# Consensus or Controversy: Do Recent Advances Shift the Debate for the Use of Echocardiography Versus Cardiac Magnetic Resonance Imaging of the Right Ventricle in Pulmonary Arterial Hypertension?

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Pulmonary arterial hypertension (PAH) is a progressive, often lethal condition originating in the pulmonary arteriolar tree. It is typically manifested in stereotypical changes in the right ventricle (RV). RV dysfunction is an important mediator of patient symptoms in PAH, and RV failure is the most common cause of mortality in PAH patients. Because of the physiologic importance of the RV, RV imaging is critical in the initial diagnostic evaluation and serial assessment of PAH patients, and can provide indirect insight into the status of the disease at the level of the pulmonary vasculature. This article will focus on whether technological advances in imaging have shifted the debate toward which modality is optimal both for routine clinical practice and for a possible surrogate endpoint in PAH clinical trials.

Pulmonary arterial hypertension (PAH) is a progressive, often lethal condition characterized by pulmonary vascular remodeling, pathologic rise in right ventricular (RV) afterload, and increase in pulmonary artery (PA) pressures.[1-3] Though PAH is a disease originating in the pulmonary arteriolar tree, it is typically also manifested in stereotypical changes in the RV, which is normally morphologically smaller and thinner-walled than the left ventricle (LV), in keeping with its design to deliver blood flow through a low-resistance pulmonary circuit.

However, as pulmonary vascular resistance (PVR) increases, RV hypertrophy, RV dilatation, and ultimately RV dysfunction occur.[4,5] Indeed, RV dysfunction is an important mediator of patient symptoms in PAH, and RV failure is the most common cause of mortality in PAH patients.[6,7]

Because of the physiologic importance of the RV, RV imaging is critical in the initial diagnostic evaluation and serial assessment of PAH patients, and can provide indirect insight into the status of the disease at the level of the pulmonary vasculature. Moreover, newer therapies for the treatment of patients with PAH are now being investigated, which may directly impact RV function, rather than solely causing pulmonary vasodilatation.[8] Despite this critical role in the pathophysiology of PAH, imaging assessment of RV structure and function has infrequently been used as a primary endpoint in large, randomized clinical trials of PAH therapeutic agents, and controversy still exists as to the most appropriate method of RV imaging in both clinical and research settings.

Two-dimensional (2D-TTE) and Doppler transthoracic echocardiography (DE) has been a mainstay of the clinical assessment of patients with PAH. However, due to the complex 3-dimensional geometry of the RV, an accurate assessment of RV volumes and ejection fraction (EF) has been challenging to obtain via traditional 2D-TTE.[9] However, echocardiography is inexpensive, widely available, and can provide important hemodynamic information via Doppler.

Cardiac magnetic resonance imaging (CMR) has been considered the gold standard for imaging of the RV due to its ability to provide accurate RV volumes, right ventricular ejection fraction (RVEF), and to simultaneously evaluate for evidence of congenital heart disease and shunts.[10] Challenges with CMR have included requirement for breath holding, lack of widespread availability, expense associated with magnetic resonance imaging (MRI) equipment, and issues with noncompatible implanted devices and claustrophobia. Over the past decade, there have been dramatic advances in 2D-TTE, 3-dimensional echocardiographic (3D-TTE) technology, and increased understanding of the prognostic significance of existing surrogates of RV function by echocardiography. Similarly, CMR technology has continually evolved to allow faster acquisition, tissue characterization, and flow dynamics.

The question remains as to whether these technological advances have shifted the debate toward which modality is optimal both for routine clinical practice and for a possible surrogate endpoint in PAH clinical trials. This debate forms the topic of this article.

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## ECHOCARDIOGRAPHY: FOUNDATION FOR RV ASSESSMENT IN CLINICAL PRACTICE AND PAH CLINICAL TRIALS

Doppler echocardiography and 2D-TTE is frequently the first diagnostic test employed in the evaluation of patients with known or suspected PAH, in part because of its widespread availability, ease and speed of image acquisition, lack of ionizing radiation, and because patients with what may ultimately prove to be PAH are often initially referred for evaluation of unexplained dyspnea. Echocardiography also has the advantage of providing hemodynamic evaluation such as an estimate of PA pressures and LV filling pressure, and the ability to evaluate for valvular heart disease and LV systolic and diastolic dysfunction.[4,11,12]

Traditional 2D-TTE has been more limited in terms of the assessment of RV structure and function in part because of the triangular, crescentic geometry of the RV, which is difficult to image from a single echocardiographic view and makes volumetric assumptions used in quantitative assessment of left ventricular ejection fraction (LVEF) untenable for calculating RVEF.[13] However, despite the inability of 2D-TTE to provide RV volumes and RVEF, a number of surrogates of RVEF have been developed and validated using 2D, M-mode, and tissue Doppler.

## NEW EVIDENCE AND APPLICATIONS FOR EXISTING SURROGATES OF RV STRUCTURE AND FUNCTION

2D-TTE assessments of RV function have generally used single-plane measurements acquired from the apical 4-chamber view. Several of these measurements rely on the unique contractile pattern of the RV, in which the majority of global RV contraction occurs in the longitudinal axis vs the transverse axis in both the normal RV and in patients with PAH.[14]

Tricuspid annular plane systolic excursion (TAPSE) is perhaps the most common of these surrogates, obtained by measuring the displacement of the lateral tricuspid annulus between systole and diastole either by M-mode or 2D-TTE. The great advantage of TAPSE is that it is very simple to acquire, does not require specialized equipment or high endocardial definition, and is easily reproducible.[13,15] TAPSE has proven to be a useful measurement that has correlated well with RVEF by radionuclide angiography and 3D-TTE.[15,16] In the past decade, TAPSE has also been shown to correlate well with invasive hemodynamic variables such as cardiac index and clinical outcomes such as survival in patients with PAH.[17,18] Low TAPSE values have correlated with lower stroke volume index and have been associated with higher transplant free mortality.[19]

Similar to TAPSE, tissue Doppler peak systolic velocity of the lateral tricuspid annulus (TD S') is another measure of longitudinal contraction of the RV, which, as the nomenclature implies, uses tissue Doppler rather than M-mode or 2D. A TD S' velocity of less than 10 cm/s is suggestive of RV dysfunction,[20] and low TD S' velocities are associated with a reduced cardiac index [21] and correlate with invasively derived stroke volume index.[21,22] While these longitudinal measures of RV function have been increasingly validated in the last decade, some of their limitations have also become apparent. TAPSE has not correlated well with RVEF in patients with repaired congenital heart disease,[23] and the reason for this observation may be that post cardiac surgery, there is a fundamental change in the global contractile pattern of the RV, with greater proportion of contraction in the transverse axis and lower TAPSE values overall.[24]

Right ventricular fractional area change (RVFAC) may prove a better surrogate of RV function in the post cardiac surgery patients, because it incorporates both longitudinal and transverse components of RV contraction into a single measurement. RVFAC is defined as the ratio of end-diastolic area minus end-systolic area divided by end-diastolic area obtained from the apical 4-chamber view. RVFAC of less than 36% is defined as RV dysfunction.[9]

Though RVFAC has many of its own limitations, when measured carefully, it correlates well with RVEF and global RV function.[25,26] The major disadvantage of RVFAC is that it requires superior endocardial definition compared to TAPSE and TD S' to allow the reader to delineate both systolic and diastolic areas appropriately, and can have greater variability based on the imaging alignment used to optimize the 2D-TTE image as well as due to subjective assessment of where the endocardium is defined. As a result, the measurement of RVFAC is typically less reproducible than TAPSE and TD S' in clinical practice.

The last DE measurement of RV function commonly employed in PAH patients is the RV myocardial performance index (MPI) or Tei index. This can be measured using either pulse wave Doppler or (in the current era) more frequently with tissue Doppler; the latter is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by RV ejection time. MPI is a combined measurement of both RV systolic and diastolic function and has the potential advantage of being relatively independent of heart rate, loading conditions, and tricuspid regurgitation.[9,27] The MPI has correlated well with clinical and hemodynamic variables such as cardiac index and PA pressures in PAH and chronic thromboembolic pulmonary hypertension (PH), has been predictive of survival, and has been used as an outcome measure in previous studies of PAH therapy.[28-30]

Current guidelines suggest the use of 2 or more quantitative metrics of RV function in patients with PH and/or RV dysfunction,[9] and as a result, TAPSE, TD S', and RVFAC form the basis for quantitative assessment of RV function in many PAH centers, whereas MPI is more commonly used in research settings as its calculation is somewhat cumbersome. However, these metrics are now being supplemented by newer measurements, including noninvasive estimates of PVR, RV strain imaging, and 3D assessment of RV volumes and RVEF.

## NEWER DEVELOPMENTS IN ECHOCARDIOGRAPHIC IMAGING OF THE RV

### *Noninvasive Estimates of PVR*

An accurate and simple noninvasive measurement of PVR is one of the "holy

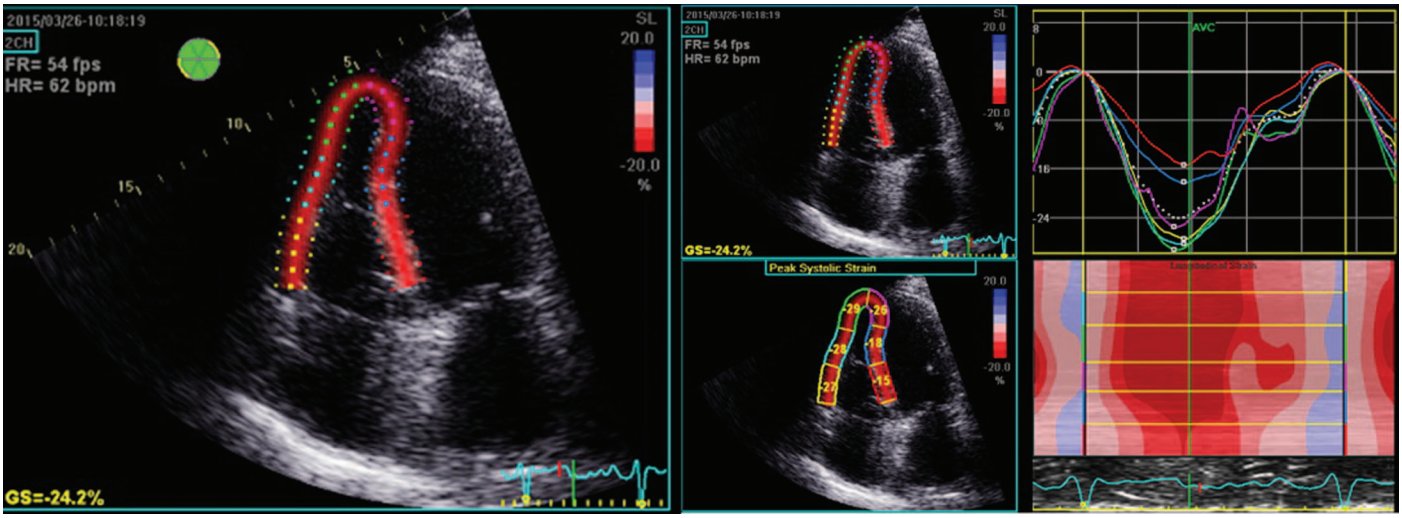


Figure 1: Right ventricular strain imaging from apical 4-chamber view demonstrating global and regional longitudinal strain.

grails" of the noninvasive assessment of the RV in PAH, because conventionally this information could only be provided by catheterization, and knowledge of PVR might prove extremely valuable to helping clinicians better phenotype patients with known or suspected PH. Two broad approaches have been employed in terms of the echocardiographic estimation of PVR: the first being fully quantitative and providing an exact PVR estimate via a formula for PVR, while the second has been semi-quantitative, providing an estimated range of PVR.

The fully quantitative measures of PVR have sought to mimic the catheterization-based PVR calculation by dividing an estimate of transpulmonary pressure gradient, typically based on tricuspid regurgitant jet velocity, by an estimate of RV stroke volume or PA flow. Abbas et al published the first such formula, which was reasonably accurate when compared to invasively derived PVR at relatively low PVR,[31] but was less reliable at higher PVR.[32] Moreover, this formula was inherently a measure of total pulmonary resistance rather than PVR per se, as it did not include a measure of left atrial pressure in the calculation. This element was incorporated by a revised formula developed by Dahiya and Marwick using the pulse wave/tissue Doppler E/E' ratio as a left atrial pressure estimate: PVR = (pulmonary artery systolic pressure [PASP] – E/E')/right ventricular outflow tract (RVOT) velocity time integral (VTI). This formula was subsequently validated in a cohort of PAH patients with a broader range of PVR values including at high PVR.[33]

An alternative approach to this fully quantitative assessment has been a semi-quantitative method evaluating the pulse wave Doppler profile in the RVOT. In patients with pulmonary vascular disease, the normally smooth and parabolic RVOT pulse wave Doppler envelope becomes notched, presumably due to wave reflection from the incident wave of ejected blood against the stiff, non-compliant pulmonary vascular tree.[34] The stiffer and more noncompliant the pulmonary vasculature, the earlier the reflected wave returns, causing the notch to fall earlier in the RVOT pulse wave Doppler profile. In their study, Arkles et al demonstrated that PAH patients with a mid-systolic notch typically had PVR >5 Wood units.

In an attempt to combine both of these approaches, Opotowski et al incorporated the presence of Doppler notching in the RVOT into a revised fully quantitative equation to estimated PVR: (PVR = (PASP/RVOT VTI) + 3 if notch present). This was validated in a larger cohort of patients with PAH and correlated with invasively derived PVR better than the Abbas formula across PVR values.[35]

### *RV Strain Imaging*

More recently, strain imaging, which measures the deformation of myocardial tissue rather than translational motion, has been applied to imaging of the RV using both tissue Doppler imaging as well as newer speckle-tracking technology. RV strain imaging can be obtained as global and regional longitudinal strain, as well as radial and circumferential strain, though in practice RV longitudinal strain is most commonly reported. The advantage of strain and strain rate imaging over other contemporary methods to assess RV function is that it is less influenced by translational motion of the RV than other metrics such as TAPSE, may be more sensitive for detecting early RV dysfunction, and can provide information regarding regional variations in RV function Figure 1).[36-38]

RV global longitudinal strain has correlated well with invasive hemodynamic variables, has been associated with survival in patients with PAH,[39,40] and overall may be more accurate as a measure of global RV function than traditional longitudinal measurements. RV strain does have some important limitations in that, similar to RVFAC, it is somewhat dependent on endocardial definition to provide accurate speckle tracking of the RV septum and free wall.[41] Strain imaging is also somewhat variable based on the ultrasound equipment used to acquire images and the specific vendor, although vendor-independent platforms have also been developed recently. Lastly, there is a relative paucity of normative data for strain imaging in the RV. Nevertheless, RV strain imaging is gaining greater traction

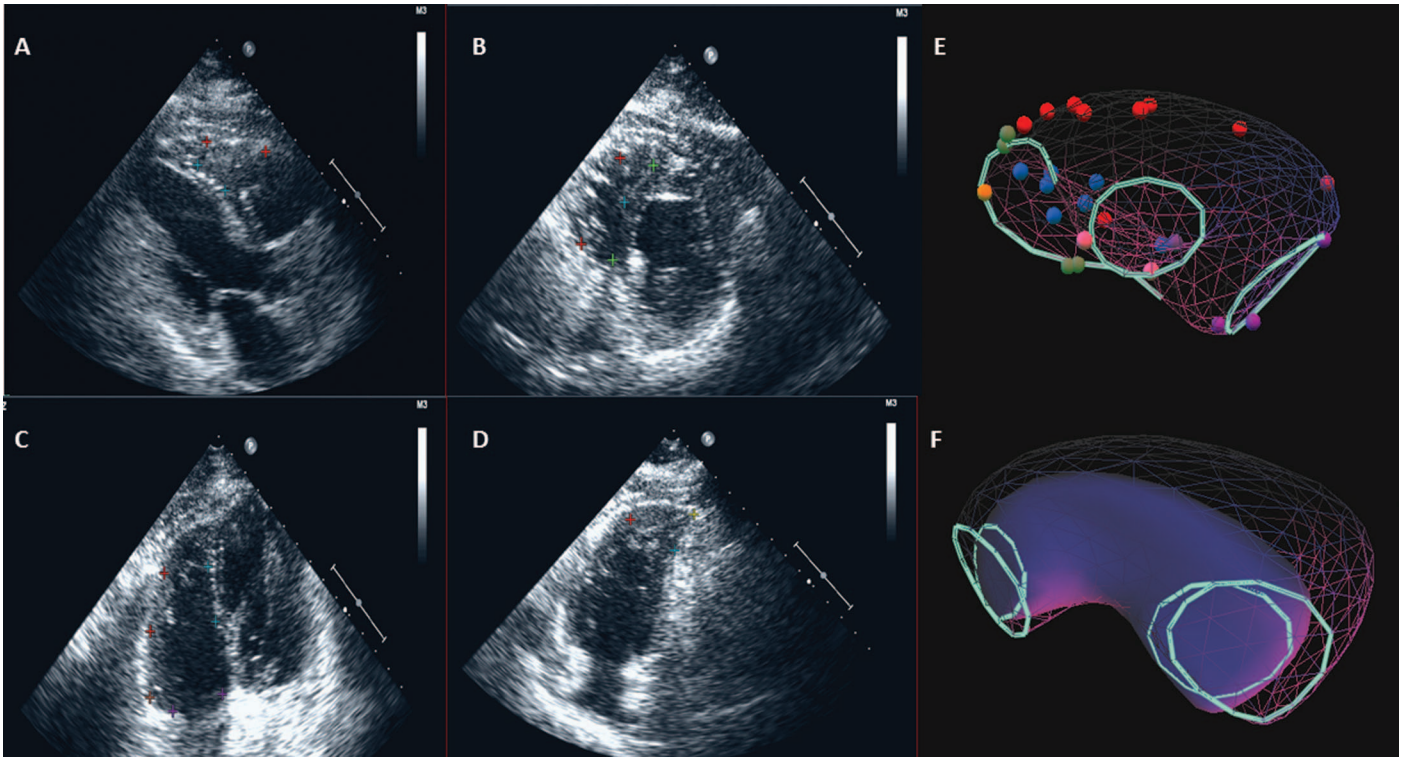


Figure 2: Definition of anatomic points from standard 2D-TTE views using the Ventripoint system (Panels A–D) to generate 3D reconstruction of the RV (Panel E) in both diastole and systole (Panel F).

in both clinical and research settings as a measure of RV function in PAH patients, and is likely to be at least one imaging endpoint in future PAH clinical trials.

### *Real-Time 3D Echocardiographic Imaging*

With continued advancement in ultrasound technology, 3D imaging of the RV has become increasingly employed. This had initially required a full volume acquisition of the RV, typically from the apical 4-chamber view over several beats, with breath holding and a summation method of discs to reconstruct RV volumes.[42,43] Challenges in 3D imaging include limited spatial and temporal resolution, and the difficulty in imaging the entire RV from a single echocardiographic view, especially with a very dilated RV, which is often seen in PAH. In addition, offline reconstruction of the RV to render RV volumes and EF could be quite time-consuming, and artifacts could be introduced due to motion over a breath hold. The major advantage, however, is that 3D-TTE could provide an estimate of RV volumes and RVEF, and can supplement the 2D and DE assessment in select patients.[42,44]

A variety of small clinical studies have demonstrated that RV volumes and RVEF by 3D-TTE have good agreement with those generated by CMR, although 3D-TTE tended to slightly underestimate RV volumes.[42,43] Newer 3D-TTE systems now permit the acquisition of 3D RV volumes in real time over a single beat, speeding up acquisition and reducing the likelihood of artifacts introduced over several beats of acquisition. Single-beat 3D-TTE has proven feasible—obtainable in 96% of patients in a small study of PAH patients, and again has shown good agreement with CMR volumes with tendency to slightly underestimate stroke volume and RVEF.[45]

### *Knowledge-Based 3D Reconstruction of the RV From 2D Anatomical Landmarks: The Ventripoint System*

Some of the disadvantages of traditional 3D-TTE imaging might be overcome by use of a newer technology termed knowledge-based reconstruction. This utilizes a knowledge database of RV geometry in PAH to interpolate RV contours between known anatomical landmarks such as the RV apex, septum, tricuspid and pulmonic annulus. Using a proprietary probe and reconstruction software, this technology allows for rapid 3D reconstruction of RV volumes and RVEF from standard 2D-TTE images (Figure 2), without the requirement for imaging the entire RV in a single view. This technology was first evaluated in a small cohort of patients with repaired Tetralogy of Fallot in comparison to CMR, and showed similar RV volumes and EF.[46] Knowledge-based reconstruction was then studied in 27 patients with PAH in comparison to CMR, and the 3D-TTE volumes correlated well with CMR, but in contrast to traditional 3D-TTE, RV volumes were slightly higher using knowledge-based reconstruction vs CMR.[47]

The commercial application of this technology is the Ventripoint imaging system, which was evaluated in a multicenter clinical trial in PAH patients in comparison to CMR. Though full results of the study have not been published to date, the Ventripoint system reportedly generated similar volumes to

CMR performed within 24 hours of the Ventripoint echocardiogram, and based on the results of this trial data, the Ventripoint system has been approved by the United States Food and Drug Administration for RV quantification. To date there has been relatively little clinical experience with this technology in PAH patients outside of the clinical trial arena, but this system certainly has the potential to significantly enhance routine echocardiographic assessment of RV volume and EF. Using the Ventripoint technology might be a less costly secondary endpoint in future PAH clinical trials.

### CMR Should Be Utilized in Both Clinical Practice and PAH Clinical Trials

To advance the field of PAH, imaging must offer more than a simple, subjective evaluation of RV size and function. CMR, with its 3D capabilities and tissue characterization techniques, not only provides accurate diagnostic information, but data obtained from CMR can be used for risk stratification purposes and for gauging treatment response. In addition, CMR can provide substantial mechanistic insight into this disease so that therapy can be targeted more effectively.

## ASSESSMENT OF RV MASS, VOLUME, AND FUNCTION IS BEST PERFORMED BY CMR

CMR is the gold standard for assessment of RV mass, volume, and function.[48,49] No other noninvasive technique can provide accurate and reproducible measurements of these parameters without any radiation or contrast exposure. In 64 patients with PAH, decreased stroke volume index and RV end-diastolic volume index by CMR were significantly associated with poor outcomes.[50] The statistical significance for RV end-diastolic volume was even greater when corrected for age, gender, and body surface area.[51] In a separate study evaluating 110 patients with incident PAH, both a decrease in RVEF at baseline and a change in RVEF by only 5% over 12 months were associated with poor survival in a multivariate analysis.[52]

In an effort to overcome the 2D limitations of echocardiography, 3D-TTE was developed to measure RV volumes and function. Feasibility and reproducibility have been studied in normal and abnormal right ventricles, but there are very little data in patients with PAH. In addition, 3D-TTE tends to underestimate RV volumes compared to CMR even in healthy hearts.[53] Despite technological advances in the last 3-5 years, offline analysis remains time-consuming, and expertise is needed to acquire the appropriate 2D image. Furthermore, CMR appears to be more cost effective in detecting incremental changes in RVEF and RV end-diastolic volume—an attractive quality when considering imaging modalities for clinical trials.[54]

Few of the pivotal trials for current PAH therapies examined imaging parameter changes, but several smaller studies found significant changes in CMR-derived mass, volume, and RVEF with these medications.[55-59] 2DE-derived parameters have also been explored as potential endpoints, but the superior accuracy, reliability, and reproducibility of CMR makes it ideal for clinical studies. Recently, the EURO-MR study showed significant changes in CMR indices of RV function and 6-minute walk distance after 12 months of PH-directed therapy.[60] Although future PAH-therapy trials should include CMR parameters for greater insight into how these drugs work, the clinical relevance of a change in these measurements must be established before they can be considered true clinical endpoints.

## NEWER DEVELOPMENTS IN CMR IMAGING OF THE RV

### *RV Strain Imaging*

One of the most promising novel imaging techniques is RV myocardial strain. Strain is a measure of myocardial deformation and is calculated as the percentage change in length of the myocardium during relaxation and contraction. Strain can be measured in the longitudinal, circumferential, and radial directions. For RV strain, global longitudinal strain, which averages the peak systolic strain throughout the RV myocardium, is the most commonly reported parameter.

A variety of CMR methods, many based on conventional tagging techniques, have been used to calculate myocardial deformation of the RV. Recently, multimodality tissue tracking of the RV has been shown to correlate well with other CMR strain techniques as well as RVEF, and can be applied retrospectively to standard cine images.[61]

While 2DE-derived RV strain has the potential to provide a more accurate assessment of RV function compared to conventional 2D-TTE parameters, CMR-derived RV strain may shed additional light on the mechanism by which the RV becomes dysfunctional. For example, little data exist regarding RV circumferential strain because short-axis images of the RV with 2D-TTE are difficult to obtain for speckle-tracking analysis. CMR, due to its multiplanar capabilities and improved spatial resolution, can easily measure this variable. This parameter is potentially important, as Kind et al showed that transverse wall motion of the RV might be a better reflection of RV function than longitudinal wall motion.[62,63]

In addition, while regional RV longitudinal strain is highly variable by 2D-TTE and rarely reported, regional strain by CMR is more feasible, reliable, and may detect changes in RV structure prior to a decrease in RVEF.[64,65] Although not yet studied in the RV, changes in regional tissue velocities by CMR-derived tissue phase mapping might also identify early myocardial disease before a decline in ventricular function is detected.[66]

### *Delayed Contrast Enhancement and T1 Mapping Imaging*

A great strength of CMR is its ability to characterize tissue and detect abnormal areas of myocardium. Not only does RV dysfunction play a key role in the pathophysiology of PAH, but, in one study, an RVEF less than 35% was better than PVR at predicting adverse outcomes.[52] This suggests that there are changes within the RV myocardium itself that contribute significantly to the overall disease process.

Delayed contrast enhancement of the RV insertion points is a common finding in PAH patients and reflects either

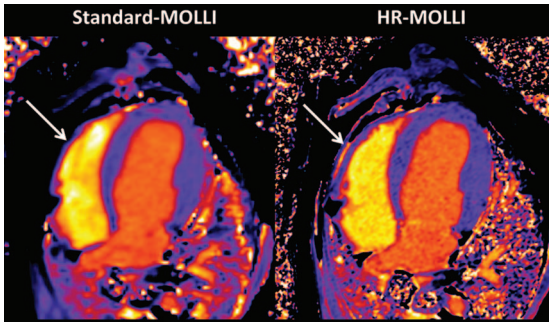


Figure 3: Comparison of standard CMR technique (Standard-MOLLI) for T1 mapping to high-resolution CMR technique (HR-MOLLI) for T1 mapping. Note the better resolution of the RV free wall (white arrows). MOLLI = modified look-locker inversion recovery.

fibrosis or myocardial fiber disarray in this region of the heart. Multiple publications have explored the clinical significance of this finding.[67-70] Although the existence and extent of delayed enhancement consistently correlates with increased RV mass, volumes, and PA pressure, it does not appear to independently predict outcomes.[71-73]

While delayed contrast enhancement identifies regional myocardial abnormalities, a recently developed MRI technique, T1 mapping, allows quantification of diffuse myocardial fibrosis with or without the use of contrast.[74-78] A recent paper showed a strong correlation between T1 mapping values of the RV insertion points and indices of RV dysfunction.[79] However, a better use of T1 mapping might be the detection of diffuse interstitial fibrosis in the RV.[80] Higher resolution sequences, which are required for the thin-walled RV myocardium, are in development and show promise for fibrosis quantification (Figure 3). Detection of fibrosis within the RV myocardium may serve as a therapeutic target for future PAH therapies.

### *RV Perfusion Imaging*

A critical component of RV failure is a decline in coronary perfusion of the RV and subsequent RV ischemia. 2D-TTE, while standard for assessing wall motion abnormalities of the LV, cannot evaluate RV perfusion. However, myocardial perfusion reserve can be evaluated by CMR using contrast and a vasodilator such as adenosine or regadenoson. In a small study of 25 patients referred for PAH evaluation, the myocardial perfusion reserve index for both LV and RV were significantly decreased compared to controls.[81] Furthermore, a decrease in RV myocardial reserve index significantly correlated with a decline in RV workload and RVEF. Similar to markers of fibrosis, RV MPI may also be used as a measure for the effectiveness of PAH therapies.

### *Pulmonary Vasculature Imaging*

While the RV plays a key role in the pathophysiology of PAH, its function is strongly affected by the pressure and resistance within the pulmonary vasculature. Both 2D-TTE and CMR can evaluate pulmonary vasculature hemodynamics with Doppler and velocity-encoded imaging, respectively. In general, velocity-encoded imaging allows flow measurement in any vessel of the heart by multiplying the cross-sectional area of the vessel by the spatial mean velocity of blood flow. Like 2D-TTE, studies have shown that it is feasible to calculate a variety of hemodynamic parameters using CMR such as mean PA pressure, PVR, cardiac output, and PA acceleration time.[82-84]

One of the unique features of CMR is that, unlike 2D-TTE, it is possible to visualize the main PA and its branches. This allows one to measure parameters such as PA distensibility, which correlates strongly with severity of disease in PAH patients.[85,86] In addition, 4D flow imaging by CMR measures all 3 directional components of the velocities of blood flow relative to time course of the cardiac cycle.[87] This allows visualization of altered patterns of flow in the PA, and might be useful in providing greater mechanistic insight into the consequences of pulmonary vascular remodeling (Figure 4). Using 4D flow of PA, wall shear stress was found to be significantly decreased in PAH patients compared to controls.[88] In addition, vortices of blood flow are common in the main PA in patients with PAH, and the vortex duration appears to correlate significantly with mean PA pressure.[89,90]

## CONCLUSION

The technologic and evidence base for both echocardiography and CMR in imaging the RV in PAH have clearly evolved dramatically in the last decade, but ultimately how have these advances impacted the question of which is the optimal RV imaging modality? While proponents of each modality may continue to fuel debate over which may be more effective in imaging the RV, in reality a general consensus is that these

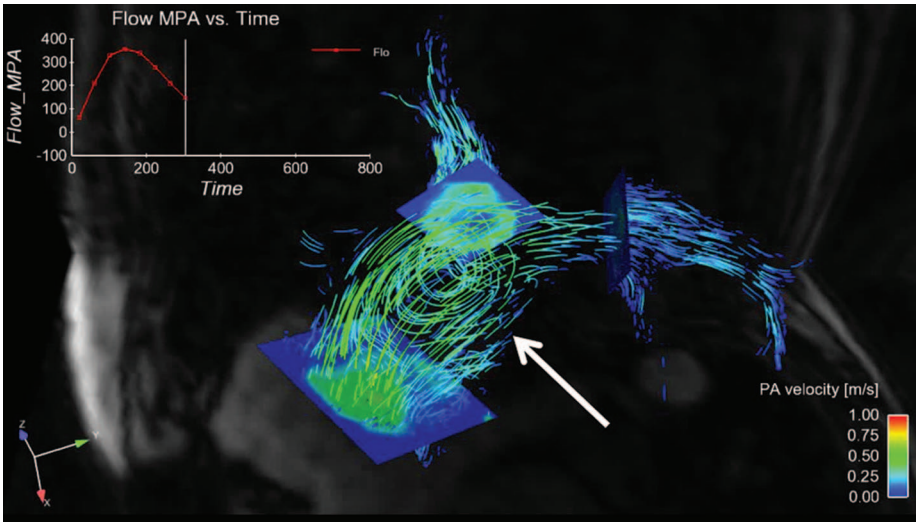


Figure 4: 4D flow of the PA in a patient with PAH. Note the slower PA velocities and flow vortex in the main PA (white arrow).

imaging modalities are in fact complementary, each providing potentially unique information.

2D-TTE will remain the clinical workhorse of RV evaluation in PAH because it provides simple, reproducible, and meaningful single-plane surrogates of RV function. Newer echocardiographic techniques such as RV strain, 3D-TTE, and Ventripoint are promising in providing measurements of RV function, RV volumes, and RVEF without the limitations of CMR, but further technological improvements are necessary before these techniques can be incorporated into standard clinical practice.

Until then, CMR will remain the gold standard for measuring RV size and function. Beyond that, CMR can provide additional information on RV tissue characterization, perfusion imaging, and 4D flow imaging of the PA. Further research is needed to determine the clinical utility of these novel MRI measurements. RV imaging for PAH is rapidly evolving. Understanding what echocardiography and MRI currently have to offer is essential for the comprehensive evaluation and management of this patient population.

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