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Echocardiography

Relationship of Echocardiographic Indices to Pulmonary Capillary Wedge Pressures in Healthy Volunteers

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OBJECTIVES We sought to determine the relationship between different echocardiographic indices and pulmonary capillary wedge pressures (PCWP) in normal volunteers.

BACKGROUND Indices based on tissue Doppler (TDE) and color M-mode (CMM) echocardiography have been proposed to reflect left (LV) ventricular filling pressures. These include the ratio of early diastolic transmitral velocity (E) to early myocardial velocity measured by TDE (E′) and the ratio of E to the wave propagation velocity (Vp) measured from CMM images. These indices, however, have not been validated in normal individuals.

METHODS We studied seven volunteers during two phases of preload altering maneuvers, baseline, with two stages of lower body negative pressure, and repeat baseline with two stages of volume loading. The PCWP obtained from right heart catheterization was compared with diastolic indices using pulsed Doppler, TDE and CMM echocardiography.

RESULTS The PCWP ranged from 2.2 to 23.5 mm Hg. During preload alterations, significant changes in E and septal E′ (both $p < 0.05$) but not lateral E′ or Vp were observed. Furthermore, E, septal E′ and E/Vp correlated with PCWP (all $r > 0.80$) but not combined E and TDE indices (both $r < 0.15$). Within individuals, a similar linear relationship was observed among E/Vp, E and septal E′ (average $r > 0.80$).

CONCLUSIONS In subjects without heart disease, E, septal E′ and E/Vp correlate with PCWP. Because the influence of ventricular relaxation is minimized, the ratio E/Vp may be the best overall index of LV filling pressures. (J Am Coll Cardiol 2000;36:1664–9) © 2000 by the American College of Cardiology

The assessment of left ventricular (LV) filling pressure is a common clinical problem in patients with established heart disease and usually requires invasive hemodynamic monitoring to follow the progression of disease or the response to therapy. Several noninvasive Doppler echocardiographic indices have been proposed to estimate LV filling pressures measured either directly or from pulmonary capillary wedge pressures (PCWP) during right heart catheterization (1,2). Two recently validated indices use either the ratio of early transmitral filling velocities (E) to the corresponding early diastolic annular velocity (E′), as measured using tissue Doppler echocardiography (TDE) (3,4) or to the early diastolic LV flow propagation velocity (Vp) as measured using color M-mode (CMM) Doppler echo (5). In these previous studies, however, only patients with known cardiovascular disease undergoing invasive left or right heart catheterization were included. Thus, whether these indices may apply to subjects without cardiovascular disease is unknown. Ideally, a single index should be appropriate in both normal and abnormal hearts, since cardiac status is often not known in the clinical setting.

The goal of this study, therefore, is to validate and compare different echocardiographically derived indices to pulmonary artery capillary wedge pressures in healthy volunteers without known cardiac disease. Moreover, a secondary goal was to obtain additional insight into how a wide range of ventricular filling pressures might influence the interpretation of these indices.

METHODS

Experimental protocol. After Institutional Review Board approval by the University of Texas Southwestern Medical Center, Presbyterian Hospital of Dallas and written, informed consent, seven healthy volunteers (six men and one woman; mean age, 37.2 ± 8.9 years) underwent standard right heart catheterization. All volunteers were normotensive, nonsmokers, and were not taking any medications. Exclusion factors included the following: family history of heart disease, abnormal screening ECG or exercise stress test, abnormal lipid/cholesterol blood profiles and prior hospitalizations for any cause. A 6F, balloon-tipped, flow-directed pulmonary arterial catheter (Edwards Swan-Ganz; Baxter) was placed under fluoroscopic guidance through an antecubital vein into the pulmonary artery. With the balloon

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Abbreviations and Acronyms

A	= late transmitral filling velocities
ANOVA	= analysis of variance
CMM	= color M-mode
DT	= transmitral deceleration time
E	= early transmitral filling velocities
E'_{lat}	= early diastolic annular velocities measured in the lateral region of the mitral annulus
E'_{sep}	= early diastolic annular velocities measured in the septal region of the mitral annulus
LBNP	= lower body negative pressure
LV	= left ventricular
PCWP	= pulmonary capillary wedge pressure
TDE	= tissue Doppler echocardiography
Vp	= early diastolic flow propagation velocity

inflated, the catheter was advanced into the pulmonary capillary wedge position, which was confirmed both fluoroscopically and by the presence of characteristic pressure waveforms. All intracardiac pressures were referenced to atmospheric pressure, with the pressure transducer (Transpac IV; Abbott) zero set at 5 cm below the sternal angle in the supine position. Pressure waveforms were amplified (Hewlett Packard 78534A and Astromed ASC909) and displayed on a strip chart recorder (Astromed MT 95000) with at least 0.5 mm Hg resolution. The mean PCWP was determined visually at end-expiration. Following satisfactory measurement of baseline central venous and PCWP, each volunteer was placed in a Plexiglas lower-body negative pressure (LBNP) box that was sealed at the level of the iliac crests. This apparatus was custom designed to allow for changes in LBNP while maintaining the ability to rotate patients into a lateral position to obtain optimal transthoracic echocardiographic images and therefore allowed for Doppler imaging sampling at similar locations within the ventricle without difficulty. Measurements were obtained under six different hemodynamic conditions for a total of 30 measurements: baseline, −15 mm Hg LBNP, −30 mm Hg LBNP, repeat baseline, following rapid 15-ml/kg normal saline solution infusion (100 ml/min) and following an additional 15-ml/kg normal saline solution infusion (100 ml/min). Hemodynamic measurements and echocardiographic evaluations were performed at each stage following at least 5 to 10 min of physiologic stabilization. All volunteers tolerated the complete protocol without complications.

Echocardiographic evaluation. Echocardiographic data were obtained at baseline and during each stage of preload alteration using an ATL (Advanced Technology Laboratories; Bothell, Washington) HDI 5000CV (software version 10.1) echocardiograph. The images obtained included apical four-chamber and two-chamber views, pulsed-wave Doppler of the LV inflow at the mitral leaflet tips, CMM of flow through the mitral valve for evaluation of transmitral flow propagation velocity and pulsed-wave tissue Doppler at the septal and lateral mitral annulus for evaluation of both systolic and diastolic myocardial velocities (TDE). All images were recorded on a half-inch SVHS tape and stored digitally to a 3½-inch magnetic-optical disk for later off-line image analysis.

All data were measured off-line from the magneto optical disk using an image review system (MedArchive; Secure Archive, Inc; Indianapolis, Indiana) on a pentium-based computer running software (Windows 95). Measurements performed on the images included peak E- and A-wave velocities and early deceleration time (DT) of the LV inflow pulsed-wave Doppler. From the CMM of the LV filling, flow propagation velocity (from mitral annulus to left ventricular apex) was derived in an automated fashion in which the values of each pixel were decoded and the slope of the isovelocity contour at 50% of the maximum E-wave velocity was determined (Fig. 1) (6). This technique of Vp determination has been recently described and has been shown to have a low intraobserver and interobserver variability (8% and 12%, respectively, $r > 0.95$, $p < 0.001$) (7). The peak velocities of the early filling wave were measured from the tissue velocity flow profiles of the septal (E'_{sep}) and lateral (E'_{lat}) regions of the mitral annuls. At least three measurements were taken of each parameter and then averaged. Echocardiographic analysis was performed by a single experienced sonographer (L.C.) and validated by an experienced physician (M.S.F.), both of whom were blinded to the pressure measurements.

Statistics. All statistics were performed using software (Systat 7.0; SPSS Inc; Chicago, Illinois). One way-repeated measures analysis of variance (ANOVA) was used for grouped data obtained under each stage tested to test for significant changes in a given variable (e.g., PCWP) with changes in loading conditions. However, linear regression analysis was performed to determine a relationship between each echocardiographic variable and all PCWP measurements in the entire population. Similar regression analysis was also performed to determine a relationship between variables and PCWP for each individual. Analysis of covariance was performed on variables that had a strong linear correlation with PCWP ($r > 0.75$) within individuals to determine if the linear relationships observed for the entire dataset could be applied to the responses of individuals. Each variable in question (e.g., E/Vp) served as the dependent variable, the individual volunteer served as the grouping variable and PCWP was the covariate. For all statistics, a p value < 0.05 was considered statistically significant.

RESULTS

Under baseline conditions, PCWP ranged from 8.0 to 13.3 mm Hg (average: 10.3 ± 2.0 mm Hg). The effects of LBNP are summarized in Table 1 and the effects of saline solution infusion are summarized in Table 2. Predictably, saline solution infusion resulted in a significant increase in PCWP while LBNP significantly decreased PCWP ($p <$ 0.001 by ANOVA). Similarly, with saline solution infusion,

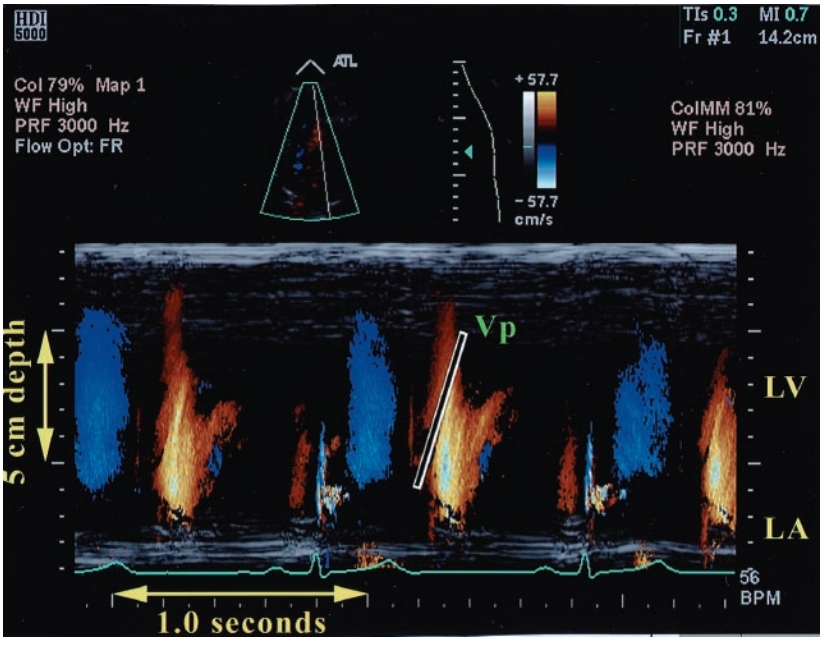

Figure 1. Representative color M-mode image demonstrating Vp determination. Spatiotemporal relationship of diastolic flow from left atrium (LA) to left ventricle (LV) is shown color encoded.

E and E'_{sep} (both $p \leq 0.05$) increased while DT decreased slightly ($p = 0.08$). However, no significant change was observed in E'_{lat}, A or Vp (all $p > 0.20$). Conversely, with LBNP, compared to baseline, both E and E'_{sep} decreased, but no significant change was observed in A, DT, Vp or E'_{lat} (all $p > 0.20$). Of the combined indices, preload altering maneuvers resulted in significant changes in only E/Vp ($p < 0.01$ by ANOVA). The LBNP or saline solution infusion did not result in statistically significant changes in E/A, E/E'_{lat} or E/E'_{sep}.

Overall, for individual echo variables, both E and E'_{sep} correlated strongly with PCWP and although E'_{lat}, Vp and DT also correlated with PCWP, the relationship was less strong (Table 3). For the single indices, the best correlates with PCWP were E ($r = 0.86$, $p < 0.001$) and E'_{sep} ($r = 0.81$, $p < 0.001$). Of the combined ratios, E/Vp correlated strongest with PCWP ($r = 0.81$, $p < 0.001$, Fig. 2). However, no relationship was observed between PCWP and E/E'_{sep} ($r = 0.14$, $p > 0.05$, Fig. 3A) or E/E'_{lat} ($r = 0.17$, $p > 0.05$, Fig. 3B).

The relationship between echocardiographic variables and PCWP for each individual was also determined. For all seven patients, a correlation was observed among PCWP and E ($r = 0.90 \pm 0.067$), E'_{sep} ($r = 0.82 \pm 0.026$) and E/Vp ($r = 0.85 \pm 0.14$). Analysis of covariance performed on each of these indices demonstrated a similar relationship to changes in PCWP within individuals as was observed for the entire group (each $p > 0.15$).

Table 1. Effects of Lower Body Negative Pressure on Hemodynamics and Doppler Indices

	Baseline	LBNP −15 mm Hg	LBNP −30 mm Hg	p ANOVA
PCWP (mm Hg)	10.3 ± 2.0	5.4 ± 1.6	4.0 ± 1.4	< 0.001
RAP (mm Hg)	8.5 ± 2.1	4.4 ± 2.0	2.5 ± 1.2	< 0.001
Heart rate (beats/min)	66.6 ± 6.6	75.0 ± 12.0	82.0 ± 7.1	0.04
E (cm/s)	77.7 ± 14.2	58.8 ± 8.8	53.6 ± 10.8	0.02
A (cm/s)	58.3 ± 11.8	45.3 ± 16.5	54.5 ± 7.4	0.20
DT (ms)	212.7 ± 37.5	247.5 ± 52.0	234.6 ± 55.6	0.56
Vp (cm/s)	53.8 ± 8.5	47.6 ± 7.9	47.1 ± 3.6	0.98
E'_{sep} (cm/s)	11.4 ± 1.6	10.3 ± 1.1	7.7 ± 1.6	< 0.01
E'_{lat} (cm/s)	15.0 ± 6.0	11.8 ± 3.0	10.1 ± 1.6	0.15
E/E'_{sep}	7.05 ± 2.06	5.83 ± 0.88	7.37 ± 2.03	0.31
E/E'_{lat}	6.18 ± 1.53	5.19 ± 1.86	5.54 ± 1.55	0.79
E/Vp	1.45 ± 0.17	1.25 ± 0.16	1.13 ± 0.17	0.01
E/A	1.36 ± 0.25	1.39 ± 0.33	1.27 ± 0.35	0.82

A = late transmitral filling velocity; DT = deceleration time of early transmitral velocity wave; E = early transmitral filling velocity; E'_{lat} = early diastolic tissue velocities measured from the region of the left ventricular free wall; E'_{sep} = early diastolic myocardial tissue velocities measured from the region of the intraventricular septum; LBNP = lower body negative pressure; PCWP = pulmonary artery capillary wedge pressure; RAP = right atrial pressure; Vp = color M-mode early diastolic propagation velocity (cm/s); ANOVA = analysis of variance.

Table 2. Effects of Saline Solution Infusion on Hemodynamics and Doppler Indices

	Baseline Repeat	Saline Solution 15 mg/kg	Saline Solution 30 mg/kg	p ANOVA
PCWP (mm Hg)	10.7 ± 1.9	16.0 ± 2.6	20.0 ± 3.3	< 0.001
RAP (mm Hg)	8.3 ± 2.0	11.6 ± 1.7	13.6 ± 1.6	0.003
Heart rate (beats/min)	69.0 ± 6.9	84.3 ± 6.9	92.9 ± 9.5	0.04
E (cm/s)	70.8 ± 8.2	87.5 ± 14.6	103.3 ± 16.8	0.02
A (cm/s)	58.3 ± 11.0	53.7 ± 12.1	65.7 ± 10.0	0.70
DT (ms)	214.2 ± 52.7	195.7 ± 28.8	169.5 ± 27.2	0.08
Vp (cm/s)	47.0 ± 7.6	56.8 ± 6.7	56.1 ± 4.9	0.70
E'_{sep} (cm/s)	11.0 ± 1.3	14.1 ± 1.5	14.0 ± 2.2	< 0.01
E'_{lat} (cm/s)	15.2 ± 2.5	17.4 ± 1.7	17.3 ± 3.1	0.21
E/E'_{sep}	6.48 ± 0.77	6.22 ± 0.89	7.61 ± 12.33	0.24
E/E'_{lat}	4.56 ± 0.27	5.04 ± 0.80	6.10 ± 1.29	0.17
E/Vp	1.49 ± 0.15	1.55 ± 0.23	1.83 ± 0.20	0.02
E/A	1.33 ± 0.61	1.73 ± 0.57	1.59 ± 0.28	0.75

A = late transmitral filling velocity; DT = deceleration time of early transmitral velocity wave; E = early transmitral filling velocity; E'_{lat} = early diastolic myocardial tissue velocities measured from the region of the left ventricular free wall; E'_{sep} = early diastolic myocardial tissue velocities measured from the region of the intraventricular septum; LBNP = lower body negative pressure; PCWP = pulmonary artery capillary wedge pressure; RAP = right atrial pressure; Vp = color M-mode early diastolic propagation velocity (cm/s); ANOVA = analysis of variance.

DISCUSSION

Our results indicate that in patients without underlying cardiac disease, simple transmitral velocity and tissue Doppler indices can provide an accurate assessment of LV filling pressures. Furthermore, we have shown that combined pulsed Doppler and CMM (E/Vp) is a more reliable index of PCWP than combined pulsed and tissue Doppler (E/E'_{sep} or E/E'_{lat}).

In the present study, the relationship between E and PCWP was the strongest of all Doppler variables measured. Although this observation may be valid in patients with normal ventricular diastolic function, previous work by Choong et al. (8) has shown that E is strongly dependent on both preload and relaxation. In their study on instrumented dogs, they showed through changes in left atrial pressures and ventricular relaxation that E was directly related to left atrial V-wave pressure ($r = 0.58$, $p < 0.0001$) and LV EDP ($r = 0.50$, $p < 0.0001$) and inversely related to tau ($r = -0.32$, $p < 0.004$). To overcome the confounding effects of relaxation on using E as an index of LV filling pressures, investigators have proposed using combined ratios. In combing E with a relaxation *dependent*, but relatively preload *independent* Doppler index, the effects of changes in relaxation can be minimized. Rossvoll and Hatle (9) have shown previously that combined transmitral Doppler parameters and pulmonary venous flow variables can approximate LV filling pressures. But, recent work by Farias et al. (10) has demonstrated the difficulty of applying these combined pulmonary venous and transmitral relationships in a general population.

Previous work has shown that myocardial Doppler velocity indices, such as E′ (measured either from the septal or lateral regions of the mitral annulus), are inversely related to tau (11) and thereby ideally suited to offset the effects of relaxation on E in estimating PCWP. Several investigators have shown that the E/E′ relationship is valid for determining filling pressures in various patient populations with underlying cardiac disease. Nagueh and colleagues have validated the relationship between E/E′ and PCWP in patients with either impaired or pseudonormal relaxation

Table 3. Relationship Between Echocardiographic Indices and Pulmonary Capillary Wedge Pressures

				Relationship to PCWP			
Index	Min	Max	Ave	SEE	Slope	Intercept	Pearson
RAP (mm Hg)	1.00	15.70	8.2 ± 4.2	2.14	0.65	1.01	0.94
E (cm/s)	40.0	123	76.3 ± 20.4	3.00	3.02	41.8	0.86
A (cm/s)	33.0	81.0	52.3 ± 13.4	5.29	1.06	41.1	0.47
DT (ms)	120.0	320.0	211.3 ± 47.1	4.95	−4.41	261.8	−0.55
Vp (cm/s)	35.0	66.7	51.6 ± 7.74	5.02	0.69	42.8	0.51
E'_{sep} (cm/s)	5.4	16.2	11.5 ± 2.6	3.46	0.36	7.43	0.81
E'_{lat} (cm/s)	7.0	24.0	14.6 ± 4.1	4.55	0.45	9.60	0.63
E/E'_{sep}	4.38	11.94	6.7 ± 1.6	5.85	0.04	6.3	0.14
E/E'_{lat}	2.71	8.44	5.4 ± 1.9	5.82	0.03	5.0	0.17
E/Vp	0.89	2.09	1.5 ± 0.28	3.44	0.04	1.02	0.81
E/A	0.73	2.57	1.5 ± 0.4	5.40	0.03	1.17	0.42

A = late transmitral filling velocity; DT = deceleration time of early Doppler transmitral velocity wave; E = early transmitral Doppler filling velocity; E'_{lat} = early diastolic myocardial tissue velocities measured from the lateral region of the mitral annulus; E'_{sep} = early diastolic myocardial tissue velocities measured from the septal region of the mitral annulus; PCWP = pulmonary artery capillary wedge pressure; RAP = right atrial pressure; SEE = standard error of the estimate (in mm Hg); Vp = color M-mode early diastolic propagation velocity (cm/s); Min = minimum; Max = maximum; Ave = average.

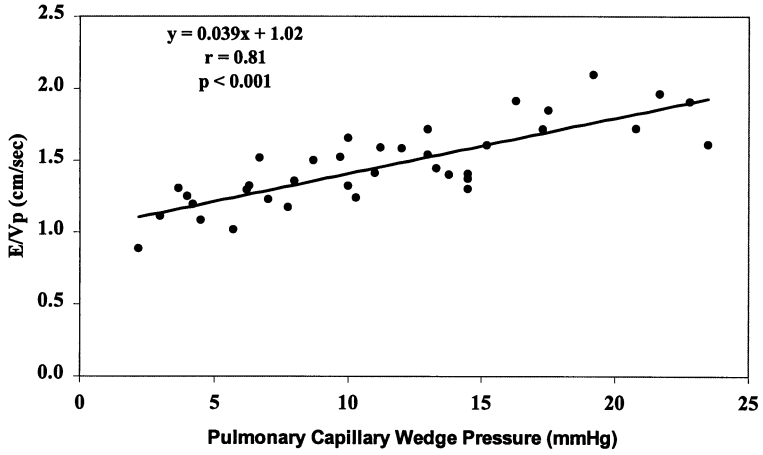

Figure 2. Relationship between PCWP and E/Vp. Linear regression analysis demonstrating the relationship between PCWP and E/Vp.

(3) or with sinus tachycardia (12). Sundereswaran et al. (4) also validated this relationship in patients following cardiac transplantation. However, a significant limitation to a general application of the results of these studies is that each was performed in patients undergoing right heart catheterization for acute complications of their underlying cardiac disease, and as such, these results have not been validated in patients who are not acutely ill. In our study of healthy volunteers, no relationship was observed between either E/E'_{sep} or E/E'_{lat} and PCWP, thereby limiting the global application of this index.

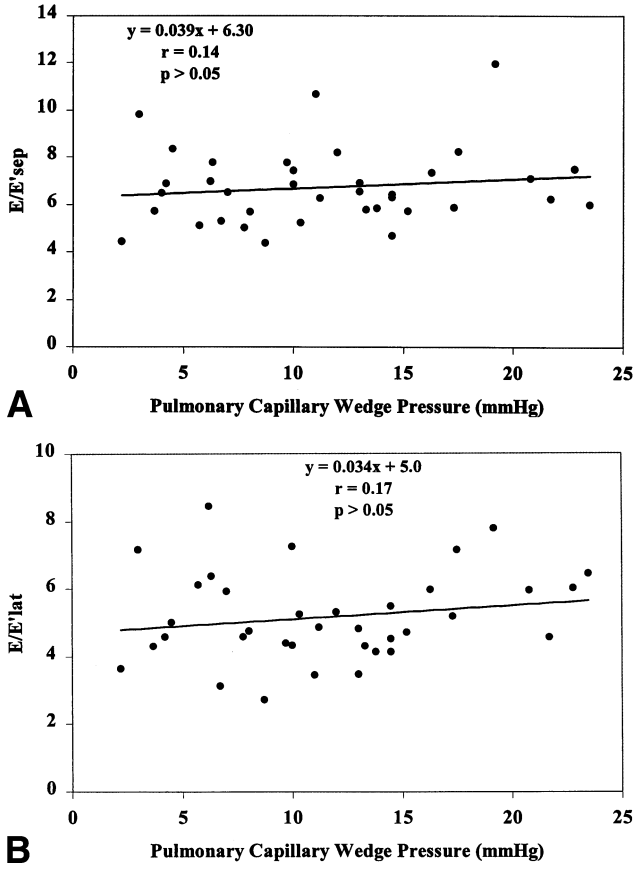

Figure 3A and B. Relationship between PCWP versus E/E′sep and E/E′lat. Linear regression analysis demonstrating the relationship between PCWP versus E/E'_{sep} (A) and E/E'_{lat} (B).

Furthermore, in this present study, we provide new evidence that in normal individuals, tissue Doppler indices vary substantially across a wide range of filling pressures and, in fact, can be used to predict the PCWP, rather than be independent of it. In addition, we show that the effects of alteration in preload on E′ differ when measurements are obtained from the lateral versus the septal region of the mitral annulus. This observation emphasizes the importance in distinguishing between these two methods when each is applied to either clinical or research applications.

The physiologic basis for the discrepancy regarding the effect of preload on E'_{sep} is based on recent evidence suggesting that preload affects E'_{sep} in ventricles with normal relaxation. We have shown in dogs undergoing pharmacologic alterations in relaxation that the influence of preload on E'_{sep} decreased with worsening tau (13). Thus, while E'_{sep} was strongly preload dependent with preserved relaxation, it was minimally preload dependent with impaired relaxation. This inverse relationship can explain why, as shown by others, the ratio of E/E′ can be applied to estimating PCWP in patients with impaired relaxation. Conversely, these findings can also explain why in our study of normal volunteers, E/E'_{sep} did not correlate with PCWP.

Recent attention has also focused on Vp as a preload independent index of ventricular relaxation, a finding that has been validated recently in a combined human and animal study (14). Early work by Brun et al. (15) demonstrated an inverse relationship between Vp and tau. Garcia et al. (5) also previously demonstrated that incorporating Vp into the relationship between E and PCWP could correct for the effects of alterations in ventricular relaxation. When the results from this current study were combined with the actual data of Garcia et al. (5) from ICU patients undergoing diagnostic pulmonary artery catheterization, despite significantly greater filling pressures than those observed in our study (mean PCWP, 15.1 ± 5.1; range, 7 to 25 mm Hg;

n = 45; $p < 0.001$ vs. our results), an E/Vp ratio >1.5 was a consistently strong predictor of elevated PCWP. For the combined data set, the ratio of E/Vp >1.5 predicted a PCWP > 12 mm Hg (sensitivity, 79%; specificity, 89%; positive predictive value, 93%; negative predictive value, 70%).

Clinical applications. The potential clinical application of these findings is broad. Currently, the accurate assessment of LV filling pressures, in itself a valuable index of both ventricular performance and a qualitative measure of intravascular fluid volume status, requires invasive right-heart catheterization. Although right-heart catheterization with a pulmonary artery catheter is performed routinely in an ICU setting, the inherent invasiveness and subsequent risks preclude widespread application. Therefore, the value of our study to both clinical medicine and physiology research for the estimation of LV filling pressures noninvasively is readily apparent. In addition, the echocardiographic techniques employed can be applied easily outside of a hospital setting, such as in the assessment of patients with suspected acute coronary syndromes or the rapid evaluation of patients with hemodynamic instability of unknown etiology.

Study limitations. The small number of subjects studied and the assumption of their individual freedom from cardiac disease are limitations of our study. The assumption of freedom from cardiac disease is supported by the lack of valvular disease or wall motion abnormalities observed by the echocardiographic evaluations. Furthermore, baseline ejection fractions were 72 ± 4% (end-diastolic volumes, 126 ± 12 ml; end-systolic volumes, 36 ± 8 ml) and noninvasive estimation of the time constant of ventricular relaxation (16) (average, 30.1 ± 7.0 ms) suggested normal values for healthy subjects. Although our study is limited in the number of volunteers studied, a unique component is that multiple measurements (5,6) were obtained in each volunteer. In addition, while other studies have performed a single repeat measurement, usually after an intervention, to our knowledge, our study is the first to perform several physiologic perturbations to provide a wide range of filling pressures within a given individual.

CONCLUSIONS

In patients with preserved systolic and diastolic function, simple transmitral or myocardial tissue Doppler velocities can provide an accurate assessment of PCWP. However, in patients whose ventricular function is either abnormal or unknown, the ratio of E/Vp should also be determined in conjunction with early diastolic transmitral and myocardial tissue Doppler velocity information for the assessment of both diastolic function and filling pressure.

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