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The Role of Echocardiography in the Evaluation of Pulmonary Arterial Hypertension

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The evaluation of pulmonary arterial hypertension (PAH) requires a multimodality approach that combines invasive and noninvasive imaging studies to ensure accurate diagnosis and classification. Given the complexity of the hemodynamic relationships between the left heart, pulmonary circulation, and right heart, the diagnosis of PAH is often a challenging task. Right heart catheterization is the gold standard for diagnosis, providing the hemodynamic information that defines the disease. Nonetheless, echocardiography continues to be a valuable tool in the approach to the patient with suspected PAH. Echocardiographic assessment generates a wealth of information about the response of the right heart to elevated pulmonary pressures and provides essential diagnostic and prognostic data to the clinician. Numerous measurements can be used to identify alterations in right heart morphology, pressure, and function; although each variable in isolation may have little utility, meaningful information is revealed when multiple parameters are considered together. In this article, we will review the echocardiographic measurements employed in assessment of the right heart and seek to clarify the role of echocardiography in the diagnostic workup of PAH. (Echocardiography 2016;33:105–116)

Key words: pulmonary arterial hypertension, echocardiography, right ventricular function

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature, defined hemodynamically by a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg at rest.[1] The World Health Organization recognizes 5 groups of pulmonary hypertension (PH): (1) PAH; (2) PH due to left heart disease; (3) PH due to lung diseases and/or hypoxia; (4) chronic thromboembolic PH; and (5) PH with unclear multifactorial mechanisms.[2] From a broader perspective, these groups can be divided on the basis of precapillary and postcapillary etiology. Precapillary PH encompasses groups 1, 3, 4, and 5, and postcapillary PH corresponds to group 2.[3] Postcapillary PH is further divided into passive (transpulmonary gradient [TPG] $\leq$ 12 mmHg) or active (TPG $>$ 12 mmHg) PH.[4] The latter can be considered as PH out of proportion to what is expected based on the severity of left heart disease and is frequently observed both in mitral valve disease and advanced cardiomyopathy. While distinguishing pre- from postcapillary PH guides treatment and prognosis, the diagnosis may be elusive. The parameters required to make the distinction must be obtained from invasive hemodynamic assessment; thus, right heart catheterization (RHC) is the gold standard for the diagnosis and classification of PH.[5]

Despite its central diagnostic role, RHC is invasive and expensive and cannot practically be performed on all patients. Two-dimensional (2D) transthoracic Doppler echocardiography, in contrast, is noninvasive, affordable, and readily available.[6] Its contribution to the diagnostic workup of PAH has been a subject of much attention and debate. Numerous echocardiographic parameters have been investigated, yet a consensus is lacking regarding the overall utility of echocardiography in PAH. Echocardiographic imaging may offer clues regarding the etiology, but some measurements are better suited for this purpose than others. Although widely regarded as a valuable screening tool,[7] the potential for a larger role of echocardiography remains unsettled.

This paper will explore the cardiac consequences of PAH and address the strengths and

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limitations of echocardiography in diagnosing and monitoring this complex disorder. The echocardiographic measurements involved in the evaluation of PAH focus on the estimation of right heart pressures and the morphology and function of the right ventricle (RV), the structure that endures the bulk of the disease burden. However, evidence of left heart, valvular or pericardial disease is often necessary for making the clinically crucial distinction between pre- and postcapillary PH.

Measurement of Right Heart Pressures:

Right Atrial Pressure:

Right atrial pressure (RAP) is frequently approximated by inferior vena cava (IVC) diameter and collapsibility during a sniff test (Table I). The IVC diameter should be measured just proximal to the entrance of hepatic veins, ~1–2 centimeters from the RA (Fig. 1A,B). The following scale is applied: for IVC diameter <2.1 cm with >50% collapse on inspiration, RAP is assumed to be 3 mmHg. For IVC diameter ≥2.1 cm with <50% collapse on inspiration, RAP is assumed to be elevated to 15 mmHg. If there is an abnormality in only one of the parameters, a value of 8 mmHg is assigned.[8] In such situations, it may be preferable to utilize another surrogate for RAP, such as the tricuspid E/E′ ratio (a value >6 is considered abnormal and indicates elevated RAP) or the pattern of hepatic vein flow (Fig. 1C,D).[9] At low or normal RA pressures, there is systolic predominance in hepatic vein flow. As RAP increases, the velocity of the systolic wave decreases; as a result, the ratio of the systolic to diastolic wave velocity in the setting of elevated RAP is <1 and the systolic filling fraction (systolic vti/[systolic vti + diastolic vti]), where vti is the velocity time integral, is <0.55.[10] While RAP clearly provides information about the state of the right heart, it reflects left-sided filling pressures as well; in this regard, RAP has been shown to correlate with pulmonary capillary wedge pressure in patients with chronic heart failure.[11]

TABLE I

Echocardiographic Measurements

Right Heart Measurements
Pressure
Right atrial pressure – IVC diameter and collapsibility with sniff[8]
Pulmonary artery systolic pressure – $4v^2$ + RAP, where v is the peak velocity in m/sec of the TR jet[10]
Mean pulmonary artery pressure – (1) $4v^2$ + RAP, where v is the peak velocity in m/sec of the early diastolic PR jet[18] (2) 79 – (0.45 × PA acceleration time),[12] or 90°– (0.62 × PA acceleration time) for acceleration time <120 milliseconds[12] (3) RAP + RV-RA mean systolic gradient[20]
Pulmonary artery diastolic pressure – $4v^2$ + RAP, where v is the peak velocity in m/sec of the PR jet at end-diastole[10]
Morphology
RV linear dimensions – basal, mid-cavity, longitudinal[8]
RV free wall thickness
RA area
Function
Fractional area change – (end-diastolic area – end-systolic area/end-diastolic area) × 100[10]
Tricuspid annular plane systolic excursion
RV S′
RV index of myocardial performance – (isovolumic relaxation time + isovolumic contraction time)/ RV ejection time[10]
RV isovolumic acceleration
Left Heart Measurements
Function
LV E/E′ ratio
LV eccentricity index

RV and Pulmonary Artery Systolic Pressure:

Through the application of the simplified Bernoulli equation, velocity of the tricuspid regurgitant (TR) jet can be used to calculate systolic RV pressure (RVSP): RVSP = $4v^2$ + RAP, where v is the peak velocity in m/sec of the TR jet and RAP is estimated from IVC diameter and collapsibility with sniff (Fig. 2A). Pulmonary artery systolic pressure (PASP) is equal to RVSP in the absence of pulmonic stenosis or RV outflow obstruction.[10] TR velocity ≥2.8–2.9 m/sec is considered abnormal, but it must be noted that this cutoff may not be accurate in the elderly or the obese.[12] Although the practice of estimating PASP by echocardiogram was introduced in 1984,[13] its accuracy remains controversial; the strength of correlation between PASP and RHC varies widely across the literature[5,14–16] with the relationship tending to weaken at pressure extremes.

The reasons for the lack of agreement in the literature are manifold. The PASP calculation requires 2 measurements, each with the potential for error. Velocity measurements are dependent on the intercept angle between the ultrasound beam and the direction of flow, necessitating interrogation of TR signals from multiple sampling sites and appropriate selection of the signal with the highest velocity.[10] Moreover, the measurement is not reliable in the setting of severe TR, in which early equalization of RV and RA pressures produces a "clipped" Doppler envelope.[10] Finally, RAP estimates may contribute to inaccurate PASP; in one study, they accounted for nearly half of the cases of echocardiographic pressure overestimation.[16]

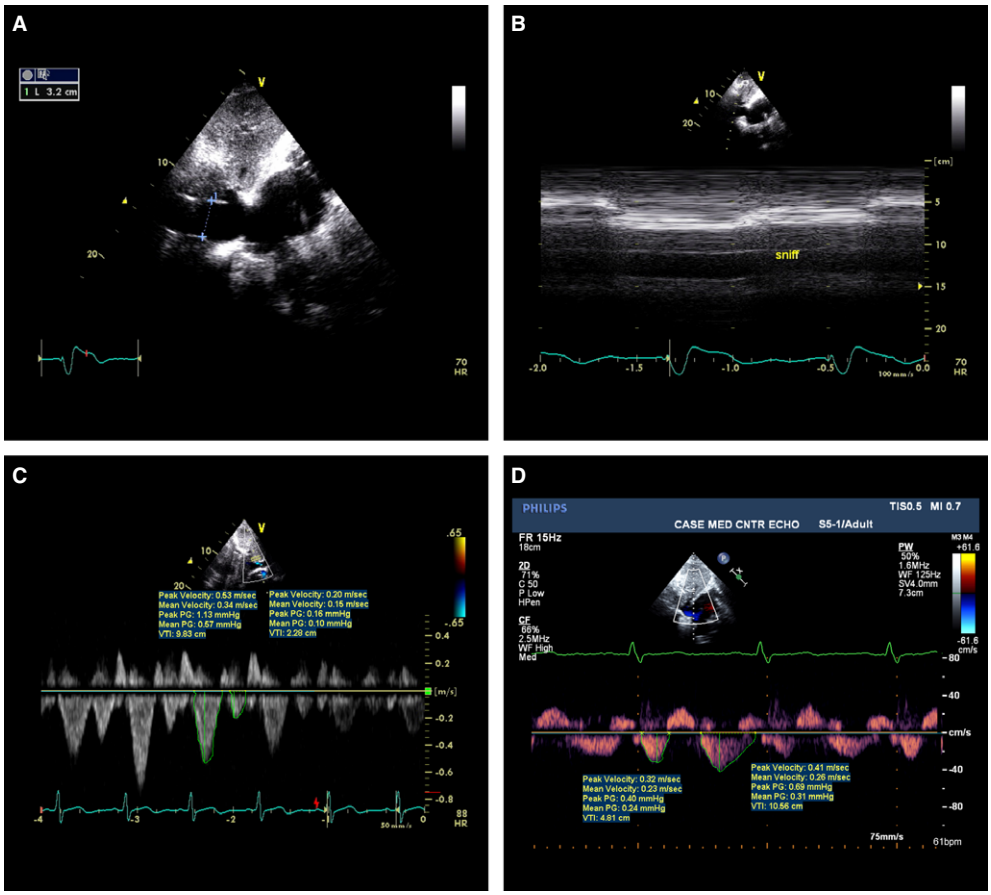

Figure 1. RA pressure estimates from the IVC size and the pattern of hepatic vein flow. Elevated RA pressure evident from a two-dimensional echocardiogram of a markedly dilated IVC **A.** and an M-mode echocardiogram of the IVC before and during a sniff **B.** spectral Doppler of hepatic venous flow demonstrating greater systolic than diastolic flow, indicative or normal RA pressure **C.** spectral Doppler of hepatic venous flow demonstrating greater diastolic than systolic flow, indicative of elevated RA pressure **D.** RA = right atrial; IVC = inferior vena cava.

It is also important to recognize that the accuracy of PASP varies across study populations. In patients with severe underlying lung disease, for example, PASP has a poor positive predictive value for the diagnosis of PH. In one study of lung transplant candidates, PASP as determined by echocardiography was inaccurate (defined as a difference of > 10 mmHg from RHC) in 52% of patients and would have considerably overdiagnosed PH if used as the sole imaging modality.[17]

Mean and Diastolic PA pressure:
As with TR velocity, the velocity of the pulmonary regurgitant (PR) jet in early diastole and end-diastole can be applied to estimate mPAP and pulmonary artery diastolic pressure (PADP), respectively, using the simplified Bernoulli equation. The following equation yields mPAP: $4v^2$ + RAP, where v is the peak velocity in m/sec of the early diastolic PR jet.[18] PADP can be calculated in a similar manner: $4v^2$ + RAP, where v is the peak velocity in m/sec of the end-diastolic PR jet (Fig. 2B).[10]

Pulmonary arterial acceleration time is the time from the onset to the peak of the pulmonary artery flow waveform as measured from pulsed Doppler (Fig. 2C).[10] PH is associated with an abnormal PA flow pattern characterized by rapid acceleration,[19] mid-systolic closure, and a second peak in late systole ("flying W sign"). PA acceleration time can be used to estimate mPAP with the following validated equations: mPAP = 79 – (0.45 × PA acceleration time),[12] or mPAP = 90 – (0.62 × PA acceleration time), if the acceleration time < 120 milliseconds.[19] However, heart rate- and sample location dependency and high measurement variability have limited its utility.

A third method for the estimation of mPAP is based on the addition of RA pressure to the RV-RA mean systolic gradient. This calculation has been shown to be more accurate than mPAP

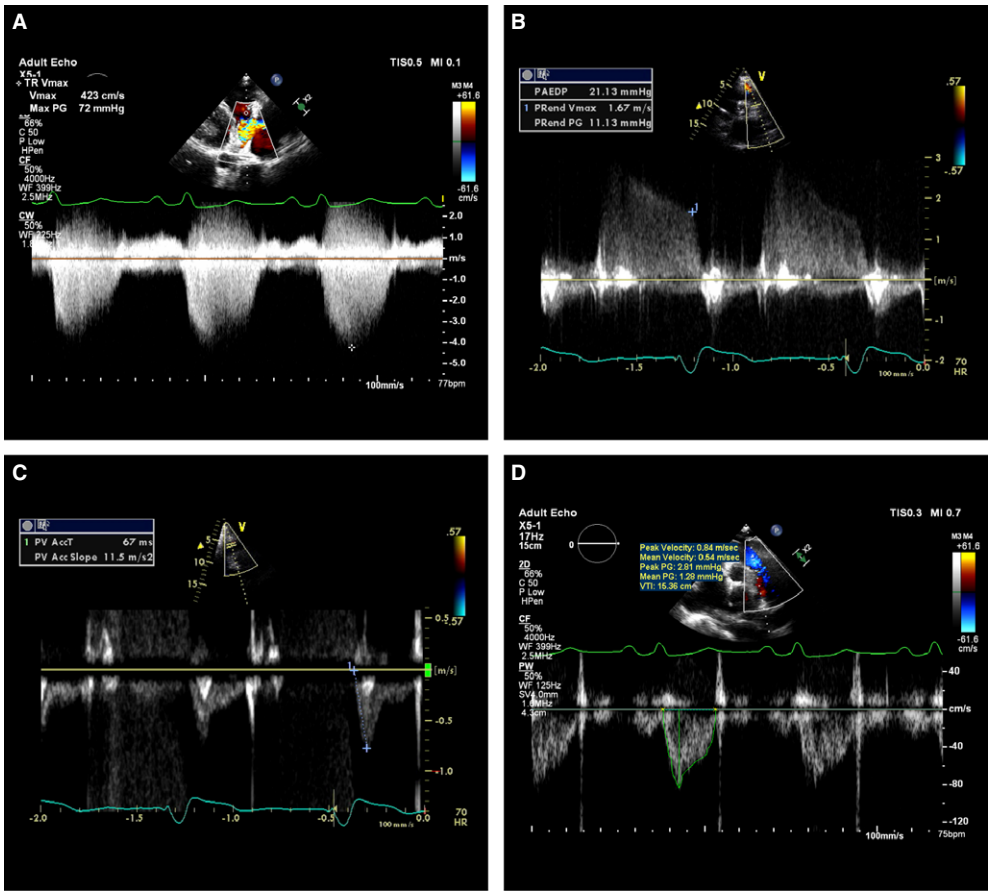

Figure 2. Measurement of right heart pressures. **A**. RV systolic pressure derived from the maximal tricuspid regurgitant jet; **B**. PA end-diastolic pressure derived from the pulmonary regurgitant jet; **C**. mean PA pressure derived from the acceleration time of PA systolic flow; **D.** RV outflow tract velocity time integral used to derive pulmonary vascular resistance. RV = right ventricular, PA = pulmonary arterial.

estimates derived from the PR jet; in fact, the mean difference between mPAP as determined by the RV-RA mean systolic gradient and RHC-derived mPAP was −1.6 mmHg, in comparison with −13.9 mmHg using the PR method.[20]

Pulmonary Vascular Resistance:
Invasively, pulmonary vascular resistance (PVR) is determined by the ratio of the transpulmonary pressure gradient to transpulmonary flow.[21] A value >3 Woods units (WU) favors a diagnosis of PAH in the presence of other requisite hemodynamic parameters (mPAP ≥ 25 mmHg with PCWP ≤ 15 mmHg). Noninvasively, PA acceleration time can be used as a surrogate for PVR. Shorter acceleration times are associated with higher PVR for heart rates within the normal range (60–100 beats per minute).[10] In particular, a PA acceleration time <90 milliseconds can identify patients with PVR ≥3 WU with 84% sensitivity and 85% specificity.[22]

A second method to assess PVR employs the ratio of TR velocity (TRV) to the time-velocity integral of the right ventricular outflow tract (TVI_{RVOT}) (Fig. 2D). The equation (TRV/TVI_{RVOT}) + 0.16 was shown to provide a good estimate of PVR, but was inaccurate when very elevated (PVR > 6 WU). The ratio TRV/TVI_{RVOT} >0.175 is considered abnormal and suggests an elevated PVR (>2 WU), while TRV/TVI_{RVOT} > 0.275 indicates a PVR > 6 WU.[21] In the latter instance, the ratio TRV^2/TVI_{RVOT} provides a more accurate noninvasive estimate of PVR. These ratios have been validated in multiple studies, the largest of which included 150 patients in an analysis comparing PVR as determined by catheterization to PVR as estimated by TRV/TVI_{RVOT} and TRV^2/TVI_{RVOT}.[21]

While PVR has inherent value in identifying significant PAH, it can also be applied to quantify RV afterload through the equation E_a = PVR/HR, where E_a represents arterial elastance. This

calculation yields a value of the afterload against which the RV must pump.[23]

The Right Ventricle:

As the clinical manifestations of PAH are largely determined by right ventricular adaptation, an understanding of the anatomy and function of the normal RV is critical. The RV is comprised of 3 regions: the smooth muscular inlet, the trabecular apex, and the infundibulum (or conus).[8,12] Although the volume of the RV is larger than that of the left ventricle (LV), RV mass is just one-fifth[8] to one-sixth[24] of the LV mass. The RV's contractility differs from the LV as well, reflecting the arrangement of its muscular layers. The RV wall is made up almost entirely of 2 muscle layers: a superficial circumferential layer and a deep longitudinal layer. Lacking an intermediate circumferential layer, RV contraction is primarily a longitudinal event.[8] RV pump function relies on 2 additional components aside from contraction of the longitudinal muscle layer: (1) inward movement of the free wall creating a "bellows" effect, and (2) traction on the free wall at sites of attachment, induced by contraction of the LV.[25] In contrast to the LV, rotational movements contribute minimally to RV contraction.

With its low mass and large volume, the RV is well designed to pump blood into the low-resistance, highly distensible pulmonary vascular bed.[24] Because of the low pressure of the pulmonary system, the RV is able to expel the same stroke volume as the LV at one-fifth the stroke work.[26] In comparison with the LV, the thin-walled RV is highly sensitive to changes in afterload.[8] The LV can withstand a pressure-overloaded state for a longer period of time than the RV; thus, ventricular enlargement occurs early in the course of pulmonary relative to systemic hypertension.[27] The initial response of the RV to PAH is homeometric (i.e., the Anrep effect); the chamber displays increased contractility and myocardial hypertrophy, with relative preservation of volume and function.[12,23] In the face of persistently elevated afterload, homeometric adaptation is inadequate and RV-arterial coupling fails. The RV thus undergoes heterometric adaptation, with gradual chamber dilation. The increase in RV dimensions coincides with deterioration of systolic and diastolic function. This maladaptive response is associated with eccentric remodeling, in contrast to the early concentric remodeling.[27] In addition, the morphology of the interventricular septum (IVS) is affected for several reasons: (1) higher RV pressures alter the relative pressure gradient between the 2 ventricles, which determines the configuration of the septum; (2) RV enlargement is limited in the rightward direction because of the nondistensible pericardium, and after a certain point, further increases in volume occur in a predominantly leftward direction; and (3) there is a late systolic delay in isovolumic relaxation of the RV.[28] Collectively, these changes promote the characteristic leftward septal bowing.

From an echocardiographic perspective, the RV is uniquely challenging to image. While the LV lends itself to geometric modeling, the RV is difficult to measure given its retrosternal position (which is poorly penetrated by ultrasound waves) and its hazy endocardial border owing to its coarse trabeculations.[29] Furthermore, the shape of the RV is complex and difficult to model geometrically, being crescentic in the coronal (or frontal) plane and triangular in the sagittal (or short axis) plane.[30]

Accordingly, no echocardiographic measurement in isolation can yield an accurate diagnosis; rather, multiple parameters are necessary to obtain a comprehensive view of the right heart. These measurements fall into 2 classes: morphological and functional.

Morphological:

Right ventricular linear measurements: Right ventricle enlargement is a predictor of mortality and treatment failure in patients with PAH, reflecting RV maladaptation to elevated afterload.[27,31]

Measurement of the linear dimensions of the RV is an integral component of echocardiographic evaluation. There are 3 particular dimensions that should be obtained at end-diastole from a RV-focused apical four-chamber view: basal, mid-cavity, and longitudinal.[8] RV enlargement is diagnosed by diameter >41 mm at the base, 35 mm at mid-cavity, or 83 mm longitudinally (Fig. 3A).[32] Of note, these values are not adjusted for age, sex, race, or body size and should therefore be employed with some caution.[12] RV size should also be interpreted in the context of LV size; in some cases, an enlarged RV may reflect global cardiac dilatation rather than an RV-specific change.[8]

The RVOT differs from the remainder of the RV in its embryologic origin[33] and merits consideration as a discrete entity for imaging purposes. The RVOT is the last part of the RV to be activated in systole,[34] and it contracts in a predominantly radial rather than longitudinal fashion.[35] With these unique features, its contribution to global systolic function is distinct from the contribution of the rest of the RV chamber. Structurally, it is made up of the subpulmonary infundibulum and

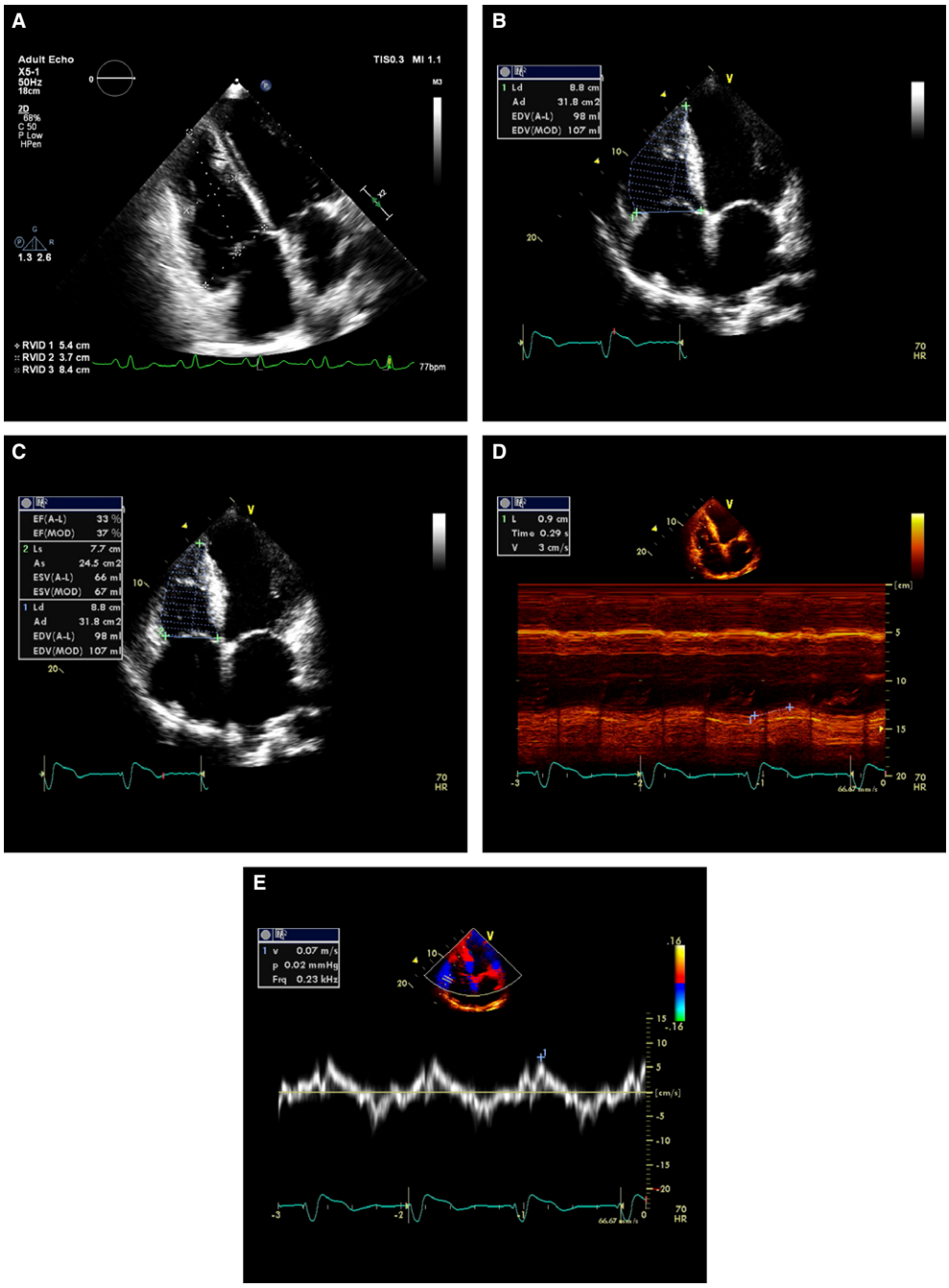

Figure 3. Morphological and functional measurements of the right ventricle. **A.** Right ventricular dimensions from the RV-focused view; RV area at end-diastole **B.** and end-systole **C.** used to calculate fractional area shortening; RV systolic longitudinal function measured from M-mode TAPSE **D.** and tissue Doppler RV S' **E.** RV = right ventricular.

the pulmonary valve.[10] Evaluation of the RVOT requires measurement at end-diastole of the proximal diameter, obtained in the parasternal long-axis view, and the distal diameter, obtained in the parasternal short-axis view.[12] Enlargement is diagnosed by a proximal diameter > 35 mm and a distal diameter > 27 mm. Although RVOT dimensions are simple to obtain, they may be unreliable in patients with skeletal deformities involving the spine or sternum.[12]

It is important to recognize that the lack of a fixed reference point for the RV makes underestimation or overestimation of RV size a common problem.[12] In addition, the measurements are largely dependent on the probe and patient position and body habitus.[8]

Free wall thickness: Right ventricle free wall thickness is an indicator of the degree of RV hypertrophy. Increased thickness can be observed not only in the setting of pressure overload but in infiltrative diseases and hypertrophic cardiomyopathies.[12,36] It should be measured in end-diastole, preferably in the subcostal or parasternal long-axis view.[10] Thickness >5 mm is indicative of RV hypertrophy, although the prognostic value of this cut point is debated.[12] RV thickness is not specific for PAH and does not help with the distinction between precapillary and postcapillary PH, but it does have good correlation with SPAP.[37]

Functional:

Fractional area change: Right ventricle fractional area change (FAC) is defined by the equation: FAC = [(end-diastolic area − end-systolic area)/(end-diastolic area)] × 100, with FAC <35% indicating systolic dysfunction (Fig. 3B).[10] RV pump function is a critical determinant of the severity of symptoms associated with PAH and is a valuable prognostic indicator.[38] The parameters necessary for this equation are best obtained in the apical four-chamber view.[39] As with other RV measurements, FAC is plagued by suboptimal visualization of the RV chamber and endocardium and therefore has relatively high inter- and intra-observer variability.[39] Despite these limitations, it has been shown to correlate with RV ejection fraction (EF) as determined by cardiovascular magnetic resonance imaging[12] and has also been shown to predict survival.[6] Furthermore, FAC is an independent risk predictor of heart failure, sudden death, stroke, and/or mortality after myocardial infarction.[40]

Tricuspid annular plane systolic excursion: Tricuspid annular plane systolic excursion (TAPSE), representing systolic displacement of the tricuspid annulus toward the RV apex, has been shown to closely correlate with RVEF (Fig. 3C).[39,41]

Tricuspid annular plane systolic excursion is widely regarded as a simple and highly reproducible measurement, as it does not depend on geometric assumptions or visualization of the endocardial border.[39,41] TAPSE <17 mm is considered abnormal,[32] although studies have shown that TAPSE <18 mm is associated with significantly reduced survival and TAPSE <15 mm is associated with particularly poor outcomes.[41] Its main drawback is manifested in the setting of regional RV wall-motion abnormalities. TAPSE assumes that the systolic motion of the tricuspid annulus is analogous to the function of the entire RV; although true in most cases, this relationship deteriorates when wall motion is not uniform throughout the chamber.[12]

RV S′: The tricuspid annular excursion during systole (RV S′) can be measured with tissue Doppler and similar to TAPSE, RV S′ provides an estimate of longitudinal systolic RV function (Fig. 3D). Values <9.5 cm/sec are considered abnormal.[32] S′ is a reproducible parameter that correlates well with other measures of RV systolic function, and it has been validated by population-based studies in healthy individuals.[12] It shares the same principal drawback as TAPSE, in that it extrapolates a function from a single portion of the RV to represent global wall function. In addition, being a Doppler technique, it is highly intercept angle dependent.

Myocardial Performance Index: While the aforementioned parameters have addressed systolic function, the right ventricular index of myocardial performance (RIMP) provides an integrated assessment of both systolic and diastolic function. RIMP is calculated by the equation (IVRT + IVCT)/RVET, where IVRT is isovolumic relaxation time, IVCT is isovolumic contraction time, and RVET is right ventricular ejection time. These measurements can be obtained with either pulsed-wave or tissue Doppler, but tissue Doppler minimizes error related to RR interval variability and is therefore the preferred method.[10] The upper limit of normal is 0.54 for tissue Doppler and 0.43 for pulsed-wave Doppler. Unlike many other measures of RV function, RIMP requires no geometric assumptions.[42] It is reproducible and well validated in the literature,[12] and it is an independent predictor of adverse outcomes in patients with PAH.[43] It must be interpreted with caution in patients with elevated RA pressures, atrial fibrillation, or other conditions associated with heart rate variability.[10]

RV Isovolumic Acceleration:

Right ventricular myocardial acceleration during isovolumic contraction (IVA) is a sensitive, relatively load-independent, tissue Doppler parameter of RV contractility used primarily to detect subclinical RV disease (e.g., in patients with obstructive sleep apnea, obstructive lung disease, and scleroderma without PH). It is calculated as the tissue Doppler-derived peak myocardial velocity during isovolumic contraction divided by the time to peak velocity. It is also used to assess RV contractile reserve[44]; thus, in a small study of patients with PAH, the change in IVA with dobutamine correlated with

the change in cardiac output and the hemodynamic response to stress.[45]

Right Atrial Imaging:

Area:

The right atrium (RA) promotes filling of the RV through 3 main functions: it acts as a reservoir for systemic venous return during ventricular systole, a passive conduit in early ventricular diastole, and a contracting pump during late ventricular diastole.[10] The muscular walls of the RA are particularly thin, such that the chamber responds to volume and pressure overload by dilating rather than undergoing hypertrophy.[46] In the setting of PAH, RA enlargement reflects chronic remodeling secondary to TR and RA hypertension.[39] In fact, RA enlargement is one of the classic features of prolonged PH and tends to parallel RV systolic and diastolic dysfunction.[46] Right-to-left shift of the interatrial septum is another marker elevated RAP; septal bowing can be observed throughout the cardiac cycle.[12]

RA area should be measured at the end of ventricular systole, when chamber size is at its maximum, by planimetry in the apical four-chamber view (Fig. 4).[12] The tracing should extend from the lateral aspect of the tricuspid annulus to the septal annulus, closely following the endocardium.[10] An area >18 cm^2 is considered abnormal.[10] Although area is easily obtained, volume is the preferred measure of RA size and should be measured with a single plane area-length or disk summation method. Normal values for RA volume are 25 $\pm$ 7 mL/m^2 in men and 21 $\pm$ 6 mL/m^2 in women.[32]

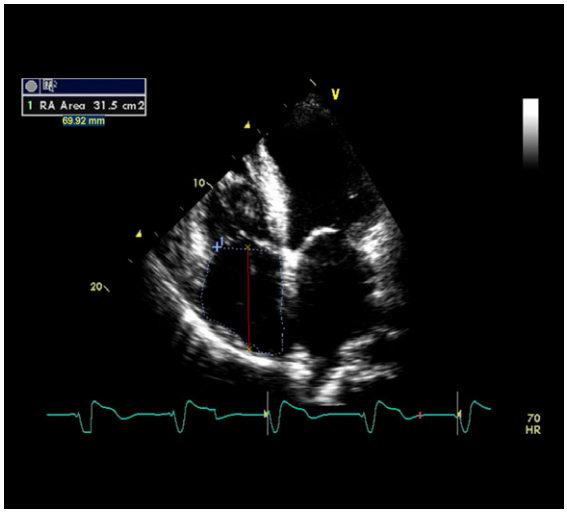

Figure 4. Measurement of right atrial (RA) area from the four-chamber view at atrial end-diastole (ventricular end-systole).

Left Ventricular Imaging:

LV E/E′ ratio:

In addition to the echocardiographic assessment of LV volume, systolic function, and mass, Doppler can be used to assess diastolic function. Early diastolic filling is manifested by the E-wave, while E′ represents the velocity of the mitral annulus during early diastole. In the presence of diastolic dysfunction and increased LA pressure, E′ will be low and E will be high, resulting in an elevated E/E′ ratio.

The E/E′ ratio is particularly helpful in separating precapillary from postcapillary PH. LV filling pressures are typically normal in pure precapillary PH, reflected by an E/E′ < 10. On the other hand, elevated LV filling pressures are a hallmark of postcapillary PH. Patients in this group classically have an elevated E/E′ ratio.[8,47]

LV Eccentricity Index:

The curvature of the IVS provides insight into the relationship between the 2 ventricles in terms of volume and pressure, as the septum is affected differently by each. In the setting of RV volume overload, the septum shifts leftward and flattens in mid-to-late diastole, leaving LV morphology intact at end-systole.[12] On the other hand, septal shift and flattening occur mainly during systole in response to RV pressure overload. Septal flattening, producing a characteristic D-shape when viewed from the parasternal short axis, is one of the echocardiographic hallmarks of PAH (Fig. 5).[15]

The phenomenon of systolic bowing can be expressed in terms of the LV eccentricity index (EI), a ratio of the LV anteroposterior and septolateral dimensions.[48] These dimensions should be measured in the short-axis view at the mid-papillary level during end-diastole.[48] A value >1 is abnormal and suggests RV overload. EI is highly reproducible, largely because it relies on left heart measurements. It can be used to predict the presence of precapillary PH[48] and has prognostic utility, particularly when evaluated alongside TAPSE.[39]

Exercise Stress Echocardiography:

While there currently is little evidence supporting the addition of an exercise criterion to a definition of PH,[7] several recent studies describe the predictive value of 6-minute walk (6 MW) stress echocardiography. By increasing cardiac output, stress testing may unmask subtle pulmonary vascular disease and facilitate early diagnosis.[49] In particular, exercise testing can elicit abnormal mPAP-cardiac output (Q) responses which may precede the development of overt PH. In one study in patients with connective tissue disease, subjects with increased ΔmPAP/ΔQ during

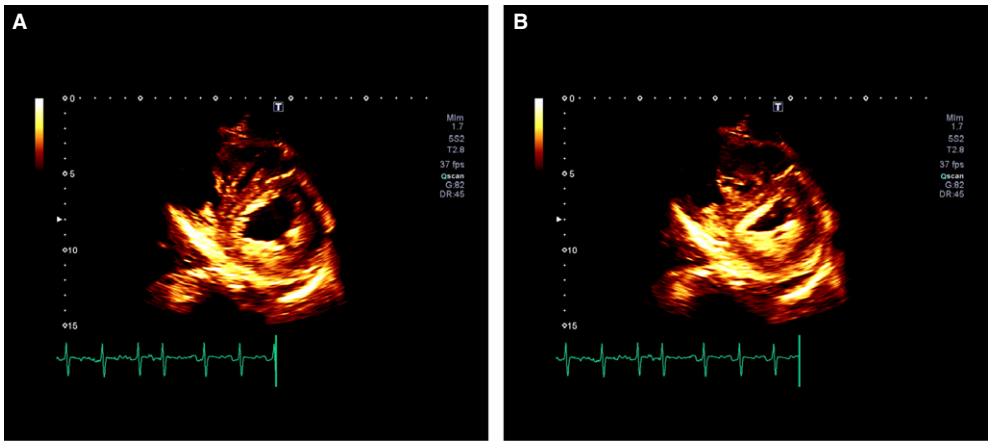

Figure 5. Position of the IVS reflecting RV overload. **A**. Flattening of the IVS at end-diastole, indicative of RV volume overload; **B**. flattening of the IVS at end-systole, indicative of RV pressure overload. IVS = interventricular septum; RV = right ventricular.

6 MW testing had significantly shorter event-free survival than their counterparts with a normal ratio.[50] These results suggest that among high-risk populations, 6 MW stress echocardiography has the potential to identify patients most likely to develop PH.

Prediction Models:

The diagnostic accuracy of echocardiography in PH increases when multiple parameters are evaluated concurrently. Recent studies have applied this principle to develop echocardiographic prediction rules for the diagnosis and classification of PH. In one of the earliest prediction studies, the authors identified 3 echocardiographic variables that could collectively distinguish precapillary from postcapillary PH using the following scoring model: +1 point for a LA anterior-posterior dimension <3.2 cm, +1 point for a mid-systolic notch or acceleration time of PA flow <80 milliseconds, −1 point for lateral mitral E/E′ >10, and −1 point for a LA anterior-posterior dimension > 4.2 cm. PVR increased stepwise with scores from −2 to +2, and a score ≥0 was 100% sensitive and 63% specific for precapillary PH.[51] Building upon this work, D'Alto et al.[48] created an improved prediction rule based on 5 variables: right heart chamber larger than left, LV EI > 1.2, dilated IVC without inspiratory collapse, E/E′ ratio ≤ 10, and location of the RV (i.e., whether it forms the apex of the heart). They found that this score had a positive predictive value of 67.9% and a negative predictive value of 77.5% for precapillary PH. In a smaller study, it was shown that the E/E′ ratio and E/A ratio could be applied to reliably predict postcapillary PH.[52]

Such prediction models can be strengthened by the incorporation of other noninvasive data, such as laboratory and pulmonary function tests. For instance, in the largest study to date on a noninvasive screening algorithm for the diagnosis of precapillary PH, the investigators employed a two-step approach for the detection of PAH. The first tier consisted of 6 nonechocardiographic variables, while the second tier consisted of 2 echocardiographic variables: RA area and TR velocity. With this stepwise approach, the prediction rule failed to detect only 4% of PAH patients (false negatives).[53] Of note, this study focused exclusively on patients with systemic sclerosis, limiting the ability to generalize to other causes of PH. Moreover, the positive predictive value of a prediction model is dependent on the incidence of disease in the study population.

The idea of an echocardiographic prediction model to minimize the need for invasive analysis is certainly attractive, but no current consensus exists. While the echocardiographic changes of PAH have been extensively studied individually, the literature on their combined utility is relatively sparse and further investigation is needed.

Emerging Modalities:

3D Echocardiography:

2D echocardiography is limited in its ability to assess RV volume and EF. 3D echocardiography can fill in these gaps with impressive accuracy.[54] It underestimates volume less frequently and has less intra- and inter-observer variability compared with conventional echocardiography.[8] Comprehensive shape analysis is also possible with 3D imaging, and such data may highlight subtle differences across different categories in PH.[55] An RV EF value <45% is considered abnormal, although age and gender values are available.[32]

Speckle Tracking Echocardiography:
Myocardial strain is defined as the change in distance between 2 points divided by the initial length, and strain rate is its derivative.[6] Wall motion measurements obtained by conventional echocardiography (displacement and velocity) cannot separate active from passive movement of a myocardial segment, but strain and strain rate imaging are able to make this distinction.[56] Speckle tracking echocardiography (STE) enables objective and quantitative evaluation of regional and global myocardial function.[57] Although most studies have focused on STE in the evaluation of LV function, recent research has validated it for the RV as well.[58,59] Briefly, this imaging technique is rooted in the ability to map displacement of speckles during the cardiac cycle. STE offers a comprehensive view of myocardial deformation (strain and strain rate) in 3 primary planes (longitudinal, radial, and circumferential), is not limited by angles of insonation or cardiac translational movement,[57] and has acceptable intra-observer and inter-observer variability.[56] RV strain and strain rates can be obtained with Doppler tissue imaging (DTI), but the angle dependency of DTI is a disadvantage. Strain imaging can identify the early signs of RV dysfunction, and these parameters can be followed throughout treatment.[8] While free wall STE global RV strain is feasible for clinical use, normative data are limited and subject to vendor and software differences; a value less negative than −20% is considered abnormal.

Furthermore, RV strain is a powerful predictor of clinical outcome in PAH. Worsening RV strain is associated with an increased risk of all-cause and cardiopulmonary mortality.[60] This relationship persists even after adjustment for WHO functional class, cause of PH, PASP, PVR, and RAP. In one study, RV free wall strain less negative than −12.5% was found to predict subsequent right-sided heart failure and clinical deterioration.[61] Similarly, another study stratified patients by RV strain quartile and found that survival decreased as strain increased.[60] Few other echocardiographic parameters have demonstrated such reproducible prognostic utility.

Prognostic Role of Echocardiography:
Of the measurements described, some of the strongest predictors of adverse outcome include right heart dimensions, TR, TAPSE, and RV strain (Table II).[23,37,62] RIMP is another powerful prognostic indicator, reflecting integrated (systolic and diastolic) function of the RV.[42] In addition, the presence of pericardial effusion portends a poor prognosis.[23] These findings underscore the critical importance of RV function in the natural history of PAH.

Conclusion:
Echocardiography is a powerful screening tool for PAH, and it allows for the study of the pathologic changes observed in the right heart in response to chronically elevated afterload. It is poised to become even more valuable as imaging techniques continue to advance. Its availability, cost-effectiveness, and safety make it an ideal modality for the assessment of right heart structure and function. Further research is needed in the area of prediction models to detect and classify PH, as the development of a well-validated algorithm could diminish the need for invasive testing.

TABLE II

Echocardiographic Prognostic Indices

Echocardiographic Indices	Supporting Studies	Sample Size	Follow-Up	Outcome
Pericardial effusion	Raymond et al. (2002)[63]	81	12 months	Death, lung transplantation
	Brierre et al. (2010)[43]	79	12 months	Death
RA Size	Bustamante-Labarta et al. (2002)[64]	25	29 months	Death, heart–lung transplantation
RIMP	Brierre et al. (2010)[43]	79	12 months	Death
RV dimensions	Van Wolferen et al. (2007)[31]	64	12 months	Death
	Ghio et al. (2011)[65]	72	38 months	Death
RV free wall strain	Sachdev et al. (2011)[61]	80	24 months	Death
	Fine et al. (2013)[60]	575	16.5 months	Death
TAPSE	Forfia et al. (2006)[41]	63	19.3 months	Death
	Brierre et al. (2010)[43]	79	12 months	Death
	Ameloot et al. (2014)[66]	78	3.5 years	Death
TR	Bustamante-Labarta et al. (2002)[64]	25	29 months	Death, heart–lung transplantation

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