Review Article

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Echocardiographic evaluation of diastolic function in the setting of pulmonary hypertension

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Abstract
Heart failure due to diastolic dysfunction and pulmonary hypertension are frequent comorbid conditions with significant morbidity and mortality. Identifying the presence and etiology of diastolic dysfunction in the setting of pulmonary hypertension remains challenging despite profound therapeutic and prognostic implications. Additionally, there is little guidance in identifying and parsing etiology of diastolic dysfunction in patients found to have pulmonary hypertension. This review discusses the complex interplay between left ventricular diastolic dysfunction and pulmonary hypertension. With an explicit focus on the use of echocardiography for determination of diastolic dysfunction and etiology of pulmonary hypertension, this review also provides a comprehensive review of the literature and provides a framework by which to assess diastolic dysfunction echocardiographically in the setting of pulmonary hypertension.

Keywords
pulmonary hypertension, diastolic dysfunction, echocradiography

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Introduction

With a growing incidence and prevalence worldwide, heart failure remains a condition with limited treatment options and poor prognosis.[1,2] Left ventricular diastolic dysfunction, defined by impaired relaxation of the myocardium, is a hallmark of heart failure in patients who present with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF).[3] The presence of even asymptomatic diastolic dysfunction portends a worse prognosis for patients regardless of the underlying etiology.[4–6] Pulmonary hypertension frequently coexists with left heart diastolic dysfunction.[7–10] Since both pulmonary hypertension and diastolic dysfunction can be a primary cause of symptoms such as exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and exercise intolerance, distinguishing the *primary* cause of symptoms and pathology carries significant prognostic and therapeutic implications.

A key determinant in the primary cause of symptoms in patients with both diastolic dysfunction and pulmonary hypertension is the evaluation of left atrial filling pressures and left ventricular end-diastolic pressures (collectively referred to as left sided filling pressures).[8,11–13] Invasive cardiac catheterization with or without provocation by exercise or fluid challenge is the gold standard for measuring left-sided filling pressures; however, it can be associated with misclassification of patients with concomitant pulmonary hypertension due to technical/interpretative errors or lack of evidence of elevated filling pressures in the absence of provocative maneuvers.[5,12,14,15] Non-invasive assessment of left sided filling pressures allows for a more global structural assessment of the heart to provide additional clues that may aid in the differentiation of the primary cause of symptoms. In addition, non-invasive approaches eliminate periprocedural risk, potentially reducing health care costs and allowing for a potential method for serial monitoring of response to therapies. While recent guidelines have created a more simplified and unified approach to the non-invasive

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assessment of diastolic function in echocardiography with a focus on a disease-oriented approach, there is limited guidance on and data supporting the accurate assessment of diastolic function in pulmonary hypertension.[3]

Thus, the following review aims to further discuss this complex interplay between diastolic dysfunction and pulmonary hypertension, as well as provide a framework by which diastolic function can more accurately be estimated in the setting of pulmonary hypertension.

Complex interplay between left ventricular diastolic function and pulmonary vascular function

While many previous studies have focused on the complex coupling between the right ventricle and pulmonary artery that is well studied in the setting of pulmonary hypertension,[16,17] there also exists a complex interaction between the left ventricle and pulmonary circulation.

A number of studies have reviewed the role of left ventricular impaired relaxation resulting in passive congestion and chronic pulmonary vascular changes.[18,19] Other studies have also shown that the chronic pulmonary vascular changes, whether primary or secondary, can themselves impair diastolic relaxation of the myocardium globally.[8,18,20–22] Additionally, the presence of pulmonary hypertension is associated with progressive structural changes on both the right and left side of the heart.[23,24]

Pulmonary hypertension as a consequence of left ventricular diastolic dysfunction

The most commonly understood mechanism by which left ventricular diastolic dysfunction and pulmonary hypertension coexist is in the setting of pulmonary hypertension secondary to left sided heart disease. Pulmonary hypertension is classically divided into five groups by the World Health Organization (WHO) (Table 1),[25] with group 2 representing patients with pulmonary hypertension due to elevated left heart filling pressures that are thought to be the primary cause of pulmonary hypertension. Defined invasively by a measured mean pulmonary artery pressure (PAP) $\geq$ 25 mmHg and a mean pulmonary arterial wedge pressure (PAWP) $>$ 15 mmHg at rest, group 2 PH patients are further subdivided into patients with isolated post-capillary pulmonary hypertension (Ipc-PH) and combined pre- and post-capillary pulmonary hypertension (Cpc-PH).[26] The latter condition is characterized by the development of pulmonary vascular remodeling leading to increased pulmonary vascular resistance,[27] Group 2 PH is the most prevalent form of pulmonary hypertension in developed countries and is rapidly becoming the most prevalent form of pulmonary hypertension worldwide,[11,25,28] and studies utilizing provocative maneuvers such as exercise or fluid challenge with right heart catheterization suggest that the true prevalence of group 2 PH may be underestimated due to misclassification (Figs. 1 and 2).[11,12,29] A number of studies have now evaluated the prevalence of occult post-capillary pulmonary hypertension in patients who are initially diagnosed with pulmonary arterial hypertension (PAH). In one study of 287 patients who all underwent fluid challenge for evaluation of pulmonary hypertension, 22% of them were found to have elevated PAWP $\geq$ 15 mmHg after fluid challenge.[11] In another cohort of 53 patients with scleroderma-associated pulmonary hypertension, 45% of patients had evidence of occult post-capillary pulmonary hypertension after fluid challenge.[30] However, when using a stricter threshold for an

Table 1. Pulmonary hypertension group classifications, according to the World Health Organization.

Group	Pathogenesis	Examples
1 – Pulmonary Arterial Hypertension	Primary pulmonary arterial remodeling	Idiopathic, heritable (BMPR2, Alk-1, ENG, SMAD9, CAV1, KCNK3), medication-induced, disease associated (e.g. scleroderma, HIV, portopulmonary hypertension), congenital heart disease, schistosomiasis
2 – Pulmonary Hypertension from Left Heart Disease	Chronic congestion leading to increased pulmonary pressures and vascular remodeling	Congestive heart failure, chronic valvular disease (mitral, aortic), congenital outflow obstructions
3 – Pulmonary Hypertension due to Primary Pulmonary Disease	Chronic pulmonary vascular destruction or hypoxic constriction	Chronic obstructive lung disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, high altitude related, developmental lung disorders
4 – Chronic Thromboembolic Pulmonary Hypertension	Pulmonary thromboembolisms cause increase in pulmonary pressures	Recurrent pulmonary embolisms, possible hypercoagulability
5 – Pulmonary Hypertension Due to Systemic Disease	Various systemic vasculopathies or inflammatory conditions that lead to pulmonary vascular disease	Hematologic disorders (hemolytic anemia, myeloproliferative disorders, splenectomy), Systemic disorders (Sarcoidosis, pulmonary histiocytosis), Metabolic disorders (glycogen storage diseases, Gaucher disease, thyroid disorders), Others (segmental pulmonary hypertension, chronic renal failure, tumor obstruction, fibrosing mediastinitis)

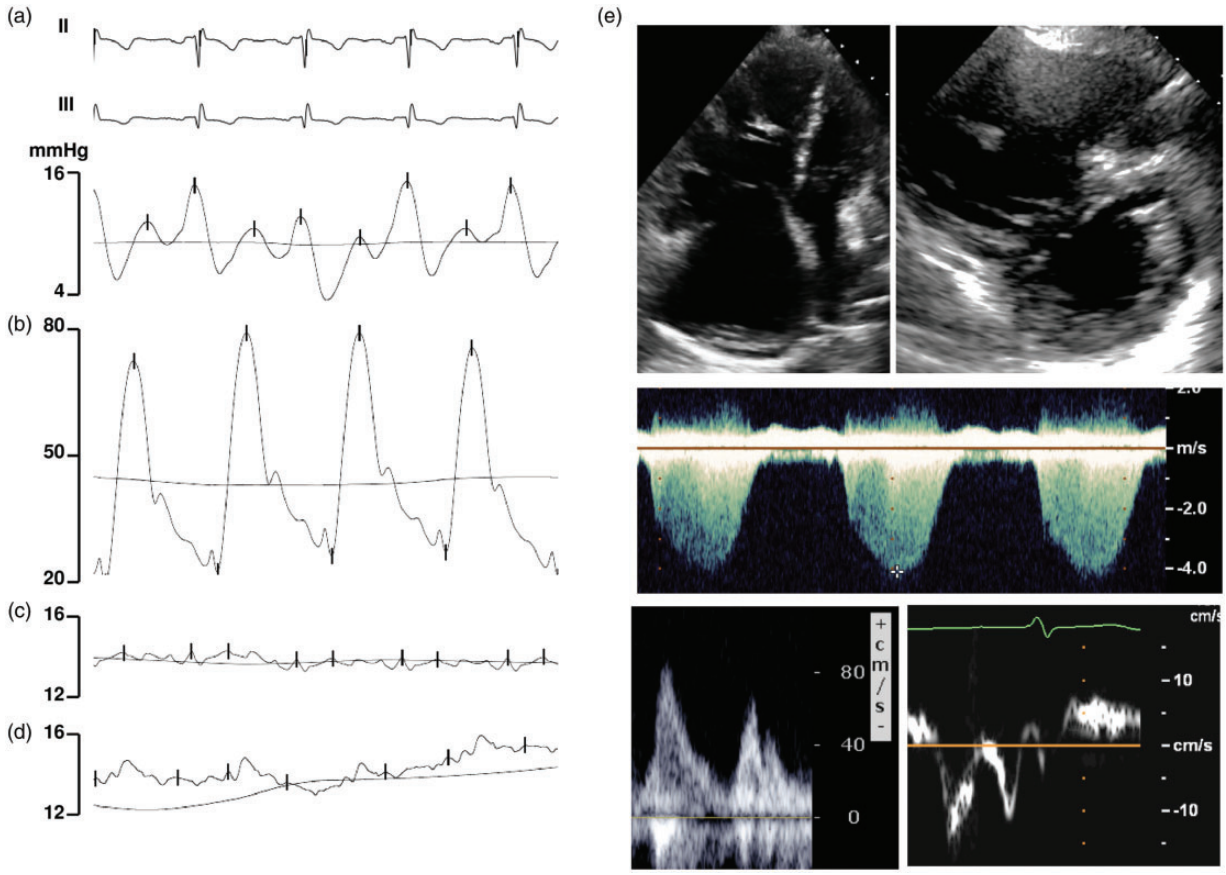

Fig. 1. Right heart catheterization in a patient with pulmonary arterial hypertension shows normal RAP (a), elevated pulmonary pressures (b), normal PAWP at rest (c), and no change in PAWP with fluid challenge (d). The same patient on echocardiogram shows evidence of right atrial and ventricular enlargement, septal bowing, elevated tricuspid regurgitation velocity, normal mitral in-flow velocity pattern, and normal mitral annular tissue doppler velocity patterns (e).

abnormal fluid challenge, D'Alto et al. found, in their cohort of 190 patients, that about 7% of patients would be reclassified as having post-capillary pulmonary hypertension.[29] All in all, the presence of patients with occult post-capillary pulmonary hypertension has decreased the accuracy of current estimates of prevalence. Notably, current guidelines do not yet routinely recommend provocative challenge for identifying patients with occult post-capillary pulmonary hypertension.

The prevalence is further affected by the accepted threshold of 25 mmHg. There is substantial data suggesting that patients with "borderline" pulmonary hypertension have a higher risk of mortality and hospitalization.[31–35] Many of these patients have increased left sided filling pressures by cardiac catheterization,[32] and left atrial and ventricular structural changes,[11] suggesting left ventricular diastolic dysfunction as the driver of pathology.

Impaired left ventricular diastolic filling as a result of PAH

It has been noted that a subset of patients who are diagnosed with PAH also exhibit left ventricular diastolic dysfunction. Two possible mechanisms have been proposed to contribute to this pathogenesis.

One mechanism that has been proposed is impaired diastolic filling of the left ventricle as a consequence of significant pre-capillary pulmonary hypertension. This occurs due to ventricular interdependence, a phenomenon in which left and right ventricular volumes/pressures are interdependent due to the presence of an interventricular septum and pericardial sac that limits volume expansion of the heart.[20–22,36–38] Under normal conditions, this interdependence is minimal and without clinical consequences, but significant pulmonary hypertension can significantly impair left ventricular diastolic filling by significantly altering the geometry of the left ventricle due to septal bowing from a pressure and volume overloaded right ventricle (Fig. 3). Notably, impaired ventricular filling as a result of enhanced ventricular interdependence is functionally distinct from intrinsic impaired myocardial relaxation. In addition, prior studies investigating this method have shown up to a 3 mmHg increase in PAWP.[14,29,39,40] Thus, while it is important to consider these changes in filling pressures when determining the etiology of pulmonary hypertension, ventricular interdependence may not be the sole cause of

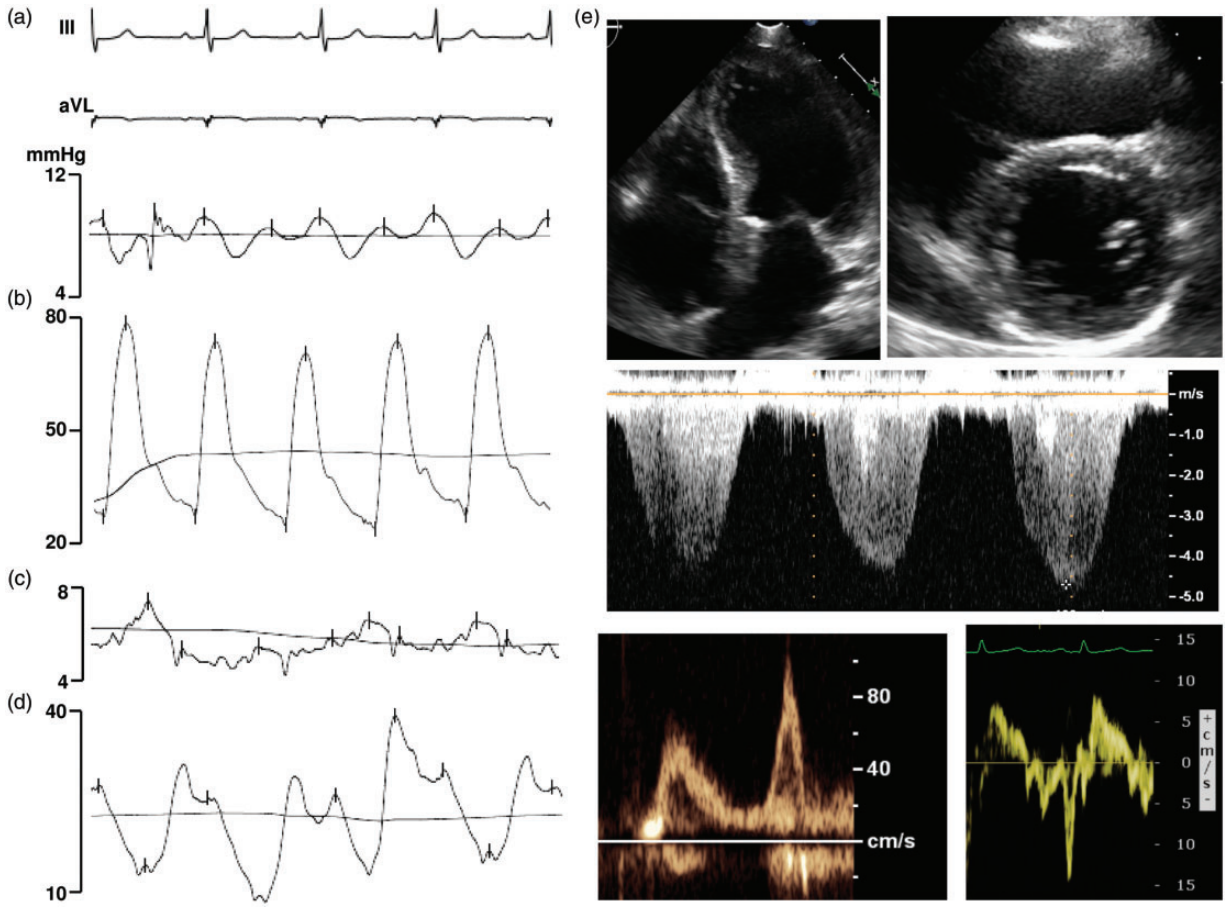

Fig. 2. Right heart catheterization in a patient with inducible post-capillary pulmonary hypertension shows normal RAP (a), elevated pulmonary pressures (b), and normal PAWP at rest (c). Notably, there is a marked increase in PAWP with fluid challenge (d). Echocardiogram shows evidence of a left ventricle larger than right, left atrial enlargement, normal septal shape, elevated tricuspid regurgitation velocity, abnormal mitral in-flow velocity pattern, and abnormal mitral annular tissue doppler velocity patterns (e).

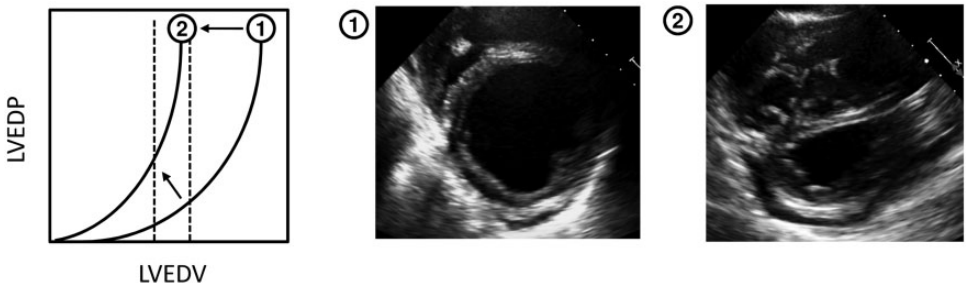

Fig. 3. Due to ventricular interdependence of the right and left ventricle, pressure and volume overload in the setting of pulmonary arterial hypertension can lead to impaired diastolic filling of the left ventricle. This results in a pressure volume relationship under normal conditions (1) that shifts to increased pressure for any given volume (2).

significant left ventricular diastolic dysfunction in patients with PAH.

The second mechanism that has been proposed in various studies is common genetic pathogenesis that gives rise to both pulmonary vascular remodeling and cardiomyopathy. This is supported by a number of studies that have found contractile deficits in isolated myocytes from the left ventricle and septum of patients with idiopathic PAH (IPAH) as well as systemic sclerosis-associated PAH.[41,42] In addition, in a cohort of patients with IPAH, heritable PAH, connective tissue disease PAH, and chronic thromboembolic disease-related PAH, non-invasive assessment of LV diastolic function by cardiac magnetic resonance imaging (cMRI) suggested global impairment in LV diastolic

function in patients with PAH compared with controls.[43] While it is possible that diastolic dysfunction is an acquired change in the LV of patients with PAH, LV diastolic impairment has also been identified in children with PAH by echo.[44] While cardiac manifestations of PAH have been studied in patients in certain forms of PAH,[37] the overlap between diastolic cardiomyopathy and PAH remains incompletely understood.

Non-invasive evaluation of diastolic function by echocardiography

Non-invasive evaluation of diastolic function is possible through multiple imaging modalities.[45] In particular, cardiac MRI is increasingly being utilized for assessment of cardiac structure and function. This has been discussed extensively in a number of recent review articles,[46,47] although not studied specifically in the setting of pulmonary hypertension. The present review focuses on echocardiography as it is currently the most commonly used method for assessing diastolic function non-invasively.

Recommendations for echocardiographic determination of diastolic function have recently been updated, with increased emphasis on high specificity of diagnosis and reproducibility of measures.[3] The four recommended variables that are reproducibly associated with diastolic dysfunction are the mitral annular tissue Doppler velocity e' (septal e' < 7 cm/sec and/or lateral e' < 10 cm/sec), left atrial maximal volume index (> 34 ml/m^2), average mitral in-flow velocity to annular tissue doppler velocity ratio (E/e' > 14), and peak tricuspid regurgitant velocity (>2.8 m/s). Notably, the recommended cutoffs are based on prior studies showing high specificity for diastolic dysfunction.[48] Further characterization of the severity, or grade, of diastolic dysfunction is then based on the number of abnormal parameters as well as the E velocity and E/A ratio (Fig. 4).

The applicability, accuracy, and performance of these and prior non-invasive algorithms for estimation of diastolic function has been a point of significant controversy in the literature. Studies have highlighted the cutoffs for variables as misclassifying both unaffected and affected individuals, and they have pointed out the pitfalls in a static cutoff that does not account for dynamic normal changes that occur with aging.[49] Epidemiologic studies have also highlighted the significant differences in prevalence of diastolic dysfunction various population cohorts between prior and current guidelines (Table 2), with variation in the prevalence of diastolic dysfunction up to 30% between different guidelines and a significant proportion still being labeled as "indeterminant" based on guidelines.[50,51] The ability of the guidelines to accurately distinguish normal vs abnormal left sided filling pressures has shown mixed results. While some studies have suggested high degree of correlation between non-invasive and invasive measures of left sided filling pressures in patients,[13,52–54] other studies have suggested a modest correlation at best.[55–58] A key difference may be that the studies that were enriched for patients with a known predisposition to abnormal left sided filling pressures, i.e. heart failure, showed poorer performance of non-invasive correlates. Of particular note is a systematic review of patients from 9 studies of patients with diastolic heart failure to compare invasive hemodynamics with echocardiographic parameters, and 18 studies to compare

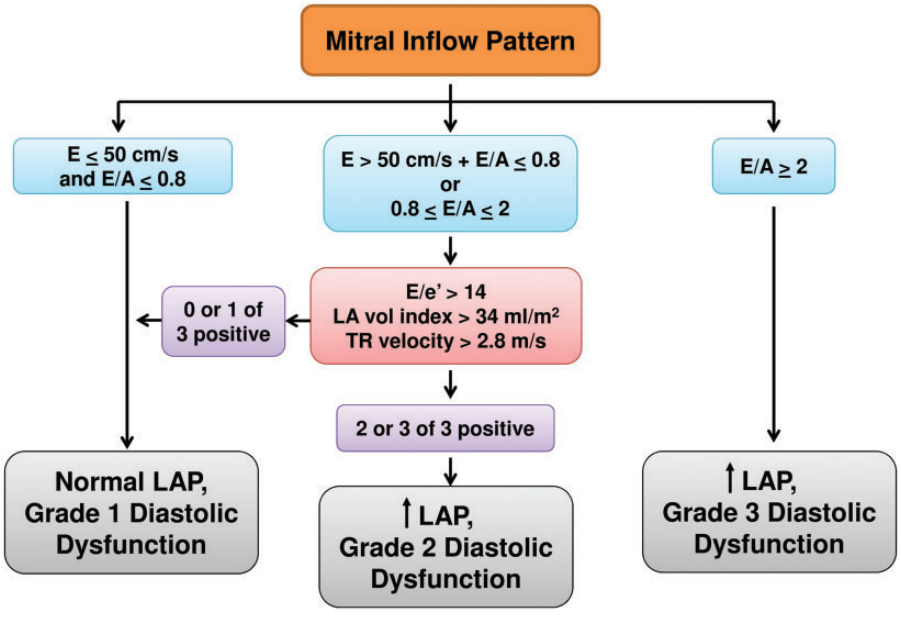

Fig. 4. Determination of diastolic function and left atrial pressure estimation by echocardiogram, adapted from the American Society of Echocardiography 2016 guidelines. LAP: left atrial pressure estimate.

Table 2. Prior algorithms proposed for non-invasive estimation of diastolic function.

Algorithm	Criteria
VALIDD	Age 45–54: lateral e' < 10
	Age 55–65: lateral e' < 9
	Age > 65: lateral e' < 8
Redfield	No DD: 0.75 < E/A < 1.5, DT > 140, and E/e' < 10;
	Mild DD: E/A < 0.75, E/e' < 10
	Moderate DD: 0.75 < E/A < 1.5, DT > 140, and E/e' >= 10;
	Severe DD: E/A > 1.5, DT < 140, and E/e' >= 10
	Indeterminate: All others
ASE 2009	No DD: Lat e' >= 10 and septal e' >= 8
	DD: Lat e' < 10, septal e' < 8, and LAVI > 34
	Grade 1 DD: DD as above, E/A < 0.8, and DT > 200
	Grade 2 DD: DD as above, 0.8 < E/A < 1.5, and 160 < DT < 200
	Grade 3 DD: DD as above, E/A > 2, and DT < 160
ASE 2016	Four factors: LAVI >= 34, septal e' < 7, lateral e' < 10, and TR vel > 2.8
	No DD: < 2 factors present
	DD: >2 factors present
	Indeterminate: 2 factors present

DD: diastolic dysfunction; DT: deceleration time; LAVI: left atrial volume index.

echocardiographic parameters to clinical outcomes.[55] In aggregate, the systematic review found only modest evidence to support the use of current guidelines in the assessment of elevated left sided filling pressures using average E/e' with a pooled correlation coefficient of 0.56 in all 9 studies. There was additionally a modest association between E/e' and major adverse cardiac events or heart failure hospitalization (pooled hazard ratio of 1.05 per unit increase in E/e'). This would suggest that further refinement of the thresholds of diastolic function variables may be necessary to more accurately identify abnormal left sided filling pressures in patients with a higher pre-test probability for abnormal left sided filling pressures, i.e. patients who suffer from heart failure or post-capillary pulmonary hypertension.

Pitfalls in diastolic function assessment: tricuspid regurgitation velocity

Although used in current algorithms to identify the presence or absence of diastolic dysfunction, tricuspid regurgitant velocity, when detectable, is elevated in all etiologies of pulmonary hypertension, thus limiting its specificity.[8,18,20–22,35] The classic approach to non-invasive estimation of pulmonary pressures is the use of a tricuspid regurgitant velocity using Bernoulli's equation. When added to an estimation of the right atrial pressure by assessment of the inferior vena cava (IVC), this pressure reasonably approximates invasively measured pulmonary artery systolic pressure.[59,60] When simultaneously measured and interpreted by readers with high inter-reader reproducibility, the correlation between TR velocity derived and invasively measured PA systolic pressures is high.[59,61,62] However, in clinical populations, this correlation declines to 0.6–0.8.[63–65] This is thought to be due to a number of pitfalls in the use of tricuspid regurgitant velocity as the sole determinant of pulmonary artery pressures. In conditions of a compensated right ventricle in the setting of high pulmonary and right ventricular pressures, and in conditions of equalization of pressures between the right atrium and right ventricle, tricuspid regurgitant velocity may be artificially low, and may underestimate the degree of pulmonary hypertension. Additionally, the estimation of pulmonary pressures is dependent on accurate assessment of the right atrial pressure by IVC assessment, which has diagnostic limitations. The presence of any primary right sided valvular disease can further affect accurate assessment of pulmonary pressures by this method. Finally, the TR velocity envelope is often incomplete or "cut-off" in severe TR, leading to underestimation of PA systolic pressure.[63,65–68]

Pitfalls in diastolic function assessment: left atrial pressure estimation in pulmonary hypertension

One of the seminal studies that formulated the basis of the guidelines for assessment of diastolic dysfunction due to pulmonary hypertension studied 70 patients with idiopathic pulmonary hypertension and 35 normal control patients who underwent simultaneous right heart catheterization and echocardiography.[69] The study importantly noted the difference between groups in the ratio of mitral in-flow E velocity and mitral annular tissue velocity e' (E/e') if the tissue doppler velocity was measured on the septal or lateral aspect of the mitral annulus. Ruan et al. showed that the septal E/e' was universally reduced in patients with idiopathic pulmonary hypertension when compared with controls, but lateral E/e' was no different.[69] They also suggested that lateral E/e' correlated well with a normal or reduced PAWP, although correlation coefficient was only 0.45. On the basis of this study, the most recent diastolic function guidelines suggest using only lateral E/e' in the presence of pulmonary hypertension to determine cardiac vs non-cardiac etiology.[3] While a seminal study in the non-invasive evaluation of diastolic function in pulmonary hypertension, this study has a number of limitations. All patients had idiopathic pulmonary hypertension, and their delineation did not account for subsequent observations that a subset of these patients actually have diastolic dysfunction when subjected to provocative maneuvers.[11] In addition, the correlation, which was modest at best based on a coefficient of 0.45, correlated highly with low or normal PAWP. Thus, the study did not shed light on the accuracy of lateral E/e' in estimating an abnormal left sided filling pressure in pulmonary hypertension.

Recently, Leung et al. has evaluated the accuracy of the 2016 ASE guidelines in estimating elevated resting left sided

filling pressures in the setting of suspected pulmonary arterial hypertension.[58] Over 8 years, 94 patients were identified with resting echocardiogram and invasive right heart catheterization within 3 months of each other. The recommend algorithm for estimating elevated left sided filling pressures had a sensitivity of 89.5% and negative predictive value of 81.8% in identifying elevated PAWP, but 100% sensitivity and negative predictive value in identifying elevated LVEDP. However, the algorithm had low specificity (39% for PAWP and 32% for LVEDP).[58] Similar to the study by Ruan and colleagues, Leung et al. relied on resting invasive measurements and did not account for patients in whom provocative maneuvers uncovered occult diastolic dysfunction.[11,14] Thus, while promising, future work including further refinement of recommend cutoffs and prospective validation in other cohorts is necessary.

Refined algorithms for distinction of pre- and post-capillary pulmonary hypertension

The greatest sensitivity and specificity for detection of left ventricular diastolic dysfunction in the setting of pulmonary hypertension have been reported using multi-variate and multi-modality algorithms (Table 3).

Bonderman et al. identified a non-invasive algorithm that utilized the tricuspid annular plane systolic excursion (TAPSE), visual inspection of right ventricular function, and inferior vena cava (IVC) diameter as echocardiographic distinguishing factors of pulmonary arterial hypertension.[70] When combined with electrocardiographic (ECG) findings of right heart strain and biomarker evidence of elevated NT-pro B-natriuretic peptide levels, the sensitivity for pulmonary arterial hypertension was 100% but specificity was only 19.3%.[70] Condliffe et al. utilized a combination of the tricuspid regurgitant velocity and measured diameters of the RV, LV, aorta, and pulmonary artery by computed tomography (CT) as a method to distinguish pulmonary arterial hypertension in patients with scleroderma.[71]

Opotowsky et al. developed a non-invasive algorithm for identifying the subset of patients with elevated pulmonary pressures by echocardiogram that likely have PAH. Using an estimation of the left atrial pressure (LAP) based on E/e' ratio, left atrial (LA) dimension, pulmonary artery acceleration time, and the presence or absence of mid-systolic notching in the right ventricular outflow tract (RVOT) pulse wave doppler signal, they were able to identify patients with PAH with 100% sensitivity and 62.3% specificity.[72]

An alternative non-invasive algorithm using echocardiography reported by D'Alto et al. used the identification of the apex forming ventricle, left ventricle eccentricity index, the presence or absence of a dilated IVC, and E/e' ratio to predict pre- vs post-capillary pulmonary hypertension.[73] Based on these factors, D'Alto et al. reported a sensitivity of 77.5% and specificity of 67.9% for pulmonary arterial hypertension. When compared with the Opotowsky algorithm within their cohort of patients, D'Alto's algorithm showed improved performance (area under ROC 0.756 vs 0.645, $P = 0.0021$).[73]

Notably, many of the listed algorithms focused on structural echocardiographic findings and did not rely on variables used in the measure of diastolic function, with the exception of measures of E/e' and left atrial dimension.

Table 3. Various non-invasive algorithms for differentiating pre- and post-capillary pulmonary hypertension.

Algorithm	Performance for Pre-capillary PH	Criteria
Opotowsky et al.[72]	Sensitivity: 100% Specificity: 62.3% PPV: 69.3%	Score Based: DD - lower score, PAH - higher score E/e' > 10: −1 LA AP dimension > 4.5: −1 LA AP dimension < 3.5: +1 RVOT mid-systolic notch or AT < 80: +1
Bonderman et al.[70]	Sensitivity: 100% Specificity: 19%	Post-capillary PH unless following criteria met: 1. Suspicion of pre-capillary PHTN by TTE (elevated PASP, RV dysfunction, no LVH) 2. Associated medical condition to suggest pre-capillary PHTN 3. Presence of RV strain on ECG 4. BNP <= 80
Condliffe et al.[71]	Sensitivity: 98% Specificity: 58% PPV: 85% NPV: 92%	Regression-based equation to identify pre-capillary PH using following variables: 1. PASP by TTE 2. PA/aorta diameter ratio on CT 3. RV/LV dimension ratio on CT
D'Alto et al.[73]	Sensitivity: 77.5% Specificity: 67.9%	Score Based: DD - lower score, PAH - higher score 1. RV > LV size: 3 2. LV eccentricity index > 1.2: 4 3. Non-collapsible dilated IVC: 10 4. E/e' < 10: 16 5. RV forming apex: 1

Many of the measured variables, such as the determination of RV forming apex and eccentricity index, are not routine measures made in everyday clinical practice and may limit the widespread adoption of these algorithms into everyday practice. Most importantly, the algorithms above focus on identifying the presence of *resting* pulmonary arterial hypertension. As a significant subset of patients identified initially as pulmonary arterial hypertension likely have inducible post-capillary pulmonary hypertension upon provocative testing, more investigation will be needed to evaluate these and other algorithms in the growing cohort of patients with inducible pulmonary hypertension.[11,12]

Emerging modalities for assessment of diastolic function: strain imaging and diastolic stress testing

Strain imaging is increasingly used for assessment of subclinical cardiac dysfunction in various patient populations.[74–76] There has also been an emerging role for strain imaging in quantifying and identifying regions of diastolic function in the myocardium.[77] Measure of strain by ultrasonography is thought to be a surrogate measure of deformation, and strain rate is a surrogate measure of rate of deformation. In a study by Kasner et al. of 33 patients who underwent strain imaging echocardiography and invasive catheterization for pressure-volume loop analysis simultaneously, LV global strain rate was reduced in patients with diastolic dysfunction compared with controls. Additionally, LV global strain rate during early diastole and isovolumic relaxation correlated with invasively measured left ventricular relaxation constant τ, LV end diastolic pressure, and LV stiffness constant β.[77] Strain imaging in pulmonary hypertension has been used to study the mechanics of the right ventricle and response to therapy,[78–80] but this technology has not been used to study the left ventricle or distinguish pre- vs post-capillary pulmonary hypertension in the literature.

Similarly, strain imaging has been utilized to study atrial mechanics as a method by which to identify patients with abnormal cardiovascular hemodynamics. In a patient study of 69 patients, which included both patients in sinus rhythm and with atrial fibrillation, speckle tracking echocardiography (STE) was utilized to evaluate contractile function of the left atrium and compared with invasive left and right heart catheterization-derived measurements of intracardiac pressures.[81] While no differences were noted in patients with atrial fibrillation, atrial peak positive strain of less than 16% in patients in sinus rhythm was significantly predictive of a PAWP $\geq$ 18 mmHg, and more predictive than non-invasive estimates such as E/e'. This has further been studied in 49 patients, 45 of whom had pulmonary hypertension (22 of them with pulmonary arterial hypertension, 19 with left sided heart disease as the cause of pulmonary hypertension, 1 with chronic thromboembolic pulmonary hypertension).[82] Left atrial strain rate was used to derive a non-invasive estimate of PAWP, and the resulting PVR correlated strongly with catheter-derived measurements (sensitivity 85%, specificity 74%), suggesting that left atrial strain can be a useful measure of left sided filling pressures and pulmonary vascular resistance. While very promising, current limitations of this technology remain the lack of uniform algorithms for measuring strain as well as a lack of consensus on various cutoffs for determining normal vs abnormal strain.

Based on previous studies showing that provocative maneuvers such as fluid challenge or exercise can identify patients with occult post-capillary pulmonary hypertension that otherwise would have been classified as having pulmonary arterial hypertension,[11,12] non-invasive stress testing for evaluation of diastolic function has previously been studied in the setting of pulmonary hypertension.[7] Studies have shown that stress, via modalities such as exercise, can elicit changes in estimated pulmonary artery pressures,[83] tricuspid regurgitation, right and left ventricular functional changes,[84] and changes in Doppler based estimates of left ventricular filling pressures.[85] However, the application of this approach to the distinction of pre- and post-capillary pulmonary hypertension remains an area of investigation. Limitations of this technology remain technical challenges in obtaining accurate data and feasibility of upscaling this technology to serve as a broad screening tool for all patients with pulmonary hypertension.

Conclusions

Distinction of pulmonary hypertension due to left ventricular diastolic dysfunction and pulmonary arterial hypertension has both prognostic and therapeutic implications. Non-invasive methods to differentiate these sub populations offers the opportunity for better screening and monitoring of therapeutic efficacy without the risks of invasive procedures. Despite multiple non-invasive algorithms proposed for identification for distinguish pre- and post-capillary pulmonary hypertension, future studies are necessary to evaluate these algorithms in the growing subset of patients who have evidence of diastolic dysfunction only after provocation. With the growing prevalence of pulmonary hypertension worldwide and the increasing therapeutic implications of identification of the subtype of pulmonary hypertension in patients, reliable non-invasive identification of diastolic dysfunction in pulmonary hypertension may have profound impact on diagnosis and management.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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References

1. Kovács SJ. Diastolic function in heart failure. *Clin Med Insights Cardiol* 2015; 9s1: CMC.S18743.
2. Savarese G and Lund LH. Global public health burden of heart failure. *Card Fail Rev* 2017; 3: 7–11.
3. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; 29: 277–314.
4. Wan S-H, Vogel MW and Chen HH. Pre-clinical diastolic dysfunction. *J Am Coll Cardiol* 2014; 63: 407–416.
5. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction. *Circulation* 2016; 134: 73–90.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. *J Am Coll Cardiol* 2013; 62: e147–e239.
7. Pellikka PA, Nagueh SF, Elhendy AA, et al. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr* 2007; 20(9): 1021–1024.
8. Lam CSP, Roger VL, Rodeheffer RJ, et al. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol* 2009; 53: 1119–1126.
9. Fayyaz AU, Edwards WD, Maleszewski JJ, et al. Global pulmonary vascular remodeling in pulmonary hypertension associated with heart failure and preserved or reduced ejection fraction. *Circulation* 2017; 137(17): 1796–1810 .
10. Strange G, Playford D, Stewart S, et al. Pulmonary hypertension: prevalence and mortality in the Armadale echocardiography cohort. *Heart* 2012; 98: 1805–1811.
11. Robbins IM, Hemnes AR, Pugh ME, et al. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Hear Fail* 2014; 7: 116–122.
12. Andersen MJ, Olson TP, Melenovsky V, et al. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Hear Fail* 2015; 8: 41–48.
13. Andersen OS, Smiseth OA, Dokainish H, et al. Estimating left ventricular filling pressure by echocardiography. *J Am Coll Cardiol* 2017; 69: 1937–1948.
14. Borlaug BA. Invasive assessment of pulmonary hypertension: time for a more fluid approach? *Circ Heart Fail* 2014; 7: 2–4.
15. Rosenkranz S and Preston IR. Right heart catheterisation: best practice and pitfalls in pulmonary hypertension. *Eur Respir Rev* 2015; 24: 642–652.
16. Haddad F, Hunt SA, Rosenthal DN, et al. Right ventricular function in cardiovascular disease, Part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation* 2008; 117: 1436–1448.
17. Haddad F, Doyle R, Murphy DJ, et al. Right ventricular function in cardiovascular disease, Part II: Pathophysiology, clinical importance, and management of right ventricular failure. *Circulation* 2008; 117: 1717–1731.
18. Guazzi M and Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation* 2012; 126: 975–990.
19. Opitz CF, Hoeper MM, Gibbs JSR, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension. *J Am Coll Cardiol* 2016; 68: 368–378.
20. Nelson GS, Sayed-Ahmed EY, Kroeker CA, et al. Compression of interventricular septum during right ventricular pressure loading. *Am J Physiol Heart Circ Physiol* 2001; 280: H2639–H2648.
21. Gorter TM, Willems TP and van Melle JP. Ventricular interdependence in pulmonary arterial hypertension: providing small pieces of a complex puzzle. *Eur J Heart Fail* 2015; 17: 1–2.
22. Santamore WP, Lynch PR, Heckman JL, et al. Left ventricular effects on right ventricular developed pressure. *J Appl Physiol* 1976; 41: 925–930.
23. Raymond RJ, Hinderliter AL, Willis PW, et al. Echocardiographic predictors of adverse outcomes in primary pulmonary hypertension. *J Am Coll Cardiol* 2002; 39: 1214–1219.
24. Chang S-M, Lin C-C, Hsiao S-H, et al. Pulmonary hypertension and left heart function: insights from tissue doppler imaging and myocardial performance index. *Echocardiography* 2007; 24: 366–373.
25. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med* 2016; 4: 306–322.
26. Galiè N, Humbert M, Vachiery J-L, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J* 2015; 46: 903–975.
27. Gerges C, Gerges M, Lang MB, et al. Diastolic pulmonary vascular pressure gradient. *Chest* 2013; 143: 758–766.
28. Hoeper MM, McLaughlin VV, Dalaan AM Al, et al. Treatment of pulmonary hypertension. *Lancet Respir Med* 2016; 4: 323–336.
29. D'Alto M, Romeo E, Argiento P, et al. Clinical relevance of fluid challenge in patients evaluated for pulmonary hypertension. *Chest* 2017; 151: 119–126.
30. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *Eur Respir J* 2013; 42: 1083–1091.
31. Heresi GA, Minai OA, Tonelli AR, et al. Clinical characterization and survival of patients with borderline elevation in pulmonary artery pressure. *Pulm Circ* 2013; 3: 916–925.
32. Assad TR, Maron BA, Robbins IM, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol* 2017; 2: 1361.
33. Maron BA, Hess E, Maddox TM, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the veterans affairs clinical assessment, reporting, and tracking program. *Circulation* 2016; 133: 1240–1248.
34. Maron BA, Brittain EL, Choudhary G, et al. Redefining pulmonary hypertension. *Lancet Respir Med* 2018; 6(3): 168–170.
35. Brittain EL, Duncan MS, Chang J, et al. Increased echocardiographic pulmonary pressure in HIV-infected and uninfected individuals in the veterans aging cohort study. *Am J Respir Crit Care Med* 2018; 197(7): 923–932 .
36. Hardegree EL, Sachdev A, Fenstad ER, et al. Impaired left ventricular mechanics in pulmonary arterial hypertension: identification of a cohort at high risk. *Circ Heart Fail* 2013; 6: 748–755.

37. van der Bruggen CE, Happé CM, Dorfmüller P, et al. Bone morphogenetic protein receptor type 2 mutation in pulmonary arterial hypertension. *Circulation* 2016; 133: 1747–1760.
38. Brittain EL, Talati M, Fessel JP, et al. Fatty acid metabolic defects and right ventricular lipotoxicity in human pulmonary arterial hypertension. *Circulation* 2016; 133: 1936–1944.
39. Gan CT-J, Lankhaar J-W, Marcus JT, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol* 2006; 290: H1528–H1533.
40. Wain-Hobson J, Sabatier R, Koné M, et al. Increase of pulmonary artery wedge pressure above 15 mm Hg in patients with pre-capillary pulmonary hypertension. *IJC Heart Vessels* 2014; 4: 161–169.
41. Manders E, Bogaard H-J, Handoko ML, et al. Contractile dysfunction of left ventricular cardiomyocytes in patients with pulmonary arterial hypertension. *J Am Coll Cardiol* 2014; 64: 28–37.
42. Hsu S, Kokkonen-Simon KM, Kirk JA, et al. Right ventricular myofilament functional differences in humans with systemic sclerosis–associated versus idiopathic pulmonary arterial hypertension. *Circulation* 2018; 137: 2360–2370.
43. Knight DS, Steeden JA, Moledina S, et al. Left ventricular diastolic dysfunction in pulmonary hypertension predicts functional capacity and clinical worsening: a tissue phase mapping study. *J Cardiovasc Magn Reson* 2015; 17: 116.
44. Burkett DA, Slorach C, Patel SS, et al. Left ventricular myocardial function in children with pulmonary hypertension. *Circ Cardiovasc Imaging* 2016; 9: e005527.
45. Salerno M. Multi-modality imaging of diastolic function. *J Nucl Cardiol* 2010; 17: 316–327.
46. Caudron J, Fares J, Bauer F, et al. Evaluation of left ventricular diastolic function with cardiac MR imaging. *RadioGraphics* 2011; 31: 239–259.
47. Webb J, Fovargue L, Tøndel K, et al. The emerging role of cardiac magnetic resonance imaging in the evaluation of patients with HFpEF. *Curr Heart Fail Rep* 2018; 15: 1–9.
48. Caballero L, Kou S, Dulgheru R, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. *Eur Heart J Cardiovasc Imaging* 2015; 16: 1031–1041.
49. Popović ZB, Sato K and Desai MY. Is universal grading of diastolic function by echocardiography feasible? *Cardiovasc Diagn Ther* 2018; 8: 18–28.
50. Rasmussen-Torvik LJ, Colangelo LA, Lima JAC, et al. Prevalence and predictors of diastolic dysfunction according to different classification criteria. *Am J Epidemiol* 2017; 185: 1221–1227.
51. Almeida JG, Fontes-Carvalho R, Sampaio F, et al. Impact of the 2016 ASE/EACVI recommendations on the prevalence of diastolic dysfunction in the general population. *Eur Heart J Cardiovasc Imaging* 2018; 19: 380–386.
52. Balaney B, Medvedofsky D, Mediratta A, et al. Invasive validation of the echocardiographic assessment of left ventricular filling pressures using the 2016 diastolic guidelines: head-to-head comparison with the 2009 guidelines. *J Am Soc Echocardiogr* 2018; 31(1): 79–88.
53. Sato K, Grant ADM, Negishi K, et al. Reliability of updated left ventricular diastolic function recommendations in predicting elevated left ventricular filling pressure and prognosis. *Am Heart J* 2017; 189: 28–39.
54. Lancellotti P, Galderisi M, Edvardsen T, et al. Echo-Doppler estimation of left ventricular filling pressure: results of the multicentre EACVI Euro-Filling study. *Eur Heart J Cardiovasc Imaging* 2017; 18: 961–968.
55. Nauta JF, Hummel YM, van der Meer P, et al. Correlation with invasive left ventricular filling pressures and prognostic relevance of the echocardiographic diastolic parameters used in the 2016 ESC heart failure guidelines and in the 2016 ASE/EACVI recommendations: a systematic review in patients with heart failure with preserved ejection fraction. *Eur J Heart Fail* 2018; 20(9): 1303–1311.
56. Sharifov OF, Schiros CG, Aban I, et al. Diagnostic accuracy of tissue Doppler index E/e' for evaluating left ventricular filling pressure and diastolic dysfunction/heart failure with preserved ejection fraction: A systematic review and meta-analysis. *J Am Heart Assoc* 2016; 5(1): pii: e002530.
57. Hummel YM, Liu LCY, Lam CSP, et al. Echocardiographic estimation of left ventricular and pulmonary pressures in patients with heart failure and preserved ejection fraction: a study utilizing simultaneous echocardiography and invasive measurements. *Eur J Heart Fail* 2017; 19(12): 1651–1660.
58. Leung EC, Swiston JR, AlAhmari L, et al. EXPRESS: Validity of algorithm for estimating left sided filling pressures on echocardiography in a population referred for pulmonary arterial hypertension. *Pulm Circ* 2018; 8(1): 204589321774047.
59. Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation* 1983; 68: 302–309.
60. Parasuraman S, Walker S, Loudon BL, et al. Assessment of pulmonary artery pressure by echocardiography—A comprehensive review. *IJC Heart Vasc* 2016; 12: 45–51.
61. Yock PG and Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. *Circulation* 1984; 70: 657–662.
62. Masuyama T, Kodama K, Kitabatake A, et al. Continuous-wave Doppler echocardiographic detection of pulmonary regurgitation and its application to noninvasive estimation of pulmonary artery pressure. *Circulation* 1986; 74: 484–492.
63. Janda S, Shahidi N, Gin K, et al. Diagnostic accuracy of echocardiography for pulmonary hypertension: a systematic review and meta-analysis. *Heart* 2011; 97: 612–622.
64. Rich JD, Shah SJ, Swamy RS, et al. Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. *Chest* 2011; 139: 988–993.
65. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med* 2009; 179: 615–621.
66. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23: 685–713.
67. van Riel ACMJ, Opotowsky AR, Santos M, et al. Accuracy of echocardiography to estimate pulmonary artery pressures with exercise: a simultaneous invasive-noninvasive comparison. *Circ Cardiovasc Imaging* 2017; 10: e005711.
68. O'Leary J, Assad T, Xu M, et al. Lack of a tricuspid regurgitation velocity and pulmonary hypertension: absence of evidence is not evidence of absence. *J Am Coll Cardiol* 2017; 69: 1891.

69. Ruan Q and Nagueh SF. Clinical application of tissue doppler imaging in patients with idiopathic pulmonary hypertension. *Chest* 2007; 131: 395–401.
70. Bonderman D, Wexberg P, Martischnig AM, et al. A noninvasive algorithm to exclude pre-capillary pulmonary hypertension. *Eur Respir J* 2011; 37: 1096–1103.
71. Condliffe R, Radon M, Hurdman J, et al. CT pulmonary angiography combined with echocardiography in suspected systemic sclerosis-associated pulmonary arterial hypertension. *Rheumatology* 2011; 50: 1480–1486.
72. Opotowsky AR, Ojeda J, Rogers F, et al. A simple echocardiographic prediction rule for hemodynamics in pulmonary hypertension. *Circ Cardiovasc Imaging* 2012; 5: 765–775.
73. D'Alto M, Romeo E, Argiento P, et al. Echocardiographic prediction of pre- versus postcapillary pulmonary hypertension. *J Am Soc Echocardiogr* 2015; 28: 108–115.
74. Rhea IB, Rehman S, Jarori U, et al. Prognostic utility of blood pressure-adjusted global and basal systolic longitudinal strain. *Echo Res Pract* 2016; 3: 17–24.
75. Rhea IB, Morris K, Sawada S, et al. Prevalence, etiology, and clinical implications of reduced longitudinal systolic strain in renal transplant candidates. *Echocardiography* 2016; 33: 1676–1682.
76. Rhea IB, Uppuluri S, Sawada S, et al. Incremental prognostic value of echocardiographic strain and its association with mortality in cancer patients. *J Am Soc Echocardiogr* 2015; 28: 667–673.
77. Kasner M, Gaub R, Sinning D, et al. Global strain rate imaging for the estimation of diastolic function in HFNEF compared with pressure–volume loop analysis. *Eur J Echocardiogr* 2010; 11(9): 743–751.
78. D'Alto M, Romeo E, Argiento P, et al. Pulmonary arterial hypertension: the key role of echocardiography. *Echocardiography* 2015; 32: S23–S37.
79. Hammerstingl C, Schueler R, Bors L, et al. Diagnostic value of echocardiography in the diagnosis of pulmonary hypertension. *PLoS One* 2012; 7: e38519.
80. Fadel BM, Al-Mahdi B, Al-Admawi M, et al. Echocardiographic assessment in a patient with vasoreactive pulmonary hypertension. *Echocardiography* 2013; 30: 419–425.
81. Hewing B, Theres L, Spethmann S, et al. Left atrial strain predicts hemodynamic parameters in cardiovascular patients. *Echocardiography* 2017; 34: 1170–1178.
82. Tossavainen E, Henein MY, Grönlund C, et al. Left atrial intrinsic strain rate correcting for pulmonary wedge pressure is accurate in estimating pulmonary vascular resistance in breathless patients. *Echocardiography* 2016; 33: 1156–1165.
83. Himelman RB, Stulbarg M, Kircher B, et al. Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography in chronic pulmonary disease. *Circulation* 1989; 79: 863–71.
84. Nootens M, Wolfkiel CJ, Chomka EV, et al. Understanding right and left ventricular systolic function and interactions at rest and with exercise in primary pulmonary hypertension. *Am J Cardiol* 1995; 75: 374–377.
85. Van Iterson EH, Olson TP, Borlaug BA, et al. Comparisons of noninvasive methods used to assess exercise stroke volume in heart failure with preserved ejection fraction. *Med Sci Sport Exerc* 2017; 49: 1758–1768.