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ORIGINAL RESEARCH

Tissue Doppler Image-Derived Measurements During Isovolumic Contraction Predict Exercise Capacity in Patients With Reduced Left Ventricular Ejection Fraction

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OBJECTIVES We explored the incremental value of quantification of tissue Doppler (TD) velocity during the brief isovolumic contraction (IVC) phase of the cardiac cycle for the prediction of exercise performance in patients referred for cardiopulmonary exercise testing (CPET).

BACKGROUND Experimental studies have shown that rapid left ventricular (LV) shape change during IVC is essential for optimal onset of LV ejection. However, the incremental value of measuring IVC velocities in clinical settings remains unclear.

METHODS A total of 82 subjects (age 53 ± 14 years, 56 men) were studied with echocardiography and CPET. Reduced LV ejection fraction (EF) (EF <50%) was present in 38 (46%) subjects. Pulsed-wave annular TD velocities were averaged from the LV lateral and septal annulus during isovolumic contraction (IVCa), ejection, isovolumic relaxation, and early and late diastole (Aa) and compared with peak oxygen consumption (VO_2) and percentage of the predicted peak VO_2 (% predicted peak VO_2) obtained from CPET.

RESULTS Patients with reduced EF had lower IVCa (6.3 vs. 4.5 cm/s, $p = 0.04$), ejection (7.7 vs. 5.5 cm/s, $p < 0.001$), and Aa velocities (7.9 vs. 6.6 cm/s, $p = 0.04$). Similarly, % predicted peak VO_2 was lower in patients with reduced EF (52.9% vs. 73.1%, $p < 0.001$) and correlated with the variations in IVCa ($r = 0.7$, $p = 0.001$). Multivariate analysis of 2-dimensional and Doppler variables in the presence of reduced LV EF revealed only IVCa and Aa as independent predictors of % predicted peak VO_2 ($r^2 = 0.612$, $p = 0.02$ for IVCa and $p = 0.009$ for Aa). The overall performance of IVCa in the prediction of exercise capacity was good (area under the curve = 0.86, $p < 0.001$).

CONCLUSIONS Assessment of TD-derived IVC and atrial stretch velocities provide independent prediction of exercise capacity in patients with reduced LV EF. Assessment of LV pre-ejectional stretch and shortening mechanics at rest may be useful for determining the myocardial functional reserve of patients with reduced EF. (J Am Coll Cardiol Img 2010;3:1–9) © 2010 by the American College of Cardiology Foundation

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The isovolumic contraction (IVC) phase of the cardiac cycle initiates interactions between cardiac myofilaments through energy-dependent calcium fluxes in the myoplasm and sarcolemma (1,2). Approximately 50% of total myocardial oxygen consumption (VO_2) is expended for a rapid rise in left ventricular (LV) pressure during IVC (3). In vitro experiments using skinned muscle preparations have suggested that this energy-dependent early shortening sequence may stretch activate the cardiac muscle tissue for modulating the force and duration of contraction (4–6). Shortening mechanics during IVC thus may be important for functionally adapting to physiological states with high energy consumption and VO_2 such as exercise.

Transient reshaping of LV geometry during IVC is registered on tissue Doppler (TD) imaging as biphasic longitudinal myocardial velocity spikes (7). The positive component of TD-derived IVC velocity spikes has been shown to correlate with the rate of change in LV pressure (8). Furthermore, IVC velocity spikes are associated with the energy efficient sequence of LV intracavity blood flow redirection through vortex ring formation (9–12). In the present study, we evaluated the incremental value of TD-derived peak positive IVC velocity as a noninvasive parameter for the prediction of exercise efficiency in patients referred for cardiopulmonary exercise testing (CPET). We hypothesized that TD-derived IVC velocity would be independently related to peak VO_2 and predicted peak oxygen consumption (% predicted peak VO_2).

ABBREVIATIONS AND ACRONYMS

Aa = annular tissue velocity during late diastolic period

CPET = cardiopulmonary exercise test

Ea = annular tissue velocity during early diastolic period

EF = ejection fraction

IVC = isovolumic contraction phase

IVCa = annular tissue velocity during isovolumic contraction period

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

MET = metabolic equivalent

ROC = receiver-operator characteristic

TD = tissue Doppler

VCO_2 = carbon dioxide production

VE = minute ventilation

VO_2 = oxygen consumption

% predicted peak VO_2 = predicted peak oxygen consumption

METHODS

Between January 2007 and August 2008, 193 patients with complaints of dyspnea underwent CPET for objective assessment of exercise capacity and a detailed transthoracic echocardiographic examination at Mayo Clinic Arizona. Patients with moderate or severe valve lesions (n = 30, 15.5%), paced rhythm or ventricular assist device (n = 38, 19.7%), atrial fibrillation (n = 10, 5.1%) and significant lung disease (n = 5, 2.6%), liver or renal failure (n = 61, 31.6%), and congenital heart disease (n = 25, 13.0%) were excluded from the study. Based on left ventricular ejection fraction (LVEF), patients were classified into 2 groups: reduced LVEF (EF <50%; n = 38, 46%) and normal LVEF (EF ≥50%; n = 50, 54%).

Echocardiography. Echocardiography and CPET were performed within 1 week (2.5 ± 2.3 days). All patients were examined at rest in the left lateral decubitus position. The echocardiographic techniques and calculations of different cardiac dimension and volumes were performed according to the recommendations of the American Society of Echocardiography (13). LVEF by 2-dimensional echocardiography was obtained by modified biplane Simpson's method from apical 4- and 2-chamber views. LV dimensions and wall thickness were made in parasternal long axis with M-mode cursor positioned just beyond the mitral leaflet tips, perpendicular to the long axis of the ventricle. LV diameter in diastole and systole, LV mass, and fractional shortening were measured. Left atrial volume was calculated from areas measured in apical 2- and 4-chamber views and indexed by body surface area. Left atrial total emptying fraction was calculated by dividing differences between largest and smallest left atrial volume with largest left atrial volume.

Mitral flow velocities. The mitral flow velocities were recorded with pulsed-wave Doppler with the sample volume placed at the tip of the mitral valve tips from the apical 4-chamber view. From the mitral valve inflow velocity curve, peak E-wave velocity and its deceleration time, and peak A-wave velocity were measured.

TD imaging. Myocardial velocities were recorded using a standard pulse-wave Doppler technique as previously described (14). High-frequency signals in IVC velocities were filtered using a Nyquist limit adjusted to a velocity range of −15 to 20 cm/s. Gains were minimized to allow for a clear tissue signal with minimum background noise as shown in Figure 1. Peak contraction and relaxation velocities were averaged from the lateral and septal corners of mitral valve annulus during IVC (IVCa), systolic ejection (Sa), and early (Ea) and late (Aa) diastolic phases of the cardiac cycle at a speed of 100 mm/s (Fig. 1). We also measured isovolumic acceleration at the lateral and medial mitral annulus as the slope of the pre-systolic velocity curve expressed in m/s^2 (15).

CPET. All patients underwent a maximal exercise

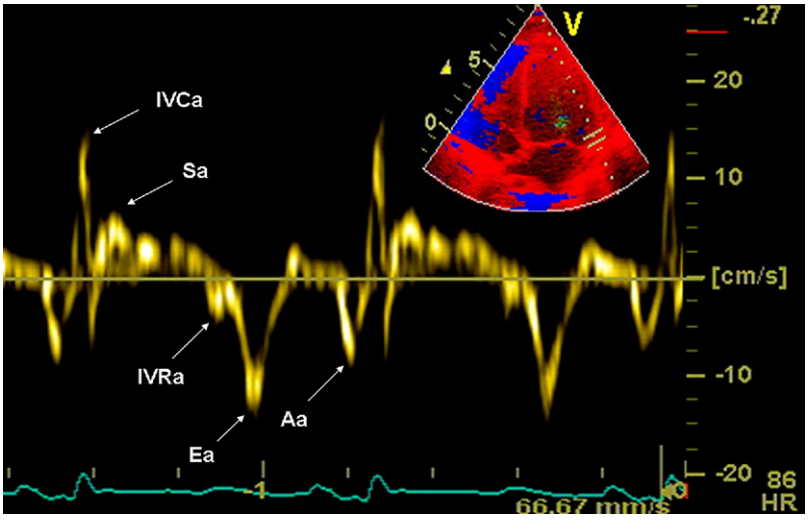


Figure 1. Measurement of Annular Tissue Velocities

Peak contraction and relaxation velocities were averaged from the lateral and septal corners of mitral valve annulus during isovolumic contraction (IVCa), systolic ejection (Sa), isovolumic relaxation (IVRa), early (Ea), and late (Aa) diastolic phases of the cardiac cycle at a speed of 100 mm/s.

stress test on an electrically braked stationary cycle ergometer using ramp protocol (n = 9, 11%) or treadmill test using modified ramp protocol (n = 73, 89%). Previous studies have shown the prognostic thresholds of peak VO_2 and minute ventilation/carbon dioxide production (VE/VCO_2) slope in patients with heart failure to be similar irrespective of mode of exercise (16). Patients were encouraged to exercise to exhaustion. During the test, patients wore a tightly fitting facemask which was connected to a capnograph and a sample tube enabling online ventilation and metabolic gas exchange measurement. Ventilatory expired gas analysis (as well as spirometry) was performed using a metabolic cart (Medgraphics CPX ULTIMA Cardio 2, Minneapolis, Minnesota). Exercise was started at a work load of 30 W, with further increment of 10 W every minute. All patients were encouraged to exercise to exhaustion, with a peak respiratory exchange greater than 1.1. Peak VO_2 was defined as the highest O_2 consumption during any stage of maximal exercise that could be sustained for 1 min (or 30 s). Data are expressed as relative values and as percentages of the predicted VO_2 as well. Metabolic equivalents was defined per convention as equivalent to the consumption of 3.5 ml of oxygen per kilogram of body mass per minute (17). The VO_2, VCO_2, VE, respiration rate, respiratory exchange ratios (VCO_2/VO_2), and other standard respiratory parameters were monitored continuously breath by breath and averaged every 15 s. A 4-lead electrocardiogram recorded heart rate continuously.

Table 1. Clinical Characteristics

	LVEF <50% (n = 38)	LVEF ≥50% (n = 44)	p Value
Men (n)	27 (71.1%)	29 (65.9%)	0.40
Mean age (yrs)	52 ± 13	53 ± 14	0.86
LVEF (%)	26 ± 10	66 ± 8	<0.001
Body mass index (kg/m^2)	29.2 ± 6.4	28.5 ± 6.0	0.65
Left bundle branch block	10 (26.3%)	3 (6.8%)	0.03
Diabetes	12 (31.6%)	7 (15.0%)	0.10
Hypertension	12 (31.6%)	23 (52.3%)	0.06
Current medication			
ACEI or ARB	26 (68.4%)	14 (31.8%)	0.002
Beta-blocker	25 (65.8%)	23 (52.3%)	0.16
Calcium-channel blocker	1 (2.6%)	6 (13.6%)	0.081
Digoxin	15 (39.5%)	3 (6.8%)	<0.001
Diuretics	30 (78.9%)	18 (40.9%)	<0.001
Nitrates	1 (2.6%)	1 (2.3%)	0.72
Etiology			
Idiopathic	10 (26.3%)	8 (18.2%)	0.54
Ischemic	17 (44.7%)	5 (11.4%)	0.002
Hypertensive	4 (10.5%)	11 (25.0%)	0.02
Hypertrophic	1 (2.6%)	19 (43.2%)	<0.001
Miscellaneous*	6 (15.9%)	1 (2.3%)	—

Values are n (%) or mean ± SD. *Miscellaneous etiologies included drug-induced and post-partum cardiomyopathy in 2 patients each and arrhythmogenic right ventricular dysplasia and infiltrative disease for 1 patient each for the subgroup with reduced ejection fraction and tachycardiomyopathy in 1 patient for the subgroup with normal ejection fraction.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction.

Statistical analysis. All continuous data were reported as mean ± SD, and categorical data as percentage. To determine intraobserver variability, 1 observer (G.C.) measured the myocardial velocities in 25 randomly selected patients. Intraobserver variability was calculated as the difference in 2 measurements of the same subject by 1 observer divided by the mean value. To evaluate the interobserver variability, the myocardial velocities were obtained in 68 patients by 2 independent observers (E.C. and G.C.), each without knowledge of the results obtained by the other. Interobserver variability was calculated as the difference in 2 measurements of the same subjects by 2 different observers divided by the mean value. Independent *t* test was used for comparisons of continuous variables between patients with normal and reduced EF. Pearson's correlation coefficient was used to reveal relations between 2 continuous variables. The receiver-operator characteristic (ROC) curve was plotted to determine the sensitivity and specificity to predict exercise capacity, and Delong Delong Clarke-Pearson method (Analyse-it software, Microsoft Excel, Redmond, Washington) was used to compare diagnostic power of ROC curves (18). Multiple stepwise regression analysis was used to evaluate the relationship between % predicted peak VO_2 and clinical and echocardiographic variables. Variables that showed significant correlations ($p < 0.1$) with % predicted peak VO_2 on simple regression analysis were selected. Statistical analysis was performed with commercially available software (SPSS 12.0 software, SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

Table 2. 2-Dimensional, M-Mode, and Doppler Echocardiographic Data

	LVEF <50% (n = 38)	LVEF ≥50% (n = 44)	p Value
LVEF (%)	26.3 ± 9.7	66.0 ± 7.7	<0.001
IVS (mm)	10.1 ± 3.0	14.7 ± 6.7	<0.001
LVPW (mm)	10.0 ± 2.5	12.2 ± 3.8	0.003
LVESD (mm)	56.1 ± 11.8	29.2 ± 8.4	<0.001
LVEDD (mm)	64.8 ± 10.7	46.7 ± 7.7	<0.001
LVESV (ml)	147.3 ± 87.0	44.0 ± 29.4	<0.001
LVEDV (ml)	198.2 ± 88.9	102.4 ± 40.0	<0.001
LV mass index (g/cm^2)	144.9 ± 54.1	126.5 ± 53.4	0.13
Relative wall thickness*	0.3 ± 0.1	0.6 ± 0.2	<0.001
Indexed LA volume (ml/m^2)	40.5 ± 14.6	39.7 ± 17.8	0.83
LA total emptying fraction (%)	49.7 ± 23.2	58.5 ± 16.8	0.12
E velocity (m/s)	0.83 ± 0.26	0.84 ± 0.37	0.90
A velocity (m/s)	0.58 ± 0.27	0.68 ± 0.28	0.14
E/Ea	14.6 ± 6.6	13.4 ± 7.8	0.50
E/A	1.73 ± 1.08	1.34 ± 0.62	0.07
Deceleration time (ms)	159 ± 52	201 ± 56	0.001
IVRT (ms)	74 ± 35	97 ± 41	0.08
Right ventricular systolic pressure (mm Hg)	45.3 ± 17.9	34.9 ± 13.2	0.12

*2 × left ventricular posterior wall thickness (LVPW)/left ventricular end-diastolic dimension (LVDd).
IVRT = isovolumic relaxation time; IVS = interventricular septal thickness; LA = left atrial; LVEDD = left ventricular end-diastolic dimension; LV = left ventricular; LVESD = left ventricular end-systolic dimension; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; 2D = 2-dimensional; other abbreviations as in Table 1.

RESULTS

Baseline clinical features of the patients and the underlying etiologies are shown in Table 1.

Echocardiographic data. Patients with reduced LVEF had thinner interventricular septum ($p < 0.001$) and posterior walls ($p = 0.003$). However, there were no significant differences in LV mass index, indexed left atrial volume, and left atrial total emptying fraction (Table 2). There were no significant differences in transmitral early and late inflow velocities, E/Ea, and E/A (Table 2). However, cardiac index was significantly reduced ($p = 0.003$) in patients with reduced EF.

Pulse-wave TD data. The absolute intraobserver differences for measuring TD velocities during IVC were 0.06 ± 1.2 cm/s and the corresponding intraobserver variability were 1.2 ± 2.4%. Annular velocities averaged from the septal and lateral corners of mitral annulus were significantly reduced in patients with reduced EF during IVC (6.3 vs. 4.5 cm/s, $p = 0.04$), ejection (7.7 vs. 5.5 cm/s, $p < 0.001$), and late diastolic (7.9 vs. 6.6 cm/s, $p = 0.04$) phases of the cardiac cycle (Table 3). Similarly, isovolumic acceleration measured during the pre-ejection period and averaged from the septal and the lateral corners of mitral annulus was significantly reduced in patients with reduced EF (1.37 ± 0.53 m/s^2 vs. 1.85 ± 0.61 m/s^2, $p = 0.001$).

CPET. Maximum exercise duration (Table 4) was significantly lower in patients with reduced LVEF (363 ± 123 s vs. 443 ± 102 s, $p = 0.006$). Similarly, exercise variables like MET at peak VO_2 ($p < 0.001$), peak VO_2 at maximal exercise ($p = 0.001$), and % predicted peak VO_2 ($p < 0.001$) were significantly lower, while VE/VCO_2 ($p = 0.04$) and VE/VO_2 ($p = 0.03$) were significantly increased in patients with reduced LVEF.

Correlation between echocardiographic parameters and CPET. Correlations between TD velocity, isovolumic acceleration and peak VO_2, and % pre-

Table 3. Tissue Doppler-Derived Longitudinal LV Annular Dynamics

	LVEF <50% (n = 38)	LVEF ≥50% (n = 44)	p Value
Medial			
IVCa (cm/s)	4.3 ± 1.8	6.3 ± 2.3	<0.001
IVA (m/s^2)	1.40 ± 0.61	1.94 ± 0.69	0.001
Sa (cm/s)	4.9 ± 1.9	7.0 ± 1.8	<0.001
IVRa (cm/s)	4.2 ± 1.8	4.0 ± 2.1	0.585
Ea (cm/s)	5.0 ± 2.3	7.1 ± 2.9	<0.001
Aa (cm/s)	5.8 ± 2.9	7.6 ± 2.8	0.008
Ea/Aa	1.1 ± 0.7	1.1 ± 1.0	0.967
Lateral			
IVCa (cm/s)	4.8 ± 2.9	5.4 ± 2.6	0.392
IVA (m/s^2)	1.34 ± 0.56	1.75 ± 0.71	0.007
Sa (cm/s)	6.1 ± 3.7	8.4 ± 3.3	0.006
IVRa (cm/s)	4.2 ± 2.5	4.6 ± 2.8	0.353
Ea (cm/s)	8.2 ± 4.1	8.1 ± 3.6	0.912
Aa (cm/s)	7.1 ± 3.4	8.2 ± 3.3	0.157
Ea/Aa	1.3 ± 0.6	1.1 ± 0.7	0.293
Average			
IVCa (cm/s)	4.5 ± 2.0	6.3 ± 2.2	0.042
IVA (m/s^2)	1.37 ± 0.53	1.85 ± 0.61	0.001
Sa (cm/s)	5.5 ± 2.1	7.7 ± 2.1	<0.001
IVRa (cm/s)	4.1 ± 1.6	4.3 ± 2.2	0.611
Ea (cm/s)	6.6 ± 2.9	7.6 ± 3.1	0.160
Aa (cm/s)	6.6 ± 2.9	7.9 ± 2.8	0.044
Ea/Aa	1.2 ± 0.5	1.1 ± 0.6	0.783

Aa = annular late diastolic wave; Ea = annular early diastolic wave; IVA = isovolumic acceleration; IVCa = annular isovolumic contraction wave; IVRa = annular isovolumic relaxation wave; LV = left ventricular; LVEF = left ventricular ejection fraction; Sa = annular ejection wave.

dicted peak VO_2 for the entire group and for patients with reduced and preserved EF are shown in Table 5. For patients with reduced EF, of all the echocardiographic and clinical parameters assessed, annular velocities during the IVC period and late diastolic period showed the best correlations (Fig. 2) and were independent predictors for % predicted peak VO_2 (Table 6, Online Table 1). The overall performance of IVCa, isovolumic acceleration, and Aa (Fig. 3) in the prediction of exercise capacity was good (area under the curve 0.86, p = 0.001 for IVCa; 0.74, p = 0.02 for isovolumic acceleration; and 0.82, p = 0.003 for Aa).

DISCUSSION

The main findings of this study are: 1) TD-derived IVCa and Aa velocities are significantly attenuated in patients with reduced LVEF; and 2) IVCa and Aa are the only 2 independent echocardiographic predictors for exercise capacity in patients with reduced LVEF. To the best of our knowledge, this is the first study that has evaluated the relationship between isovolumic contraction velocities and exercise performance in patients undergoing CPET.

Echocardiographic predictors of exercise capacity in heart failure patients. Conventional measures of LV function such as resting EF and Doppler indexes such as peak A velocity or E/A are load-dependent and poorly associated with symptoms and exercise capacity (19–24). Previous studies have correlated TD-derived parameters like early diastolic lengthening velocities (Ea) and E/Ea ratio with the extent of exercise limitation in patients with reduced LVEF (25–28). Recent investigations have further suggested the combined use of systolic ejection and early diastolic TD parameter, rather than isolated measurements, would be essential for proper characterization of the extent of exercise intolerance (29). The duration of the total isovolumic period is a major determinant of peak VO_2 (30,31). Moreover, TD-derived isovolumic indexes were previously suggested to be relatively load-independent and therefore more sensitive markers of myocardial contractility than parameters measured during ejection and diastolic filling phases (32,33). The specific contribution of IVC period and the relationship between IVC velocity and peak VO_2, however, were previously unknown. Our investigation suggests that IVC contraction and LV

Table 4. Cardiopulmonary Exercise Test

	LVEF <50% (n = 38)	LVEF ≥50% (n = 44)	p Value
Exercise duration (s)	363 ± 123	443 ± 102	0.006
RER at Max VO_2	1.2 ± 0.1	1.5 ± 0.6	0.183
Basal HR (beats/min)	81 ± 18	76 ± 21	0.192
Basal RR (per min)	18 ± 3	18 ± 5	0.836
Basal SBP (mm Hg)	114 ± 16	126 ± 19	0.004
Basal DBP (mm Hg)	69 ± 11	76 ± 13	0.019
Max HR (beats/min)	120 ± 23	129 ± 27	0.139
Max RR (per min)	34 ± 7	31 ± 7	0.098
Max SBP (mm Hg)	127 ± 28	150 ± 41	0.025
Max DBP (mm Hg)	73 ± 12	82 ± 17	0.022
MET at Max VO_2	4.4 ± 1.4	5.8 ± 1.7	<0.001
Peak VO_2 (ml/kg/min)	15.4 ± 5.0	20.0 ± 6.3	0.001
% Predicted peak VO_2 (%)	52.9 ± 14.2	73.1 ± 17.5	<0.001
VE/VCO_2 at Max VO_2	38.4 ± 8.9	33.9 ± 8.3	0.041
VE/VO_2 at Max VO_2	45.2 ± 8.7	39.3 ± 9.5	0.030

DBP = diastolic blood pressure; HR = heart rate; LVEF = left ventricular ejection fraction; Max = maximal; MET = metabolic equivalents; RER = respiratory exchange ratio; RR = respiratory rate; SBP = systolic blood pressure; VCO_2 = carbon dioxide production; VE = minute ventilation; VO_2 = oxygen consumption.

Table 5. Correlation Between Tissue Doppler Velocity and Exercise Capacity

	Overall Group (n = 82)				LVEF <50% (n = 38)				LVEF ≥50% (n = 44)			
	Peak VO_2		% Predicted VO_2		Peak VO_2		% Predicted VO_2		Peak VO_2		% Predicted VO_2	
	r	p Value	r	p Value	r	p Value	r	p Value	r	p Value	r	p Value
IVCa	0.32	0.006	0.40	0.001	0.45	0.01	0.69	<0.001	0.15	0.35	0.08	0.62
IVA	0.17	0.14	0.29	0.01	0.08	0.67	0.33	0.05	0.08	0.64	0.04	0.80
Sa	0.26	0.02	0.49	<0.001	0.35	0.04	0.51	0.002	0.03	0.88	0.17	0.28
IVRa	0.03	0.82	0.04	0.72	0.26	0.14	0.45	0.009	0.19	0.23	0.20	0.22
Ea	0.20	0.08	0.14	0.22	0.32	0.06	0.42	0.01	0.05	0.74	0.15	0.34
Aa	0.25	0.03	0.39	0.001	0.44	0.01	0.71	<0.001	0.01	0.97	0.05	0.76
Ea/Aa	−0.21	0.07	−0.14	0.21	−0.27	0.12	−0.35	0.04	−0.18	0.25	−0.05	0.74
E/Ea	−0.19	0.11	−0.13	0.27	−0.42	0.01	−0.54	0.001	−0.04	0.80	−0.14	0.38

Abbreviations as in Tables 3 and 4.

stretch velocities resulting from atrial contraction, rather than ejection or early diastolic phase lengthening velocities, provide superior prediction of the exercise performance. In contrast to IVC velocity, IVC acceleration showed weaker correlation with % predicted peak VO_2 (r = 0.34, p = 0.044) (Online Fig. 1). The diagnostic power of IVC velocity and acceleration for predicting % predicted peak VO_2 >50% were, however, similar (0.80 vs. 0.76, p = NS for the entire group and 0.86 vs. 0.74, p = 0.06 for LVEF <50%).

During electromechanical coupling, influx of Ca^{2+} activates both energy-producing and energy-consuming processes, providing mechanisms for cardiac muscle to dramatically increase contraction without any change in energetic intermediates (34). Early activated regions of the LV contract, stretching the late activated regions (9). This sequence of early shortening and stretch during IVC provides an intrinsic servo-mechanism for dynamically modulating the force of cardiac muscle contraction and the timing of cross-over into diastole (4–6). LV stretch due to atrial contraction precedes isovolumic contraction, and both may dynamically modulate the forces operating in the ejection and early diastolic phases of the cardiac cycle. For example, in our study we found that IVC velocity correlated with ejection phase velocities (Online Fig. 2). This relationship between the phases of the cardiac cycle may be a potential reason why the diagnostic yield of TD imaging for predicting exercise capacity is improved when Aa and IVCa velocities are incorporated. Witte et al. (35) stressed the role of annular tissue velocity in the late diastolic period and its correlation with peak VO_2. Late diastolic

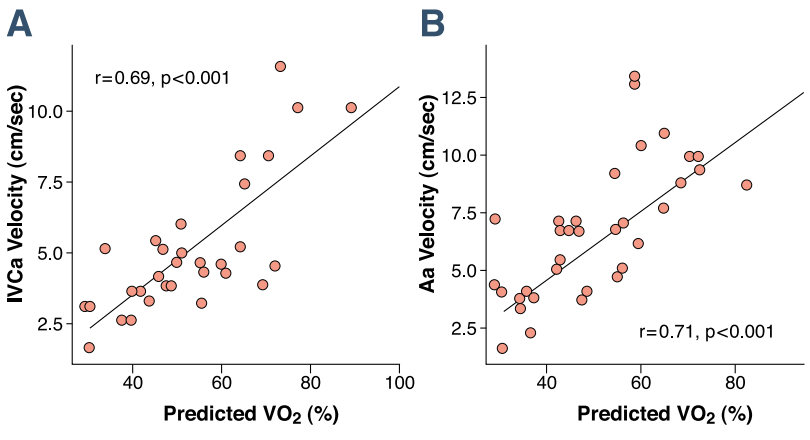


Figure 2. Annular Velocities and % Predicted Peak VO_2 >50%

Correlation between annular tissue Doppler velocity and % predicted peak oxygen consumption (VO_2) in patients with left ventricular systolic dysfunction. Abbreviations as in Figure 1.

stretch velocities reflect left atrial function and the adaptive capacity of the left atrium to compensate for increased diastolic volume and filling pressure of the LV in heart failure patients (36–38). Moreover, the peak of Aa and the positive IVCa velocity spike transit on a continuum as seen on the TD-derived spectral velocity waveforms. The correlation of IVCa and Aa with % predicted peak VO_2 may thus reflect atrioventricular events that operate on a continuum and prime the LV for optimal systolic ejection and diastolic suction.

Prognostic value of CPET in heart failure patients. The term "VO_2 max" refers to a plateau in peak oxygen uptake in line with increasing workload during exercise. However, congestive heart failure patients are normally unable to exercise to such a level; therefore, the term peak VO_2 is used. Peak VO_2 is affected by sex and age. In addition, because oxygen uptake is relativized for body mass, heavier patients with a similar fitness level will have a lower peak VO_2. Therefore, when considering an individual patient, one must consider adjustments for age, sex, and body mass of the patient. Assessment of peak VO_2 threshold can also be problematic in some heart failure patients due to deconditioning, lack of motivation, and difficulty exercising with a facemask/mouthpiece in situ. In 1996, Stelken et al. (39) suggested the use of the % predicted peak VO_2 for identifying patients at risk for future cardiac event. In their study, % predicted peak VO_2 cut point ≤50% was sensitive in detecting more events than the use of absolute peak VO_2 value. Subsequently, Osada et al. (40) reported that for peak VO_2 ≤14 ml/kg, peak exercise systolic blood pressure and % predicted peak VO_2 (≤50%) in heart transplant recipients were the 2 most important predictors for the combined end point of death or listing as status 1 transplantation priority. Interestingly, for our study the comparison of TD and exercise parameters revealed superior correlation coefficients between TD parameters and % predicted peak VO_2 than with peak VO_2. Furthermore, ROC analysis showed TD parameters were able to predict % predicted peak VO_2 >50%, whereas similar observations were not seen for peak VO_2. The role of % predicted peak VO_2 thus needs more careful assessment in future investigations.

Study limitations. The present study only evaluated the myocardial velocity using TD imaging in the longitudinal direction. Further studies would be required for understanding the value of measuring 2- and 3-dimensional strain deformation using Doppler and angle-independent techniques such as speckle tracking. Future studies would also need to compare the clinical value of measuring LV torsional mechanics in predicting exercise capacity, particularly for the group of patients with preserved EF in whom the longitudinal velocities were unable to predict exercise capacity in our study.

Table 6. Multiple Regression Analysis for % Predicted VO_2 in Patients With LVEF <50%

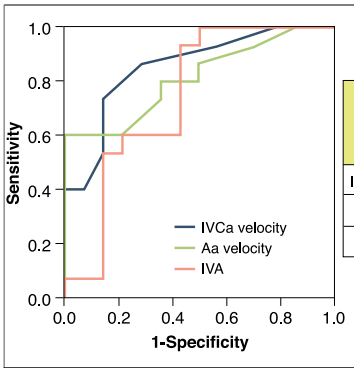
Model	Unstandardized Coefficients		Standardized Coefficients		
	Beta	Standard Error	Beta	τ	Significance
Coefficient	24.915	4.990	—	5.000	<0.001
Aa	250.743	88.243	0.464	2.842	0.009
IVCa	241.003	99.207	0.397	2.429	0.023

$r^2 = 0.612$, % predicted $VO_2 = 24.915 + 250.743 \times Aa + 241.003 \times IVCa$

Dependent variable: % predicted VO_2, excluded variables are ejection fraction, left atrial fractional area change, annular ejection wave velocity, E/annular early diastolic wave, annular early diastolic wave velocity, annular early diastolic wave/Aa, annular isovolumic relaxation wave velocity, and E/A that showed p value <0.1 in simple regression analysis (shown in Online Table 1).
Abbreviations as in Tables 3 and 4.

CONCLUSIONS

Pulsed-wave mitral annular isovolumic velocities measured by TD imaging are useful clinical



Variables	Area	Standard Error	p Value	95% Confidence Interval	
				Lower Bound	Upper Bound
IVCa velocity	0.86	0.071	0.001	0.716	0.994
Aa velocity	0.82	0.080	0.003	0.655	0.969
IVA	0.74	0.098	0.026	0.550	0.935

Figure 3. Diagnostic Value of Tissue Doppler-Derived Measurements

The receiver-operator characteristic curve analysis of IVCa, Aa, and isovolumic acceleration (IVA) for prediction of % predicted peak volume of oxygen >50% in patients with left ventricular systolic dysfunction. Area under the curve was 0.86, p value was 0.001 for IVCa; area under the curve was 0.82, p value was 0.003 for Aa; and area under the curve was 0.74, p value was 0.026 for IVA. A cutoff value of 3.8 cm/s for IVCa had 88% sensitivity and 72% specificity, while a cutoff value of 5.8 cm/s for Aa had 81% sensitivity and 65% specificity, and 0.96 m/s for IVA had 95% sensitivity and 50% specificity for predicting % predicted volume of oxygen >50%. Abbreviations as in Figure 1.

variables for predicting cardiopulmonary exercise capacity in patients with reduced LV systolic function. Peak stretch and shortening velocities during late diastolic and IVCs of cardiac cycle are significantly attenuated in patients with reduced LVEF and are the only 2 independent echocardiographic predictors of the extent of exercise limitation.

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Key Words: left ventricular dysfunction ■ tissue velocity ■ exercise capacity.

▶ APPENDIX

For a supplementary table and figures, please see the online version of this article.