ORIGINAL RESEARCH

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Echocardiographic Detection of Occult Diastolic Dysfunction in Pulmonary Hypertension After Fluid Challenge

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Background**—**Identification of occult diastolic dysfunction often requires invasive right heart catheterization with provocative maneuvers such as fluid challenge. Non-invasive predictors of occult diastolic dysfunction have not been identified. We hypothesized that echocardiographic measures of diastolic function are associated with occult diastolic dysfunction identified at catheterization.

Methods and Results**—**We retrospectively examined hemodynamic and echocardiographic data from consecutive patients referred for right heart catheterization with fluid challenge from 2009 to 2017. A replication cohort of 52 patients who prospectively underwent simultaneous echocardiography and right heart catheterization before and after fluid challenge at Monaldi Hospital, Naples, Italy. In the retrospective cohort of 126 patients (83% female, 56+14 years), 27/126 (21%) had occult diastolic dysfunction. After adjusting for tricuspid regurgitant velocity and left atrial volume index, E velocity (odds ratio 1.8, 95% CI 1.1–2.9, *P*=0.01) and E/e′ (odds ratio 1.9, 95% CI 1.1–3, *P*=0.005) were associated with occult diastolic dysfunction with an optimal threshold of E/e′ >8.6 for occult diastolic dysfunction (sensitivity 70%, specificity 64%). In the prospective cohort, 5/52 (10%) patients had diastolic dysfunction after fluid challenge. Resting E/e′ (odds ratio 8.75, 95% CI 2.3–33, *P*=0.001) and E velocity (odds ratio 7.7, 95% CI 2–29, *P*=0.003) remained associated with occult diastolic dysfunction with optimal threshold of E/e′ >8 (sensitivity 73%, specificity 90%).

Conclusions**—**Among patients referred for right heart catheterization with fluid challenge, E velocity and E/e′ are associated with occult diastolic dysfunction after fluid challenge. These findings suggest that routine echocardiographic measurements may help identify patients like to have occult diastolic dysfunction non-invasively. **(*J Am Heart Assoc.* 2019;8:e012504. DOI: 10.1161/JAHA.119.012504.)**

Key Words: echocardiography • heart failure • pulmonary hypertension

Heart failure is a highly prevalent and morbid condition with growing incidence worldwide,[1] with at least half of patients who now present with heart failure with preserved ejection fraction (or HFpEF).[2] Many of these patients have concomitant pulmonary hypertension (PH), and early identification of post-capillary PH has both prognostic and therapeutic implications. Echocardiography is essential to the evaluation of heart failure, and guidelines exist to identify diastolic dysfunction non-invasively.[3] However, up to 50% of patients with HFpEF have normal resting diastolic function parameters on echocardiography.[4,5] Published non-invasive algorithms exhibit modest accuracy in identifying underlying diastolic dysfunction in this patient population,[6] highlighting the difficulty in clinical diagnosis of diastolic dysfunction. Despite multiple potential etiologies that contribute to HFpEF,[7] elevated left sided filling pressures are not only important for diagnosis[8,9] but also correlate with symptoms.[10,11]

Recent studies have suggested that up to 25% of patients initially diagnosed with pulmonary arterial hypertension are found to have occult diastolic dysfunction after provocative maneuvers such as exercise or fluid challenge.[12–14] This finding has generated considerable interest in identifying non-invasive methods by which to identify these patients.[15–19] Left ventricular hypertrophy and left atrial enlargement have been associated with occult diastolic dysfunction after fluid challenge, but these metrics are non-specific and binary.[13] To

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Clinical Perspective

What Is New?

- Differentiation of primary pulmonary arterial hypertension from pulmonary hypertension due to left heart disease, particular in patients with preserved ejection fraction, often requires catheterization and provocative challenge with fluid or exercise.
- The use of 2 echocardiographic measures of diastolic function, mitral in-flow velocity (E) and the ratio of mitral in-flow to mitral annular tissue doppler velocity (E/e′), can identify occult diastolic dysfunction in patients with pulmonary hypertension.

What Are the Clinical Implications?

- These findings suggest that a subset of patients can be classified non-invasively, and future investigations of non-invasive imaging after fluid challenge may improve diagnostic accuracy.

date, no studies to date have evaluated the association between echocardiographic measures of diastolic function and the hemodynamic response to provocative maneuvers during RHC.

Thus, we examined the ability of quantitative markers of diastolic function to identify individuals with diastolic dysfunction after fluid challenge. The findings from a retrospective cohort were replicated in a prospective research-based cohort undergoing simultaneous echocardiography and right heart catheterization.

Methods

The present study was approved by the Institutional Review Board at Vanderbilt University Medical Center, IRB #130268 and #170726, as well as Monaldi Hospital IRB in Naples, Italy IRB #774/15. The data, methods used in the analysis, and materials used to conduct the research will not automatically be made available for purposes of reproducing the results or replicating the procedure.

Patient Selection: Retrospective Cohort

We extracted data on all patients referred for right heart catheterization between 2009 and 2017 at Vanderbilt University Medical Center who underwent a fluid challenge and a clinically indicated echocardiogram. In 2009, our catheterization laboratory adopted the practice of performing fluid challenge in all patients referred for evaluation for PH with a suspicion for pulmonary arterial hypertension, as well as any patient in the cardiac catheterization laboratory whose resting hemodynamics showed a mean pulmonary artery pressure >25 mm Hg and pulmonary arterial wedge pressure (PAWP) <15 mm Hg. Patients were excluded if they had persistent atrial fibrillation, atrial flutter, congenital heart disease, prior valve surgery, aortic stenosis, mitral stenosis, or moderate or severe aortic or mitral regurgitation. Clinical data extracted included demographics (age, sex, weight), coexisting cardiac risk factors (hypertension, diabetes mellitus, obstructive sleep apnea, coronary artery disease, and dyslipidemia), right heart catheterization data (baseline data, post-fluid challenge, and post-nitric oxide and oxygen therapy), and data from the nearest echocardiogram. Co-morbid conditions were defined based on either the presence of the condition in the patient's medical history or problem list, or the report of a previous myocardial infarction (specifically for coronary artery disease). No time limits were imposed upon time between nearest echocardiogram and right heart catheterization data, but sensitivity analysis was done on significant findings to determine the effect of time between echocardiogram and right heart catheterization on findings.

Right Heart Catheterization: Retrospective Cohort

Invasive measurements were made by experienced interventional cardiologists and tracings were manually reviewed.[20] Fluid challenge was performed with a 500 mL rapid infusion of normal saline through an 8 Fr catheter over 5 to 10 minutes as previously described,[13] corresponding to 5.62±1.37 mL/kg on average for each patient. All patients referred for evaluation of PH were evaluated for fluid challenge. PH was defined by a mean pulmonary artery (PA) pressure ≥25 mm Hg. Resting diastolic dysfunction was defined by a PAWP ≥15 mm Hg at the time of resting right heart catheterization. For this study, occult (post-fluid) diastolic dysfunction by RHC was defined by PAWP ≥18 mm Hg after fluid challenge, based on previous studies and recent consortium reports on the definitions of abnormal fluid challenge.[12,21] Fluid challenge was conducted in all patients with PAWP ≤15 mm Hg, and at the discretion of the interventionalist in patients with PAWP ≥15 mm Hg or RAP ≥15 mm Hg. Cardiac output was measured by thermodilution method.

Echocardiography: Retrospective Cohort

Echocardiography was performed as part of a routine clinical care of patients. Studies were all performed between 2009 and 2017 at Vanderbilt University Medical Center on a Philips IE-33 or CX-50 ultrasound system (Philips Corporation, Amsterdam, Netherlands). Baseline measurements were acquired and measured in accordance with American Society of Echocardiography guidelines.[3,22,23] All patients underwent standard measurements in parasternal long, parasternal short, right ventricular in-flow, apical 4 chamber, apical 3 chamber, and subcostal views. Chamber size and function of the left atria and ventricles was quantified primarily by volume estimation by Biplane method. Right ventricular size and function were quantified by RV fractional area change, tricuspid annular plane systolic excursion (TAPSE), and tissue doppler velocity of the RV free wall (lateral S′ velocity). Diastolic function measurements were made in accordance with current guidelines and included tricuspid regurgitation velocity, mitral in-flow E and A velocities, both septal and lateral mitral valve tissue doppler e′ and a′ velocities, and mitral E velocity deceleration times. Calculated E/e′ ratio was based on the average e′ value obtained from septal and lateral aspects of the mitral valve. The highest measured tricuspid regurgitation velocity regardless of view was used for analysis. Echocardiographic data were reviewed by an experienced cardiologist (V.A.) blinded to each patient's invasive hemodynamic data. In cases in which multiple echocardiograms were performed for a specific patient, the echocardiogram closest in date to the right heart catheterization was used for analysis.

Prospective Cohort

A prospective cohort comprised 52 patients who underwent simultaneous echocardiogram and right heart catheterization (RHC) before and after fluid challenge at Monaldi Hospital, Naples, Italy. All consecutive patients referred between January 1, and December 31, 2016, were enrolled in the study. The presence of an uncorrected intra- or extracardiac shunt and the presence of atrial fibrillation or flutter were considered exclusion criteria. All patients provided written informed consent. Echocardiography was performed with a portable VIVID-I echo machine (General Electric, USA) according to the American Society of Echocardiography guidelines (3). Hemodynamic and echocardiographic measurements were obtained by 2 experienced interventional cardiologists and an experienced non-invasive cardiologist simultaneously at baseline and immediately after intravenous administration of 7 mL/kg of saline >5 to 10 minutes, corresponding to 498±95.6 mL per patient on average. Fluid challenge was avoided in patients with a PAWP >25 mm Hg because of the high risk of pulmonary edema. Clinical data and coexisting risk factors were collected for all patients.

Statistical Analysis

Statistical analysis was completed using the R studio package (R Foundation for Statistical Computing, Vienna, Austria). Figures were generated in the R studio software and Prism (GraphPad software, La Jolla, CA, http://www.graphpad.com). Non-parametric Kruskal–Wallis test or Chi-square test was used to compare between the 3 groups of patients (no diastolic dysfunction, occult diastolic dysfunction, and resting diastolic dysfunction) for all clinical, demographic, and hemodynamic parameters. Nemenyi post-hoc test was used to identify significant differences between subgroups for Kruskal–Wallis test. The Kruskal–Wallis and Nemenyi post-hoc tests were performed with the *PMCMR plus* package,[24] and the chi-square test was performed using the *stats* package.[25] A $P<0.05$ was considered significant. Receiver operative curves, sensitivity, specificity, and area-under-the-curve analyses were completed using the *ROCR* package in R.[26] Non-linear univariate and multivariate odd ratios of variables was conducted with the *RMS* package in R using maximum likelihood estimation.[27] Clinical variables were selected a priori based on clinical knowledge. We did not perform adjusted analysis on the replication cohort in order not to overfit the model.

Results

Patient Baseline Characteristics

In the Vanderbilt cohort, a total of 126 patients were identified who met inclusion criteria (Table 1), with exclusion criteria including patients who underwent right heart catheterization without fluid challenge and patients without echocardiographic images and data available for review (Figure 1). The cohort was 83% female with a mean age of 56±14 years and a median interval between right heart catheterization (RHC) and echo of 40 days (IQR 4–165 days). The cohort consisted of 71/126 (56%) patients without evidence of diastolic dysfunction, 28/126 (22%) patients with resting diastolic dysfunction, and 27/126 (21%) patients with inducible or occult diastolic dysfunction. Baseline characteristics were notable for an increased body mass index in patients with occult or resting diastolic dysfunction when compared with patients without diastolic dysfunction, and a decreased prevalence of diabetes mellitus in the occult diastolic dysfunction group when compared with patients with no diastolic dysfunction or resting diastolic dysfunction (Table 1).

The overall prevalence of PH in our patient cohort was 89% (112/126). Among patients with PH, 71 (57%) had pre-capillary PH, 28 (22%) had resting post-capillary PH, and 27 (21%) had occult diastolic dysfunction after initial hemodynamics suggested pre-capillary PH. Patients with resting diastolic dysfunction had an increased right atrial pressure and lower mean pulmonary artery mean pressures when compared with patients with occult diastolic dysfunction (Table 1). The patients without diastolic dysfunction had

Table 1. Baseline Demographics and Hemodynamics for Patient Groups

	Fluid Challenge Response		
	No DD	Occult DD	Resting DD
Demographics	n=71	n=27	n=28
Age, y	54±14.5	57±12.3	62±14
BMI	30±7	31±7	34±10
Sex (% female)	76	85	96
Overweight, %	62	70	79
Obese, %	34	48	54
Diabetes mellitus, %	58	26*	46
Hypertension, %	42	44	29
Hyperlipidemia, %	52	33	39
Coronary artery disease, %	51	33	64
Obstructive sleep apnea, %	59	30*	36
Medications			
Beta blocker, %	18	18	33
ACE/ARB, %	12	6	20
Diuretic, %	59	82	87
Aldosterone antagonist, %	12	18	33
Calcium channel blocker, %	18	24	33
Nitrate, %	0	12	7
PDE-5 inhibitor, %	53	24*	0*
Prostaglandins/analogues, %	29	0*	0*
Endothelin receptor antagonists, %	47	0*	0*
Hemodynamics			
Heart rate	78±15	75±12	78±13
MAP, mm Hg	94±15	96±14	93±17
RAP, mm Hg	9±6	9±5	15±6*
Mean PAP, mm Hg	45±14	38±13	49±19
PAWP pre-fluid, mm Hg	10±3	13±3	22±7*
RAP pre-fluid, mm Hg	9±6	9±5	15±6*
RAP post-fluid, mm Hg	10±5	10±4	17±5*
TPG, mm Hg	35±13	25±13*	27±17*
DPG, mm Hg	19±10	13±10*	12±12*
PVR, wood units	8±5	5±4*	6±5
Cardiac index, L/min per m^2	2.6±0.7	2.9±0.7	2.8±0.8

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; DD, diastolic dysfunction; DPG, diastolic pulmonary gradient; MAP, mean arterial pressure; PDE, phosphodiesterase; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TPG, transpulmonary gradient.
*Represents significant differences compared with "No DD" with threshold of $P<0.05$.

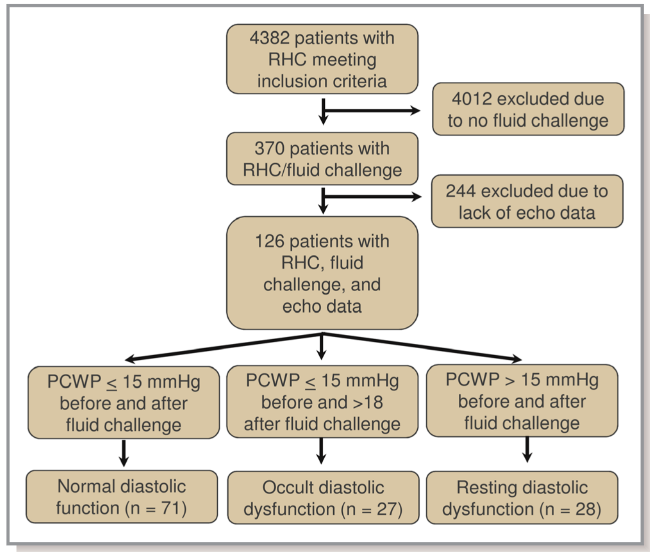

Figure 1. Flowchart diagram depicting patients who were evaluated for inclusion in the current study and patients excluded from the current study. Echo indicates echocardiogram; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization.

higher resting transpulmonary gradient, diastolic pulmonary gradient, and pulmonary vascular resistance (PVR) when compared with patients with occult or resting diastolic dysfunction. This is consistent with our referral population, which has a high prevalence of pulmonary arterial hypertension. There was no difference in baseline heart rate, mean arterial pressure, or cardiac index between groups.

Baseline Echocardiographic Measures

Echocardiographic measurements showed no significant differences in LV chamber size, LV chamber function, or wall thickness between groups (Table 2). However, patients with pre-capillary PH had a lower right ventricular outflow tract velocity time integral than patients with occult or resting diastolic dysfunction. Additionally, LA volume index was higher in patients with resting diastolic dysfunction, and E velocity was higher in patients with occult and resting diastolic dysfunction when compared with the pre-capillary PH group.

Association of Echocardiographic Measures With Invasive Hemodynamics in the Retrospective Cohort

In a univariate analysis of variables recommended for the evaluation of diastolic function,[3] the early diastolic mitral-inflow velocity (E velocity) was significantly higher for patients with occult or resting diastolic dysfunction on RHC as compared to no diastolic dysfunction. There was additionally

Table 2. Resting Echocardiographic Parameters for Patient Groups

	Fluid Challenge Response		
	No DD	Occult DD	Resting DD
E, cm/s	74±24	89±28*	86±26*
A, cm/s	76±21	81±26	76±27
MV_Decel, ms	223±74	210±48	219±68
Lateral e′, cm/s	11±4	9±3	9±4
Medial e′, cm/s	7±2	7±2	7±2
TR velocity, m/s	3.7±1.1	3.4±1.1	3.5±1.1
LA vol index, mL/m^2	22±8	22±8	27±10*
RVOT VTI, cm	13±4	15±3*	16±6*
PV AT, ms	96±41	107±40	101±33
E/e′	8.7±4.1	11.5±4.9*	11.8±6.6*
E/A	1.1±0.8	1.2±0.6	1.4±1.1
IVSd, cm	1.1±0.2	1.1±0.2	1.1±0.2
LVPWd, cm	1.0±0.2	1.1±0.2	1.0±0.2
LVIDd, cm	4.1±0.7	4.1±0.6	4.2±0.7
LVIDs, cm	2.6±0.6	2.6±0.5	2.6±0.7
EF, %	63±9	62±7	60±9
LVOT VTI, cm	19±5	21±5	20±7
TAPSE, cm	1.6±0.5	1.8±0.4	1.8±0.6
Lateral S′ velocity, cm	12±5	12±4	13±2
RV fractional area change, %	28±9	33±10	30±9

A indicates atrial kick-associated mitral in-flow peak velocity; DD, diastolic dysfunction; E, early diastolic mitral in-flow peak velocity; e′, mitral annular tissue Doppler velocity; EF, ejection fraction; IVSd, interventricular septal diameter; LA, left atrium; LVIDd, left ventricular end-diastolic internal diameter; LVIDs, left ventricular end-systolic internal diameter; LVOT, left ventricular outflow tract; LVPWd, left ventricular posterior wall thickness at end-diastole; PV AT, pulmonary valve acceleration time; RVIDd, right ventricular end-diastolic internal diameter; RVOT, right ventricular outflow tract; TAPSE, tricuspid annular plane systolic excursion; VTI, velocity time integral.
*Represents significant differences compared with “No DD” with threshold of $P<0.05$.

a concomitant elevation in the ratio of E velocity to average mitral annular tissue doppler velocity (e′ velocity) (E/e′) in patients with occult or resting diastolic dysfunction. Finally, the patients with resting diastolic dysfunction had a significantly greater left atrial volume index (LAVI) compared to patients with occult or no diastolic dysfunction (Figure 2, Table 2). There were no differences in the deceleration time (DT), a-wave mitral in-flow velocity, lateral or septal mitral annular tissue doppler velocities (e′ velocity), ratio of early and atrial-kick related mitral-inflow velocity ratio (E/A ratio), or tricuspid regurgitation velocity. In multivariate analysis adjusting for tricuspid regurgitation velocity and left atrial volume index, parameters recommended for determination of diastolic function by echocardiography,[3] E velocity (OR 1.8, 95% CI 1.1–2.9, P=0.01) and E/e′ (OR 1.9, 95% CI 1.1–3, P=0.005) were significantly associated with occult diastolic dysfunction. E/e′ remained significantly associated with occult diastolic dysfunction after univariate adjustment for obstructive sleep apnea, coronary artery disease, hyperlipidemia, diabetes mellitus, hypertension, or obesity (Figure 3A). E/e′ also remained significantly associated with occult diastolic dysfunction after adjustment for echocardiographic variables known to be associated with occult diastolic dysfunction[13] (E/A ratio, presence of left ventricular hypertrophy, left atrial volume index, and TR velocity) (Figure 3B). Receiver Operating Curve (ROC) analysis suggested an optimal threshold of E/e′ >8.6 for identification of occult diastolic dysfunction (sensitivity 70%, specificity 64%) (Figure 4).

To determine whether the time between echocardiogram and right heart catherization affected the association between E/e′ and occult diastolic dysfunction, univariate analysis of E/e′ was repeated for each quartile of time between echocardiogram and right heart catheterization and showed that E/e′ remained significantly associated with occult diastolic dysfunction in all quartiles except for the last quartile (Figure 3C). Left ventricular transmural pressure was also measured to determine whether fluid loading affected E/e′ through increased pericardial restraint, and no significant difference in LV transmural pressure was noted between all groups (Figure 3D). Notably, patients with occult diastolic dysfunction after fluid loading had a larger increase in PAWP pressure after fluid loading (Figure 3E) that was out of proportion to the increase in right atrial (RA) pressure (Figure 3F), suggesting that fluid loading primarily identified patients with left sided filling impairments.

Prospective Cohort

The cohort was 63% female with an average age of 52±12 years. In the prospective cohort, 6/52 (11%) had resting diastolic dysfunction and 5/52 (10%) had occult diastolic dysfunction after fluid challenge. Patients with diastolic dysfunction had a higher prevalence of diabetes mellitus, hyperlipidemia, and coronary artery disease compared with patients without occult diastolic dysfunction (Table 3), and by echocardiogram had no significant changes except for mitral in-flow E velocity and E/e′ ratio (Table 4). Univariate analysis confirmed resting E/e′ (OR 8.75, 95% CI 2.3–33, P=0.001) and E velocity (OR 7.7, 95% CI 2–29, P=0.003) were associated with occult diastolic dysfunction (Figure 5A). The optimal ROC threshold for identifying occult diastolic dysfunction in the replication cohort was E/e′ >8 (sensitivity 73%, specificity 90%) (Figure 5C).

Simultaneous echocardiography pre- and post-fluid challenge showed that resting E/e′, post-fluid E/e′, and change in E/e′ after fluid challenge all were significantly greater in patients with diastolic dysfunction compared with no diastolic dysfunction (Figure 5B). Receiver operating curve

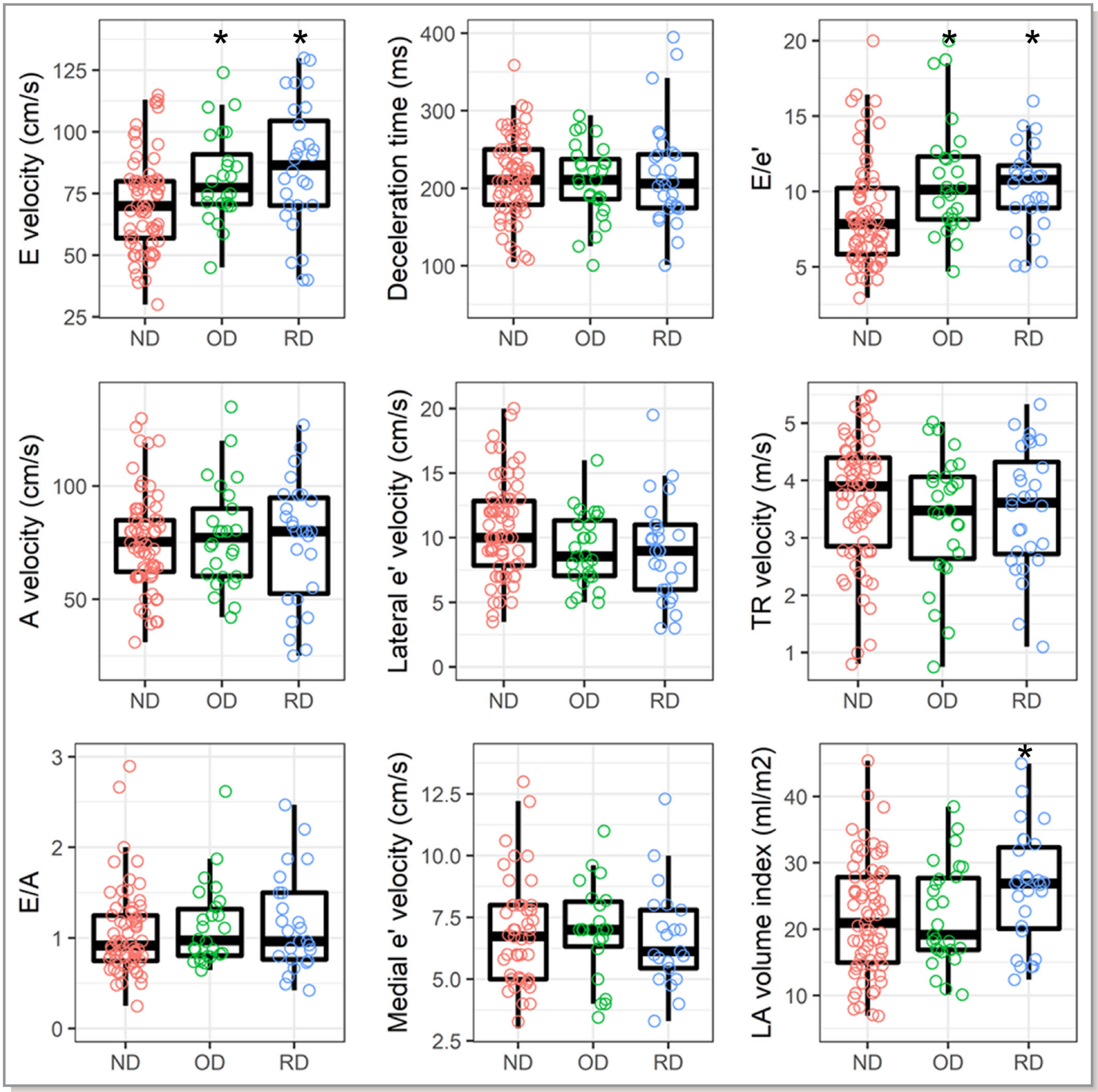

Figure 2. Diastolic function echocardiographic parameters for between patient groups with no diastolic dysfunction, inducible diastolic dysfunction, and resting diastolic dysfunction. *$P<0.05$ when compared with group with no diastolic dysfunction. LA indicates left atrial; LVTMP, left ventricular transmural pressure; ND, no diastolic dysfunction; OD, occult diastolic dysfunction; RD, resting diastolic dysfunction; TR, tricuspid regurgitation.

analysis showed that an increase in E/e′ by 6 or greater (AUC 0.69) or a post-fluid E/e′ of greater than or equal to 12 (AUC 0.90) was associated with diastolic dysfunction (Figure 5C), similar to previous studies comparing left atrial pressure to E/e′ changes in patients with hypertrophic cardiomyopathy.[28] In a univariate analysis, pre-fluid E/e′ remained significantly associated with occult diastolic dysfunction after adjustment for change in E/e′, but not post-fluid E/e′ (Figure 5D).

Discussion

In our study, the measures of mitral in-flow velocity, E velocity, and the ratio of mitral in-flow velocity and tissue doppler, E/e′, were significantly associated with occult diastolic

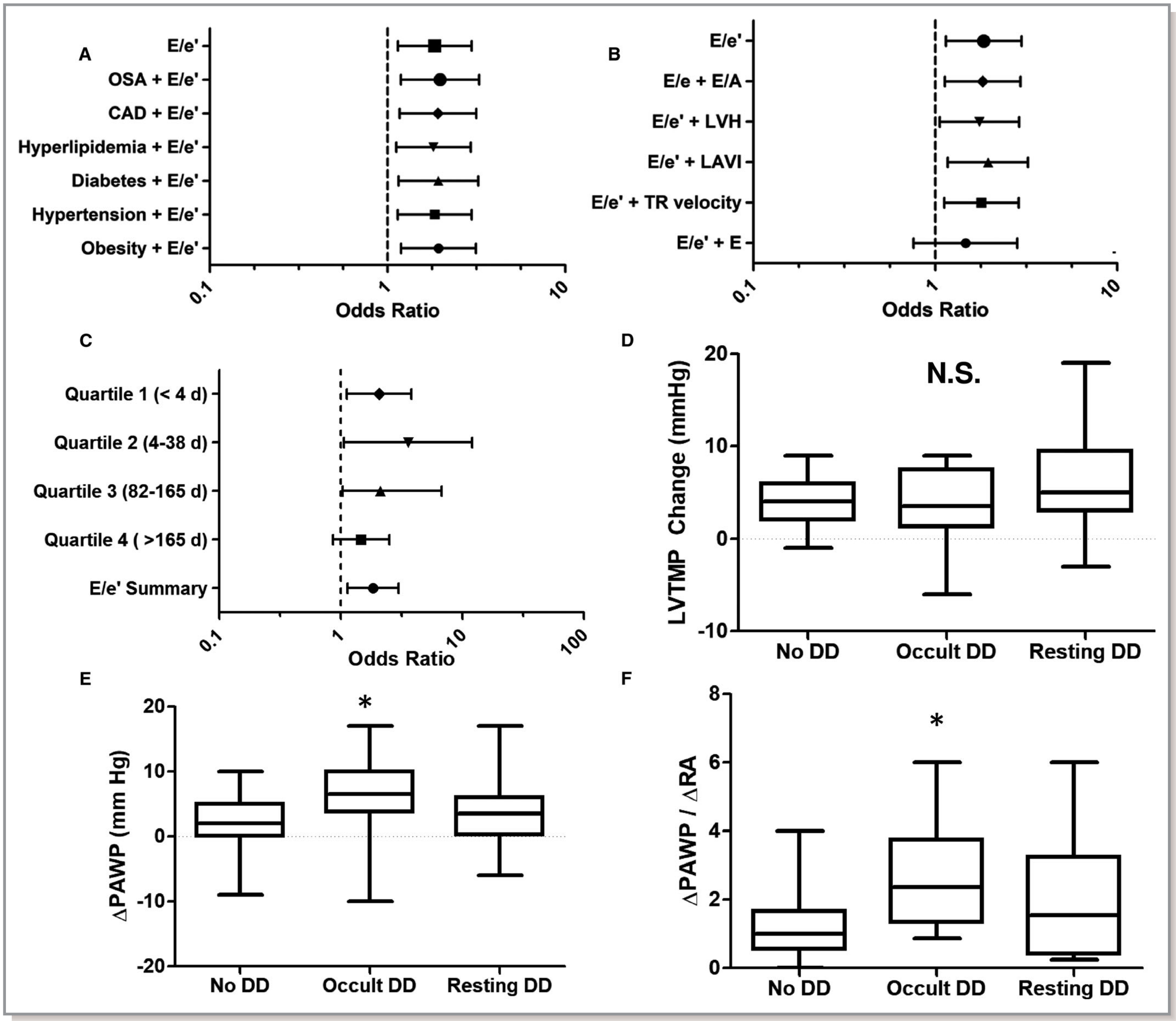

Figure 3. Univariate odds ratios of E/e′ predicting inducible diastolic dysfunction after adjusting for clinical comorbidities (**A**) and echocardiographic variables (**B**). **C**, Univariate odds of E/e′ predicting occult diastolic dysfunction separated by quartiles of time between right heart catheterization and echocardiogram. **D**, Left ventricular transmural pressure change between all 3 groups after fluid loading. **E**, Change in pulmonary arterial wedge pressure with fluid loading. **F**, Change in PAWP pressure normalized to change in RA pressure in all 3 groups. *$P<0.05$ compared with the no diastolic dysfunction group. CAD indicates coronary artery disease; DD, diastolic dysfunction; LAVI, left atrial volume index; LVH, left ventricular hypertrophy; OSA, obstructive sleep apnea; PAWP, pulmonary arterial wedge pressure; TR, tricuspid regurgitation.

dysfunction identified at the time of RHC with fluid challenge. This was confirmed both retrospectively in a cohort of patients who underwent clinically indicated echocardiography and RHC, as well as prospectively in a separate cohort of patients who underwent simultaneous echo and RHC before and after fluid challenge. The present results show that in patients referred for RHC for suspicion of PH, occult diastolic dysfunction can be identified by echocardiography of resting E/e′ >8, change in E/e′ >6 with fluid challenge, or post-fluid challenge E/e′ >12.

Previous studies have suggested mixed degrees of correlation between non-invasive and invasive measures of PAWP,[29–36] leading to controversy over the use of non-invasive PAWP estimates for identifying post-capillary pulmonary venous congestion in patients. This controversy is partially explained by studies showing the relative lack of precision, but high accuracy, in estimating PAWP non-invasively. As argued previously by D'alto et al,[37] correlation studies do not adequately distinguish between accuracy for diagnosis of elevated filling pressures and precision of

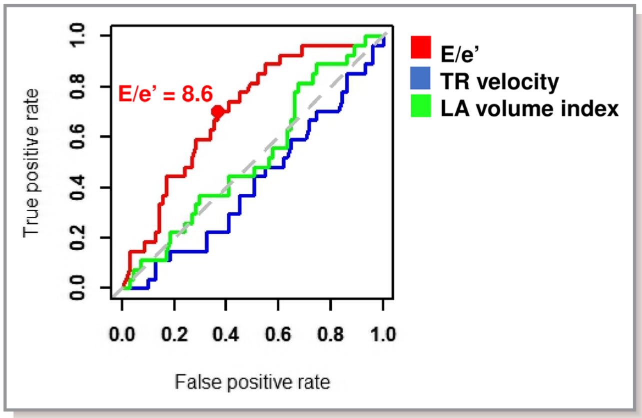

Figure 4. Receiver operating curve for each diastolic function variable shows only E/e′ as a significant predictor of inducible diastolic dysfunction. The optimal cutoff is 8.6 with area under the curve of 0.70, sensitivity of 70%, and specificity of 64%. LA indicates left atrial; TR, tricuspid regurgitation.

invasive PAWP estimation. Via Bland-Altman analysis, they showed minimal bias between invasively and non-invasively measured PAWP with a mean difference of 2±5 mm Hg between the measurements over a large range of PAWP values in their cohort. However, for any given PAWP measurement, the difference between non-invasive and invasively measured PAWP varied considerably, consistent with low precision. These findings suggest that non-invasive measurement of PAWP is accurate on a population level, or when repeated multiple times, and thus can be a valuable screening tool on a population level to identify disease conditions that require evidence of elevated PAWP as a diagnostic criterion. Our findings complement existing literature by showing that variables used in the non-invasive estimation of PAWP can also help to identify patients with diastolic dysfunction found only after a provocative maneuver such as fluid challenge.

Current American Society of Echocardiography guidelines suggest an E/e′ threshold of 14 as a parameter for determining the presence or absence of diastolic dysfunction, defined in their guidelines primarily by evidence of elevated PAWP.[3] European Society of Cardiology consensus statements have suggested a similar threshold of E/e′ ≥15 with requirement of additional echocardiogram measurements or biomarker evidence to support elevated filling pressures to make a diagnosis of diastolic dysfunction if E/e′ is between 8 and 15.[8] Our studies suggest that a lower threshold is necessary to identify patients with occult diastolic dysfunction. In particular, our study suggests that a lower E/e′ threshold may raise suspicion for diastolic dysfunction in certain conditions such as PH, where one might expect a higher prevalence of diastolic dysfunction.[38] The current echocardiographic guidelines for evaluating diastolic function

Table 3. Baseline Demographics and Hemodynamics for Patient Groups in the Validation Cohort

	Fluid Challenge Response	
	No DD	Occult or Resting DD
Demographics	n=41	n=11
Age, y	51±12	56±13
BMI	27±4	26±4
Sex (% female)	68	45
Overweight, %	49	55
Diabetes mellitus, %	7	45*
Hypertension, %	32	63
Hyperlipidemia, %	12	72*
Coronary artery disease, %	7	63*
Obstructive sleep apnea, %	7	18
Hemodynamics		
Heart rate	78±15	75±12
MAP, mm Hg	94±15	96±14
RAP, mm Hg	7±4	6±2
Mean PAP, mm Hg	36±16	34±11
PAWP, mm Hg	9±3	16±5*
TPG, mm Hg	27±16	18±9
DPG, mm Hg	15±11	8±7
PVR, Wood Units	6±5	4±2
Cardiac index, L/min per m^2	2.8±0.7	2.9±0.7
Post-fluid mean PAP, mm Hg	42±15	39±10
Post-fluid PAWP, mm Hg	12±3	22±3*

BMI indicates body mass index; DPG, diastolic pulmonary gradient; MAP, mean arterial pressure; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TPG, transpulmonary gradient.

*Represents significant differences compared with "No DD" with threshold of $P<0.05$.

do not provide guidance for identifying patients with occult diastolic dysfunction. Our findings suggest that both resting E/e′ and post-fluid challenge E/e′ can be used diagnostically to raise or decrease suspicion for occult diastolic dysfunction in these patients.

In our study, tricuspid regurgitation velocity and left atrial volume did not significantly associate with occult diastolic dysfunction. This differs from previous studies that have shown statistically significant differences between groups with HFpEF and normal controls for both parameters.[39] Our retrospective referral cohort was enriched for PH, which limited the ability to discriminate groups based on tricuspid regurgitant velocity. While left atrial volume index did differ in patients with resting diastolic dysfunction, it did not differentiate patients with occult diastolic dysfunction. While this may be a reflection of the chronicity of elevated filling pressures,

Table 4. Resting Echocardiographic Parameters for Patient Groups in the Prospective Cohort

	Fluid Challenge Response	
	No DD	Occult or Resting DD
LVOT diameter, cm	20±1.2	21±1.4
RVSP, mm Hg	58±24	51±19
TAPSE, cm	2.0±0.4	2.1±0.5
LVOT VTI, cm	20±5	22±3
TRV, m/s	3.4±0.8	3.0±0.8
IVC diameter	1.7±0.4	1.7±0.6
E velocity, cm/s	58±20	85±18*
Average e′ velocity, cm/s	10.6±4	10.2±4
E/e′	5.7±1.8	9.6±3.8

DD indicates diastolic dysfunction; E, early diastolic mitral in-flow peak velocity; e′, mitral annular tissue Doppler velocity; IVC, inferior vena cava; LVOT, left ventricular outflow tract; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; VTI, velocity time integral.
*Represents significant differences compared with "No DD" with threshold of $P<0.05$.

which is thought to result in greater left atrial remodeling with time,[40–42] limitations in the resolution of our imaging modality may also account for this finding. Other modalities such as cardiac magnetic resonance imaging have shown that left atrial volume distinguishes subsets of patients with PH,[43] although occult diastolic dysfunction was not specifically evaluated via provocative maneuvers.

We acknowledge several limitations in our study. Our retrospective cohort was derived from a referral sample with wide variation in timing between echo and right heart catheterization. However, the findings did not differ when we restricted the time interval between echocardiogram and RHC were stratified by quartile. Our retrospective cohort was also limited to patients who had both an echocardiogram and right heart catheterization data available for review, and thus exclusion of a number of patients could have affected the profile of patients with occult diastolic dysfunction. The decreased incidence of diabetes mellitus in the retrospective cohort, as an example, was not expected and inconsistent with prior studies suggesting a higher incidence of diabetes mellitus in patients with occult diastolic dysfunction.[13] We suspect this may have been related to selection bias in the current study for patients with both echocardiogram and catheterization data.

We thus replicated the findings of the retrospective cohort in a prospective cohort to address some of the limitations of the retrospective cohort. The prospective cohort included consecutive patients who underwent simultaneous catheterization and echocardiography before and after fluid loading. Thus, while not randomized to ensure equal prevalence of comorbidities, the prospective cohort likely reflects a more accurate comorbidity profile of patients with occult diastolic dysfunction that is consistent with previous reports.[13] Despite multiple differences in the baseline characteristics of patients in the retrospective and prospective cohorts, most notably of which is body mass index and the weight-adjusted volume of fluid administered, the consistency of our findings in each cohort strengthen the conclusion that E/e′ may be a useful echocardiographic marker of patients with occult diastolic dysfunction who present with pulmonary hypertension.

Our study also did not explicitly control for the operator variability in the performance of right heart catheterization between institutions, or even within institution. However, this likely reflects real world practice in that operators generally follow accepted guidelines for performance of right heart catheterization, but operator-to-operator variability would most likely only bias towards the null hypothesis by introducing an additional source of error. Thus, the significant association between E/e′ and E velocity and occult diastolic dysfunction that is consistent and reproducible between 2 separate cohorts is likely more reflective of real-world practice.

Our study was also limited in that echocardiographic parameters collected were limited to those pre-specified. A number of other parameters not investigated in this study could affect the results and warrant future investigation. Regional hypokinesis of the left ventricle could have possibly affected our measurement of E/e′, and our current study did not account for regional hypokinesis between groups. However, risk factors for hypokinesis such as coronary artery disease were not significantly different between groups. Additionally, the current study did not evaluate parameters such as interventricular septal geometry, left atrial reservoir function, or strain, all of which have been shown to contribute to left ventricular diastolic function.[44–46] Finally, while our study did exclude patients with atrial fibrillation or atrial flutter to limit influence of arrhythmia on mitral in-flow parameters, it did not explicitly exclude patients with pacemaker that could affect mitral in-flow variables.

Our study was limited to the use of fluid challenge as the provocative maneuver for identification of diastolic dysfunction. This is reflective of institutional practices. Exercise has also been used as a method of provocation with suggestions that it is a more sensitive, and possibly specific, indicator of occult diastolic dysfunction.[47–50] However, previous studies have shown that measurement of end-expiratory PAWP can lead to overestimation of PAWP.[51,52] This may account, in part, for studies that show a greater magnitude of change of PAWP with exercise as compared with fluid challenge.[50] Exercise provocation requires additional equipment that is not readily available in all cardiac catheterization laboratories. In contrast, volume expansion with saline does not require

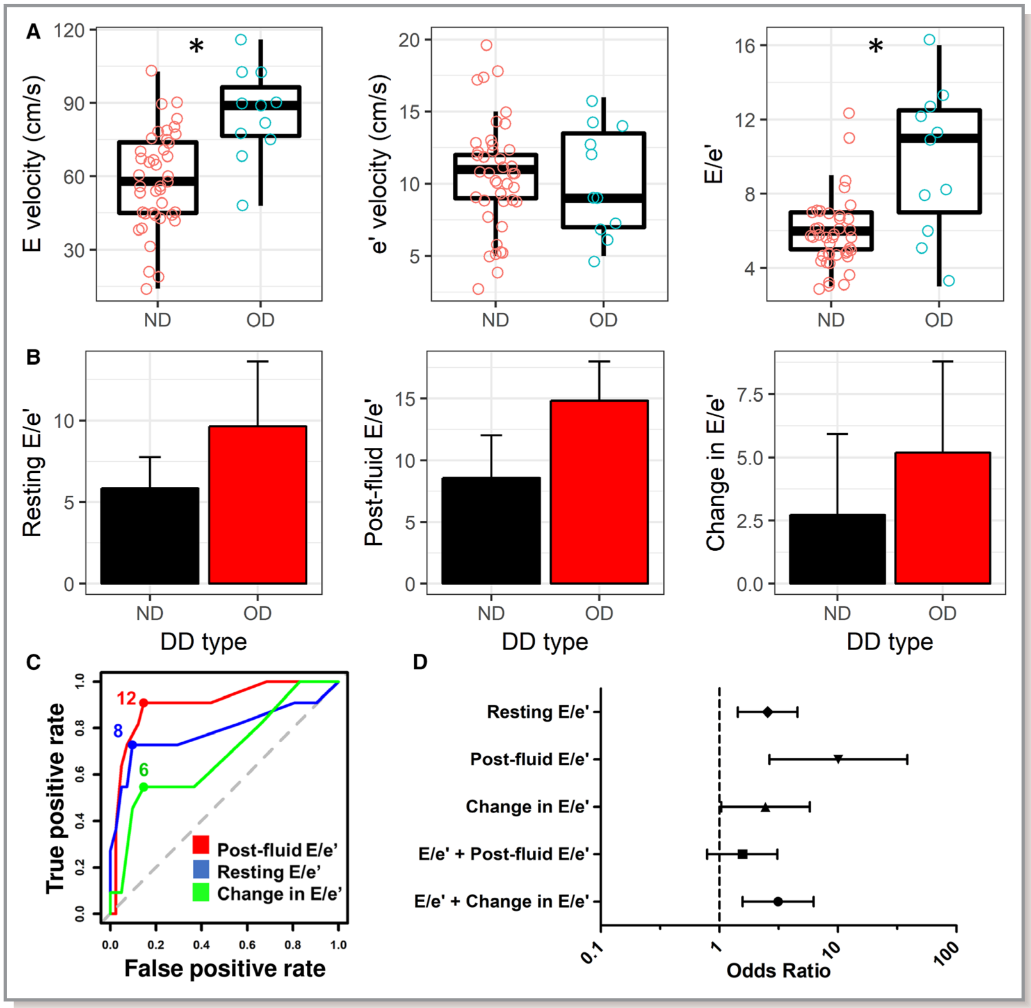

Figure 5. **A**, Diastolic function parameters mitral in-flow E velocity, mitral annular tissue doppler e′ velocity, and E/e′ ratio in patients with no diastolic dysfunction and occult diastolic dysfunction in the second cohort. **B**, Average pre-fluid resting E/e′, post-fluid E/e′, and change between resting and post-fluid E/e′ in patients with and without occult diastolic dysfunction after fluid challenge. **C**, Receiver operating curve for resting, post-fluid, and change in E/e′ between resting and post-fluid challenge as a predictor of occult diastolic dysfunction. **D**, Univariate odds ratios of resting E/e′, post-fluid E/e′, and change in E/e′ predicting occult diastolic dysfunction after fluid challenge. Resting E/e′ remains a significant predictor of occult diastolic dysfunction after adjusting for change in E/e′, but not after adjusting for resting E/e′. **P*<0.05 compared with the no diastolic dysfunction group. DD indicates diastolic dysfunction; ND indicates no diastolic dysfunction; OD, occult diastolic dysfunction.

additional equipment, remains cost effective, and is highly reproducible[12,13] with recent studies suggesting prognostic significance to an abnormal fluid challenge.[53] Thus, while potentially less sensitive, volume expansion challenge does potentially eliminate variability in measurements and may serve as a more easily standardized method of provocation.

Finally, although the patients in the retrospective cohort underwent catheterization using a clinical protocol, we manually review all hemodynamic tracings for accuracy. The measurement of left sided filling pressure can vary significantly, and our study relied on measurements of PAWP as an estimate of left-sided filling pressures. While we acknowledge limitations in this method as opposed to direct measurement of left ventricular end diastolic pressure, previous studies suggest a mean difference of 1.6 mm Hg with almost no bias in patients who had both left ventricular end diastolic pressure and PAWP measurements.[54] Direct comparison of left ventricular end diastolic pressure and PAWP was not possible in our cohort.

Conclusions

Mitral in-flow E velocity and E/e′ are associated with occult diastolic dysfunction after right heart catheterization with fluid challenge in both a large retrospective cohort and prospective cohort. A threshold of resting E/e′ >8 and a post-fluid/E/e′ ≥12 optimally identifies patients with occult diastolic dysfunction. These findings suggest that routine echocardiographic measurements may help raise suspicion for occult diastolic dysfunction. Given the important therapeutic and prognostic implications of identifying diastolic dysfunction in patients with HFpEF and PH, our findings contribute to the growing body of literature suggesting that further refinement of current guidelines may be necessary to better identify diastolic dysfunction in this patient population.

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Disclosures

None.

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