Clinical Usefulness of an Echo-Doppler Model in Predicting Elevated Pulmonary Capillary Wedge Pressure in Patients With Heart Failure

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Although several tissue-Doppler imaging (TDI) models for pulmonary capillary wedge pressure (PCWP) estimation have been reported, their reliability remains uncertain. Our previous theoretical and experimental analyses suggest that right atrial pressure (RAP) corrected by tissue-Doppler imaging tricuspid/mitral annular peak systolic velocities (S_T/S_M) (RAP × S_T/S_M) reliably predicts elevated PCWP. We sought to investigate its clinical usefulness for predicting elevated PCWP in heart failure (HF) patients. Ninety-eight patients admitted with HF who underwent right heart catheterization were prospectively studied. RAP and PCWP were measured by right heart catheterization. Simultaneously, S_T/S_M, early diastolic transmitral flow velocity to mitral annular velocity ratio (E/Ea), and diameter of inferior vena cava at inspiration (IVCDi), a noninvasive surrogate for RAP, were measured by echocardiography. RAP correlated with IVCDi ($R^2 = 0.57$). A significantly stronger correlation was observed between IVCDi corrected by S_T/S_M (IVCDi × S_T/S_M) and PCWP than between E/Ea and PCWP ($R^2 = 0.47$ vs 0.18). Receiver-operating characteristic analyses indicated that IVCDi × S_T/S_M >16 mm predicted PCWP >18 mm Hg with 90% sensitivity and 77% specificity, and the area under the curve was 0.86, which was significantly larger than that of E/Ea (area under the curve=0.72). In conclusions, IVCDi × S_T/S_M is a new useful noninvasive model to predict elevated PCWP in HF patients. **(Am J Cardiol 2019;123:1464−1469)**

Several echocardiographic methods have been developed for noninvasive estimation of pulmonary capillary wedge pressure (PCWP).[1−7] Among them, the ratio of early transmitral velocity to tissue Doppler mitral annular early diastolic velocity (E/Ea) is a potentially useful tool.[5−7] Nevertheless, the reliability of these echocardiographic methods remains a major issue,[8−10] and there is a need to develop a novel noninvasive and reliable method. We recently proposed a model to predict PCWP from right atrial pressure (RAP) corrected by the ratio of peak systolic velocity of tricuspid annulus (S_T) to that of mitral annulus (S_M) measured by tissue-Doppler imaging (TDI) echocardiography.[11] The aim of this study was to investigate the clinical usefulness of our model to predict PCWP in patients with heart failure (HF).

Methods

We prospectively enrolled 174 consecutive patients aged 20 years or older admitted to our institution with a diagnosis of acute or chronic HF, who underwent right heart catheterization (RHC) for hemodynamic assessment between August 2013 and March 2014 (Supplementary Figure S1). HF was diagnosed by at least 2 experienced cardiologists according to the Framingham HF criteria.[12] Patients with severe valvular diseases, prosthetic valves, acute coronary syndrome, atrial septal defect, coronary to pulmonary artery fistula, use of intravenous nitroglycerin between RHC and echocardiography, inadequate PCWP waveform, insufficient IVCD data, and change of rhythm from atrial tachycardia to sinus rhythm during RHC were excluded. Finally, 98 patients (acute HF [n = 17], chronic HF [n = 81]) were included in this study. We further examined the reliability of our model in patients with severe LV (left ventricular)

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Sources of funding: This work was supported by a Grant-in-Aid for Scientific Research [26293160] (S.Y.), the Grants-in-Aid from the Japanese Ministry of Health, Labor, and Welfare, Tokyo, Japan [H24-009] [H26-001] (S.Y.) and a Grant-in-Aid for Young Scientists [26-6-2] (T.M.) from the Japan Cardiovascular Research Foundation.

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See page 1469 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.01.053

Table 1
Clinical characteristics

Variable	All patients (n = 98)	Left Ventricular Ejection Fraction <35 % (n = 51)	Left Ventricular Ejection Fraction ≥35 % (n = 47)
Age, years	62.4 ± 14.7	61.4 ± 13.6	63.5 ± 15.9
Male	62 (63.3%)	37 (72.6%)	25 (53.2%)†
Body mass index (kg/m^2)	22.6 ± 3.4	22.2 ± 3.6	22.9 ± 3.2
New York Heart Association class III or IV	27 (27.6%)	21 (41.2%)	12.8%*
Atrial fibrillation	23 (23.5%)	11 (21.6%)	25.5%
Hypertension	40 (40.8%)	24 (47.1%)	34.0%
Dyslipidemia	34 (34.7%)	19 (37.3%)	31.9%
Diabetes mellitus	17 (17.4%)	12 (23.5%)	10.6%
Left ventricular ejection fraction (%)	38.6 ± 16.8	25.0 ± 6.5	53.4 ± 11.2
Hemoglobin (g/dL)	13.3 ± 1.9	13.4 ± 1.8	13.1 ± 2.0
Creatinine (mg/dL)	1.3 ± 1.8	1.6 ± 2.4	1.0 ± 0.7
Brain natriuretic peptide (pg/mL)	443.2 ± 552.4	597.7 ± 660.4	275.5 ± 338.1*
Etiology of heart failure			
Ischemic cardiomyopathy	14 (14.3%)	7 (13.7%)	7 (14.9%)
Non-ischemic cardiomyopathy	67 (68.4%)	40 (78.4%)	27 (57.5%)†
Valvular heart diseases	2 (2.0%)	1 (2.0%)	1 (2.1%)
Pulmonary hypertension	8 (8.2%)	1 (2.0%)	7 (14.9%)†
Others	7 (7.1%)	2 (3.9%)	5 (10.6%)
Medical treatments during hospitalization			
Angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers	65 (66.3%)	37 (72.6%)	28 (59.6%)
β-blockers	52 (53.1%)	27 (52.9%)	25 (53.2%)
Digitalis	15 (15.3%)	12 (23.5%)	3 (6.4%)†
Loop diuretics	49 (50.0%)	31 (60.8%)	17 (36.2%)†
Mineralocorticoid receptor antagonists	31 (31.6%)	20 (39.2%)	11 (23.4%)

Data are expressed as mean ± SD where appropriate.

*p <0.01, †p <0.05 against left ventricular ejection fraction <35%.

Hypertension is defined according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: blood pressure ≥140/90 mm Hg.

Dyslipidemia is defined according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III: total cholesterol levels ≥240 mg/dl or the use of lipid-lowering drugs; triglyceride levels ≥200 mg/dl; high-density lipoprotein cholesterol levels <40 mg/dl; and low-density lipoprotein cholesterol levels ≥160 mg/dl.

dysfunction defined as LV ejection fraction (LVEF) <35% and ≥35%. This study was approved by the institutional review board, with a waiver of individual consent (M25-018), and registered under the Japanese UMIN Clinical Trials Registration (UMIN000017025).

With the patient at a steady state, RAP, pulmonary artery pressure and PCWP were measured using a balloon-tipped catheter (Thermodilution Catheter 3000, Biosensors International Pte. Ltd., Singapore) at the end of expiration in a supine position. The wedge position was verified by fluoroscopy and phasic changes in pressure waveforms. The investigator performing pressure measurements was blinded to the echocardiographic data. Data of RAP, pulmonary artery pressure, and PCWP represent the average of 5 cardiac cycles. Fluid-filled transducers were balanced before measurement with 0 level set at the mid-axillary line. Cardiac index was determined using the estimated Fick principle.

Echocardiography was performed using the Vivid q cardiovascular ultrasound system (General Electric, Piscataway, New Jersey) within 30 minutes after hemodynamic measurements. Two-dimensional images were acquired in supine position using a phased array transducer in the standard parasternal, apical, and subcostal views. From the subcostal view, longitudinal image of the inferior vena cava was recorded throughout the respiratory cycle (Supplementary Figure S2A). From the apical 4-chamber view, the pulsed Doppler sample volume was placed at the mitral valve tip and mitral inflow was recorded. From the apical 4-chamber view, the tricuspid and mitral annular velocities were obtained with pulsed tissue Doppler by placing 5-mm wide sample volumes at the free wall side of the tricuspid annulus (Supplementary Figure S2B) and at the medial and lateral sides of the mitral annulus, respectively (Supplementary Figure S2C). Gains were adjusted to eliminate background noise and obtain clear tissue signals. Five to 10 cardiac cycles were recorded. The sonographer measuring the parameters was blinded to the hemodynamic data.

Analysis was performed using an offline station by 2 independent observers who were blinded to all hemodynamic data. All reported echocardiographic data were averaged from 3 consecutive cycles in sinus rhythm and 7 consecutive cycles in atrial fibrillation. The LV dimension, volume, ejection fraction, and severity of valvular disease were assessed in accordance with the American Society Echocardiography Guidelines.[13,14] The IVCD at inspiration (IVCDi) and at expiration (IVCDe) were measured within

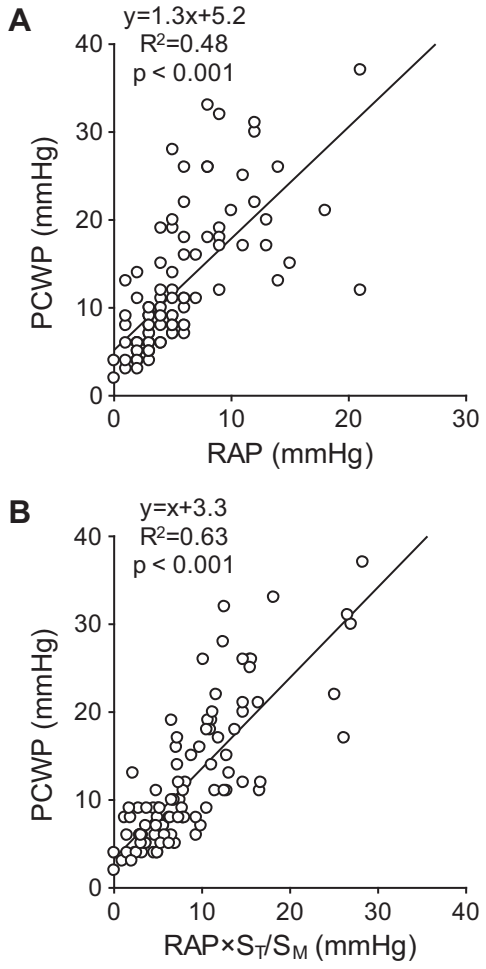

Figure 1. Correlation between pulmonary capillary wedge pressure and invasive parameters. (*A*) Relation between right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP), and (*B*) between RAP × S_T/S_M and PCWP. S_T/S_M, ratio of tricuspid to mitral annular peak systolic velocity.

2 cm from the IVC-right atrial junction. IVC collapsibility index (IVCCI) was calculated using the formula: ([IVCDe−IVCDi]/IVCDe) × 100. The mitral inflow velocity was traced and the following variables were derived: peak velocity of early (E) and late (A) filling, and deceleration time (DT) of the E wave velocity. The following measurements were obtained from the TDI: peak systolic velocities at free wall side of the tricuspid annulus (S_T) (Supplementary Figure S2B) and at lateral side of the mitral annulus (S_M) (Supplementary Figure S2C), and early (Ea) diastolic velocities at medial and lateral sides of the mitral annulus. Data of Ea represent the average of Ea measured at the medial and lateral mitral annulus.

Intraobserver and interobserver variabilities were assessed in 12 randomly selected patients. Intraobserver variability was assessed by repeating the measurements offline from video recordings on 2 occasions 2 weeks apart. To test the interobserver variability, the measurements were performed offline from video recordings by a second observer who was unaware of the results of the first examination. Variability was expressed as the mean percent error, derived as the absolute difference between the 2 sets of observations, divided by the mean of observations.[5]

All data are presented as mean ± SD. Between-group comparison was performed by unpaired 2-sided *t* test for continuous variables, or by chi-square test for categorical variables. Linear regression analysis and the coefficient of determination (R^2) were used to determine the strength of association among the variables. Receiver-operating characteristic (ROC) curve analysis was used to determine optimal cut-off values for selected variables to detect PCWP >18 mm Hg.[15] Sensitivity, specificity, and positive and negative predictive values were calculated for each cut-off value, using standard techniques. The area under the ROC curve (AUC) was determined as a summary measure for diagnostic accuracy of the variables. To compare R^2 value of each correlation and AUC value of each ROC curve, we used a bootstrap technique (1000 replicates).[16,17] p value less than 0.05 was considered statistically significant. Statistical analyses were performed by custom-made programs developed using Microsoft Excel and SPSS for Windows version 21.0 (IBM, Corp., Armonk, New York).

Results

Clinical characteristics of the 98 patients are shown in Table 1. Patients with LVEF <35% had higher prevalence of NYHA III or IV and nonischemic etiology, and higher BNP level compared to those with LVEF ≥35%. The hemodynamic and echocardiographic measurements are summarized in Supplementary Table S1. Prevalence of PCWP >18 mm Hg and E/Ea were higher, and Ea and S_M levels were lower in LVEF <35% group compared to LVEF ≥35% group.

A significant correlation was observed between RAP and PCWP, and also between RAP × S_T/S_M and PCWP (Supplementary Table S2). In all 98 patients, coefficient of determination observed between RAP × S_T/S_M and PCWP (Figure 1) was significantly larger than that between RAP and PCWP (Figure 1; p <0.05). Among IVCDe, IVCDi, and IVCCI, IVCDi correlated most strongly with RAP irrespective of LVEF (Supplementary Table S2). Therefore, we chose IVCDi as the noninvasive surrogate for RAP in subsequent analyses.

A significant but weak correlation was observed between E/Ea and PCWP, and between DT and PCWP, while a significant and strong correlation was observed between IVCDi × S_T/S_M and PCWP, especially in patients with LVEF <35% (Supplementary Table S2). In all 98 patients, the coefficient of determination observed between IVCDi × S_T/S_M and PCWP (Figure 2) was significantly larger than that between E/Ea and PCWP (Figure 2; p <0.05). This difference was larger (Figure 2 vs Figure 2) in patients with LVEF < 35%, whereas smaller (Figure 2 vs. Figure 2) in patients with LVEF ≥35% than that observed in all 98 patients. Moreover, correlation between IVCDi × S_T/S_M and PCWP observed in patients with acute HF was similar to that observed in patients with chronic HF (Supplementary Figure S3).

The ROC curves for IVCDi × S_T/S_M and E/Ea in predicting PCWP >18 mm Hg in all 98 patients are shown in

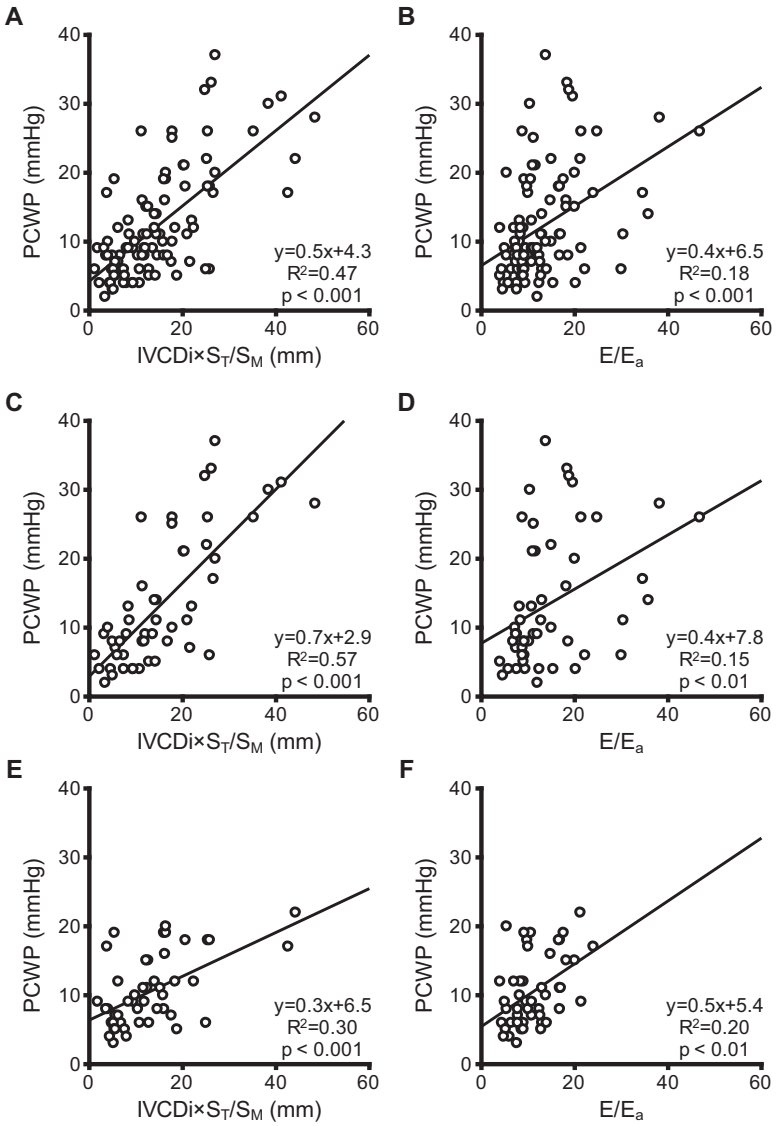

Figure 2. Correlation between pulmonary capillary wedge pressure and noninvasive parameters. (*A*) Relation between IVCDi × S_T/S_M and pulmonary capillary wedge pressure (PCWP) and (*B*) between E/Ea and PCWP in all 98 patients. (*C*) Relation between IVCDi × S_T/S_M and PCWP and (*D*) between E/Ea and PCWP in patients with LVEF <35%. (*E*) Relation between IVCDi × S_T/S_M and PCWP and (*F*) between E/Ea and PCWP in patients with LVEF ≥35%. IVCDi × S_T/S_M, diameter of inferior vena cava at inspiration corrected by ratio of tricuspid to mitral annular peak systolic velocity; E/Ea, ratio of early diastolic transmitral flow velocity to mitral annular velocity.

Figure 3. The AUC of ROC curve for IVCDi × S_T/S_M was significantly larger than that for E/Ea ($p < 0.05$). At the cut-off value, IVCDi × S_T/S_M >16 mm had 90% sensitivity, 77% specificity, 50% positive predictive value, and 97% negative predictive value; whereas E/Ea >11 had 75% sensitivity, 58% specificity, 31% positive predictive value, and 90% negative predictive value. When analysis was conducted in patients with LVEF <35%, the AUC of ROC curve for IVCDi × S_T/S_M in predicting PCWP >18 mm Hg was also significantly larger than that for E/Ea ($p < 0.05$; Figure 3). At the cut-off value, IVCDi × S_T/S_M > 17 mm had 93% sensitivity, 83% specificity, 70% positive predictive value, and 97% negative predictive value; whereas E/Ea > 13 had 67% sensitivity, 72% specificity, 50% positive predictive value, and 84% negative predictive value. In contrast, in patients with LVEF ≥35%, the AUC of ROC curve for IVCDi × S_T/S_M in predicting PCWP >18 mm Hg was larger than that for E/Ea, but not with statistical significance (Figure 3). At the cut-off value, IVCDi × S_T/S_M >16 mm had 80% sensitivity, 74% specificity, 27% positive predictive value, and 97% negative predictive value; whereas E/Ea >17 had 40% sensitivity, 88% specificity, 29% positive predictive value, and 93% negative predictive value.

The interobserver and intraobserver reproducibilities are shown in Supplementary Table S3. Less than 10% differences were noted in each of S_T, S_M, and IVCDi. When combined as IVCDi × S_T/S_M, the difference increased but remained acceptable, that is,. less than 10% on average.

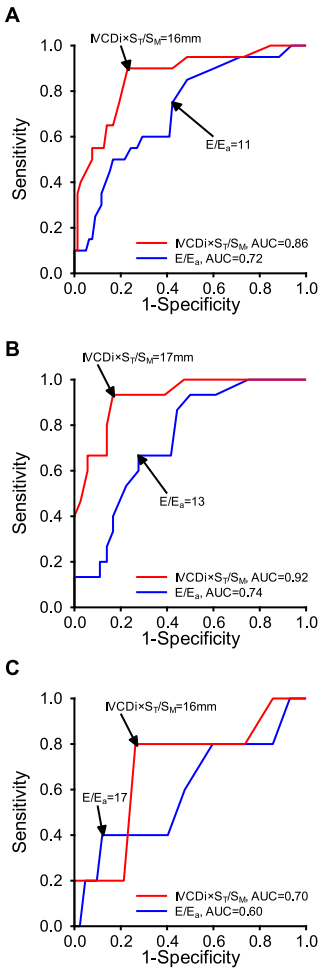

Figure 3. ROC curves analysis for the prediction of elevated pulmonary capillary wedge pressure (>18 mm Hg) using IVCDi × S_T/S_M and E/Ea in all 98 patients (*A*), in 51 patients with LVEF <35% (*B*) and in 47 patients with LVEF≥35% (*C*). IVCDi × S_T/S_M, diameter of inferior vena cava at inspiration corrected by ratio of tricuspid to mitral annular peak systolic velocity; E/Ea, ratio of early diastolic transmitral flow velocity to mitral annular velocity; AUC, area under the curve. Red curve indicates ROC for IVCDi × S_T/S_M, and blue curve, ROC for E/Ea. (Color version of figure is available online.)

Discussion

The present findings indicate that the new echocardiographic TDI model using IVCDi × S_T/S_M is a noninvasive, reliable, and reproducible diagnostic method to predict elevated PCWP in clinical cases. Importantly, the predictive performance of IVCDi × S_T/S_M is significantly superior to that of E/Ea, which is currently the most widely used noninvasive indicator for elevated PCWP. We further highlight that the new model is useful especially in severely impaired LV systolic function with LVEF <35%.

Among the noninvasive Doppler-based estimation models including tricuspid and pulmonary regurgitation pressure gradient, and mitral inflow velocity indexes such as E wave velocity, E/A ratio, and DT,[1–4] E/Ea has been shown to correlate relatively strongly with PCWP.[5,7,18] It was originally hypothesized that since E wave velocity is directly influenced by LV preload and relaxation while Ea reflects LV relaxation, correcting E wave velocity for the influence of LV relaxation (the E/Ea ratio) improves its relation with LV preload, that is, PCWP.[5] However, rigidly controlled experiments disclosed that Ea is influenced also by LV preload.[19,20] Furthermore, both E and Ea are indexes obtained in early diastole and may reflect many factors involving LV recoil, suction and previous systolic function, whereas PCWP is the mean value of diastolic pressure.[21] In fact, several clinical studies found that E/Ea failed to accurately estimate PCWP, especially in advanced HF patients with severely impaired LV systolic function.[8,9,22] These previous findings may limit the general use of E/Ea as a surrogate for PCWP.

In the present study conducted in clinical cases, we evaluated our previously reported echo-Doppler model that is able to predict PCWP from RAP corrected by S_T/S_M obtained from TDI echocardiography in canine RV or LV failure models.[11] The theoretical background and rationale of the model is summarized in Supplementary Appendix. In this study, we used IVCD as a noninvasive surrogate for RAP, because IVCD has been reported to correlate with RAP ($0.36 \leq R^2 \leq 0.74$) and is widely used to estimate RAP in patients with HF.[23–25] Indeed, in the present population, IVCD and RAP correlated reasonably well ($0.38 \leq R^2 \leq 0.57$, Supplementary Table S2). Furthermore, results of the present study confirmed previous reports that IVCDi correlated better with RAP than with IVCDe or IVCCI.[24,26] We thus chose IVCDi as an alternative to RAP to assess PCWP. With further improvement of the correlation by S_T/S_M correction, IVCDi × S_T/S_M permitted prediction of PCWP with reasonable accuracy, and was significantly superior to that of E/Ea. This was especially the case in patients with severe LV dysfunction (LVEF <35%) (Figure 3), a patient population with strong requirement for hemodynamic assessment. Given the high sensitivity of IVCDi × S_T/S_M in predicting PCWP >18 mm Hg, clinicians may be able to use this model easily and safely to rule out severe pulmonary congestion, consequently minimizing pulmonary artery catheterization in HF patients.

There are several potential limitations of the present study which should be acknowledged. First, the sample size was small, and a significant number of patients were excluded from this study, thereby limiting the ability to generalize the findings. Second, we enrolled a diverse spectrum of acute or chronic HF patients reflecting the real clinical situation. However, the etiological differences that may affect the diagnostic performance of our new TDI model remain to be verified. Third, we excluded patients with severe valvular disease, prosthetic valves, and acute coronary syndrome from our study population. In these patients, the relation between TDI parameters and LV filling can be confounded, or the unstable hemodynamics may change even during the interval between RHC and echocardiography. Forth, we did not perform expanded validation. Large-scale validation studies in multicenter settings are warranted. Finally, there was poor correlation between E/Ea and PCWP in our population, especially in those with advanced systolic HF. Nevertheless, this poor correlation was compatible with previous reports,[8,10,27] and we believe our new model overcomes the disadvantage of E/Ea even in advanced systolic HF.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.01.053.

Appendix

For the physiological principle of our model obtained from previous studies, and supplementary tables and figures, please see the online version of this report.

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