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Contribution of Ventricular Diastolic Dysfunction to Pulmonary Hypertension Complicating Chronic Systolic Heart Failure

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OBJECTIVES The aim of the study is to clarify the clinical role of Doppler-echocardiographic parameters of left ventricular diastolic dysfunction (LVDD) as determinants of pulmonary hypertension in patients experiencing left ventricular systolic dysfunction (LVSD) with and without the presence of functional mitral valve regurgitation (FMR).

BACKGROUND Pulmonary hypertension (pulmonary venous or mixed pulmonary venous-arterial hypertension) complicating LVSD is associated with poor outcomes beyond that of LVSD alone. The view of the contribution of LVDD as a determinant of pulmonary hypertension is controversial and not well defined as a tool in clinical practice.

METHODS Data from patients with LVEF ≤40% undergoing Doppler-echocardiography evaluations during the period from August 2001 to December 2004 were analyzed. Pulmonary systolic pressure (PSP), parameters of diastolic function (mitral valve [MV] transmitral flow velocity [E]/mitral annular diastolic velocity [e′] ratio, MV deceleration time [DT]), quantitated effective regurgitant orifice area (EROA) of FMR, and clinical characteristics were evaluated. Pulmonary hypertension was defined as an estimated PSP ≥45 mm Hg.

RESULTS Criteria were met in 1,541 patients; one-third (n = 533) demonstrating PSP ≥45 mm Hg (58 ± 10 mm Hg, range 45 to 102 mm Hg). Patients with pulmonary hypertension were older with higher E/e′ ratio, EROA, and lower DT and LVEF. In multivariate analysis, pulmonary hypertension was independently predicted not only by severity of FMR (EROA ≥20 mm^2, odds ratio: 3.8, $p < 0.001$) but also by parameters of LVDD (E/e′ ratio ≥15, odds ratio: 3.31, $p < 0.001$; DT ≤150 ms, odds ratio: 3.8, $p < 0.001$). Receiver-operating characteristics curve analysis showed that EROA, E/e′ ratio, and DT provided significant incremental value in predicting pulmonary hypertension (c-statistic 0.830, $p < 0.001$).

CONCLUSIONS Patients with LVSD commonly have secondary pulmonary hypertension, which is largely determined by the severity of LVDD even with adjustment for FMR and low LVEF. Thus, measures of LVDD in routine clinical practice where PSP may not be estimated are important physiologic descriptors of hemodynamic status and are cumulatively linked in the prediction of pulmonary hypertension. (J Am Coll Cardiol Img 2011;4: 946–54) © 2011 by the American College of Cardiology Foundation

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Left ventricular systolic dysfunction (LVSD) is a major factor in the development of symptomatic congestive heart failure. However, an important landmark in the progression from uncomplicated left ventricular (LV) dysfunction to congestive heart failure is the development of pulmonary venous or mixed pulmonary venous/arterial pulmonary hypertension (PH). In clinical series, the frequency of PH is variable, but its development is associated with an augmented mortality/morbidity beyond that of LV dysfunction alone (1–4). Therefore, defining the causes of PH and the clinical markers associated with PH carries significant implications for patient management. In that regard, the role of left ventricular diastolic dysfunction (LVDD) remains to be clarified.

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Doppler echocardiography (D-E) is an essential tool in the assessment of patients with LV dysfunction, not only because it allows noninvasive quantitation of severity, pulmonary pressures, and functional mitral regurgitation (FMR), but also provides indirect measures of diastolic function. In previous studies, these measures were important independent determinants of filling pressures in the context of LVSD (5–7). Particular emphasis has been placed on the ratio of transmitral flow to mitral annular diastolic velocities (E/e′ ratio) (8), which is easily measured and, in validation studies, found to correlate with catheter-measured filling pressures, and thus serve as a core measure of ventricular diastolic function (6,7). However, early diastolic filling flow velocity, which is central to E/e′ calculation, is affected by the severity of FMR (9), which is commonly associated with LV dysfunction (10). The value of Doppler-derived indirect measures of LV diastolic function in estimating LV filling pressures has been questioned (11). Hence, in routine clinical practice, the value of basic Doppler-derived variables of diastolic function in patients with LVSD, particularly the E/e′ ratio, remains controversial.

Some salient issues in this context remain to be addressed. First, FMR is an important contributor to hemodynamic alterations in LVSD (5,12,13), and its interaction with measures of LVDD, particularly E/e′ ratio, in relation to the development of PH, is poorly understood (14). Second, the links between E/e′ ratio and PH accounting for FMR and other LVDD measures in LVSD have not been evaluated in a large series providing ample statistical power. Third, the practical value of these indices, particularly E/e′ ratio, in routine clinical practice is unclear. Therefore, in our clinical echocardiography practice in which quantification of LV systolic function, pulmonary systolic pressure (PSP), FMR, and LV diastolic function is commonly obtained, we examined the clinical merit of these physiologic contributors to the presence and prediction of PH in patients with LVSD.

METHODS

A retrospective analysis was conducted in a cohort of patients with LV systolic heart failure (HF) of ischemic and nonischemic etiologies and a quantitative measure of PSP who were evaluated at the Mayo Clinic, Rochester, during the period of August 1, 2001, to December 31, 2004. All patients underwent clinical D-E evaluation and were included in this analysis if the following criteria were met: 1) age >18 years; 2) presence of LVSD defined by a left ventricular ejection fraction (LVEF) ≤40%; 3) PSP measurable by D-E using tricuspid regurgitation velocity; 4) normal right ventricular systolic function; 5) measurable diastolic LV function by assessment of mitral valve (MV) E/e′ ratio and MV deceleration time (MV DT); and 6) quantitative assessment of FMR. Exclusion criteria were as follows: 1) atrial fibrillation; 2) organic mitral, tricuspid, or aortic valvular disease or status post any valve replacement/repair; 3) infiltrative, constrictive, or hypertrophic cardiomyopathy; 4) myocardial infarction within 6 months of index D-E; 5) chronic obstructive pulmonary disease or sleep apnea; 6) congenital heart disease; 7) tachycardia-related dysrhythmia with heart rate persistently >100 beats per min; 8) primary pulmonary arterial hypertension or pulmonary thromboembolic disease; 9) serum creatinine ≥2.0 mg/dl, 10) history of chest radiation therapy; 11) collagen vascular diseases; 12) status after cardiac or lung transplantation. The study was approved by the Mayo Foundation Institutional Research Review Board and included only those patients who provided informed consent as required by Minnesota Statute 144.335/CRF 21 (Part 50).

Doppler echocardiography. A clinical, comprehensive 2-dimensional and D-E examination was per-

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
D-E = Doppler echocardiography
DT = deceleration time
E = transmitral flow velocity
e′ = mitral annular diastolic velocity
EROA = effective-regurgitant-orifice area
FMR = functional mitral regurgitation
HF = heart failure
LV = left ventricular
LVDD = left ventricular diastolic dysfunction
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
MV = mitral valve
OR = odds ratio
PH = pulmonary hypertension
PSP = pulmonary systolic pressure
ROC = receiver-operating characteristic

formed in all patients (15,16), and the original clinical measurements were used for analysis without remeasurement. LV size and function were measured according to American Society of Echocardiography recommendations (17). Continuous wave Doppler was used to assess maximal tricuspid regurgitation flow velocity to estimate the systolic pressure gradient between the right ventricle and right atrium. Right ventricular systolic pressure was then calculated by adding an estimated right atrial pressure (18,19). For the purposes of analysis, this derived pressure was considered to be identical to PSP after demonstrating the absence of any organic abnormality of the pulmonary or tricuspid valves. PH was defined as PSP ≥45 mm Hg based upon reported cut-point assessments (4,20). The FMR was quantified by D-E or by proximal isovelocity surface area (PISA) methodology using measurements of mitral and aortic stroke volumes and also quantitative 2-dimensional echocardiography using measurements of LV volume and stroke volume. That allowed calculation of the effective mitral regurgitant orifice area (EROA), and in patients with no or trace mitral regurgitation by color flow imaging, the EROA was considered to be zero. Early transmitral flow velocity (E) and early diastolic mitral annular velocity (e′) were measured with D-E in the apical 4-chamber view to provide an estimate of LV diastolic function and pulmonary pressure (21). The ratio of peak E to peak e′ was calculated (mitral E/e′ ratio) from the average of at least 3 cardiac cycles. The deceleration time of the E-wave was also measured. Left atrial volume was calculated using the biplane area length method at end systole (22). Using pulse wave D-E, the cardiac index was calculated as the product of aortic stroke volume and heart rate adjusted for body surface area.

Statistical analyses. Data are presented as mean ± SD or median with 25th and 75th percentiles for continuous data, and as number and percentage for categorical data. Two-sample *t* tests were used to compare continuous variables, and signed-rank analysis was used to compare medians of values with nonparametric distributions, with statistical difference accepted for $p < 0.05$. Multiple linear regression analysis was used to assess associations among continuous clinical and 2-dimensional D-E variables with PSP. Logistic regression analysis was performed using all the independent variables to assess their relative contribution (odds ratio [OR]) to the development of PSP ≥45 mm Hg. The incremental value of each clinical and D-E variable in predicting the development of PSP ≥45 mm Hg was assessed in terms of the construction of receiver-operating characteristic (ROC) curves. The c-statistic (area under the ROC curve), as a measure of risk discrimination for PH, was calculated after the addition of each variable to the base model. The significance of the incremental c-statistic value was then determined. The Charlson index summating the patient's individual comorbidities including specific heart failure-related morbidity was calculated to aid in the characterization of the study cohort (23). Analyses were done using SAS software version 9 (SAS Institute, Cary, North Carolina) or S-plus version 7 (Insightful Corp., Durham, North Carolina).

RESULTS

Clinical and D-E characteristics. Patient demographic and clinical characteristics are shown in Table 1. Whereas a large number of patients met the initial requirement of LVEF ≤40% and a reported quantitative measure of PSP (n = 5,516), a smaller number met the specific study inclusion/exclusion criteria and having all the stipulated quantitative D-E measurements (n = 1,541). Pulmonary hypertension defined as a calculated systolic pressure ≥45 mm Hg was used in the analyses of the different variables as also shown in Table 1. Patients with elevated PSP were older, more frequently female, and with lower LVEF and higher Charlson index. The specific HF component within this comorbidity index was also higher in the patients with elevated PSP (44% vs. 31%, $p < 0.001$). Patients were receiving standard oral HF medications, and there were no differences identified in the distribution of these medications between patients with and without elevations in PSP. Median B-type natriuretic peptide concentrations were higher in the patients with elevated PSP (580 vs. 175 pg/ml, $p < 0.01$). Several Doppler-derived hemodynamic parameters were also different. Most notable were parameters of LVDD (E/e′ ratio, MV DT). Approximately one-third of the patient cohort had PSP ≥45 mm Hg (n = 533) and of these, 190 patients (36%) had PSP ≥60 mm Hg. An E/e′ ratio ≥15 was present in 78% and MV DT ≤150 ms in 65% of patients with PSP ≥45 mm Hg (both cut-points reflecting moderate or greater LVDD). The parameter of moderate or greater FMR, EROA ≥20 mm^2, was present in 31% of this subgroup, but nearly one-half (45%) demonstrated an EROA <10 mm^2 consistent with no to trivial

Table 1. Clinical, Demographic, and Doppler-Echocardiographic Characteristics of Patient Cohort

	Overall (n = 1,541)	PSP <45 mm Hg (n = 1,008)	PSP ≥45 mm Hg (n = 533)	p Value
Age, yrs	68 ± 14	66 ± 14	71 ± 14	<0.001
Sex, % male (n)	65.2%	70.2% (705)	56.1% (299)	0.001
Systemic BP, mm Hg	Systolic: 124 ± 22	124 ± 20/	125 ± 25/	0.753
	Diastolic: 70 ± 13	70 ± 13	70 ± 14	
Heart rate, beats per min	73 ± 16	71 ± 14	78 ± 14	0.001
Body mass index, kg/m^2	28.1 ± 6.9	28.2 ± 5.8	28.0 ± 8.6	0.338
Charlson Comorbidity Index	3.02 ± 2.99	2.90 ± 2.99	3.25 ± 2.98	0.03
Creatinine, mg/dl	1.3 ± 0.49	1.2 ± 0.42	1.3 ± 0.59	0.040
Potassium, mEq/l	4.3 ± 0.51	4.3 ± 0.50	4.3 ± 0.52	0.160
BNP, pg/ml	495 ± 539	306 ± 365	763 ± 626	<0.01
	317 (118–725)	175 (63–416)	580 (343–972)	
Cardiac index, l/min/m^2	2.7 ± 0.7	2.7 ± 0.6	2.6 ± 0.8	0.015
LVEF, %	30.5 ± 8.3	32.0 ± 7.6	27.8 ± 9.0	<0.001
LA volume, ml	73 ± 29	67.1 ± 26.1	84.3 ± 30.7	0.001
PSP, mm Hg	40 ± 15	31.4 ± 6.4	57.6 ± 10.5	<0.001
MV EROA, mm^2	8 ± 12	4.2 ± 8.2	14 ± 14	<0.001
EROA ≥20 mm^2	240 (16)	77 (7.6)	163 (31)	
EROA 10–19 mm^2	273 (18)	133 (13.2)	140 (26.3)	
MR volume, ml/beat	32 ± 15	29 ± 13	34 ± 16	<0.001
MV E/e′ ratio	17 ± 9	13.9 ± 6.9	21.8 ± 10.5	0.001
E/e′ ≥15	773 (50.2)	359 (36)	414 (78)	0.01
MV DT, ms	193 ± 61	209.5 ± 60.2	163 ± 50.9	<0.001

Values are mean ± SD, median (25th and 75th percentiles), or n (%).
BNP = brain natriuretic peptide; DT = deceleration time; E = transmitral flow velocity; e′ = mitral annular diastolic velocity; EROA = effective regurgitant orifice area; LA = left atrial; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MV = mitral valve; PSP = pulmonary systolic pressure.

FMR. In the cohort as a whole, 66% of patients had an EROA <10 mm^2.

Associations with PSP are presented as quintiles of the parameters of diastolic dysfunction—E/e′ ratio (Fig. 1) and MV DT (Fig. 2)—and the severity of FMR (EROA) (Fig. 3). The LVEF was less significantly related to an elevated PSP (Fig. 4) than the Doppler-derived parameters of LVDD. In multivariate logistic regression analysis, using clinical and quantitative 2-dimensional and Doppler-derived variables in modeling for PSP ≥45 mm Hg, LVDD parameters along with age were highly significant predictors of elevated PSP (Table 2). The strongest determinants were MV E/e′ ratio ≥15, MV DT ≤150 ms, and MV EROA ≥20 mm^2. In contrast, LVEF was not an independent determinant of elevated PSP (OR: 1.25, p = 0.465). The results of the ROC curve analysis for the determinants of PSP ≥45 mm Hg are shown in Figure 5. The incremental prognostic value of each determinant was demonstrated by the addition of each variable to the model (Table 3). Significant contributions occurred with the addition of the parameters of LVDD (MV DT ≤150 ms and E/e′ ratio ≥15) to the model (c-statistic of 0.804, p < 0.001) from baseline model of age only (c-statistic 0.605). Adding other markers of elevated filling pressure (left atrial volume and serum creatinine concentration) to this model did not significantly

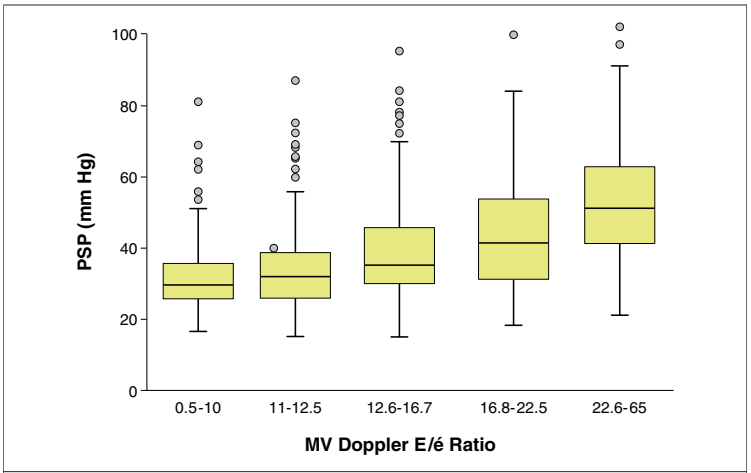

Figure 1. Box-Plot of Association of Mitral E/e′ Ratio by Quintiles With PSP

Data are presented as medians (**line inside the box**), interquartile ranges (IQR) of 25th to 75th percentiles (**limits of the box**), and 1.5 times IQR above and below the 75th and 25th percentiles (**error bars**). p < 0.001 across quintiles. E/e′ = transmitral flow velocity/mitral annular diastolic velocity ratio; MV = mitral valve; PSP = pulmonary systolic pressure.

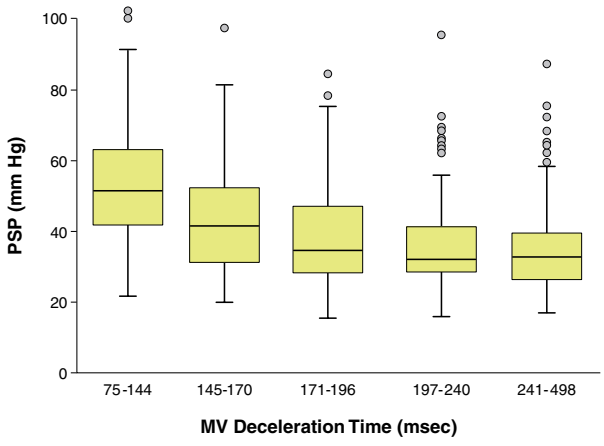

Figure 2. Box-Plot of Association of MV Deceleration Time (ms) by Quintiles With PSP

Data are presented as described for Figure 1. Abbreviations as in Figure 1.

add to predictive power (p = 0.165 for c-statistic increment to 0.830).

An issue relating to standard clinical practice was the study requirement that all patients meet prespecified selection criteria, (i.e., that all patients had to have a quantitative D-E assessment, particularly for FMR). That was felt to be the best design for vigorous data analysis as a basis for study conclusions. However, many patients in routine clinical practice do not have quantitative measurements of all the study specified D-E parameters (for various reasons including technical limitations or a focused evaluation based upon the echo referral question). Therefore, many patients have only qualitative assessments of FMR. Thus, we undertook the same analysis in the larger initial cohort who met the basic selection criteria of LVEF ≤40% and a measured PSP (n = 5,516) and included qualitative measures of FMR (none-trivial, mild, moderate-severe, and severe). By this analysis, the parameters of LVDD (E/e′ ratio ≥15; OR: 2.78, 95% confidence interval [CI]: 2.29 to 3.37, p < 0.001) and MV DT ≤150 ms (OR: 3.23, CI: 2.59 to 4.05, p < 0.001)], FMR [OR: 4.55 [none-trivial vs. severe], CI: 3.30 to 6.30, p < 0.001], and age (OR: 5.92, CI: 3.32 to 10.67, p < 0.001) remained robust predictors of PH. Also, LVEF (OR: 1.82, CI: 1.22 to 2.71, p = 0.003) was predictive. These findings support these parameters of LVDD and FMR being effective predictors of PH even when less stringent patient selection criteria are applied.

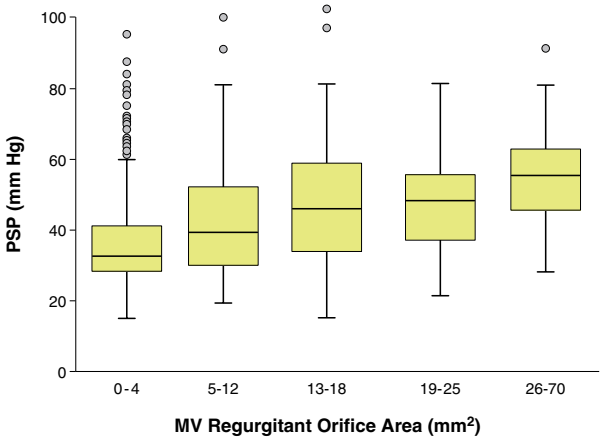

Figure 3. Box-Plot Analysis of Association of MV EROA (mm²) by Quintiles, Using Quantitative Doppler Echocardiography, as Measure of FMR Severity, With PSP

Data are presented as described for Figure 1. EROA = effective regurgitant orifice area; FMR = functional mitral valve regurgitation; other abbreviations as in Figure 1.

DISCUSSION

The findings of this study indicate that in a large cohort of patients with systolic HF being evaluated in routine clinical practice, PH is present in approximately one-third of patients. PH is not an isolated finding and is generally accompanied by left atrial enlargement and B-type natriuretic peptide elevation. It is associated with older age (>70 years), and also with several D-E–derived hemodynamic variables: the parameters of LVDD (E/e′ ratio ≥15 and MV DT≤150 ms), and the presence and severity of FMR. In this cohort, these variables are independent and cumulative predictors of PSP ≥45 mm Hg. Thus, the greater the number of individual predictors identified extends the probability of PH being present or at risk of developing when PSP is not or cannot be measured by D-E techniques. While these variables reflect a physiologic relationship among LVDD, FMR, and PSP, their clinical use does not assure the absolute prediction of PH in the individual patient. Rather, the presence of these markers of LVDD and FMR in clinical practice should inform the risk of developing PH and lead to further assessment and the use of therapeutic options to prevent the progression to decompensated HF.

The Doppler-derived parameters of LVDD showed a high frequency in this cohort being present in 78% of patients with PSP ≥45 mm Hg and were shown to be independent predictors of PH. The severity of FMR with EROA ≥20 mm² was also associated with PH independently of all other variables. This indicator was present, however, in only one-third of patients with PSP ≥45 mm Hg but more than one-half (55%) had an

EROA ≥10 mm^2, indicating the presence of at least mild-moderate FMR. It also should be noted that in the patients with PSP <45 mm Hg, an E/e′ ratio ≥15 was present in 36%, whereas MV DT ≤150 ms and EROA ≥20 mm^2 were present in only 12% and 8%, respectively. By inference, that suggests the presence of elevated left-sided filling pressure and, therefore, the presence of post-capillary pulmonary venous hypertension and no apparent contribution of a pre-capillary pulmonary arterial hypertension component (20,21,24). It would thus appear that, in addition to age, the degree of LVDD and FMR are the most potent determinants of an elevation in PSP in this large cohort. Extent of LVEF reduction, while shown in univariate analysis to be a determinant of PH, was, however, not predictive after adjusting for the other variables.

Mitral E/e′ ratio is accepted as a reliable measure of ventricular diastolic function and an estimate of ventricular filling pressure (8,14,16,24). Elevated filling pressures in patients with congestive HF are driven to a large extent by abnormalities of myocardial relaxation during diastole. The discordance between slow relaxation (low e′) of the LV and a high E velocity suggests the presence of a high pressure gradient between the left atrium and LV in early diastole. A high E/e′ ratio has been considered a good marker of elevated LV filling pressure and diastolic dysfunction on the basis of this discordance. Thus, E/e′ ratio is linked to PH in the context of LVSD, as well as other left-sided heart disease (25). However, the clinical reliability of mitral E/e′ ratio and MV DT as estimators of LV filling pressure and PH is not unchallenged (11,26). In a study of 106 patients who underwent echocardiography and hemodynamic catheterization evaluations, discordant findings between mitral E/e′ ratio and pulmonary capillary wedge pressure were reported (11). The patients enrolled were being admitted for acute decompensated HF and were receiving adjustments in their medical therapy and, therefore, were not in a steady-state condition, which might be expected to influence correlations with hemodynamic measurements. Also, in that study, no direct measurements of LV end diastolic pressure were undertaken, pulmonary capillary wedge pressure displayed no association to E/e′ ratio, and only a weak negative correlation with MV DT was demonstrated. These findings contrast with prior studies that established these D-E parameters as being reflective of LV filling pressures (16,24) and also with the results of the current study. Our data lend support to a role, in conjunction with standard-of-care clinical assessment, for these Doppler-derived measurements of diastolic function in assessing patients with LVSD for high risk PH. The findings of our study in this respect are hypothesis generating.

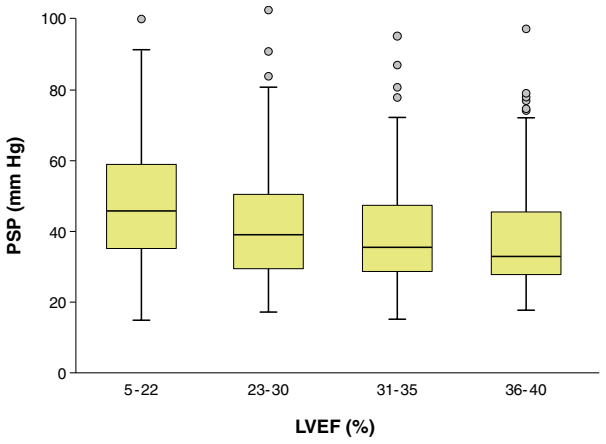

Figure 4. Box-Plot Analysis of Association of LVEF by Quartiles With PSP

Data are presented as described for Figure 1. LVEF = left ventricular ejection fraction; other abbreviation as in Figure 1.

FMR has also been reported to be a marker of poor outcome in patients with LVSD (14,27,28). The contribution, however, of FMR to the development of PH in patients with chronic LVSD is not clear. The severity of FMR would be expected to influence diastolic function through an effect on LV volume overload. Quantitative D-E assessment of FMR is, however, subject to loading conditions of the heart and may, therefore, provide varying results. The findings of the current study indicate that more severe FMR, as reflected in EROA ≥20 mm^2, is an independent determinant of PH, but may lack sensitivity. Nearly one-half (45%) of the patients with PSP ≥45 mm Hg demonstrated an EROA <10 mm^2. The contribution of FMR per se to the development of PH may be through longer-

Table 2. Logistic Regression Analysis, Odds Ratio for Risk of PSP ≥45 mm Hg

	OR	95% CI	p Value
Age, yrs	8.39	3.71–19.33	<0.001
LVEF, %	1.25	0.68–2.29	0.465
MV EROA ≥20 mm^2	3.72	2.59–5.45	<0.001
MV EROA 10–19 mm^2	2.13	1.53–3.0	<0.001
MV E/e′ ratio ≥15	3.31	2.48–4.43	<0.001
MV DT ≤150 ms	3.85	2.78–5.24	<0.001

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

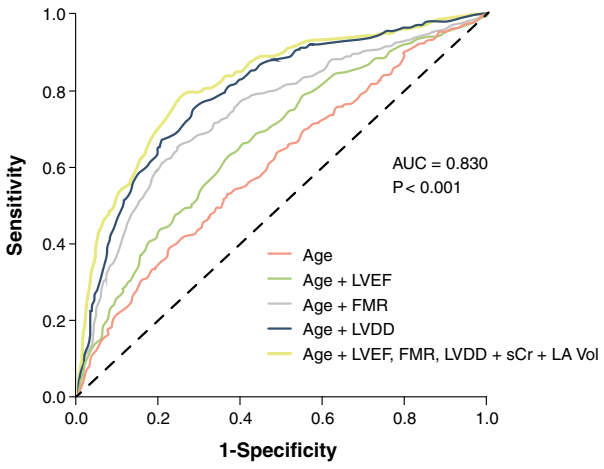

Figure 5. ROC Curve Analysis

Receiver-operating characteristic (ROC) curve analysis of incremental values of clinical and Doppler echocardiography–derived variables in the prediction of PSP ≥45 mm Hg. **Orange line** indicates age; **green line** indicates age plus LVEF; **gray line** indicates age plus functional mitral regurgitation (FMR); **dark blue line** indicates age plus left ventricular diastolic dysfunction (LVDD); and **yellow line** indicates age plus LVEF, FMR, LVDD, serum creatinine (sCR), and left atrial (LA) volume. AUC = area under the curve; other abbreviations as in Figures 1 and 4.

term consequences such as increases in left atrial pressure secondary to large regurgitation volume, and increased LV volume shifting its function to a steeper portion of the diastolic filling curve. These may add to the progression of LVDD and may be the mechanisms whereby patients with reduced systolic function and FMR experience a poorer long-term outcome. Our findings confirm the few prior studies that address FMR and suggest that FMR imparts hemodynamic consequences and impacts outcome (12,14). Also importantly, the threshold for these serious complications is lower than that of organic MV regurgitation (29).

Study limitations. In interpreting these data, several issues should be considered. Foremost is the retrospective design of the study with associated inherit limitations. Pulmonary pressures were calculated from D-E–derived data and no invasive hemodynamic measurements were obtained for comparison. The noninvasive methodology, however, has been well validated and accepted in guideline recommendations as a standard approach to the initial assessment of pulmonary pressure (6–8,24), which is the measure of interest for this study. Also, while the measures of LVDD and FMR shown in this study are independent determinants of PH, there is notable individual variability. As such, these measures should be considered as thresholds for physiologic determinants of PH more so than absolute markers for PH in the individual patient. Additionally, while we were vigorous in excluding patients with primary lung disease as a basis of elevated PSP, we cannot be certain that a few such patients were not included in the analysis; it would not be expected, however, to significantly impact the findings.

Also, given the absence of a clear consensus for a specific PSP to define pulmonary venous or mixed pulmonary venous and arterial hypertension, the cut-point for our study (PSP ≥45 mm Hg) could be considered arbitrary. Therefore, we undertook additional regression analyses by defining additional cut-points (PSP ≥50, ≥55, and ≥60 mm Hg). The results were not significantly changed (EROA ≥20 mm^2 OR: 3.63, 3.00, 2.68, respectively, $p < 0.001$; E/e′ ≥15 OR: 3.76, 5.02, 4.29, respectively, $p < 0.001$; and DT ≤150 ms OR: 3.46, 3.15, 3.78, respectively, $p < 0.001$). All were independent predictors of PH except LVEF, which remained nonpredictive. The c-statistic was not significantly changed with the highest cut-point of ≥60 mm Hg (0.839 compared with 0.830 for PSP ≥45 mm Hg, $p = 0.424$). The overall nature of this study cohort particularly without a bias for pre-specified cardiac catheterization reflects more of the routine of standard clinical practice than would be expected from clinical trial data and, therefore, contributes to a general applicability of these findings.

Table 3. Incremental Value of Clinical and Echocardiographic/Doppler Determinants of PSP ≥45 mm Hg, ROC Curve Analysis

	AUC C-Statistic	p Value
Age	0.605	
Age + LVEF	0.669	<0.001
Age + FMR (EROA ≥20 mm^2 and EROA 10–19 mm^2)	0.740	<0.001
Age + LVDD (MV E/e′ ≥15 and MVDT ≤150 ms)	0.804	<0.001
Age + LVEF + FMR + LVDD + sCr + LA volume	0.830	<0.001

AUC = area under the curve; FMR = functional mitral regurgitation; LVDD = left ventricular dystolic dysfunction; ROC = receiver-operating characteristic; sCr = serum creatinine; other abbreviations as in Table 1.

CONCLUSIONS

Pulmonary venous and mixed pulmonary venous/arterial hypertension are commonly associated with chronic LV systolic HF. Elevations in PSP appear to occur independently of the severity of LVEF reduction but are notably associated with the presence and severity of LVDD and FMR. FMR most likely contributes to the development of PH either directly through its effect on left atrial pressure/volume or by adding to the longer-term development of diastolic dysfunction through LV dilation

and changes in LV filling pressures. While measures of LVDD and FMR are not always associated with PH, these indices are strong predictors of elevated filling pressures and when present, particularly in the absence of an evaluation of PSP, should alert the clinician to the prospect of PH being present. Therefore, these predictors (age, measures of LVDD, and FMR) can contribute cumulatively in the determination of the presence and severity of PH. Prospective studies are needed to assess whether progressive changes in D-E-derived variables of LVDD such as MV E/e′ ratio and MV DT (or others) should be a primary focus for predicting and a therapeutic target for intervening in the course of LV systolic HF to limit the development of secondary PH and its maladaptive consequences.

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Key Words: Doppler echocardiography ■ functional mitral valve regurgitation ■ heart failure ■ left ventricular diastolic dysfunction ■ secondary pulmonary hypertension.