The Role of Echocardiography in the Diagnosis and Assessment of Pulmonary Hypertension


Stephen C. Mathai, MD, MHS


Paul M. Hassoun, MD

Stephen C. Mathai, MD, MHS and
Paul M. Hassoun, MD
Johns Hopkins University School of Medicine
Department of Medicine
Division of Pulmonary and Critical Care Medicine
Baltimore, MD

Pulmonary hypertension (PH) is a progressive disease of the pulmonary vasculature, characterized by elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). The definition of PH is based on measurement of the mean PAP greater than 25 mmHg. Pulmonary arterial hypertension (PAH) is also defined by mean PAP greater than 25 mmHg, but includes assessment of PVR greater than 3 Wood units and pulmonary capillary wedge pressure (PCWP) at least 15 mmHg, and thus can only be diagnosed with right heart catheterization and direct measurement of cardiac output (CO) and PCWP.[1]

Echocardiography (ECHO) is an important modality in the noninvasive assessment of PH and has been used to screen for the disease, determine right and left heart structure and function, and assess response to therapy in persons with PH. Current guidelines recommend ECHO to estimate PAP and to assess for right atrial enlargement, right ventricular enlargement, pericardial effusion, left ventricular systolic or nonsystolic dysfunction, left atrial or ventricular enlargement, and valvular disease as part of the initial evaluation of a patient suspected of having PH.[2] Although limitations to its use in PH and PAH exist, several aspects of ECHO are particularly helpful in the assessment and long-term management of patients with PH. In this review, we highlight the utility of various applications of ECHO and describe their role in the management of PH.

Estimation of PAP and PVR

The diagnosis of PH depends on direct measurement of the mean PAP by right heart catheterization. ECHO can provide an estimate of the pulmonary artery systolic pressure (PASP). Although ECHO cannot be used to establish the diagnosis of PH, it is a useful screening test, with several caveats.

Estimating PASP

The most commonly used modality to estimate PASP is Doppler ECHO. PASP can be determined by measuring the peak systolic pressure gradient from the right ventricle to the right atrium. This is calculated using the modified Bernoulli equation: $4v^2$, where v is the maximum velocity of the tricuspid valve regurgitant jet, measured by continuous wave Doppler, added to the estimated right atrial pressure. Estimation techniques for right atrial pressure vary, but a commonly employed method is to determine the variation in the size of the inferior vena cava with inspiration: complete collapse, right atrial pressure = 5 mmHg; partial collapse, right atrial pressure = 10 mmHg; and no collapse, right atrial pressure = 15 mmHg, although this method may not accurately assess right atrial pressure.[3,4] Furthermore, this method to determine PASP estimates is dependent on the presence of an analyzable tricuspid regurgitant jet and on the absence of pulmonic stenosis.

Unfortunately, the prevalence of tricuspid regurgitation in patients with a PASP greater than 35 is only 80%, although this increases to greater than 95% in patients with a PASP greater than 50.[5] In addition, the presence of analyzable tricuspid regurgitant jets seems to vary depending on underlying disease and body habitus.[6] For instance, in one study of patients with connective tissue disease, only 39% of patients had analyzable tricuspid regurgitant jets.[7] Similarly, estimates of PASP in patients with advanced lung disease such as interstitial lung disease and chronic obstructive lung disease can be difficult to obtain; in one cohort of nearly 400 patients, only 166 (44%) had adequate images and acoustic windows to allow estimates of PASP.[8]

In our study, although a relatively strong correlation between estimated PASP and measured PASP by right heart cathetarization existed (Pearson correlation r = 0.69) in the subset of patients on whom estimates were obtained, Doppler ECHO overestimated directly measured PASP by more than 10 mmHg in about 50% of patients without PH and in 30% of patients with PH. Similar findings have been observed in other cohorts of patients at risk for or with known PH, including a cohort of PAH patients from our center (**Table; Figure 1**).[4]

While some of the limitations pertaining to the inability to detect TR can be overcome with contrast Doppler ECHO using saline or other mixtures, there is much variability in the Doppler ECHO-estimated PASP that are obtained, especially in patients with underlying lung disease.[9] The interpretation of PASP estimates should include assessment of the individual patient; population-based studies have demonstrated that the resting physiologic range of PASP depends on age, sex, and body mass index and may exceed 35 mmHg in the elderly and obese.[10] Furthermore, highly-trained athletes may generate PASP of 60 mmHg with exertion, related to increased pulmonary blood flow and left atrial pressure.[11]

Key Words—echocardiography; pulmonary hypertension; pulmonary artery pressure; pulmonary vascular resistance.
Address for reprints and other correspondence: Stephen C. Mathai, Johns Hopkins University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine, 1830 E. Monument Street, 5th Floor, Baltimore, MD; email: smathai4@jhmi.edu.

Estimating mean PAP

Recent investigations of the relationship between Doppler ECHO-estimated PASP and invasively measured mean PAP have suggested that noninvasive measurement of PASP may be a useful surrogate for the mean PAP.[12-14] Of particular interest, the study by Syyed and colleagues[14] examined the relationship between the systolic, diastolic, and mean PAPs using a high-fidelity micromanometer-tipped catheter during right heart cathetarization in healthy controls and patients with various forms of cardiopulmonary disease (eg, chronic obstructive pulmonary disease, interstitial lung disease, idiopathic PAH, and chronic thromboembolic pulmonary hypertension).

The investigators measured these pressures during positional changes, during exercise, and following administration of pulmonary vasodilators to develop predictive equations relating the PASP to the mean PAP. The results demonstrated that the relationship between the components of PAP remain constant regardless of positional, exercise, and vasodilator challenges, diagnosis, or degree of PH. The following formula was derived to estimate mean PAP: mean PAP = 0.65 PASP + 0.55 mmHg. This suggests that accurate, noninvasive measurement of PASP may be more directly related to invasively determined mean PAP than previously thought.

Table. Relationship between DopplerECHO-estimated and RHC-measured PASP in various cohorts

Study	Diagnosis	N	Correlation[a]	Limitations
Bossone et al. 1999[11]	PAH	51	r = 0.31	RAP assumed 14 mmHg
Denton et al. 1997[46]	PAH-SSc	33	r = 0.83	TR present in only 20 of 33 (61%)
Hinderliter et al. 1997[19]	PAH	81	r = 0.57	TR jets obtained in 70 of 81 (86%); RAP assumed 14 mmHg
Murata et al. 199[26]	PAH-SSc	71	NA	TR jets analyzable in 28 of 71 (39%); RAP assumed 10 mmHg
Shapiro et al. 1997[47]	PAH	69	r = 0.85	Assessed ΔP, defined as 4(TR jet)^2
Shen et al. 1999[48]	PAH-SLE	84	r = 0.76	12 of 84 (14%) subjects had RHC; only 1 of 12 had PH on RHC
Arcasoy et al. 2003[7]	Lung transplant referrals	374	r = 0.69	47 of 166 (28%) had difference > 20 mmHg between Doppler ECHO and RHC
Fisher et al. 2009[8]	PAH and PH	65	r = 0.66	Doppler ECHO RAP estimates significantly differed from hemodynamic measurements; 30 of 59 (52%) had difference > 10 mmHg

RHC, right heart catheterization; PASP, pulmonary artery systolic pressure; PAH, pulmonary arterial hypertension; RAP, right atrial pressure; SSc, systemic sclerosis; TR, tricuspid regurgitation; SLE, systemic lupus erythematosus.

Other useful ECHO measures

Other ECHO methods have been used to estimate mean PAP in patients with PH. Using tissue Doppler imaging, pulmonary flow can be measured proximal to the pulmonary valve in the middle of the right ventricular outflow tract to generate velocity profiles.[15] These profiles can be quantitatively assessed to define several pulmonary flow indices including the pre-ejection period, acceleration time, and right ventricular ejection time. Acceleration time, defined as the interval from the onset to maximal velocity of forward flow in the right ventricular outflow tract, can be used to estimate mean PAP. Acceleration time varies inversely with increasing pulmonary vascular resistance in PH that is accompanied by increased pulmonary arterial elastance and wave reflection.[15,16] Thus, acceleration time may be more useful in the assessment of RV function rather than as an estimate of mean PAP.

Other studies have shown that reduced acceleration time may be a marker of latent PH in scleroderma patients with normal PASP estimates at rest.[17] The regional right ventricle (RV) isovolumetric relaxation time corrected for heart rate (IVRTc, defined as the interval between pulmonary valve closure and tricuspid valve opening) from tissue velocity recordings of the RV myocardial wall motion at the tricuspid annulus, correlates strongly with invasively-measured PASP. However, this relationship loses its significance with increasing RV dysfunction and thus has limited utility. Other measures used to estimate mean PAP include the pulmonary regurgitation velocity, which has been shown to closely approximate mean PAPs, but is not often used in clinical practice.[18]

Limitations

Although noninvasive assessment of PASP and estimates of mean PAP are useful in the screening of patients with possible PH, there are limited data that demonstrate its utility in the long-term assessment of patients with established disease. Several investigators have studied the impact of PAH-specific therapies on the estimates of PASP in patients with various forms of PH. Hinderliter and colleagues[19] assessed changes in multiple ECHO variables in patients with idiopathic PAH who were treated with intravenous epoprostenol for 12 weeks. While there were statistically significant changes in several parameters, including tricuspid regurgitant jet velocity, these changes were small in magnitude, particularly for the tricuspid regurgitant jet and unlikely to be clinically detectible. Similarly, no significant change

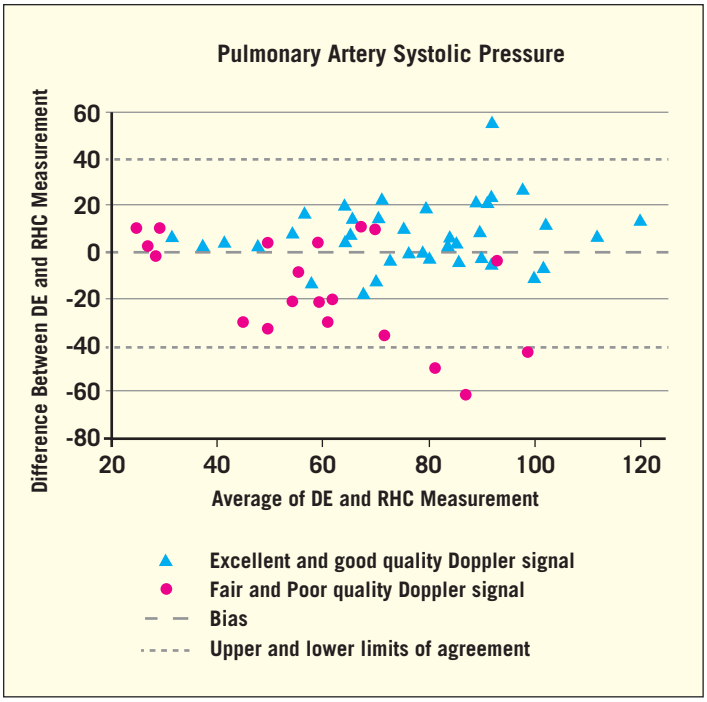

Figure 1. Bland-Altman plot of Doppler ECHO estimates of PAP and right heart catheterization measurements. The bias was –0.6 mmHg and the 95% limits of agreement were +38.8 and –40.0 mmHg. PASP, pulmonary artery systolic pressure; DE, Doppler echocardiography; RHC, right heart catheterization.Reproduced with permission from Fisher et al. *Am J Respir Crit Care Med*. 2009.[8]

in tricuspid regurgitant jet was noted in a placebo-controlled study of bosentan in PAH, despite improvements in other Doppler ECHO parameters.[20] Thus, serial changes in estimated PASP cannot be recommended to assess response to therapy in patients with PH.

Although estimating PASP may be important for screening of PH, the clinical relevance of this value beyond diagnosis is limited. As demonstrated in the National Institutes of Health registry of patients with primary pulmonary hypertension, mean PAP does not provide prognostic information unless it is significantly elevated.[21] Pulmonary vascular resistance (PVR), on the other hand, is a practical measure that assesses disease severity and predicts survival.[21,22] A reliable noninvasive estimate of PVR would likely be useful to diagnose and assess response to interventions in PH. Several investigators have recently examined the ability of ECHO to measure PVR, using the ratio of the peak tricuspid regurgitant velocity to the right ventricular acceleration time as assessed by tissue Doppler imaging.[23-26] Unfortunately, the reliability of an ECHO-derived PVR seems to depend on disease severity. While several groups found good correlations between noninvasive and invasive measures in several populations of patients with PH, including idiopathic PAH, portopulmonary hypertension, and children with PH. PH was not severe in any of these studies; the mean PVR ranged from 1.1 to 2 Wood units.[23-25]

In a larger study of 52 patients who underwent ECHO and right heart catheterization within 24 hours where the mean PVR for the group was 8.8 Wood units, the overall correlation was good (Pearson correlation r = 0.73).[26] However, in patients whose PVR was greater than 8 Wood units, there was no correlation with invasively measured PVR (r = 0.17). The investigators concluded that noninvasively measured PVR should not be used as an estimate of PVR in patients with PH.

Assessment of Right and Left Heart Structure

Pericardial effusion

The presence of pericardial effusion has been shown to be a poor prognostic factor in several studies of patients with various forms of PAH.[27,28] Although thought to be a reflection of poor RV function in patients with idiopathic PAH, it may be related to serositis in patients with connective-tissue related PAH.[28] Our clinical experience suggests that percutaneous drainage should be avoided as this may be associated with an increased risk of hemodynamic compromise and death.[29] Rather, aggressive diuresis and immunosuppression if related to serositis should be undertaken.

Left ventricle

ECHO should be used to assess for possible underlying congenital heart disease and to evaluate for possible evidence of left heart disease that may contribute to elevations in pulmonary pressures. Valvular disease, particularly mitral disease, can increase left-sided pressures and contribute to increased pulmonary pressures. Left ventricular systolic dysfunction, while a common cause of pulmonary venous hypertension, makes the diagnosis of PAH very unlikely. Nonsystolic dysfunction of the left ventricle (LV)—also known as diastolic dysfunction—may significantly contribute to PH. Several investigators have found stronger associations with pulmonary pressures related to LV nonsystolic dysfunction than to LV systolic dysfunction.[30,31] Nonsystolic dysfunction of the LV can be quantified by various ECHO parameters (mitral inflow velocity, M-mode of mitral flow propagation, pulmonary vein flow, and tissue Doppler imaging of the mitral annulus) and is often suggested by an enlarged left atrium. Combination of transmitral flow velocities by Doppler ECHO (assessing LV early filling [E wave velocity] and atrial contraction and emptying [A wave velocity]) with pulmonary venous flow measurements may enhance the detection of nonsystolic dysfunction in patients with essential hypertension, although limited data exist in other patient populations.[32] However, it is important to note that chronic RV volume overload with impingement of the LV may also lead to nonsystolic dysfunction due to decreased LV compliance. Thus, careful examination of the relationship between the RV and LV should be undertaken in each patient to distinguish between these conditions.

Right atrium

The right atrium can be dilated in PH, which reflects increased right atrial pressure as a result of elevated right ventricular diastolic pressure and tricuspid regurgitation. The size of the right atrium can be measured by ECHO in the 4-chamber apical view. Since right atrium size varies by a person's height, a corrected value, the right atrial area index, is the standard measure used to assess right atrium size.

In the multicenter study of epoprostenol therapy of patients with idiopathic PAH (the Primary Pulmonary Hypertension Study Group), right atrial area index was a strong predictor of survival in univariable analysis, but not in multivariable analysis, though it approached statistical significance.[27] When stratified by the median value, patients whose right atrial area index was above the median had a more than 50% increased risk of death compared with those below the median. We noted similar significance of right atrial area index in a cohort of patients with PAH; for every 1 cm^2/m increase in right atrial area index, patients had a 24% increased risk of death in univariable analysis.[33] Strong correlations between right atrial area index and right atrial pressure were demonstrated in both the Primary Pulmonary Hypertension Study

Group cohort and in our cohort. However, there are limited data defining the responsiveness of right atrial area index to PAH-specific therapies, thereby limiting its utility as a noninvasive surrogate marker.

Right ventricle

Morphologic assessment of the RV can be difficult because of its structure, but the variation in its geometric configuration and spatial relation with the LV that occurs with pressure and/or volume overload may be more problematic in the assessment of RV size and volume. Right ventricular hypertrophy, generally defined as an end-diastolic thickness of the free wall greater than 5 mm, usually reflects chronic increased right ventricular afterload.[34] However, other infiltrative conditions, such as amyloidosis, may also lead to right ventricular hypertrophy and need to be considered in the appropriate clinical scenario.

Measurement of RV volume parameters is more challenging because of the structure of the RV and lack of fixed structures to use as reference points. Thus, multiple geometric assumptions must be made to estimate RV volume; subsequently, correlation with RV volume measured by angiography is poor. Furthermore, determination of RV dilatation based on linear measurements is not standardized and should be interpreted with caution.

Interventricular septum

Because of the relationship of between the RV and LV during the cardiac cycle (ventricular interdependence), inferences from the assessment of the movement of the interventricular septum can be drawn. In PH, the movement of the interventricular septum reflects right ventricular function, pressure, and volume state. If there is an increase in right ventricular pressure and/or volume, the interventricular septum will shift into the LV, leading to decreased LV compliance. This in turn impairs chamber filling and reduces pulmonary venous return, ultimately influencing LV output. This relationship between the RV and LV can be assessed by the eccentricity index.

This measure, obtained by evaluating the LV geometry in the parasternal short axis view between the papillary muscle and the tips of the mitral leaflets, compares the diameter of the LV measured perpendicular to the septum to the diameter of the LV measured parallel to the septum, at both end-systole and end-diastole. This ratio is significantly increased in PH, and varies based on whether pressure or volume overload is present. In isolated RV volume overload, end-diastolic eccentricity index is significantly increased (>1). In pressure overload, the eccentricity index is greater than 1 in both end-systole and end-diastole. This measure may also be responsive to PAH-specific therapy, such as calcium channel blockers (in vasoreactive patients), epoprostenol, and bosentan, and it may predict survival in PAH[19,27,35]

Assessment of Ventricular Function

The RV is a structurally complex chamber with 2 distinct cavities: the inflow region (sinus) and the outflow region (infundibulum). The relationship between these 2 cavities during contraction and relaxation varies with increasing afterload, as that which occurs with PH. In the normal physiological situation, the RV contracts in a peristaltic motion, beginning in the sinus and moving towards the infundibulum. With increasing afterload, the RV dilates and is unable to maintain this peristaltic motion.[36] Subsequently, RV ejection fraction falls, leading to decreased stroke volume, LV filling and output, and ultimately, impaired organ perfusion.

Because the major hemodynamic predictors of survival are directly related to RV function (eg, right atrial pressure, cardiac index, pulmonary vascular resistance, a noninvasive measure of RV function would be invaluable in the assessment of patients with PH. However, given the geometry and poor endocardial definition of the RV on ECHO, estimating RV function has traditionally been challenging, and varies based on operator experience. Measures that have been studied to estimate RV function include the Tei index (also known as the myocardial performance index), RV ejection fraction, RV fractional area change, and the tricuspid annular plane systolic excursion.

Initially described in the mid-1990s, the Tei index has been employed in several large clinical studies as a noninvasive measure of RV function.[37] This measure assesses both systolic and diastolic RV function and is defined as the sum of isovolumteric contraction time and isovolumteric relaxation time divided by the RV ejection time. In randomized clinical trials of PAH-specific therapy such as intravenous epoprostenol and bosentan, improvements in RV function were noted as assessed by the Tei index.[19,20] However, despite the validity of this measure in PAH, it is rarely clinically used because of its complexity.

As discussed previously, RV ejection fraction as assessed by radionuclide angiography decreases with increasing RV afterload as a result of progressive PH. Unfortunately, assessment of RV ejection fraction by cross-sectional ECHO is challenging and of limited utility. RV fractional area change is another measure that has been studied in various PH populations.[20,27,33] However, its utility as a measure of RV function is limited as its reproducibility and reliability, prognostic significance, and response to therapy are varied.

One measure that holds promise as a simple, reproducible measure of RV function is the tricuspid annular plane systolic excursion (**Figure 2**). Despite the complexity of the RV chamber, its contraction is predominantly in the longitudinal plane because of the orientation of muscle fibers.[38] Thus, systolic performance of the RV may be estimated by the longitudinal motion of the RV; specifically, the systolic displacement of the tricuspid annulus toward the RV apex. Using 2-D Doppler ECHO, in the apical 4-chamber view with an M-mode cursor placed through the lateral tricuspid annulus, the total displacement of the annulus from end-diastole to end-systole averaged over 3 to 5 beats is measured. Using this measure, we showed strong correlations with invasive measures of RV function, including CI and RV stroke volume index.[33] In addition, tricuspid annular plane systolic excursion was a strong predictor of survival, both in a heterogeneous population of patients with PH and in a subset of patients with PAH.

Interobserver and intraobserver reproducibility was excellent, with correlations greater than 0.94 and small mean bias and 95% confidence interval by Bland-Altman analysis. Although tricuspid annular plane systolic excursion may be a useful marker of RV function in clinical practice, especially considering the ease of its application, the responsiveness of tricuspid annular plane systolic excursion to PAH-specific therapy has not yet been described. Investigators have suggested that its utility may be limited in patients with severe tricuspid regurgitation.[39] Thus, its role in the management of patients with PH remains to be defined.

Estimation of cardiac output

Estimation of cardiac output by noninvasive measures is challenging. Current methodology uses the velocity time integral (VTI) of flow through the left ventricular outflow tract (LVOT), the di-

ameter of the LVOT, and heart rate recorded during the imaging study, using the following formula:

$CO_{Doppler} = [VTI_{LVOT} \times (\text{diameter of LVOT})^2 \times (0.785)] \times \text{heart rate}$.[40]

However, this method can be fraught with variability as the estimation of the diameter of the LVOT must be squared, thus an error in this estimation will be amplified.

Our group recently studied the accuracy of ECHO-estimated CO in a large group of patients with PH and found wide 95% limits of agreement between thermodilution CO and the noninvasive estimate.[8] Although the discrepancies between the Doppler ECHO-derived estimate and the hemodynamic measurements were small when the CO was low, the accuracy diminished as CO increased, thereby limiting the utility of this modality in clinical practice.

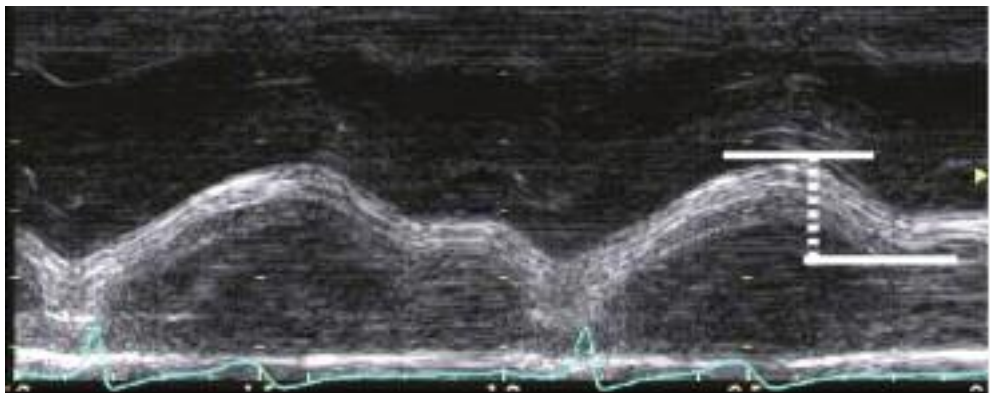

Figure 2. Measurement of the TAPSE. In the apical 4 chamber view while in M-mode, place the cursor through the RV apex and lateral tricuspid annulus and measure excursion from end-diastole to end-systole, which average over 3 to 5 heart beats. This excursion is measured in centimeters. In one cohort, patients with PAH with an TAPSE less than 1.8 cm exhibited a nearly 6-fold increased risk of death compared with those with TAPSE greater than 1.8 cm.[33] TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; PAH, pulmonary arterial hypertension.

Future Directions

With technological advances in the field of ECHO, newer measures to assess PH have emerged. An area of particular interest is tissue Doppler imaging of ventricular strain rate, which may quantify RV function. The local rate of wall deformation (the strain rate) and the amount of deformation (the strain) measured by regional velocity data have been shown to correlate strongly with invasively measured mean PAP and PVR.[41,42]

Changes in strain may precede the development of clinical RV dysfunction as assessed by tricuspid annular plane systolic excursion.[43] Three-dimensional ECHO offers promise in its ability to minimize the geometric limitations of 2-D assessment of chamber size and thus better quantify volume and pressure relationships in the RV. However, there are few studies that characterize this modality in the evaluation of PH.[44,45] Thus, despite the current utility of ECHO, there remain vast areas to explore in the noninvasive assessment of PH. Further research into (1) more accurate assessment of pulmonary pressures and PVR; (2) early detection of RV dysfunction heralding the development of PH in susceptible populations; and (3) responsiveness of any of the currently employed measures of PH to therapeutic interventions is urgently needed to enhance the recognition and longitudinal care of patients with PH.

References

1. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2004;43:5S-12S.
2. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126:14S-34S.
3. Bredikis AJ, Liebson PR: The echocardiogram in COPD: estimateing right heart pressures. *J Respir Dis.* 1998;19:191-198.
4. 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 Jan 22. [Epub ahead of print].
5. Berger M, Haimowitz A, Van Tosh A, Berdoff RL, Goldberg E. Quantitative assessment of pulmonary hypertension in patients with tricuspid regurgitation using continuous wave Doppler ultrasound. *J Am Coll Cardiol.* 1985;6:359-365.
6. Sciomer S, Badagliacca R, Fedele F. Pulmonary hypertension: echocardiographic assessment. *Ital Heart J.* 2005;6:840-845.
7. Murata I, Kihara H, Shinohara S, Ito K. Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J.* 1992;56:983-991.
8. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med.* 2003;167:735-740.
9. Jeon DS, Luo H, Iwami T, et al. The usefulness of a 10% air, 10% blood, 80% saline mixture for contrast echocardiography: Doppler measurement of pulmonary artery systolic pressure. *J Am Coll Cardiol.* 2002;39:124-129.
10. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation.* 2001;104:2797-2802.
11. Bossone E, Rubenfire M, Bach DS, Ricciardi M, Armstrong WF. Range of tricuspid regurgitation velocity at rest and during exercise in normal adult men: implications for the diagnosis of pulmonary hypertension. *J Am Coll Cardiol.* 1999;33:1662-1666.
12. Chemla D, Castelain V, Humbert M, et al. New formula for predicting mean pulmonary artery pressure using systolic pulmonary artery pressure. *Chest.* 2004;126:1313-1317.
13. Friedberg MK, Feinstein JA, Rosenthal DN. A novel echocardiographic Doppler method for estimation of pulmonary arterial pressures. *J Am Soc Echocardiogr.* 2006;19:559-562.
14. Syyed R, Reeves JT, Welsh D, Raeside D, Johnson MK, Peacock AJ. The relationship between the components of pulmonary artery pressure remains constant under all conditions in both health and disease. *Chest.* 2008;133:633-639.
15. Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. *Circulation.* 1983;68:302-309.
16. Castelain V, Herve P, Lecarpentier Y, Duroux P, Simonneau G, Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol.* 2001;37:1085-1092.
17. Huez S, Roufosse F, Vachiery JL, et al. Isolated right ventricular dysfunction in systemic sclerosis: latent pulmonary hypertension? *Eur Respir J.* 2007;30:928-936.
18. Masuyama T, Kodama K, Kitabatake A, Sato H, Nanto S, Inoue M. Continuous-wave Doppler echocardiographic detection of pulmonary regurgitation and its application to noninvasive estimation of pulmonary artery pressure. *Circulation.* 1986;74:484-492.
19. Hinderliter AL, Willis PW 4th, Barst RJ, et al. Effects of long-term infusion of prostacyclin (epoprostenol) on echocardiographic measures of right ventricular structure and function in primary pulmonary hypertension. Primary Pulmonary Hypertension Study Group. *Circulation.* 1997;95:1479-1486.
20. Galie N, Hinderliter AL, Torbicki A, et al. Effects of the oral endothelin-receptor antagonist bosentan on echocardiographic and doppler measures in patients with pulmonary arterial hypertension. *J Am Coll Cardiol.* 2003;41:1380-1386.
21. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115:343-349.
22. Sitbon O, Humbert M, Nunes H, et al. Long-term intravenous epoprostenol

infusion in primary pulmonary hypertension: prognostic factors and survival. *J Am Coll Cardiol.* 2002;40:780-788.
23. Abbas AE, Fortuin FD, Schiller NB, Appleton CP, Moreno CA, Lester SJ. A simple method for noninvasive estimation of pulmonary vascular resistance. *J Am Coll Cardiol.* 2003;41:1021-1027.
24. Farzaneh-Far R, McKeown BH, Dang D, Roberts J, Schiller NB, Foster E. Accuracy of Doppler-estimated pulmonary vascular resistance in patients before liver transplantation. *Am J Cardiol.* 2008;101:259-262.
25. Vlahos AP, Feinstein JA, Schiller NB, Silverman NH. Extension of Doppler-derived echocardiographic measures of pulmonary vascular resistance to patients with moderate or severe pulmonary vascular disease. *J Am Soc Echocardiogr.* 2008;21:711-714.
26. Rajagopalan N, Simon MA, Suffoletto MS, et al. Noninvasive estimation of pulmonary vascular resistance in pulmonary hypertension. *Echocardiography.* 2008 Nov 11. [Epub ahead of print].
27. 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.
28. Fisher MR, Mathai SC, Champion HC, et al. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum.* 2006;54:3043-3050.
29. Champion HC. The heart in scleroderma. *Rheum Dis Clin North Am.* 2008;34:181-90;viii.
30. Enriquez-Sarano M, Rossi A, Seward JB, Bailey KR, Tajik AJ. Determinants of pulmonary hypertension in left ventricular dysfunction. *J Am Coll Cardiol.* 1997;29:153-159.
31. Capomolla S, Febo O, Guazzotti G, et al. Invasive and non-invasive determinants of pulmonary hypertension in patients with chronic heart failure. *J Heart Lung Transplant.* 2000;19:426-438.
32. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y. Pulmonary venous flow and risk of cardiovascular disease in essential hypertension. *J Hypertens.* 2008;26:798-805.
33. Forfia PR, Fisher MR, Mathai SC, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med.* 2006;174:1034-1041.
34. Prakash R. Determination of right ventricular wall thickness in systole and diastole. Echocardiographic and necropsy correlation in 32 patients. *Br Heart J.* 1978;40:1257-1261.
35. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation.* 1987;76:135-141.
36. Mebazaa A, Karpati P, Renaud E, Algotsson L. Acute right ventricular failure—from pathophysiology to new treatments. *Intensive Care Med.* 2004;30:185-196.
37. Tei C, Dujardin KS, Hodge DO, et al: Doppler echocardiographic index for assessment of global right ventricular function. *J Am Soc Echocardiogr.* 1996;9:838-847.
38. Rushmer RF, Crystal DK, Wagner C. The functional anatomy of ventricular contraction. *Circ Res.* 1953;1:162-170.
39. Hsiao SH, Lin SK, Wang WC, Yang SH, Gin PL, Liu CP. Severe tricuspid regurgitation shows significant impact in the relationship among peak systolic tricuspid annular velocity, tricuspid annular plane systolic excursion, and right ventricular ejection fraction. *J Am Soc Echocardiogr.* 2006;19:902-910.
40. Ihlen H, Amlie JP, Dale J, et al: Determination of cardiac output by Doppler echocardiography. *Br Heart J* 1984;51:54-60.
41. Huez S, Vachiery JL, Unger P, Brimioulle S, Naeije R. Tissue Doppler imaging evaluation of cardiac adaptation to severe pulmonary hypertension. *Am J Cardiol.* 2007;100:1473-1478.
42. Rajagopalan N, Simon MA, Shah H, Mathier MA, Lopez-Candales A. Utility of right ventricular tissue Doppler imaging: correlation with right heart catheterization. *Echocardiography.* 2008;25:706-711.
43. Kittipovanonth M, Bellavia D, Chandrasekaran K, Villarraga HR, Abraham TP, Pellikka PA. Doppler myocardial imaging for early detection of right ventricular dysfunction in patients with pulmonary hypertension. *J Am Soc Echocardiogr.* 2008;21:1035-1041.
44. Apfel HD, Shen Z, Gopal AS, et al. Quantitative three dimensional echocardiography in patients with pulmonary hypertension and compressed left ventricles: comparison with cross sectional echocardiography and magnetic resonance imaging. *Heart.* 1996;76:350-354.
45. Tamborini G, Brusoni D, Torres Molina JE, et al. Feasibility of a new generation three-dimensional echocardiography for right ventricular volumetric and functional measurements. *Am J Cardiol.* 2008;102:499-505.
46. Denton CP, Cailes JB, Phillips GD, et al. Comparison of Doppler echocardiography and right heart catheterization to assess pulmonary hypertension in systemic sclerosis. *Br J Rheumatol.* 1997;36:239-243.
47. Shapiro SM, Oudiz RM, Cao T, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Col Cardiol.* 1997;30:343-349.
48. Shen JY, Chen SL, Wu YX, et al. Pulmonary hypertension in systemic lupus erythematosus. *Rheumatol Int.* 1999;18:147-151. ■