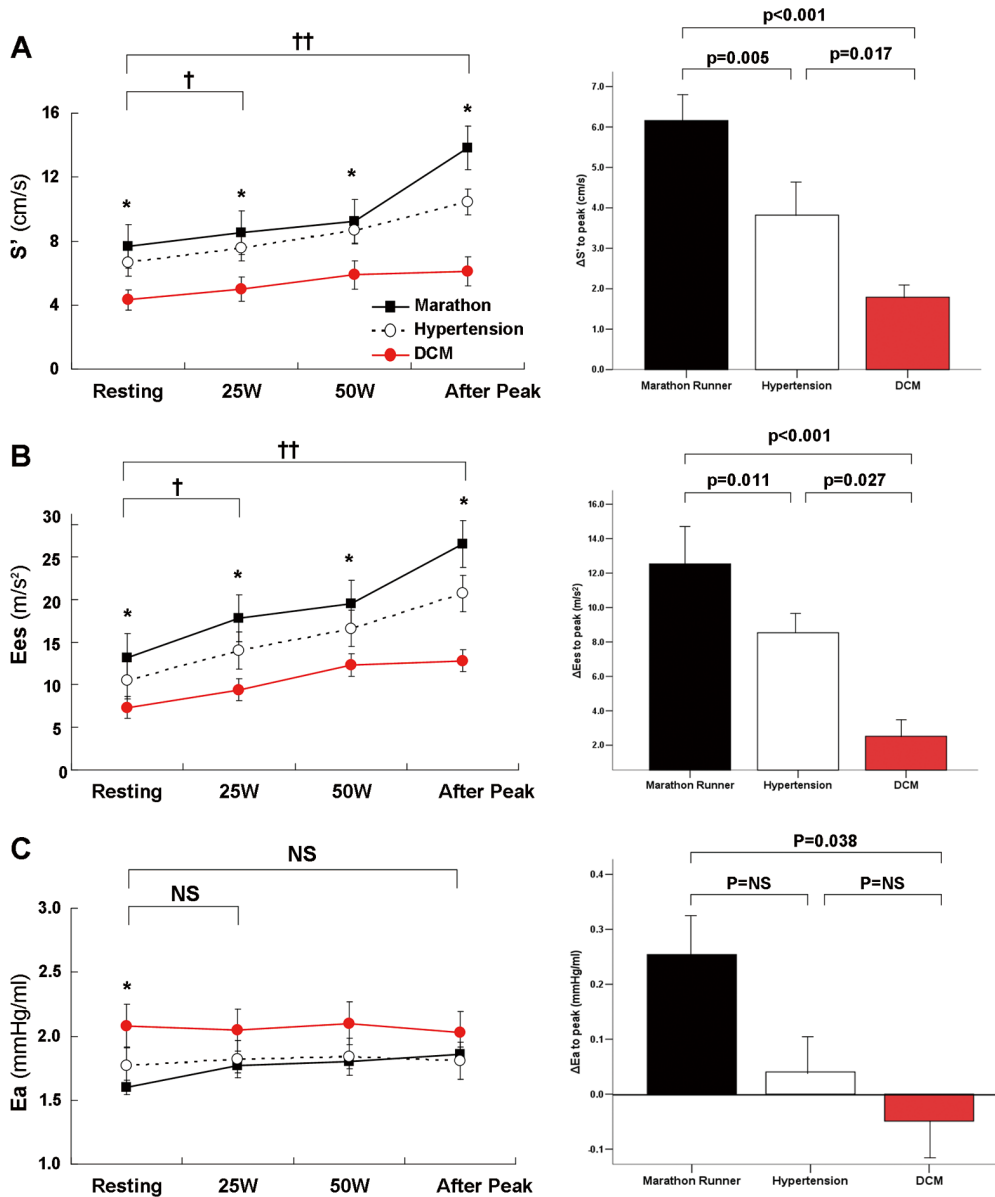
Figure 3. Exercise-induced changes in systolic mitral annular velocity (**A**), Ees (**B**) and Ea (**C**) in each group. Comparisons of their change at peak exercise between each group. Data are described as the mean±standard error. *P<0.05 between 3 groups, †P<0.05, ††P<0.001 in the patients with DCM. See text for explanation of abbreviations.

that of the hypertensive patients or marathon runners (3.21± 2.56 vs 1.86±0.77 vs 1.33±0.55, respectively, P<0.001) (**Figure 2**). In all subjects, the Ees significantly correlated with LVEF (r=0.595, P<0.001) and S' (r=0.639, P<0.001), and inversely correlated with LAVI (r=−0.330, P<0.001) and Ed (r=−0.521, P<0.001). Resting VVI was also significantly but inversely correlated with LVEF (r=−0.619, P<0.001), S'(r=−0.741, P<0.001) and correlated with LAVI (r=0.702, P<0.001) and Ed (r=0.692, P<0.001). However, their correlation coefficients were higher with VVI than with Ees alone. In the subgroup analysis of DCM, Ees also significantly correlated with LVEF (r=0.438, P=0.029), and resting VVI significantly correlated with Ed (r=0.525, P=0.007), LAVI (r=0.798, P<0.001) and the deceleration time of early mitral inflow (r=−0.464, P=0.023).

Change of Each Parameter During Exercise

The mean exercise duration of DCM patients was 438.9± 155.5 s (612.4±162.7 s in hypertensive patients and 981.0± 159.3 s in marathon runners, P<0.001). During exercise, the systemic vascular resistance index and total arterial compliance decreased in all 3 groups. The Ea, which represents total afterload, of DCM patients did not significantly change during exercise, despite a significant increase in the marathon runners. S' and Ees also significantly increased during exercise in all groups, but the degree of increase in DCM patients was significantly lower than that of the hypertensive patients or marathon runners (ΔS' to immediately after peak exercise: 1.79±1.60 vs 3.82±2.39 vs 6.16±3.33 cm/s, P<0.001; ΔEes to immediately after peak exercise: 5.5±4.6 vs 10.2±5.3 vs 13.3±8.3 m/s², respectively, P<0.001). The ΔEes in hypertensive patients was significantly lower than that of marathon runners (**Figure 3**). In addition, resting Ees
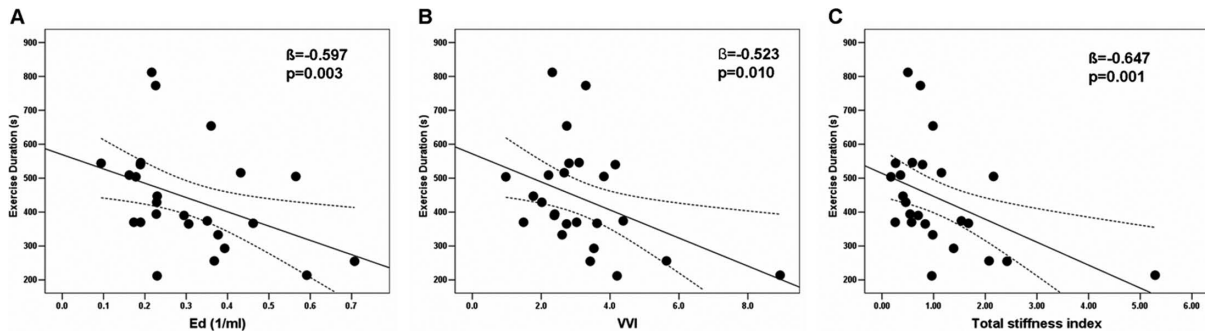
Figure 4. Correlation of Ed (**A**), VVI (**B**), and total stiffness index (**C**) with exercise duration after adjusting for age and gender. See text for explanation of abbreviations.
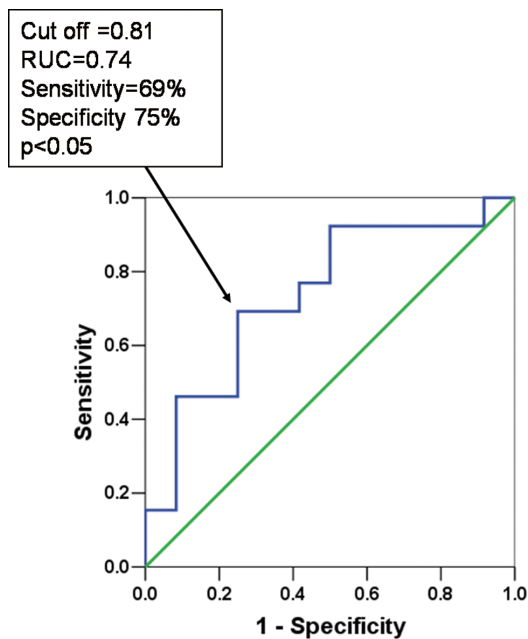

Figure 5. Prediction of impaired exercise capacity (<400 s) with total stiffness index using receiver operating characteristic analysis.

correlated with ΔS' to 25 W, representing contractile reserve to low-grade exercise, (r=0.561, P=0.004) despite no significant correlation with resting LVEF. The correlation between VVI and Ed was also maintained during exercise (at 25 W, r=0.510, P=0.047).

Determinants of Exercise Capacity in Patients With DCM
Multiple linear regression analysis including age and gender, resting Ed (β=−0.597, P=0.003) and VVI (β=−0.523, P=0.010) correlated with exercise duration, independent of age and gender (**Figure 4**). The combination of the preload index and afterload index, called the total stiffness index (Ed×VVI), had a better correlation coefficient (β=−0.647, P=0.001) with exercise duration. However, the resting SV (r=0.303, P=0.141), cardiac output (r=0.085, P=0.685), LVEF (r=−0.088, P=0.675), S' (r=0.180, P=0.388), E/E' (r=−0.288, P=0.163) and LAVI (r=−0.303, P=1.41) did not significantly correlate with exercise duration in this study. A total stiffness index of 0.811 could reliably predict impaired exercise capacity (<400 s, 69% sensitivity and 75% specificity with area under the curve of 0.74, P<0.05) (**Figure 5**).

Discussion

In this study, we found that the echo-Doppler derived ventricular elastance index and ventriculoarterial coupling index could be reliably used as an index of overall cardiovascular function in various group of subjects. Accordingly, we found that DCM patients had a higher ventricular elastance index, a lower ventricular Ees and more impaired ventriculoarterial interaction than hypertensive patients and marathon runners. The LV Ees index of hypertensive patients was also lower than that of the marathon runners, despite no significant differences in LVEF. We finally found that Ed and VVI were closely correlated at various exercise stages, and both can serve as independent determinants of exercise capacity in patients with DCM.

Ventricular Ed
In patients with heart failure, increased ventricular stiffness induces restrictive ventricular filling, thereby inducing an elevation of pulmonary capillary wedge pressure and increasing vulnerability to an acute loading change.[15] Echo-Doppler-derived E/E', a reliable index of ventricular filling, is significantly correlated with the LV end-diastolic pressure.[16] In the absence of significant aortic regurgitation, SV can be used as an indicator of ventricular filling volume. So, the combination of these 2 parameters as E/E'/SV represents the LV end-diastolic pressure/LV filling volume and can be used as the Ed index.[9,12] According to our results, Ed is a better determinant of exercise capacity than E/E' alone, independent of age and gender.

Ventriculoarterial Interaction
Another important pathophysiology of heart failure is increased afterload because of overactivation of the renin–angiotensin–aldosterone system or an increase in the peripheral catecholamine level.[17] Afterload has 2 components: a pulsatile component of central aortic mechanics and a nonpulsatile peripheral vascular resistance. The effective Ea can be used as the total arterial afterload, containing both components of afterload. These parameters can be measured noninvasively.[9,18–20] In this study, we found these indices of afterload were closely related to the ventricular diastolic functional indices at various exercise stages. Interestingly, despite no significant differences in the systemic vascular resistance index between the 3 groups, total arterial compliance and the pulsatile component of afterload significantly differed, thereby leading to differences in Ea. This finding suggests the importance of central arterial compliance, even in the patients with advanced systolic

heart failure. A normal response to afterload elevation is concomitant with an increase in LV contractility. However, the failing heart is very sensitive to afterload during ejection, and mismatched afterload–contractility can make an inefficient circulating system vulnerable to an acute loading change. The ventricular response to afterload, called Ees, is the most reliable index of ventricular end-systolic stiffness, representing load independent contractility.[21] The results of this study showed that both resting and exercise-induced Ees were significantly correlated with S', which represents a sensitive index of LV systolic function. We found that the echo-Doppler-derived Ees of the DCM patients was lower than that of the other groups. Interestingly, the Ees of the hypertensive patients was also significantly lower than that of the healthy controls, despite no significant differences in LVEF. In addition, resting Ees was related to contractile reserve for exercise in patients with DCM, with a blunted response of Ees increase in DCM patients compared with the controls. These findings suggest that echo-Doppler-derived Ees is a sensitive index of LV contractility.

Incorporation of Preload and Afterload Indexes

We also found that the combination of Ea/Ees, which represents ventriculoarterial stiffening or afterload-adjusted contractility of the cardiovascular system, and Ed can be a predictor of exercise capacity in DCM patients. Despite the fact that SV is a core component of VVI and Ed, SV did not correlate solely with exercise capacity in this study. The Ed, which represents preload, is closely related to the VVI, which represents the contractility–afterload interaction. By combining the resistance of ventricular filling and outflow with contractility, we devised a new index of total ventricular stiffness based on Ed×VVI. This index can provide information regarding the overall efficiency of the cardiovascular system. With the combination of these preload and afterload indices, we obtained a better correlation coefficient with exercise duration in this study. However, its predictive value for exercise intolerance has not been proved to be better than traditionally accepted predictive indices, such as ventricular filling indices or skeletal muscle mass, in a large-scale study. Future study should deal with this point.

Study Limitations

First, despite the fact that noninvasive measurement of Ees and Ea has been validated, Ed has not yet been validated. However, several previous studies used E/E'/SV as a reflector of ventricular elastance.[9,12] In the nature of this study, measurements of echo-Doppler-derived Ed had some clinical value regarding risk stratification. Secondly, the indices used for ventricular stiffness or ventriculoarterial coupling came from multiple calculation steps, which may cause the values to vary from those obtained by invasive measurement. Several previous studies have validated the use of echo-Doppler indices, and in clinical practice there is a need for easy and noninvasive measurement to assess prognosis and exercise capacity, and to monitor specific treatments. Therefore, it is very useful to have these noninvasively measured indices. Thirdly, although Doppler-derived Ees has been validated in the resting state, its accuracy during exercise has not. However, in this study, Ees during exercise was closely correlated with S' on exercise, which is a sensitive index of LV systolic function; therefore, Doppler-derived Ees could be used as an index of contractility during exercise. Several studies also used noninvasively

measured Ea during exercise.[18,22,23] Furthermore, we think that the main result of our study, which is that the resting VVI can predict exercise capacity, might not be significantly affected by this limitation. Future study should validate Doppler-derived Ees during exercise. Fourthly, we did not measure the LV end-systolic volume for the calculation of Ees because of the poor border delineation during exercise. Instead, we used LV outflow tract pulse-wave Doppler for the measurement of the Ees index because of its clearer image quality. The concept of Ea/Ees represents afterload-adjusted cardiac contractility, which reflects the efficiency of the cardiovascular system. Although the timing of Ea and LV outflow tract flow acceleration was different, the Ees index measured by LV outflow acceleration was invasively validated. We think the original concept of this coupling index would be preserved when we used LV outflow tract acceleration.

Conclusion

Arterial mechanics are associated with ventricular functional indices. In addition, echo-Doppler-derived ventricular stiffness and the VVI can be used to predict the exercise capacity of patients with nonischemic DCM. Therefore, in clinical practice the measurement of these indices can provide physiological insight, and may be helpful in the triage of patients according to risk stratification.

Disclosure

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