Tissue Doppler Imaging-Derived Myocardial Acceleration During Isovolumetric Contraction Predicts Pulmonary Capillary Wedge Pressure in Patients With Reduced Ejection Fraction

Alaa Mabrouk Salem Omar, PhD; Hidekazu Tanaka, MD, PhD; Kensuke Matsumoto, MD; Kazuhiro Tatsumi, MD, PhD; Tatsuya Miyoshi, MD; Mana Hiraishi, MD; Takayuki Tsuji, MD; Akihiro Kaneko, MD; Keiko Ryo, MD; Yuko Fukuda, MD; Hiroya Kawai, MD, PhD; Ken-ichi Hirata, MD, PhD

Background: Tissue Doppler imaging-obtained isovolumetric myocardial acceleration (IVA) is load independent, reportedly predicts systolic functions, and correlates with exercise capacity in patients with reduced ejection fraction (EF). We hypothesized that IVA correlates with the pulmonary capillary wedge pressure (PCWP) in patients with reduced EF.

Methods and Results: Of 113 patients, correlations between PCWP and IVA were done for all patients, 48 patients with EF $\geq 55\%$, and 65 patients with EF $< 55\%$. Results were compared to the correlation between PCWP and other echocardiographic predictors. IVA correlated moderately with PCWP in all patients ($r=0.54$, $P<0.0001$) and was comparable to the E/A and E/e' ratios. In patients with EF $\geq 55\%$, IVA lost correlation and the only predictor was the E/e' ratio ($r=0.08$, 0.58 , $P=0.58$, <0.0001). In patients with EF $< 55\%$, IVA was better than E/A and E/e' ($r=0.72$, 0.61 , 0.51 , $P<0.0001$), especially for atrial fibrillation or when E/e' fell between 8 and 15. Furthermore, IVA $> 1.60 \text{ m/s}^2$ can predict PCWP $\geq 15 \text{ mmHg}$, with a sensitivity of 95%, specificity of 73%, and an area under the curve of 0.867 ($P<0.0001$).

Conclusions: IVA can predict PCWP in patients with reduced EF, and can be considered an alternative to the E/e' ratio for patients with atrial fibrillation or E/e' ratio between 8 and 15. (*Circ J* 2012; **76**: 1399–1408)

Key Words: Echocardiography; Heart failure; Left ventricular function; Tissue Doppler imaging

Heart failure (HF) is a complex clinical condition caused by systolic or diastolic dysfunction and in either case it leads to elevation of the pulmonary capillary wedge pressure (PCWP).^{1–3} Invasive cardiac catheterization remains the gold standard for PCWP assessment.^{4,5} In clinical practice, however, PCWP can be non-invasively assessed by echocardiography using mostly diastolic parameters. Systolic variables, such as the ejection fraction (EF), do not correlate with PCWP because they are derived from the load-dependent ejection systolic phase. The isovolumetric phase, on the other hand, appears to be load independent, and therefore variables derived from this phase, such as the tissue Doppler imaging (TDI)-derived mitral annular isovolumetric velocity (IVV) and acceleration (IVA), have been suggested for assessing LV systolic function. Despite showing biphasic motion patterns in normal subjects, which may be altered if

contractility is impaired, positive wave IVV and IVA have been validated as load-independent variables useful for the assessment of myocardial contractility of both the left and right ventricles in animals as well as in humans.^{6–11} Moreover, IVV was reported to correlate with right ventricular (RV) filling pressure,¹² and both IVV and IVA have been reported to predict exercise capacity in patients with reduced EF.¹³ Ventricular torsion during ejection and its subsequent early diastolic untwist, are reported as interdependently affecting diastolic filling. Myocardial untwist also occurs during isovolumetric contraction (IC), the velocity of which reportedly seems to affect the force of cardiac contraction during ejection, and the timing of systolic cross-over into diastole in patients with reduced left ventricular (LV) EF.¹³ Therefore, it seems that understanding IC is essential to explain this systolic-diastolic interaction and its effect on diastolic filling.

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Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
Mailing address: Hidekazu Tanaka, MD, PhD, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. E-mail: tanakah@med.kobe-u.ac.jp

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Table 1. Basic Characteristics and Clinical Data of All Patients

	All (n=113)	EF $\geq$ 55% (n=48)	EF <55% (n=65)
Age (years)	62 $\pm$ 14	63 $\pm$ 15	61 $\pm$ 12
Sex (M/F)	63/50	18/30	45/20
Rhythm (sinus/AF)	92/21	43/5	49/16
Mean BP (mmHg)	89 $\pm$ 19	89 $\pm$ 20	89 $\pm$ 19
LV end-systolic volume (ml)	128 $\pm$ 66	158 $\pm$ 69	89 $\pm$ 36*
EF (%)	49 $\pm$ 17	66 $\pm$ 6	36 $\pm$ 12*
Left atrial volume (ml)	66 $\pm$ 32	63 $\pm$ 26	70 $\pm$ 36
NYHA, n (%)			
I/II/III/IV	29/49/26/9	13/21/9/2	16/28/17/6
Medication, n (%)			
ARB/ACEI	49 (43%)	21 (44%)	28 (43%)
β -blockers	37 (33%)	15 (31%)	22 (34%)
Calcium-channel blockers	34 (30%)	14 (29%)	20 (31%)
Diuretics	66 (58%)	22 (46%)	44 (67%)
Digoxin	39 (35%)	9 (19%)	30 (46%)
Etiology			
Dilated cardiomyopathy	38 (34%)	7 (15%)	31 (48%)
Aortic valve disease	24 (21%)	10 (21%)	14 (22%)
Pulmonary hypertension	14 (12%)	10 (21%)	4 (6%)
Ischemic cardiomyopathy	11 (10%)	3 (6%)	8 (12%)
Hypertrophic cardiomyopathy	8 (7%)	5 (10%)	3 (5%)
Hypertension	5 (4%)	4 (8%)	1 (1%)
Atrial septal defect	5 (4%)	4 (8%)	1 (1%)
Systemic lupus erythematosus	1 (1%)	1 (2%)	0 (0%)
Peripartum cardiomyopathy	1 (1%)	0 (0%)	1 (1%)
Other	6 (5%)	4 (8%)	2 (3%)

Data are presented as n, mean $\pm$ SD or n (%).

*P<0.01 denotes significant difference between subgroups.

EF, ejection fraction; AF, atrial fibrillation; BP, blood pressure; NYHA, New York Heart Association; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Accordingly, the objective of this study was to test the hypothesis that the TDI-derived IVA of the septal mitral annulus can predict the PCWP in patients with reduced EF.

Methods

Study Population

Between January 2008 and April 2011, we retrospectively studied 155 patients admitted to hospital for the management of HF of different causes. All patients underwent echocardiographic examination and right-heart cardiac catheterization; 42 patients (27%) were excluded from all subsequent analyses because of poor echocardiographic images (4 patients), more than mild mitral stenosis (8 patients), severe mitral regurgitation (10 patients), negative or unclear IC velocity waves (12 patients), and an interval of more than 1 week between echocardiographic and catheterization studies (3 patients); 2 patients with constrictive pericarditis and 3 patients with cardiac sarcoidosis were also excluded because of known problems in calculating PCWP using the conventional echocardiographic variables.¹⁴ Accordingly, the patient study group consisted of 113 patients. **Table 1** summarizes their basic clinical data, and etiologies and therapies for HF. The mean age was 62 $\pm$ 14 years (range, 23–87 years), 50 patients (44%) were female, and the mean EF was 49 $\pm$ 17%; 92 (81%) were in sinus rhythm and 21 (19%) had atrial fibrillation (AF). The study was approved by the institution's local ethics committee, and written informed consent was given by all patients.

Echocardiographic Examination

All echocardiographic studies were performed with a commercially available echocardiography systems equipped with a 2.5-MHz multifrequency phased array transducer (Vivid 7, GE-Vingmed, Horton, Norway or Aplio Artida, Toshiba Medical Systems, Tochigi, Japan). Digital routine grayscale 2-dimensional and tissue Doppler cine loops from 3 consecutive beats were obtained at end-expiratory apnea from standard apical views at depths of 12–20 cm. Sector width was optimized to allow for complete myocardial visualization while maximizing the frame rate. Gain settings were adjusted for routine clinical grayscale 2D imaging to optimize endocardial definitions. LVEF was calculated from the apical 2- and 4-chamber images using the biplane Simpson's technique.¹⁵ Left atrial volume was calculated using the prolate ellipse method.¹⁵ All measurements were made in $\geq$ 3 consecutive cardiac cycles and in $\geq$ 5 cycles if the patient's rhythm was AF and average values were used for the final analyses. To confirm reproducibility, 60 randomly selected measurements were redone by the same investigator but in a separate setting and by a different investigator who was blinded to all previous data.

Pulsed-Wave Doppler Examination

The pulsed-wave Doppler-derived transmitral velocity and digital color tissue Doppler-derived mitral annular velocity were obtained from the apical 4-chamber view. The early diastolic wave velocity (E), late diastolic atrial contraction wave velocity (A), and the E-wave deceleration time (E-DcT) were

Figure 1. Spectral pulsed-wave Doppler-derived parameters obtained from the septal mitral annulus.

measured using pulsed-wave Doppler recording. The pulsed-wave Doppler-derived pulmonary venous velocities were also obtained from the apical 4-chamber view. The systolic wave velocity (PV-S), early diastolic wave velocity (PV-D), and atrial contraction reverse wave velocity (PV-Ar) and the D-wave deceleration time (PV D-DcT) were measured using pulsed-wave Doppler recording. Spectral pulsed-wave tissue Doppler-derived peak systolic velocity (s'), early diastolic velocity (e'), late diastolic velocity (a'), as well as IC velocity (IVV), were obtained from the septal mitral annulus (Figure 1). Myocardial acceleration during IC (ie, IVA) was measured as IVV divided by isovolumetric acceleration time (IVAT), which was defined as the time spent in milliseconds from baseline to peak IC velocity (Figure 1). The onset of the IVAT was determined as the start of the upstroke of the IVV wave from the baseline using image zooming. All measurements made during IC were taken from the positive wave only. The E/e' ratio was calculated to estimate the LV filling pressure for all patients. Finally, the ratios IVV/s' and IVA/s' were calculated to study the relation between both phases of systole and their combined effect on PCWP.

Cardiac Catheterization Studies

Cardiac catheterization was performed within 0.94 ± 2.2 days of the echocardiographic examination. All catheter measurements were done by an investigator blinded to the echocardiographic data. All patients underwent right-heart catheterization for hemodynamic measurements using a fluid-directed balloon tipped catheter. Stroke volume was measured using either the Fick's principle or the thermodilution method. The thermodilution method was obtained by averaging 3 cardiac cycles with less than 10% variation. Fluoroscopically verified mean PCWP, right atrial, pulmonary artery and RV pressures were obtained at end expiration with the zero-level set at the mid-axillary line and represent the average of 5 cardiac cycles. LV

catheter-derived peak systolic pressure (LVSP), minimal diastolic pressure (LVMDP), and end-diastolic pressure (LVEDP) were also available for 65 patients (21 with $EF \geq 55\%$, and 44 with $EF < 55\%$). The intracavitary LV pressures were measured using a fluid-filled pigtail catheter attached to a pressure transducer after adjusting the zero-level as described before.

Statistical Analysis

All data are expressed as mean $\pm$ SD. The independent sample t-test was used to compare the mean values of different groups. Linear regression was used for correlation analyses, which were expressed as Pearson correlation coefficients between all echocardiographic variables and the invasively measured PCWP. For analysis of the independent determinants of PCWP, we used a multivariate linear regression analysis model based on stepwise selection. Receiver-operator characteristics curve (ROC) was used to test the sensitivity and specificity for the detection of $PCWP \geq 15$ mmHg. The intraclass correlation coefficient was then used to determine inter- and intraobserver reproducibility. For all tests, $P < 0.05$ was considered statistically significant. All the analyses were performed with commercially available software (SPSS version 16.0; SPSS, Inc, Chicago, IL, USA). The authors had full access to the data and take full responsibility for their integrity.

Results

Table 2 lists the echocardiographic and catheterization data for all patients, as well as for the 2 groups of patients classified according to their LVEF: 48 patients with $EF \geq 55\%$ ($65.5 \pm 6\%$), and 65 patients with $EF < 55\%$ ($36.4 \pm 11.7\%$). The E -DcT, a' , s' , PV-S, and PV-Ar, and stroke volume were significantly lower in patients with $EF < 55\%$. Other echocardiographic and catheter-derived variables were similar for both groups.

Table 2. Echocardiographic and Catheterization Measurements for All Study Patients and Subgroups

	All patients (n=113)	Patients with EF ≥55% (n=48)	Patients with EF <55% (n=65)	P value
EF (%)	49±17	66±6	36±12	<0.01
E (cm/s)	76±29	78±29	75±29	0.60
A (cm/s)*	75±25	80±26	70±24	0.06
E/A*	1.06±0.59	1.04±0.50	1.08±0.68	0.77
E-DcT (ms)	211±80	235±91	193±66	0.006
e' (cm/s)	5.6±1.9	5.9±2.1	5.4±1.7	0.18
a' (cm/s)	8.0±2.4	8.9±2.2	7.2±2.2	0.001
IVV (cm/s)	5.6±1.7	5.9±1.5	5.4±1.9	0.10
IVAT (ms)	32.5±8.8	32.9±9.9	32.1±7.9	0.64
s' (cm/s)	5.7±1.7	6.6±1.9	5.0±1.3	<0.0001
IVA (m/s ²)	1.80±0.59	1.9±0.55	1.73±0.62	0.20
IVV/s'	1.04±0.36	0.95±0.31	1.10±0.38	0.01
IVA/s' (s ⁻¹)	34±13	31±11	36±14	0.02
E/e'	14.2±5.9	13.9±6.0	14.3±5.9	0.80
PV-S (cm/s)	48±17	56±17	43±16	0.001
PV-D (cm/s)	47±16	50±16	45±15	0.08
PV D-DcT (ms)	242±76	257±83	231±69	0.07
PV-S/D	1.13±0.49	1.23±0.47	1.05±0.49	0.06
PV-Ar (cm/s)*	29±11	33±14	27±7	0.01
PCWP (mmHg)	11.2±6.8	9.9±4.7	12.3±7.8	0.07
PAP (mmHg)	21±11	21±10	21±11	0.97
RVSP (mmHg)	36±16	38±18	35±15	0.37
RVEDP (mmHg)	6.7±5.6	6.7±5.3	6.7±5.8	0.98
RAP (mmHg)	3.6±4.3	3.6±3.7	3.6±4.7	1.00
SV (ml)	66±25	73±31	61±19	0.02
LVSP†	134±36	140±37	131±36	0.40
LVMDP†	4.5±8.4	1.7±3.2	5.6±9.5	0.09
LVEDP†	14.5±6.3	13±6.5	15±6.1	0.24

*A, E/A, and PV-Ar were assessed in a subset of 92 patients with sinus rhythm. †LVSP, LVMDP, and LVEDP were calculated in 65 cases (21 with EF ≥55% and 44 with EF <55%).

EF, ejection fraction; E, early diastolic mitral flow velocity; A, late diastolic mitral flow velocity; E-DcT, early diastolic mitral flow deceleration time; e', TDI-derived septal mitral annular early diastolic velocity; a', TDI-derived septal mitral annular late diastolic velocity; IVV, isovolumetric contraction velocity; IVAT, isovolumetric acceleration time; s', TDI-derived septal mitral annular systolic velocity; IVA, isovolumetric acceleration; PV-S, pulmonary venous systolic wave velocity; PV-D, pulmonary venous diastolic wave velocity; PV D-DcT, pulmonary venous D-wave deceleration time; PV-S/D, ratio between pulmonary venous S and D velocities; PV-Ar, pulmonary venous reverse atrial wave velocity; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary artery pressure; RVSP, right ventricular systolic pressure; RVEDP, right ventricular end-diastolic pressure; RAP, right atrial pressure; SV, stroke volume; LVSP, left ventricular systolic pressure; LVMDP, left ventricular minimal diastolic pressure; LVEDP, left ventricular end-diastolic pressure.

Overall Correlations Between Echocardiographic Parameters and PCWP

For all patients, significant correlations were found between PCWP and the isovolumetric variables, IVV and IVA ($r=-0.48$, -0.54 , respectively; $P<0.0001$), as well as the diastolic variables, E/A and E/e' ($r=0.48$, 0.51 , respectively; $P<0.0001$). Weaker correlations were found for PV D-DcT and PV-S/D ($r=-0.28$, $P=0.007$; and $r=-0.38$, $P<0.0001$, respectively). The systolic parameters, EF and s', did not correlate with PCWP ($r=-0.17$, $P=0.13$ and $r=-0.1$, $P=0.18$, respectively).

Comparison of Patients With Preserved and Reduced LVEF

In patients with EF ≥55%, only E/e' correlated significantly with the invasively measured PCWP ($r=-0.58$, $P<0.0001$), whereas IVV and IVA did not ($r=-0.25$, -0.08 and $P=0.08$, 0.58 ; respectively) (Figure 2, Table 3). In patients with EF <55%, on the other hand, both IVV and IVA correlated significantly with PCWP ($r=-0.55$, -0.72 , and $P<0.0001$; respectively) (Figure 2, Table 3). Other variables that showed sig-

nificant correlations with PCWP in this group of patients were E/A ($r=0.61$, $P<0.0001$), E/e' ($r=0.51$, $P<0.0001$), PV D-DcT ($r=-0.38$, $P=0.002$), and PV-S/D ($r=-0.44$, $P<0.0001$). Of note, EF and s' did not show any correlation with PCWP in either group.

Relation Between Both Phases of Systole and Its Effect on PCWP

The ratios IVV/s' and IVA/s' were calculated for all patients to study the relation between the tissue Doppler-derived myocardial velocities of both the isovolumetric and ejection phases of contraction. Unlike IVV and IVA, both ratios were significantly higher in patients with EF <55% (IVV/s': $0.95±0.31$ vs. $1.1±0.38$, $P=0.01$; IVA/s': $31±11$ vs. $34±13$ s⁻¹, $P=0.02$; Table 2). As for IVV and IVA, both ratios correlated well with PCWP in patients with EF <55% (IVV/s': $r=-0.50$, IVA/s': $r=-0.61$, $P<0.0001$), but not in patients with EF ≥55% (Table 3). Suggested by their overall means and by ROC curve, as discussed later, a cut value of 1 in the case of IVV/s' and of

Figure 2. Dot plots of isovolumetric acceleration (IVA) in relation to pulmonary capillary wedge pressure (PCWP) for all patients (A), patients with ejection fraction (EF) $\geq 55\%$ (B) and patients with EF $< 55\%$ (C). IVA correlated significantly with PCWP for all patients and patients with EF $< 55\%$, but such a correlation was not observed for patients with EF $\geq 55\%$.

Table 3. Comparisons Between Different Variables and PCWP

	All Patients (n=113)		Patients with EF $\geq 55\%$ (n=48)		Patients with EF $< 55\%$ (n=65)			
	Linear regression		Linear regression		Linear regression		Multivariate regression model Adjusted $r^2=0.64$	
	r	P value	r	P value	r	P value	β coefficient	95%CI
IVA (m/s ²)	-0.54	<0.0001	-0.08	0.58	-0.72	<0.0001	-0.44	-9.36 to -3.95
IVV (cm/s)	-0.48	<0.0001	-0.25	0.08	-0.55	<0.0001	-0.121	-0.168 to 0.67
IVV/s'	-0.35	<0.0001	-0.17	0.26	-0.50	<0.0001	-0.021	-23.9 to 23.07
IVA/s' (s ⁻¹)	-0.40	<0.0001	-0.08	0.59	-0.61	<0.0001	-0.147	-24.9 to 7.5
E/A	0.48	<0.0001	0.14	0.36	0.61	<0.0001	0.35	1.74 to 6.32
E/e'	0.51	<0.0001	0.58	<0.0001	0.51	<0.0001	0.106	-0.155 to 0.457
PV-S/D	-0.38	<0.0001	-0.17	0.27	-0.44	<0.0001	0.063	-2.78 to 4.78
PV D-DcT (ms)	-0.28	0.007	-0.03	0.87	-0.38	0.002	-0.26	-0.57 to -0.009
EF (%)	-0.17	0.1	-0.22	0.13	-0.01	0.94	—	—
s' (cm/s)	-0.13	0.18	0.01	0.95	-0.08	0.52	—	—

All abbreviations as in Table 2.

Table 4. PCWP Values for Patients Classified According to Their EF, IVV/s', and IVA/s' Values

	IVV/s' ≥ 1		IVV/s' < 1		P value	IVA/s' ≥ 34		IVA/s' < 34		P value
	n	Mean	n	Mean		n	Mean	n	Mean	
EF $\geq 55\%$	20	8.8 $\pm$ 4.4	28	10.3 $\pm$ 4.8	0.26	15	9.33 $\pm$ 4.8	33	9.8 $\pm$ 4.7	0.75
EF $< 55\%$	35	9.8 $\pm$ 6.0	30	15.4 $\pm$ 8.7	0.003	33	8.7 $\pm$ 4.8	32	16.2 $\pm$ 8.7	< 0.0001

PCWP, pulmonary capillary wedge pressure. Other abbreviations as in Table 2.

Table 5. Analyses of Different Subgroups

	All Patients classified according to PCWP			Patients with EF $< 55\%$ classified according to E/e' (dependent: PCWP)			
	Group A (PCWP < 15 mmHg) (n=81)		P value	E/e' < 8 or > 15 (n=34)		E/e' between 8 and 15 (n=31)	
	Mean $\pm$ SD	Mean $\pm$ SD		r value	P value	r value	P value
IVV (cm/s)	5.97 $\pm$ 1.7	4.65 $\pm$ 1.44	< 0.0001	0.63	< 0.0001	0.33	0.06
IVA (m/s ²)	1.94 $\pm$ 0.57	1.42 $\pm$ 0.47	< 0.0001	0.74	< 0.0001	0.59	< 0.0001
IVV/s'	1.1 $\pm$ 0.36	0.88 $\pm$ 0.32	0.003	0.53	0.001	0.45	0.01
IVA/s' (s ⁻¹)	36 $\pm$ 13	27 $\pm$ 10	< 0.0001	0.59	< 0.0001	0.59	0.001
E/e'	12.2 $\pm$ 3.9	19.12 $\pm$ 7.07	< 0.0001	0.57	< 0.0001	0.04	0.83
E/A	0.94 $\pm$ 0.43	1.44 $\pm$ 0.83	< 0.0001	–	–	–	–
PV D-DcT (ms)	250 $\pm$ 72	222 $\pm$ 81	0.08	–	–	–	–
PV S/D	1.21 $\pm$ 0.49	0.89 $\pm$ 0.45	0.005	–	–	–	–
s' (cm/s)	5.7 $\pm$ 1.7	5.6 $\pm$ 1.93	0.72	–	–	–	–
EF (%)	49.6 $\pm$ 18	46.7 $\pm$ 15.7	0.44	–	–	–	–

All abbreviations as in Tables 2,4.

34 s⁻¹ in the case of IVA/s' were used to test differences between PCWP values in subgroups (Table 4). Among the patients with EF $< 55\%$, 35 had an IVV/s' value ≥ 1 , and 30 had IVV/s' value < 1 . The PCWP for patients with IVV/s' < 1 was significantly higher than in those with IVV/s' ≥ 1 (15.4 $\pm$ 8.7 mmHg, 9.8 $\pm$ 6.0 mmHg, respectively; $P=0.003$). Similarly, in the same group of patients, 33 had IVA/s' ≥ 0.34 s⁻¹ and 32 had IVA/s' < 0.34 s⁻¹, and the PCWP was significantly higher in patients with IVA/s' < 0.34 s⁻¹ (16.2 $\pm$ 8.7 mmHg, 8.7 $\pm$ 4.8 mmHg, $P<0.0001$). The same classification for cases with EF $\geq 55\%$ failed to show any significant difference between PCWP values.

Independent Predictors of PCWP

For patients with EF $< 55\%$, multivariate linear regression showed that IVA ($\beta=-0.44$, $P<0.0001$), E/A ratio ($\beta=0.35$, $P=0.001$), and D-DcT ($\beta=-0.26$, $P=0.009$) were independent determinants of PCWP (Table 3). Despite that E/e' showed a comparable correlation with PCWP in this group ($r=0.51$, $P<0.0001$), it was excluded from the multivariate model ($\beta=0.106$, $P=0.324$).

Detection of PCWP ≥ 15 mmHg

Next, patients were classified into 2 groups according to their PCWP. Group A consisted of 81 patients with PCWP < 15 mmHg and Group B of 32 patients with PCWP ≥ 15 mmHg (Table 5). The diastolic parameters were significantly different for both groups, as Group B showed a higher E/A ratio (1.44 $\pm$ 0.83 vs. 0.94 $\pm$ 0.43, $P<0.0001$), higher E/e' ratio (19.12 $\pm$ 7.07 vs. 12.2 $\pm$ 3.9, $P<0.0001$), lower PV-S/D ratio (0.89 $\pm$ 0.45 vs. 1.21 $\pm$ 0.49, $P=0.005$) and slightly shorter PV D-DcT (222 $\pm$ 81 vs. 250 $\pm$ 72 ms, $P=0.08$). Furthermore, patients in Group B showed significantly lower isovolumetric systolic parameters (IVV: 4.65 $\pm$ 1.44 vs. 5.97 $\pm$ 1.7, $P<0.0001$; IVA: 1.42 $\pm$ 0.47 vs. 1.94 $\pm$ 0.57, $P<0.0001$), and significantly lower IVV/s' and IVA/s' (IVV/s': 0.88 $\pm$ 0.32 vs.

1.1 $\pm$ 0.36, $P=0.003$; IVA/s': 27 $\pm$ 10 vs. 36 $\pm$ 13, $P<0.0001$, respectively), but EF and s' were not different between both groups.

The ROC curve was initiated for IVA, IVV, IVA/s', IVV/s', and E/A in patients with EF $< 55\%$. It was found that IVA of 1.60 m/s² and IVV of 4.95 cm/s had sensitivities of 95% and 71%, respectively; and specificities of 73% and 64%, respectively, for predicting PCWP ≥ 15 mmHg (IVV: area under the curve [AUC]=0.758, 95% confidence interval [CI] 0.632–0.884, $P=0.001$; IVA: AUC=0.867, 95%CI 0.782–0.952, $P<0.0001$, Figure 3A). The E/A value of 0.94 was 83% sensitive and 67% specific for detecting PCWP > 15 mmHg in this subset of patients (AUC=0.778, 95%CI 0.633–0.923, $P=0.004$, Figure 3B). In the case of IVV/s' and IVA/s' in patients with EF $< 55\%$, the ROC curve suggested that an IVV/s' value of 1 and an IVA/s' value of 34 s⁻¹ could effectively predict PCWP ≥ 15 mmHg with sensitivities of 71% and 76%, and specificities of 60% and 64%, respectively (IVV/s': AUC=0.74, 95%CI 0.606–0.868, $P=0.002$; IVA/s': AUC=0.84, 95%CI 0.723–0.95, $P<0.0001$, Figure 3A).

Advantage of IVA Over E/A and E/e'

Of the 65 patients in this study with EF $< 55\%$, 16 had AF: 7 of them had PCWP < 15 mmHg (11.6 $\pm$ 2.3), and 9 had PCWP ≥ 15 mmHg (21.1 $\pm$ 6.7). The correlation between IVA and PCWP for those patients was preserved ($r=0.63$, $P<0.0001$). In this subset of patients, we noticed that a correlation with PCWP was only obtained in cases of IVV and IVA, and none of the other variables showed a correlation with PCWP. It is worth noting that the E/e' ratio in these patients showed a moderate correlation that lost statistical significance, which might be because of the small number of patients. Finally, to confirm the previously noticed superiority of IVA over E/e' for patients with EF $< 55\%$, these patients were classified according to their E/e' value into 2 groups, the first group consisting of 34 patients with E/e' values less than 8 or more than

ROC curves in patients with EF<55%

Figure 3. Receiver-operating characteristics (ROC) curve analysis for predicting pulmonary capillary wedge pressure ≥ 15 mmHg in patients with ejection fraction (EF) $< 55\%$. **(A)** Isovolumetric contraction velocity (IVV) of 4.95 cm/s showed a sensitivity of 58% and a specificity of 75% , and the corresponding values for isovolumetric acceleration (IVA) of 1.59 cm/s² were 92% and 83% , respectively. E/A did not show statistically significant results. **(B)** IVV/s' value of 1 showed a sensitivity of 71% and a specificity of 60% , and the corresponding values for IVA/s' of 34 s⁻¹ were 76% , 64% , respectively.

15 , and the second group of 31 patients with E/e' values between 8 and 15 (≥ 8 and ≤ 15). It was noticed that both IVA and E/e' correlated significantly with PCWP for patients with E/e' less than 8 or more than 15 ($r=0.74$ and 0.57 , respectively; $P<0.0001$, Table 5). However, in patients with E/e' values between 8 and 15 , IVA correlated with PCWP and the correlation with the E/e' was lost ($r=0.59$, 0.04 , $P<0.0001$, $=0.83$, respectively, Table 5).

Comparison With LVEDP

Besides correlating with PCWP, IVA showed a statistically significant correlation with LVEDP in patients with EF $< 55\%$ ($r=0.4$, $P=0.01$). Again, this correlation was not noticed in patients with EF $\geq 55\%$ ($r=0.23$, $P=0.33$). Of note, the LVEDP showed a good overall correlation with PCWP ($r=0.61$, $P<0.0001$) and the correlation was maintained for patients with EF $\geq 55\%$ or EF $< 55\%$ ($r=0.61$ and 0.62 ; $P=0.006$ and <0.0001 , respectively).

Other Determinants of IVV and IVA

Several echocardiographic variables correlated with IVV and IVA, but the correlations were almost always found only in patients with EF $< 55\%$. Left atrial volume (LAV), s' , a' , E , E/A , E/e' , PV-S, PV-D, and PV-S/D correlated with IVV and IVA in patients with EF $< 55\%$. Multivariate linear regression analysis of patients with EF $< 55\%$ revealed that only PCWP and s' could independently predict IVV (adjusted $r^2=0.409$, β : -0.444 , 0.454 , $P=0.001$, respectively), whereas PCWP and a' could independently predict IVA (adjusted $r^2=0.555$, β : -0.586 , 0.301 , $P<0.0001$, $=0.037$, respectively). All previously mentioned echocardiographic variables correlated with IVV and

IVA only in patients with EF $< 55\%$, except for s' , E/A and E/e' , which correlated with IVV in both patients with EF $\geq 55\%$ and those with EF $< 55\%$; multivariate regression analysis showed that only E/e' could independently predict IVV in such cases (adjusted $r^2=0.269$, β : 0.535 , $P<0.0001$). Finally, no echocardiographic variable correlated with IVA in patients with EF $\geq 55\%$.

Reproducibility

The intraclass correlation coefficients for interobserver reproducibility of IVV and IVA were 0.944 (mean difference= 0.34 ± 0.54 cm/s, 95% CI 0.761 – 0.919 , $P<0.0001$) and 0.89 (mean difference= 0.2 ± 0.25 m/s², 95% CI 0.826 – 0.946 , $P<0.0001$), respectively, and the respective intraclass correlation coefficients for intraobserver reproducibility of IVV and IVA were 0.934 (mean difference= 0.29 ± 0.64 cm/s, 95% CI 0.878 – 0.956 , $P<0.0001$) and 0.91 (mean difference= 0.1 ± 0.29 m/s², 95% CI 0.838 – 0.953 , $P<0.0001$), respectively.

Discussion

This study demonstrated that TDI-derived IVA of the septal mitral annulus, despite not correlating with PCWP in patients with preserved systolic function, correlated well and independently predicted PCWP, and was better than other echocardiographic predictors in patients with systolic dysfunction, probably because it compensates for the ejection systolic dysfunction in patients with systolic HF.

Physiological Aspects of Isovolumetric Contraction

Velocities recorded by TDI during IC at the mitral annulus

show a longitudinal acceleration-deceleration pattern, the mechanism of which is not yet clear but suggests, unlike the previous understanding, a dynamic nature of IC. Whether these velocities represent myocardial deformation remains questionable. Remme et al explained this biphasic motion as an early systolic shortening that is interrupted by the longitudinal motion produced by mitral valve closure; and added that myocardial deformation does not occur during IC.¹⁶ In our study, both IVV and IVA correlated with a' only in patients with EF <55% ($r=0.35, 0.55, P=0.017, <0.0001$, respectively), suggesting that IVV may be related to the elastic potential energy of a' , which favors the findings by Remme et al. However, this does not seem enough to explain the correlations noticed in our study, especially that, again, both IVV and IVA lost such correlation with a' in patients with EF $\geq 55\%$ ($r=0.043, 0.15, P=0.784, 0.338$, respectively). IC was, however, reported in other studies to be dynamic in terms of thickening because of subendocardial fiber shortening, which, because of subepicardial sheet extension and negative angle formation, is kept within the isovolumetric constraint.^{17,18} Thus, it seems that the biphasic (positive-negative) nature of the IVV is caused by counter-directional myocardial deformations that occur in such a fashion as to cause actual deformation without changing the LV volume. The finding that, myocardial deformation during IC occurs in all directions, including the longitudinal axis, has led to a conclusion that mitral valve closure might not affect the mechanics during IC. Another reported dynamic aspect of IC is the brief period of myocardial untwist, which precedes the torsion (Twist) that occurs during ejection.^{19–22} Although variables derived from IC are reported to predict the load-independent state of contractility of both the LV and RV,^{6–11} the hemodynamic and clinical effects of the previously mentioned dynamic aspects are still not clear.

Systolic and Diastolic Interaction and the Role of Isovolumetric Contraction

Ventricular torsion during ejection and the subsequent early diastolic untwist are reported to interdependently affect diastolic filling because of the mechanical and timing relationships of the circular and helical muscular pathways of the myocardium. However, myocardial untwist also occurs pre-ejection, and an understanding of IC is said to be essential to explain this systolic–diastolic interaction.²⁰ Luo et al found that in patients with systolic HF, myocardial untwist during IC is prolonged into the ejection phase and that torsion during ejection is also prolonged into the diastolic phase.²³ Cho et al also reported that the ability of the IVV and IVA to predict the exercise capacity of patients with depressed systolic function might be explained by dynamic changes of IC that affect the force of cardiac contraction during ejection, and the timing of systolic cross-over into diastole.¹³ In our study, the fact that both IVV and IVA inversely correlated with PCWP (higher PCWP with lower IVV and IVA), and the preservation of such correlations after combining them with ejection systolic variables in the ratios IVV/ s' and IVA/ s' , supports the dynamic nature of IC and its effect on other phases of the cardiac cycle.

Defining Systolic Dysfunction

Unlike the IVV and IVA, which showed no difference between patients with and without systolic dysfunction, both IVV/ s' and IVA/ s' were significantly higher in patients with EF <55%, despite that all isovolumetric variables (IVV, IVA, IVV/ s' , and IVA/ s') were significantly lower in patients with PCWP ≥ 15 mmHg. Moreover, when IVV/ s' and IVA/ s' values were less than 1 and 34 s^{-1} , respectively, and PCWP was sig-

nificantly higher in patients with systolic dysfunction (IVV/ s' : 15.4 vs. 9.8 mmHg, $P=0.003$; IVA/ s' : 16.2 vs. 8.7 mmHg, $P<0.0001$), however did not differ in patients with preserved systolic functions. Our explanation for these findings is that, as the LV goes into ejection systolic failure, patients with preserved IC values show better hemodynamics. This suggests that the previously mentioned dynamic aspects of IC are essential for appropriate systolic function, and when preserved, can compensate for the ejection systolic dysfunction. Thus, defining systolic function and the systolic-diastolic interaction only according to ejection variables (EF and s' in our study) seems insufficient.

Another Possible Mechanism of Correlation

Lindqvist et al explained the correlation noticed between RV-IVA and right atrial pressure by the mechanics of the Frank-Starling law; that is, as the initial sarcomere length increases at end-diastole, IVV and IVA increase as a direct result of Starling forces.¹² Despite we found a similar correlation between LV-IVA and LVEDP in patients with EF <55% ($r=0.4, P=0.01$), we do not think this is enough to explain why LV-IVA in our study correlated with both LVEDP and PCWP only in the case of depressed systolic dysfunction ($r=0.4, 0.72, P=0.01, <0.0001$, respectively), and not in the case of preserved systolic function ($r=0.08, 0.23, P=0.58, 0.33$, respectively).

Lack of Correlations in Patients With Preserved Systolic Function

Despite that IC reportedly represents the load-independent state of contraction in many studies, a recent study by Lyseggen et al has questioned this concept when they found that loading the LV induced a marked decrease of IVA and dissociated it from contractility.²⁴ Our ideas on the mechanism of IVV and IVA correlation are based on the untwist-torsion exhibited in IC and ejection, respectively. Changes in torsion and untwisting mechanics within the normal conical heart are reported to be load-dependent.^{19,20,25} Conversely, dilated and failing hearts exhibit different torsion and untwisting responses, independent of loading conditions, because cardiac fiber orientation is responsible for such rotational changes.^{20,26} Accordingly, the lack of correlation with PCWP in patients with preserved systolic function noticed in our study seems reasonable, and furthermore, the effect of loading reported by Lyseggen et al does not necessarily represent the situation in patients with systolic HF, because they studied animal models that had basically preserved systolic function.

Clinical Implications

The E/e' ratio is reportedly the best predictor of PCWP in patients with preserved as well as reduced systolic function. In our study, E/e' also showed acceptable correlations in both cases ($r=0.58, 0.51$, respectively, and $P<0.0001$), but IVA showed a stronger correlation for patients with EF <55% ($r=0.72, P<0.0001$). Moreover, E/e' was not an independent predictor of PCWP in this group of patients, whereas IVA proved to be the best predictor. This was explained when we found, as also mentioned in previous studies,^{27–29} that for 31 of our patients with E/e' between 8 and 15, E/e' did not show a correlation with PCWP ($r=0.04, P=0.83$), but the correlation was preserved for IVA ($r=0.59, P<0.0001$). In addition, in patients with EF <55% and AF in our study, IVA and IVV were the only variables that correlated with PCWP.

It is important to note that IVA was the best IC predictor of PCWP, and that might denote the importance of acceleration,

which combines both velocity and temporal changes of IC. However, despite the excellent correlation, IVA is limited by its moderate reproducibility because of TDI temporal resolution. On the other hand, $IVV/s' < 1$ seems to be a simple predictor of high PCWP in patients with depressed systolic function, which represents additional information about the relation between both systolic phases. However, it lacks the temporal factor represented by IVA. For that, we still recommend echocardiographic assessment of PCWP using the well-established variables E/e' and E/A , considering IVA only as an alternative for patients with reduced systolic function who have E/e' values between 8 and 15 or AF.

Study Limitations

Unfortunately, there are several limitations. First, this study included a small number of patients in a retrospective single-center study, so future studies of larger patient populations are necessary to more accurately determine the utility of IVA for the evaluation of PCWP. It is worth noting that, because of being a retrospective analysis, available data was not sufficient to measure torsion and untwist during IC and as such future studies should also be concerned with measuring these variables and assessing their relation to PCWP. Second, TDI measurements are angle dependent, so the angle between the ultrasound beam and the LV axis must be kept small. In our study, the smallest possible angle ($<30^\circ$) was kept during measurements of IVV and IVA. Third, although we measured the TDI-derived parameters from only the septal side of the mitral annulus, it is recommended to acquire TDI measurements from at least both the septal and lateral sides of the mitral annulus and calculate their average.³⁰ The measurement of IC variables from the septal side only can, however, be justified, as it is reported to be the area with the best reproducibility and was recommended to be the site used when measuring IVA for study purposes.³¹ Fourth, the echocardiographic studies were not performed simultaneously with right-heart catheterization. Fifth, pressures were measured invasively using fluid-filled catheters, which might be less sensitive to variations in diastolic pressures. Sixth, our study population included 3 patients with right-sided HF and 21 with AF, which may have affected our results. Furthermore, 3 patients had asymmetrical septal hypertrophy among 8 patients with hypertrophic cardiomyopathy, and that could affect the values for mitral annular velocity. Finally, the normal ranges of IVV and IVA for humans are not yet established, so there is a need for a larger study using a control group of normal subjects to determine the normal ranges and cut-off values for these indices. Ruan and Nagueh reported normal values of septal IVV and IVA in 80 consecutive normal subjects to be 6.9 ± 2.7 cm/s and 2.52 ± 0.11 m/s², respectively.³²

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Disclosures

There is no ethical problem or conflict of interest with regard to this manuscript.

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