

iREVIEWS

STATE-OF-THE-ART PAPERS

MR and CT Imaging for the Evaluation of Pulmonary Hypertension



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ABSTRACT

Imaging plays a central role in the diagnosis and management of all forms of pulmonary hypertension (PH). Although Doppler echocardiography is essential for the evaluation of PH, its ability to optimally evaluate the right ventricle and pulmonary vasculature is limited by its 2-dimensional planar capabilities. Magnetic resonance and computed tomography are capable of determining the etiology and pathophysiology of PH, and can be very useful in the management of these patients. Exciting new techniques such as right ventricle tissue characterization with T1 mapping, 4-dimensional flow of the right ventricle and pulmonary arteries, and computed tomography lung perfusion imaging are paving the way for a new era of imaging in PH. These imaging modalities complement echocardiography and invasive hemodynamic testing and may be useful as surrogate endpoints for early phase PH clinical trials. Here we discuss the role of magnetic resonance imaging and computed tomography in the diagnosis and management of PH, including current uses and novel research applications, and we discuss the role of value-based imaging in PH. (J Am Coll Cardiol Img 2016;9:715–32)
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Pulmonary hypertension (PH) is a common hemodynamic abnormality that reflects a variety of diseases of the heart and pulmonary vasculature (Table 1) (1,2). Imaging is critical in the diagnostic evaluation of all types of PH. Not only does it provide the first clue that pulmonary artery (PA) pressures may be elevated, but it also allows the direct visualization of the right ventricle (RV)

and its adaptation (or maladaptation) to worsening pulmonary vascular function. Furthermore, imaging tests are essential for determining the etiology of PH. Whereas 2-dimensional (2D) Doppler echocardiography remains the most commonly used imaging modality for cardiac and hemodynamic evaluation in PH, its ability to comprehensively and accurately evaluate the RV and pulmonary vasculature is limited

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ABBREVIATIONS AND ACRONYMS

2D	= 2-dimensional
3D	= 3-dimensional
4D	= 4-dimensional
CMR	= cardiac magnetic resonance
CT	= computed tomography
CTA	= computed tomography angiography
IVS	= interventricular septum
LV	= left ventricle
MRI	= magnetic resonance imaging
NCCT	= noncontrast computed tomography
PA	= pulmonary artery
PAH	= pulmonary arterial hypertension
PC	= phase contrast
PH	= pulmonary hypertension
RV	= right ventricle
SENC	= strain encoded imaging
SV	= stroke volume
WSS	= wall shear stress

by its 2D planar capabilities. In addition, while echocardiography can assist in determining whether left heart disease or congenital heart disease is the cause of PH, several other causes of PH (e.g., lung disease, chronic thromboembolic disease) require additional imaging modalities.

Advanced imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) overcome the aforementioned limitations while providing an additional layer of mechanistic insight that is not possible with echocardiography alone. Examples of novel MRI and CT techniques include 4-dimensional (4D) flow assessment of the PA on MRI, tissue characterization of the RV on MRI, and quantification of lung perfusion on dual-energy CT. Here we discuss the current role of MRI and CT in the diagnosis and management of PH, novel research applications of these imaging techniques, a clinical assessment of the relative utility of the various imaging modalities (including echocardiography), the role of MRI in PH clinical trials, and an assessment of value-based imaging in PH.

MAGNETIC RESONANCE IMAGING

CURRENT APPROACHES IN PULMONARY HYPERTENSION.

Right ventricular size and function. The RV is a critical barometer of cardiovascular health in patients with PH. Several studies have demonstrated the prognostic significance of RV function in PH, whether evaluated indirectly using invasive hemodynamic testing (e.g., right atrial pressure, cardiac output) or directly via noninvasive imaging (e.g., RV ejection fraction) (3). Cardiac magnetic resonance (CMR) is the reference standard for the assessment of RV size and systolic function (4). Owing to the nonsymmetric, pyramidal chamber configuration, quantitation of RV size and systolic function is a unique challenge even when evaluated with CMR (5). Some investigators have advocated for orienting short-axis slices parallel to the tricuspid baseline, as such an orientation is rarely in the same plane as short-axis slices aligned for left ventricular (LV) analysis (6). However, short-axis-oriented images pose challenges in identifying the RV base plane during systole and diastole and require cross-referencing with RV 2-chamber and RV inlet-outlet imaging to ensure accurate definition of the base plane. Other authors have advocated to contour the RV from transaxial images mitigating difficulties identifying the RV base plane (6). With

this approach, Jauhiainen et al. (6) demonstrated improved reproducibility of RV volumes compared to short-axis images optimized to the RV axis.

Quantification of RV chamber size and systolic function requires electrocardiographically gated cine images. This technique often uses segmented balanced steady-state free precession imaging with effective temporal resolutions <50 ms and enabling a per-slice acquisition time on the order of 5 to 15 s, depending on heart rate, spatiotemporal resolution, and parallel imaging capabilities. Patients with slower heart rates, irregular rhythms, or dyspnea limiting breath-holding are challenging to image with CMR. Real-time cine imaging permits assessment of regional wall motion, but is limited due to necessary tradeoffs in spatial and temporal resolution (7). The use of advanced imaging acceleration techniques such as compressed sensing, radial sampling trajectories, and 3-dimensional (3D) approaches with electrocardiographic-gating and self-gated respiratory navigation are promising techniques to improve CMR image quality in patients with dyspnea or irregular rhythms, both of which commonly occur in patients with PH.

RV quantification during CMR yields accurate measures of RV size (RV end-diastolic and end-systolic volumes), stroke volume (SV), myocardial mass, and ejection fraction (8). Maladaptive changes in CMR-derived RV end-diastolic volume, end-systolic volume, and ejection fraction—indicative of RV remodeling and dysfunction—have been associated with a worse prognosis in PH patients on optimal medical therapy (3). Similarly, a reduced SV on CMR has been linked to increased mortality, both at baseline and on follow-up imaging after initiation of therapy (9).

Interventricular septal changes. The interventricular septum (IVS) is known to play a critical role in the pathophysiology of PH (10). As PA systolic pressure increases, RV systolic pressure exceeds that of the LV and the resulting IVS shift toward the LV impedes cardiac output (11). Mechanical asynchrony, wherein RV contraction time is prolonged compared with LV contraction time, is also thought to contribute to this process (12,13). In addition, as RV diastolic pressure increases with progressive RV failure, IVS flattening occurs during diastole thereby impeding LV filling, further reducing cardiac output. Because of its superior spatial resolution, CMR cine short-axis images provide a detailed view of this dynamic relationship between the RV and LV (14,15). Beyond simply correlating the degree of septal flattening to PA systolic pressure, studies using CMR have attempted to quantify the shape and deformation of the IVS using

TABLE 1 Diagnostic Criteria and Categorization of Pulmonary Hypertension

	All WHO Groups	WHO Group 1	WHO Group 2	WHO Group 3	WHO Group 4	WHO Group 5
Description	Elevated pulmonary artery pressure	Pulmonary arterial hypertension	Pulmonary venous hypertension	PH due to hypoxemia	Chronic thromboembolic PH	Miscellaneous or multifactorial PH
Major etiologies		Idiopathic, heritable, drug/toxin-induced, HIV, CTD, portal hypertension, CHD (shunts), schistosomiasis (WHO Group 1' includes PVOD and PCH)	LV systolic dysfunction, LV diastolic dysfunction, aortic valve disease, mitral valve disease	COPD, interstitial lung diseases, sleep-disordered breathing		Chronic hemolytic anemias, myeloproliferative disorders, sarcoidosis, glycogen storage disease, thyroid diseases, chronic kidney disease
Estimated prevalence	Up to 10%-20% of the general population	15 cases per million overall, 6 cases per million for idiopathic PAH	>3-4 million in the United States	20% in COPD patients with a previous hospitalization for COPD exacerbation, >50% in advanced COPD; 32%-39% in interstitial lung disease	0.5%-2% (up to 3.8%) in survivors of acute pulmonary embolism	Unclear
Diagnostic criteria	Mean PA pressure (mm Hg)	≥25	≥25	≥25	≥25	≥25
	PCWP or LVEDP (mm Hg)	—	≤15	>15	≤15	≤15
	PVR (dynes/s/cm ⁵)	—	>240	—	>240	>240

Dashes indicate data are not applicable.
CHD = congenital heart diseases; COPD = chronic obstructive pulmonary disease; CTD = connective tissue diseases; HIV = human immunodeficiency virus; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary artery; PCH = pulmonary capillary hemangiomatosis; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; PVR = pulmonary vascular resistance; WHO = World Health Organization.

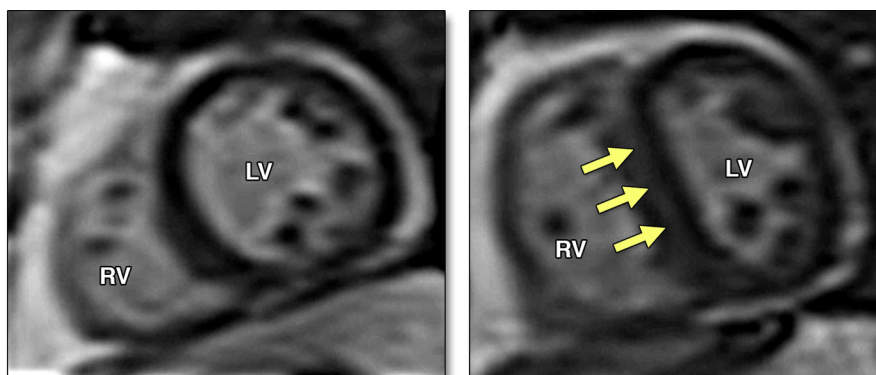
3D analysis in patients with PH (16). The changes to the IVS that occur throughout the cardiac cycle may, over time, be responsible for the delayed enhancement commonly found in the RV insertion points on CMR (17).

While CMR cine imaging provides excellent spatial resolution, free breathing sequences provide real-time physiologic assessment of IVS dynamics (Figure 1). These sequences are particularly helpful in understanding the ability of the RV to handle volume overload. During inspiration, negative intrathoracic pressure creates a suction effect in the thorax, which results in increased blood flow from the systemic veins into the right heart. Whereas some IVS flattening is expected during inspiration to accommodate the increased volume of blood, significant IVS flattening at peak inspiration is indicative of a vulnerable or dysfunctional RV.

Pulmonary vasculature function. In a number of studies, the standard phase contrast technique (2D phase contrast magnetic resonance imaging [PC-MRI], with single direction velocity encoding along the through-plane direction) has been applied to evaluate changes in blood flow in patients with pulmonary arterial hypertension (PAH). Pelc et al. (18) initially noted that main PA flow at peak systole in PAH patients was more spatially heterogeneous and demonstrated a

greater percentage of retrograde flow. Building on this observation, a number of researchers have quantified bulk flow hemodynamics in the PA. Among them, Ley et al. (19) performed a detailed study of 25 PAH patients and 25 control subjects to compare the PA peak velocity, average flow, time-to-peak velocity, velocity rise gradient, and pulmonary distensibility. In this study, CMR values were also compared with transthoracic echocardiography and right heart catheterization. In comparison to the control subjects, the PAH patients showed significantly reduced pulmonary velocities ($p = 0.002$), blood flow ($p = 0.002$), and pulmonary distensibility ($p = 0.008$). The patients also showed a shorter time-to-peak velocity ($p < 0.001$) with a steeper velocity rise gradient ($p = 0.002$). In addition, a number of authors have observed highly heterogeneous cross-sectional area flow profiles and retrograde flow in the main PA of PAH patients (20-22).

The pulsatility of deformation of the main PA is useful as an index of PA stiffness (23). A related measure called PA relative area change can also be calculated (24); decreased values of main PA relative area change indicate increased PA stiffness and have been associated with increased mortality (25). Magnetic resonance angiography can also provide information on pulmonary vascular function. Using data

FIGURE 1 Dynamic Interventricular Septal Shift From Right to Left in a Patient With Systemic Sclerosis-Associated PAH on CMR

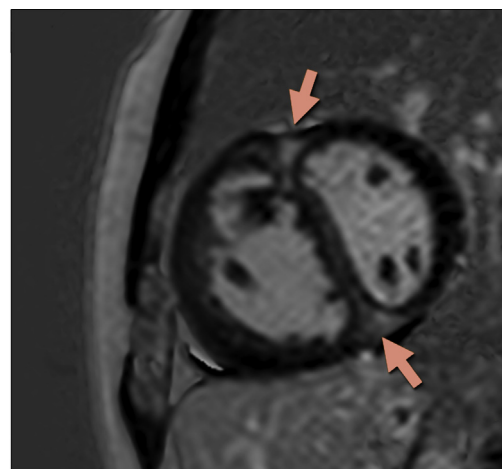
Dynamic interventricular septal shift from right to left in a patient with systemic sclerosis-associated pulmonary arterial hypertension (PAH) on cardiac magnetic resonance (CMR) imaging. **Yellow arrows** point to interventricular septal shift during inspiration. LV = left ventricular; RV = right ventricular.

from signal intensity curves on magnetic resonance angiography, Ohno et al. (26,27) found that prolonged mean transit time and decreased pulmonary blood flow were common in patients with PAH, whereas Swift et al. (28) suggested that these parameters have prognostic significance in these patients.

Right ventricular delayed enhancement. Delayed-enhancement imaging on CMR is a well-established technique to identify focal myocardial abnormalities. RV insertion point enhancement, a common finding in patients with PH, appears as regions of poorly marginated mesocardial scar in the basal-to-mid chamber along the anterior and inferior RV septal insertion points (Figure 2). This pattern of delayed enhancement is strongly associated with elevated PA pressures, as well as RV dilation and hypertrophy (29), and has also been associated with adverse outcomes in patients with PH (30). RV insertion point enhancement at the basal antero-septal insertion has been associated with reduced regional RV contractility suggesting a structure-function relationship (31). Lending support to structural alterations in this region, RV septomarginal trabeculations inserting into the basal-to-mid chamber antero-septum are significantly hypertrophied in PH subjects, correlating with elevated pulmonary pressure and vascular resistance (32). These findings suggest increased mechanical stress at the antero-septal insertion and may explain the pattern of delayed enhancement identified.

NOVEL APPROACHES IN PULMONARY HYPERTENSION. MRI approaches to the evaluation of PH are rapidly evolving. The following section includes several

techniques that are still in development and likely will not be available and ready for routine clinical use for some time. However, these novel imaging approaches can provide unique insight into the pathophysiology of PH and should be examined in prospective research studies (including PH clinical trials) to determine their utility relative to conventional imaging approaches.

FIGURE 2 Late Gadolinium Enhancement at the RV Insertion Points in a Patient With PAH on CMR

Late gadolinium enhancement at the right ventricle insertion points in a patient with pulmonary arterial hypertension on cardiac magnetic resonance imaging. **Arrows** point to late gadolinium contrast enhancement at right ventricular insertion points. Abbreviations as in Figure 1.

Right ventricular T_1 mapping. Although delayed-enhancement imaging identifies regional myocardial abnormalities, a newer MRI technique, T_1 mapping, can potentially identify diffuse myocardial abnormalities by either measuring native RV T_1 time without the need for contrast or extracellular volume fraction based on pre- and post-contrast T_1 times (33). Both metrics can be considered surrogate markers for ventricular fibrosis (34,35). A recent paper showed a strong correlation between T_1 mapping values of the RV insertion points and indices of RV dysfunction (36). However, a better use of this technique may be the detection of diffuse interstitial abnormalities in the RV (37).

Kawel-Boehm et al. (38) tested the feasibility of RV T_1 mapping using standard modified look-locker inversion recovery in 20 healthy control subjects. The investigators found that the T_1 mapping technique was possible in 90% of the subjects. The most appropriate imaging plane was the mid-ventricular short-axis view, and systole was preferred over diastole given the larger amount of myocardium that could be evaluated during systole. Interestingly, the average T_1 time of the RV myocardium was significantly longer than the LV myocardium. The investigators believed this was due to the naturally higher collagen content in the RV.

Higher resolution T_1 mapping sequences, which may be more appropriate for the thin-walled RV myocardium, are in development. Recently, an accelerated and navigator-gated look-locker imaging sequence was developed for T_1 quantification of the RV (37). The investigators found that the accelerated and navigator-gated look-locker imaging sequence provided lower intrascan variability than did standard modified look-locker inversion with clinically reasonable scan times.

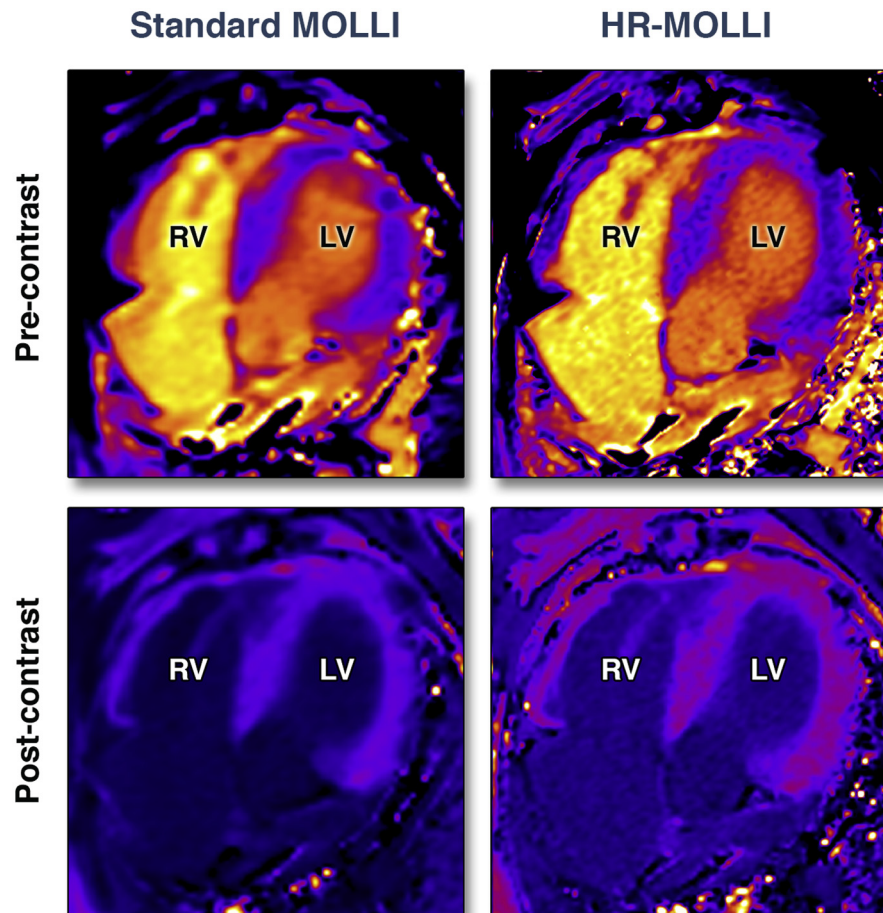
Another high-resolution T_1 mapping sequence under development is similar to standard modified look-locker inversion but the interpolated spatial resolution is reduced from 1.4×1.4 mm to 0.5×0.5 mm (Figure 3). Although results are still preliminary, this technique has the potential to detect diffuse fibrosis of the RV in heart failure. Given the importance of RV health in patients with PH, T_1 mapping (i.e., the amount of diffuse RV myocardial fibrosis) may serve as a novel tool for measuring therapeutic success in PH.

Right ventricular strain imaging. CMR has the advantage of flexible 2D slice prescription, as well as the potential for volumetric coverage of the whole heart. The quantitative evaluation of regional myocardial function using strain imaging has the potential to improve the sensitivity of CMR to regional

decrements in RV function that may precede global changes in the RV systolic function. The majority of available literature for RV analysis reports longitudinal and circumferential strains, given the limited amount of radial RV strain due to the thin RV myocardium.

Myocardial strain can be calculated using several different CMR techniques. Myocardial tagging is the most-studied, well-validated technique for assessing myocardial strain. Challenges to myocardial tagging of the RV include the wall thickness relative to tag spacing and time-intensive analysis (39). Harmonic phase analysis is a post-processing technique that tracks pixels on time-resolved tagging images, applying a constant phase constraint (40); this technique streamlines tag analysis. Displacement encoding with stimulated echoes (41), strain-encoded imaging (SENC) (42), deformation field analysis, and multimodality feature tracking (43) have also been applied to measure RV strain. Displacement encoding with stimulated echoes directly encodes tissue displacement into the image phase by encoding and decoding gradients. The resultant stimulated echo fades secondary to T_1 recovery, limiting assessment of mid to late diastolic strains. SENC shares similarities with displacement encoding with stimulated echoes and tagging, but it differs through application of tag lines parallel to the imaging plane. Myocardial deformation analysis and feature tracking are unique in that they are applied to balanced steady-state free precession cine image data, yielding strain data without the need for dedicated image acquisitions. The majority of work evaluating the utility of RV strain analysis on CMR has focused on myocardial tagging, harmonic phase analysis, or SENC techniques. Several feature-tracking software systems are available, with differing algorithms for identifying and tracking endomyocardial, epimyocardial, and intramyocardial image features over time with promising results for assessment of RV strain (43).

Strain analysis on cardiac MRI has focused on identifying early changes in RV function that precede maladaptive RV remodeling (44). Shehata et al. (45) evaluated segmental RV myocardial strains using fast SENC in a cohort of 35 patients with PAH, demonstrating reduced RV longitudinal strain in nearly all segments, with reduced RV circumferential strain in the mid-chamber. Importantly, compared with a cohort of healthy controls, in a subgroup analysis of 13 patients with PAH and preserved RV ejection fraction (51% to 61%), segmentally reduced longitudinal strain was demonstrated in the RV basal- and mid-chamber anterosseptal and RV mid-chamber anterior segments, indicating the ability to detect

FIGURE 3 RV T₁ Mapping on CMR

As compared to standard modified look-locker inversion (MOLLI), the high-resolution (HR) MOLLI images (**right**) have a higher pixel density and therefore may be more accurate for estimating extracellular volume content in the thin-walled right ventricular myocardium. Abbreviations as in [Figure 1](#).

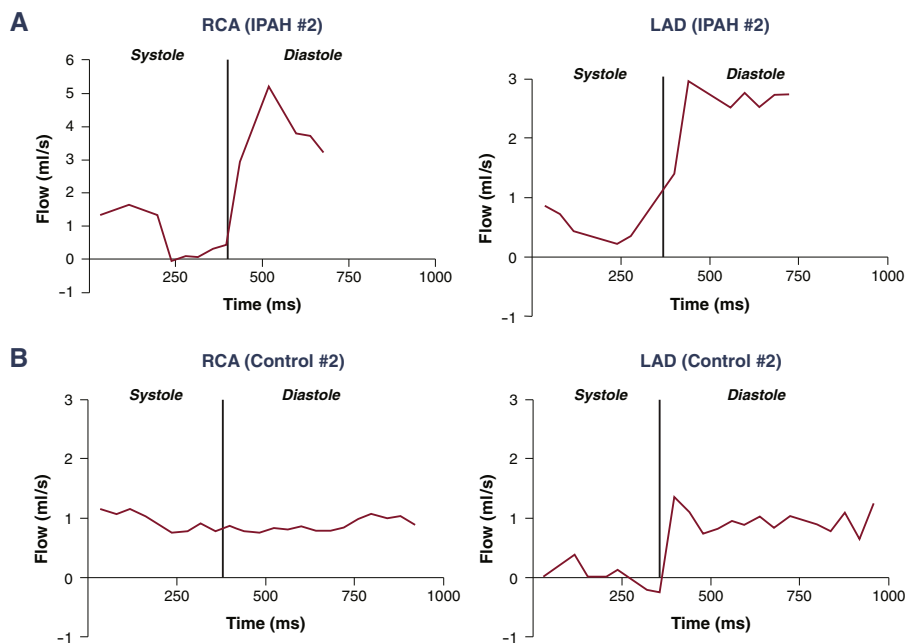
regional changes in function prior to reductions in global RV ejection fraction. Myocardial strain imaging has also been used to identify ventricular dyssynchrony in PH using myocardial tagging by determining differences in time to peak RV and LV circumferential strains (46). For example, ventricular dyssynchrony assessed by myocardial tagging has been shown to normalize following thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension (46).

Right ventricular perfusion. A critical component of RV failure in PH is a decline in coronary perfusion of the RV and subsequent RV ischemia. Coronary blood flow can be evaluated by CMR using gadolinium contrast and a coronary vasodilator such as adenosine or regadenoson, and also by PC-MRI techniques. In an

earlier study involving PC-MRI, Van Wolferen et al. (47) found that right coronary artery peak and mean systolic flow in PAH patients, compared with control subjects, was significantly decreased ([Figure 4](#)). These changes correlated inversely with RV mass and RV pressure. The results of this study help explain the effects of PH and a failing RV on coronary blood flow.

In a subsequent study of 25 patients referred for PAH evaluation, myocardial perfusion reserve index was evaluated using CMR for both the LV and RV and found to be significantly decreased when compared with that of control subjects (48). The potential to noninvasively calculate RV blood flow in patients with PH may serve to guide the initiation and/or effectiveness of PH therapies.

FIGURE 4 Representative Examples of the RCA and LAD Flow Curves, Obtained on CMR



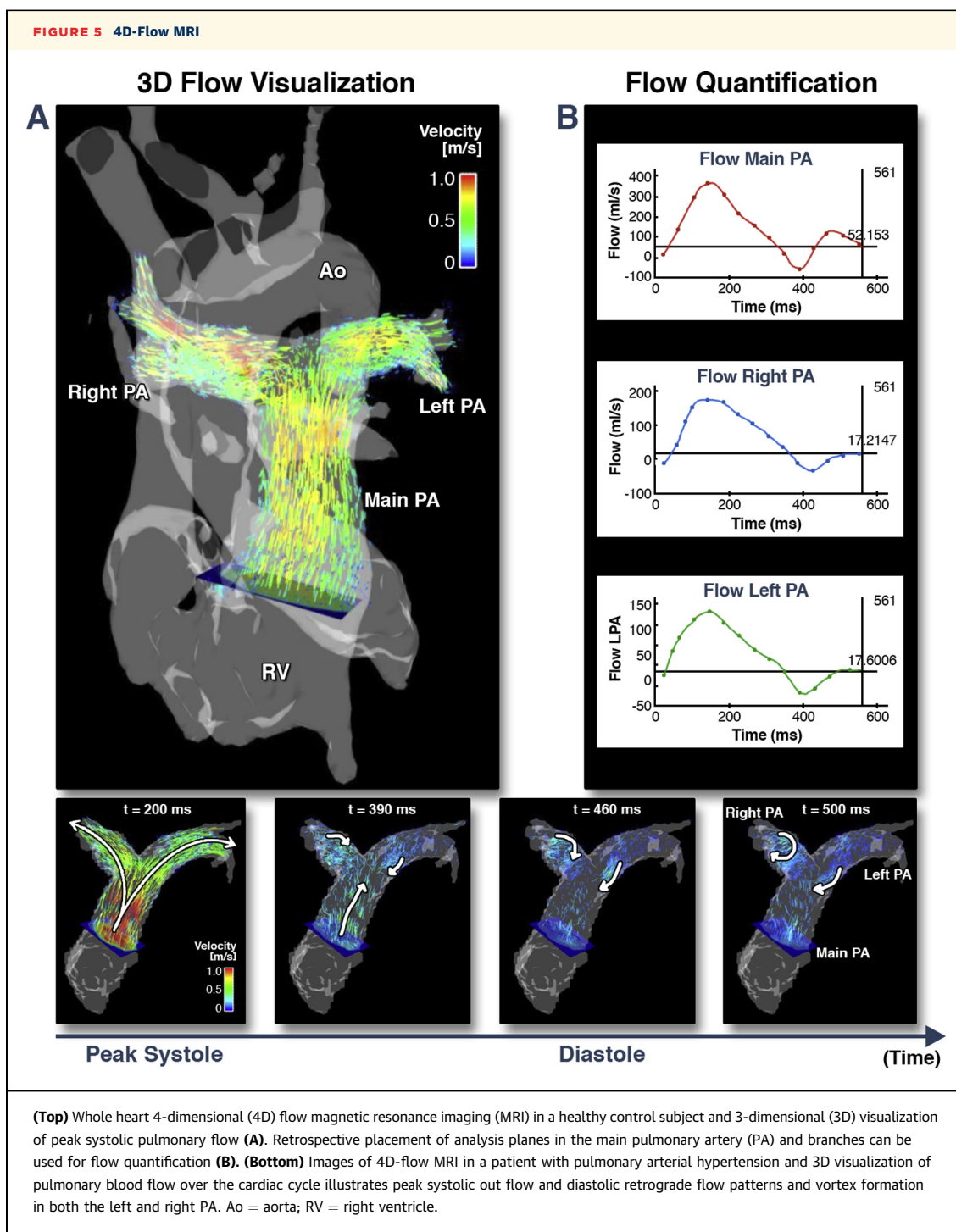
Representative examples of the right coronary artery (RCA) and left anterior descending (LAD) flow curves, obtained on cardiac magnetic resonance (CMR) imaging. **(A)** Idiopathic pulmonary arterial hypertension (IPAH); **(B)** healthy control. Systolic and diastolic phases in the cardiac cycle are indicated. Reproduced with permission from van Wolferen et al. (47).

Pulmonary artery 4D flow imaging. Functional characterization of the PA is increasingly important given that PH is not merely a disease of the distal vessels, as the proximal PA undergo dilation, remodeling, and stiffening. The distal and proximal PA changes not only contribute to decreased compliance and increased resistance, thereby increasing RV afterload, but also alter secondary flows (such as helix and vortex formation) including changes to the velocity profile shape and magnitude (49-51). To this end, PC-MRI can be employed to assess cardiovascular hemodynamics and quantify blood flow velocities in the main PA, the RV, and the RV outflow tract. In addition, PC-MRI data has been used to derive more advanced hemodynamic metrics such as pulse-wave velocity (which can characterize arterial stiffness), vorticity (which may detect diastolic RV dysfunction), and wall shear stress (WSS) (which regulates endothelial cell function and vascular remodeling) (52-54).

More recently, a number of studies have employed 4D-flow MRI (time-resolved 3D PC-MRI with 3D velocity encoding), which offers the opportunity to noninvasively measure complex 3D hemodynamic changes with full volumetric coverage of the RV and PA (49,55,56) (Figure 5). A recent study has confirmed

that volumetric analysis based on 4D-flow MRI allows for improved assessment of aortic and pulmonary peak velocities, which may be underestimated by both Doppler echocardiography and 2D PC-MRI, which are limited by 2D analysis planes and single-directional velocity encoding (57). Moreover, a number of studies have demonstrated low interobserver variability, high test-retest reliability, and good correlation between flow parameters obtained by 4D-flow MRI and 2D-cine PC-MRI (58-60).

Using 4D-flow MRI in the pulmonary circulation, Reiter et al. (49,50) observed abnormal vortex development in the main PA in patients with PAH, resulting in an abnormal boundary layer along the wall of the main PA. Notably, the time persistence of this vortex correlated with the degree of PH as measured by mean PA pressure (50). Furthermore, 4D-flow MRI and 3D-flow visualization in the PA may have the potential to provide a noninvasive vortex-based diagnosis of PH. François et al. (55) and Geiger et al. (61) similarly observed increased vortex flow patterns in the PA of patients with repaired tetralogy of Fallot. Another recent 4D flow study in a canine model of acute thromboembolic PH demonstrated that RV and LV function, PA flow, tricuspid



valve regurgitation velocity, and aorta flow could be quantified based on a single 4D-flow MRI exam (62). Fenster et al. (53) recently correlated complex RV vortex flow with multiple echocardiographic markers of RV diastolic dysfunction. In particular trans-tricuspid valve E and A velocities, E/A ratio, and e'

and a' tissue Doppler velocities were all significantly correlated with degree of vorticity.

We are only beginning to understand the role of the complex flow changes documented in these investigational studies for PH diagnosis and monitoring progression. One direct application of 4D-flow

TABLE 2 Key Parameters on MRI in the Evaluation of Patients With PH

MRI Sequence Details		Key Points
RV size and function	bSSFP ECG-gated cine Short-axis or transaxial plane	Reference standard Delineation of tricuspid valve plane challenging on short-axis imaging Superior reproducibility makes it ideal for clinical trials SV, RVEF, RV volumes are all prognostic variables in PH
Interventricular septal changes	bSSFP ECG-gated or real-time cine imaging Short-axis plane	Provides insight into degree of RV pressure and volume overload Septal shift during cardiac cycle prognostic marker in PH
PA pulsatility (relative area change)	2D PC-MRI GRE or bSSFP ECG-gated cine	PA pulsatility prognostic marker in PH
PA mean transit time	TR-MRA	Significant prognostic marker in PH MRA is also helpful in differentiating between COPD, interstitial lung disease, and chronic thromboembolic disease
RVIP delayed enhancement	LGE	RVIP associated with worse outcomes in PH
RV diffuse interstitial abnormalities	RV T ₁ mapping	RV interstitial abnormalities potentially identify diffuse fibrosis within the RV
RV strain	Myocardial tagging HARP DENSE SENC Feature tracking Deformation field analysis	Provides RV longitudinal, circumferential, and radial strain measurements Changes in regional strain potentially useful in understanding mechanism of disease
RV perfusion	First pass perfusion Vasodilator needed for stress perfusion	Detects changes in RV coronary flow Significant difference in these markers between PH patients and control subjects
PA peak velocity PA average flow PA time-to-peak velocity PA velocity-rise gradient PA and RV vortex flow PA wall shear stress	2D PC-MRI 4D-flow MRI	Significant differences in these markers between PH patients and control subjects Altered flow patterns recognized in the PA of PH patients Wall shear stress lower in PH patients compared with control subjects

2D = 2-dimensional; 4D = 4-dimensional; bSSFP = balanced steady-state free precession; DENSE = displacement encoding with stimulated echoes; ECG = electrocardiogram; GRE = gradient-recalled echo; HARP = harmonic phase analysis; LGE = late gadolinium enhancement; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PC = phase contrast; RV = right ventricle; RVEF = right ventricular ejection fraction; RVIP = right ventricular insertion point; SENC = strain encoded imaging; SV = stroke volume; TR = time resolved; other abbreviations as in [Table 1](#).

MRI to PH may be WSS, a parameter known to stimulate vasodilation via nitric oxide release from endothelial cells, vascular remodeling, and intrinsic proximal vessel characteristics (51,63,64). In this respect, 4D flow is a highly informative tool, given that altered 3D flow is not focal to the RV but is also present in the enlarged PA of PAH patients (49,50). Proximal PA stiffening and dilation as a result of collagen accumulation (or elastin loss) and pressure loading will diminish the Windkessel effect and alter the function of the dual stage RV-PA unit (65,66). It is presumed that this phenomenon increases RV afterload and alters proximal as well as distal flow dynamics. The changes can be measured in the form of bulk flow (SV, cardiac output, Q_{\max}) as well as in the form of maximum velocity and WSS. Indeed, a recent 4D-flow MRI study was able to detect differences in PA hemodynamics in patients with PAH (67). V_{\max} , Q_{\max} , SV, and WSS at all locations were significantly lower ($p < 0.05$) in PAH patients than in healthy subjects. These investigational 4D flow studies extend our understanding of the changes

occurring to structure and flow in the presence of the hypertensive RV and PA and how they may possibly affect the progression of the various forms of PH and response to therapy.

Integration of magnetic resonance imaging and invasive hemodynamic testing. Whereas MRI imaging can provide a comprehensive assessment of the RV and pulmonary vasculature in PH patients (as summarized in [Table 2](#)), the combination of invasive hemodynamic data, obtained during right heart catheterization, and main PA cross-sectional area can allow for the calculation of several indices of proximal PA stiffness, such as PA compliance, distensibility, elastic modulus, and stiffness index (β) (23,24) ([Table 3](#)). Increased proximal PA stiffness (i.e., reduced proximal PA compliance) occurs in virtually all etiologies of PH and can contribute to RV dysfunction. The PA pulsatility and relative area change measures are not true measures of PA compliance, although they are valid surrogates of PA compliance measures. Combining PA cross-sectional area change with invasive hemodynamic data can

TABLE 3 Indices of PA Stiffness Derived From CMR Imaging and Invasive Hemodynamic Testing

	Units	Formula	Definition
Pulsatility (also known as RAC)	%	$(\text{maxA} - \text{minA})/\text{minA} \times 100$ or $(\text{maxA} - \text{minA})/\text{maxA} \times 100^*$	Relative change in lumen area during the cardiac cycle
Compliance	mm ² /mm Hg	$(\text{maxA} - \text{minA})/\text{PP}$	Absolute change in lumen area for a given change in pressure
Capacitance	mm ³ /mm Hg	SV/PP	Change in volume associated with a given change in pressure
Distensibility	%/mm Hg	$(\text{maxA} - \text{minA})/\text{PP} \times \text{minA} \times 100$	Relative change in lumen area for a given change in pressure
Elastic modulus	mm Hg	$\text{PP} \times \text{minA}/(\text{maxA} - \text{minA})$	Pressure change driving a relative increase in lumen area
Stiffness index β	N/A	$\text{Ln}(\text{PASP}/\text{PADP})/[(\text{maxA} - \text{minA})/\text{minA}]$	Slope of the function between distending arterial pressure and arterial dimension

*Pulsatility (RAC) is variably defined in the published reports. Modified with permission from Sanz et al. (23).
 CMR = cardiac magnetic resonance; maxA = maximum area of the proximal pulmonary artery; minA = minimum area of the proximal pulmonary artery; PADP = pulmonary artery diastolic pressure; PASP = pulmonary artery systolic pressure; PP = pulse pressure; RAC = relative area change; other abbreviations as in Tables 1 and 2.

provide the aforementioned PA compliance measures such as the PA stiffness index β . Sanz et al. (23) calculated proximal PA stiffness measures in 94 patients who underwent both CMR and invasive hemodynamic testing, and they divided the patients into those with no PH (control), exercise-induced PH (i.e., early PH), and PH at rest. These investigators found that proximal PA stiffness increased early in PH patients compared with control subjects, thereby providing mechanistic insight into the development of PH. It is interesting to note, however, that an acute increase in pressure can also increase proximal PA stiffness via strain-stiffening, as recently demonstrated in a canine model of acute PH (24). Thus, whether increased proximal PA stiffness

(and decreased PA compliance) with PH are due to remodeling or strain remains unclear.

COMPUTED TOMOGRAPHY

CURRENT APPROACHES IN PULMONARY HYPERTENSION.

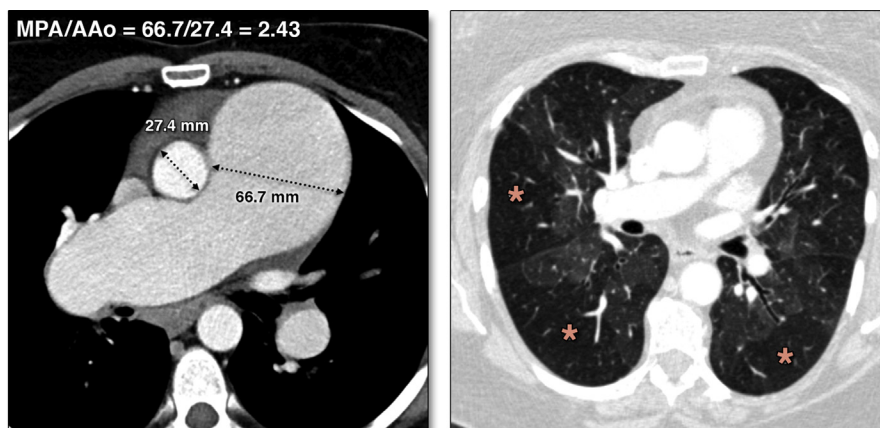
Diagnostic role of computed tomography in pulmonary hypertension. Noncontrast computed tomography (NCCT) and computed tomography angiography (CTA) are the 2 main CT techniques that have a significant role in the clinical evaluation and management of patients with PH. The pulmonary parenchymal findings on CT in patients with PH are variable and depend upon the etiology. NCCT is sufficient for the evaluation of most lung diseases given

TABLE 4 CT Findings That Are Useful for the Evaluation of PH and Its Etiologies

Noncontrast CT Findings and Caveats	
Clinical Entity	
Pulmonary hypertension	Findings suggestive of PH: dilated PA, increased main PA:AAo ratio, PA calcification, tortuosity of the PA, rapid tapering of the PA, and mosaic attenuation of the lung parenchyma. Cutoffs for main PA diameter and main PA:AAo ratio are based on data from the Framingham Heart Study. The 90th percentile cutoff values were >29 mm main PA diameter in men, >27 mm main PA diameter in women, and 0.9 main PA:AAo ratio. Additional findings of PH on CT angiography include reflux of intravenous contrast into the hepatic veins, RV dilation, RV hypertrophy, flattening or bowing of the interventricular septum, and dilation of the bronchial arteries.
Etiologies of PH	
COPD	In patients with COPD, CT can confirm the presence and characterize the type of emphysema, airway disease, and secondary features associated with COPD. Quantitative methods of assessing emphysema severity have been developed and correlate with histological and clinical indices of COPD severity. Main PA diameter and main PA:AAo ratio in COPD are linearly correlated with systolic, diastolic and mean PA pressures.
HHT	On noncontrast CT, pulmonary arteriovenous malformations present as a nodular opacity with a feeding artery and a draining vein. Contrast-enhanced CT angiography is only necessary for the evaluation of larger pulmonary arteriovenous malformations or in patients that have already undergone embolization.
ILD	Noncontrast high-resolution CT is the test of choice for the parenchymal evaluation of ILD. Caution must be used when measuring main PA diameter in patients with pulmonary fibrosis, because main PA dilation can occur in the absence of PH in these patients.
PVOD	CT features that are suggestive of PVOD include smooth septal lines, centrilobular ground glass opacities, and enlarged lymph nodes.
CTEPH	CT metrics, including main PA diameter, RV/LV diameter ratio, and RV wall thickness correlate with mean PA pressure in CTEPH.

AAo = ascending aorta; CT = computed tomography; CTEPH = chronic thromboembolic pulmonary hypertension; HHT = hereditary hemorrhagic telangiectasia; ILD = interstitial lung disease; PVOD = pulmonary veno-occlusive disease; other abbreviations as in Tables 1 and 2.

FIGURE 6 Examples of the Role of CT Imaging in PH



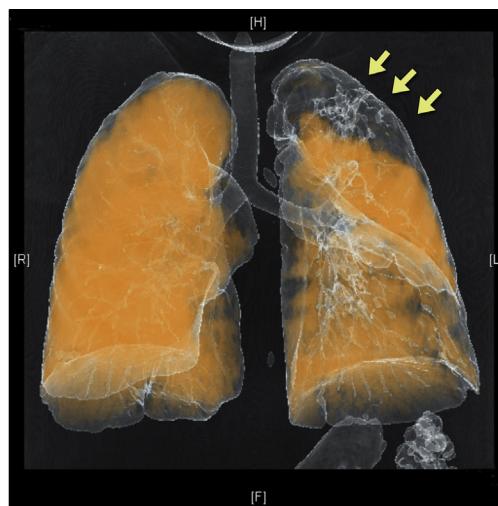
(Left) Computed tomography (CT) angiography image from a 43-year-old female with idiopathic pulmonary arterial hypertension demonstrating severe enlargement of the main pulmonary artery and increased ratio of the main pulmonary artery (MPA) to ascending aorta (AAo) diameter (2.43). **(Right)** Image from a 65-year-old female with chronic thromboembolic pulmonary hypertension. CT chest reveals “mosaic” lung attenuation due to heterogeneous lung perfusion with darker areas (*) indicating hypoperfusion.

its ability to accurately identify structural changes in the airways and parenchyma. Specifically, NCCT is indicated for the following: 1) the evaluation of the lung parenchyma in diffuse lung diseases such as chronic obstructive pulmonary disease and interstitial lung diseases; 2) the detection of pulmonary arteriovenous malformations; and 3) the diagnosis of pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis. **Table 4** lists CT findings that are useful for the diagnosis of PH and underlying PH etiologies on NCCT.

CTA, which requires the intravenous administration of iodinated contrast material, has become the reference standard for the diagnosis of acute pulmonary embolism given its ability to routinely assess PA to the subsegmental level; however, the role of CTA to screen for chronic pulmonary emboli in PH is less well established. Although CTA is not indicated in the primary imaging evaluation of PH, there are secondary signs present on CTA studies that are suggestive of PH and provide additional prognostic information. **Qualitative and quantitative computed tomography findings in pulmonary hypertension.** The most conspicuous finding on both NCCT and CTA suggestive of PH is dilation of the central PA (**Figure 6**). Other findings of PH present on both NCCT and CTA include PA calcification, tortuosity of the PA, rapid tapering of the PA, and mosaic attenuation of the lung parenchyma (**Figure 6**). Additional findings of PH on CTA include reflux of intravenous contrast into the hepatic veins, RV dilation, RV hypertrophy, flattening

or bowing of the IVS, and dilation of the bronchial arteries. Chan et al. (68) published data from a retrospective study in hospitalized patients that underwent both CT and invasive hemodynamic

FIGURE 7 Example of Dual-Source CT Demonstrating Lung Perfusion Abnormalities in a Patient With Chronic Thromboembolic PH



The left upper lung hypoperfusion (arrows) corresponded with the area of largest thrombus burden in the patient. CT = computed tomography; PH = pulmonary hypertension.

TABLE 5 Relative Costs for Imaging Tests Used in the Diagnosis and Management of PH (Centers for Medicare and Medicaid Services Data*)

CPT Code	Procedure	Technical Fee (U.S. Dollars)	Professional Fee (U.S. Dollars)	Global Fee (U.S. Dollars)
71275	CT angiography chest	228.09	102.07	330.15
75561	Cardiac MRI with contrast	307.00	131.52	427.61
93306	Transthoracic echocardiography with Doppler	165.65	64.32	229.97
93312	Transesophageal echocardiography with Doppler	186.14	123.61	309.75
78585	V/Q scan	295.37	53.90	349.27
93451	Right heart catheterization	647.88	150.20	798.08

*Data obtained from Centers for Medicare and Medicaid Services website (72).
CPT = current procedural terminology; V/Q = ventilation/perfusion; other abbreviations as in Tables 2 and 4.

testing during the same hospitalization and found a variety of CT-based indices to be significantly correlated with elevated invasively measured PA pressures. In addition to main PA diameter and main PA-to-ascending aorta diameter ratio, these investigators found that descending right and left PA diameter, RV wall thickness, RV/LV wall thickness ratio, and RV/LV diameter ratios were also highly associated with PH (68).

NOVEL APPROACHES IN PULMONARY HYPERTENSION.

One of the greatest unmet needs in PH imaging is the ability to characterize the distal pulmonary vasculature in PH—particularly PAH, which is thought to be a disease of the small pulmonary arteries. Newer CT scanners have implemented methods of performing dual-energy CT, enabling the ability to quantitatively characterize the material properties of soft tissues,

including the distal pulmonary vasculature, with CT (Figure 7). There are 2 main dual-energy CT technologies available, 1 that uses 2 x-ray sources and detector (dual-source CT) and 1 that uses a single x-ray source and detector. Dual-source CT and dual-energy CT with rapid kilovoltage switching methods have been investigated in PH and have shown promise in their ability to generate quantitative lung perfusion and pulmonary blood volume maps using the same acquisition that would be used for standard pulmonary CTA (69).

STRENGTHS AND WEAKNESSES OF ECHOCARDIOGRAPHY, MR AND CT IMAGING FOR THE EVALUATION OF PULMONARY HYPERTENSION

While the strengths of both CMR and CT relative to echocardiography are detailed in this review, there are a number of drawbacks for each imaging modality that are worth mentioning.

Echocardiography is the mainstay of screening and initial assessment of PH given its low cost, widespread availability, and potential for bedside application. In addition, 2D echocardiography is performed in real time and has a much higher frame rate than either MRI or CT and remains the gold standard for noninvasive hemodynamic assessment. Nevertheless, sonographer technique, acoustic windows, and nontomographic views are all factors that can limit its utility in the individual patient.

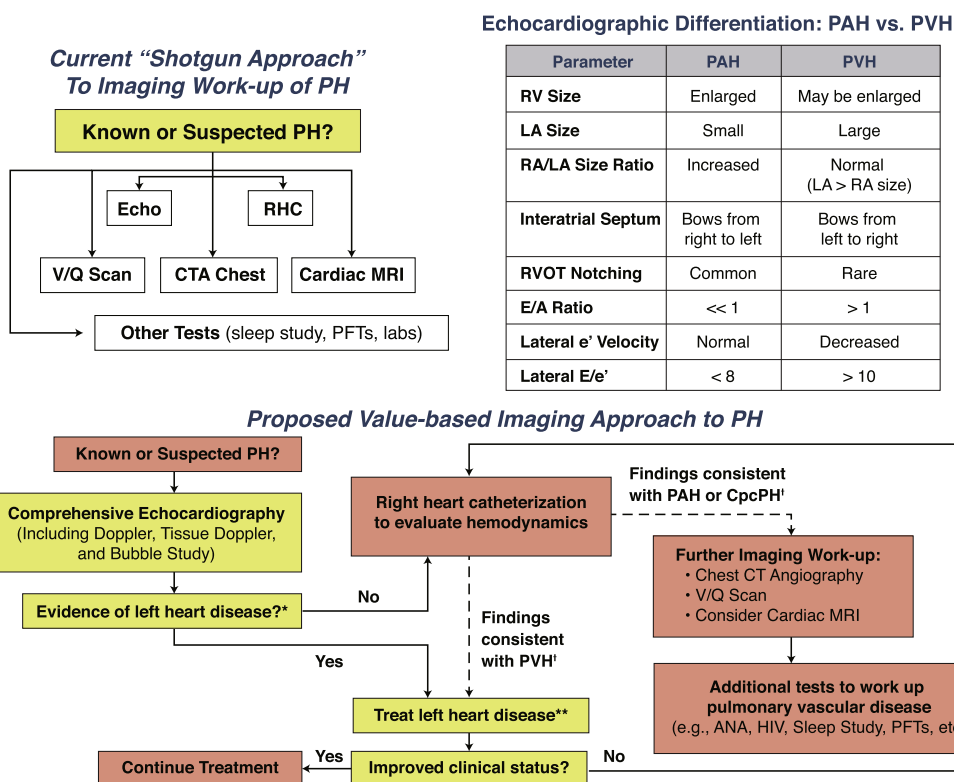
The major weakness of NCCT and CTA is the need for ionizing radiation. An additional disadvantage of

TABLE 6 Completed PH Clinical Trials With CMR Imaging-Based Endpoints

First Author (Ref. #)	Type of Study	Patients (n)	Intervention	Study Duration	CMR Endpoints	Summary of Results
Wilkins SERAPH (73)	RCT	26 PAH	Sildenafil vs. bosentan	4 months	RV mass	RV mass decreased with both sildenafil and bosentan (mean 8.8 g vs. 3 g; $p = 0.142$)
Wilkins SiPHT (74)	RCT	42 PAH	Simvastatin add-on	12 months	RV mass	Simvastatin produces a 5.2 g mean decrease in RV mass within 24 weeks that is not sustained at 12 months
Roeleveld (75)	Prospective observational study	11 PAH	Epoprostenol	12 months	RV mass RVEDV	No significant change in RV mass or RVEDV
Van Wolferen (76)	Prospective observational study	15 PAH	Bosentan with sildenafil add-on	3 months	RV mass RVEF RVEDV	On average, sildenafil add-on decreased RV mass by 8 g ($p < 0.01$) and increased RVEF by 4% ($p < 0.05$), no significant change in RVEDV
Chin (77)	Prospective observational study	16 PAH	Bosentan	12 months	RVEF RVEDV SV	No significant change in RVEF, RVEDV, or SV
Euro MR (78)	Prospective observational study	91 PH	None (physician-discretion therapy)	12 months	RVEDVI RVSVI RVEF RV mass index	Significant improvement in RVEF ($p < 0.001$) and RVSVI ($p < 0.0001$)

RCT = randomized controlled trial; RV = right ventricular; RVEDV = right ventricular end-diastolic volume; RVEDVI = right ventricular end-diastolic volume index; RVSVI = right ventricular stroke volume index; SERAPH = Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension; SiPHT = Simvastatin Pulmonary Hypertension Trial; other abbreviations as in Tables 1 to 3.

FIGURE 8 Proposed Algorithm to Enhance Value-Based Imaging in Patients With Suspected or Known PH



(Top left) The current “shotgun approach” to imaging and other tests in the work-up of PH is shown. **(Bottom)** The proposed value-based imaging algorithm for work-up of PH is shown. Because most patients with PH have left heart disease, the echocardiogram is the focus of initial work-up and if findings are consistent with pulmonary venous hypertension, treatment for left heart disease is recommended first before automatically proceeding to other tests (including invasive hemodynamic testing). **(Top right)** The table lists helpful echocardiographic clues for the differentiation between PAH and pulmonary venous hypertension (PVH). *See right upper panel for echocardiographic clues of left heart disease; other signs of left heart disease include reduced left ventricular ejection fraction, aortic valve disease, and mitral valve disease. **Treatment of left heart disease is dependent on the underlying etiology of left heart disease; however, PH in most patients with left heart disease will improve with diuresis and lowering systemic blood pressure (i.e., systemic vasodilation). †PAH is characterized by mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure ≤ 15 mm Hg; PVH is characterized by mean pulmonary artery pressure ≥ 25 mm Hg and pulmonary capillary wedge pressure > 15 mm Hg; combined post- and pre-capillary PH is characterized by PVH plus diastolic pulmonary gradient (PADP-PCWP) > 7 mm Hg or pulmonary vascular resistance > 3 Wood units. ANA = antinuclear antibody; CpcPH = combined post- and pre-capillary pulmonary hypertension; CTA = computed tomography angiography; HIV = human immunodeficiency virus; LA = left atrium; PFT = pulmonary function test; RHC = right heart catheterization; RA = right atrium; RVOT = right ventricular outflow tract; V/Q = ventilation/perfusion; other abbreviations as in Figures 1, 5, and 7.

CTA is the need for iodinated contrast material administration. However, with newer multislice scanners and iterative reconstruction techniques, the overall radiation dose and amount of contrast needed continues to improve.

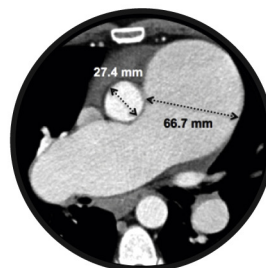
For MRI, the acquisition time continues to be lengthy despite a number of technical advancements that allow for fewer breath-holds. MRI also requires technical expertise and occasional time-consuming post-processing. PH patients receiving subcutaneous or intravenous prostacyclin treatment can be scanned, but ensuring the safety and

monitoring of these patients can increase MRI acquisition time and the requirement for specialized personnel. In addition, gadolinium-based contrast is relatively contraindicated in patients with a glomerular filtration rate < 30 ml/min/1.73 m²; however, many of the sequences used in PH (standard cines for RV size and function, velocity-encoded imaging for PA flow, and even 4D flow) do not require contrast.

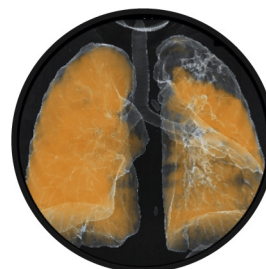
One common misconception is that cost is always a major limitation for MRI and CT. Although overall cost is higher than echocardiography, the total

CENTRAL ILLUSTRATION Utility of Computed Tomography and Magnetic Resonance Imaging in Pulmonary Hypertension**CLUES TO THE DIAGNOSIS**

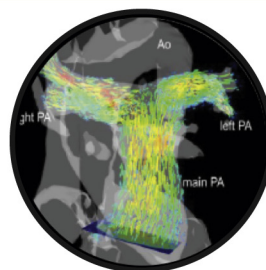
- ↑ PA diameter
- ↑ PA/Ao diameter ratio
- ↑ RV size
- Interventricular septal flattening

**ETIOLOGY**

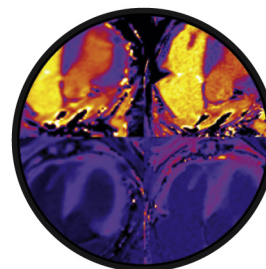
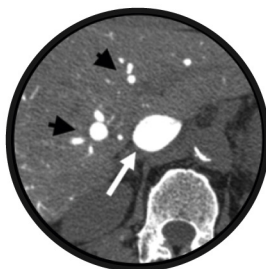
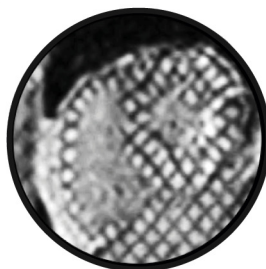
- Parenchymal lung disease
- Congenital heart disease
- PE

**PATHOPHYSIOLOGY**

- 4D PA flow characteristics
- PA wall shear stress
- PA stiffness measures

**CONSEQUENCES**

- Abnormal RV mechanics
- RV failure: contrast reflux into IVC
- RV fibrosis



Freed, B.H. et al. J Am Coll Cardiol Img. 2016;9(6):715-32.

Continued on the next page

cost is dependent on the type of MRI/CT used and whether or not contrast is given. The cost of NCCT, for instance, is only slightly higher than echocardiography, whereas the cost of MRI without contrast is similar to transesophageal echocardiography (Table 5).

THE ROLE OF COMPUTED TOMOGRAPHY AND MAGNETIC RESONANCE IMAGING IN PULMONARY HYPERTENSION CLINICAL TRIALS. Since the pivotal clinical trial of epoprostenol in 1996, the 6-min walk distance test has been the accepted exercise endpoint for studies evaluating the treatment effects of PAH in adults. Although measurable, noninvasive, easy to obtain, and cost-effective, 6-min walk distance provides little insight into the mechanism of therapeutic action. In addition, what constitutes a relevant change in 6-min walk distance is complex and not necessarily clinically meaningful despite statistical significance. An ideal surrogate should be able to predict clinically meaningful outcomes (70).

The response of the RV to increased afterload is the greatest determinant of a PH patient's symptoms and survival; therefore, parameters of RV function may be the ideal surrogate endpoints for future PH clinical trials. CMR, in particular, is well-suited for providing these parameters. Although cost-effectiveness is thought to be a major barrier for using CMR in clinical studies, Addetia et al. (71) showed that the superior reproducibility of CMR, when compared with echocardiography, in measuring RV volumes and function allowed for lower overall global fees due to the fact that fewer subjects were needed to detect changes in these measurements.

A number of small randomized controlled trials and prospective nonrandomized (observational) trials have already explored the use of CMR in PH (Table 6). Although these studies show that CMR can be used effectively in clinical trials, more work is needed to examine the clinical relevance of changes in these CMR parameters.

VALUE-BASED IMAGING FOR PULMONARY HYPERTENSION

As reimbursement patterns change in response to the rising costs of health care, it is clear that there will be a shift in incentives from volume-based to value-based imaging strategies, and the imaging of PH will be no exception to this rule. In line with these initiatives is the acknowledgment that quality and safety are of cardinal importance when selecting and performing imaging in all patients, including those with PH. Several strategies have been employed to increase the value of cardiovascular imaging overall; these include appropriateness criteria, accreditation, quality measurement, technical standards, and practice guidelines.

The imaging of PH patients is a perfect example of a clinical syndrome that can result in a high volume of imaging tests: echocardiograms, both at baseline and repeated over time, coupled with CT, MRI, and nuclear scans, not to mention a battery of other tests, including invasive hemodynamic and cardiopulmonary exercise testing, occur in a large number of these patients. In the future, health care providers will need to be much more judicious in their use of these imaging tests in order to improve both value and patient experience while keeping costs down. Furthermore, the quality of advanced imaging modalities—particularly MRI—can be quite variable. Therefore, centers of excellence for MRI imaging of complex disease states such as PH may be necessary in order to improve the value and yield of imaging tests.

An efficient algorithm for the approach to imaging of the PH patient may reduce costs and improve value. We present one such algorithm (Figure 8), which takes advantage of the fact that the majority of patients with PH have left heart disease. For example, by screening for left heart disease with echocardiography, treating, and then reimaging with echocardiography, many patients may not require further imaging tests.

CENTRAL ILLUSTRATION Continued

CT and MRI can both be helpful throughout the evaluation and management of patients with PH. **(First panel)** CT findings suggestive of PH are a common portal of referral for PH because of the widespread use of CT in the evaluation of dyspnea and respiratory failure. Both PA enlargement and RV enlargement/overload can be clues on CT for the diagnosis of PH. **(Second panel)** CT and MRI can both be helpful in the evaluation of the etiology of PH by demonstrating the presence of parenchymal lung disease or pulmonary embolism (CT) or congenital heart disease (MRI and CT). **From left to right**, these images demonstrate pulmonary fibrosis (CT), secundum atrial septal defect (MRI), and left upper lobe pulmonary embolism (CT). **(Third panel)** MRI can be useful for the evaluation of the pathophysiology of PH through the use of 4-dimensional flow characteristics and PA stiffness measurements as outlined in Table 3. **(Fourth panel)** MRI and CT can also demonstrate the consequences of PH (i.e., the effect of PH on the RV). **From left to right**, these images display MRI tagging for assessment of RV strain; CT showing reflux of contrast in the IVC and hepatic veins due to right heart failure (reproduced with permission from Aviram G, Cohen D, Steinvil A, et al. *Am J Cardiol* 2012;109:432-7); and standard and T1 mapping for assessment of diffuse RV fibrosis. Ao = aorta; CT = computed tomography; IVC = inferior vena cava; MRI = magnetic resonance imaging; PA = pulmonary artery; PE = pulmonary embolism; PH = pulmonary hypertension; RV = right ventricular.

Although algorithms such as those presented in **Figure 8** may be attractive initiatives in the era of cost containment, only randomized controlled trials of imaging algorithms versus usual care will determine whether value-based imaging strategies will truly improve patient outcomes, enhance the patient experience, and decrease costs in patients with PH.

CONCLUSIONS

MRI and CT imaging modalities are capable of determining the etiology and pathophysiology of PH and can be extremely useful in the management of these patients (**Central Illustration**). Advances in these imaging modalities are occurring at a rapid pace, with exciting new techniques such as RV tissue characterization with T_1 mapping, 4D flow of the RV and PA, and CT lung perfusion imaging paving the way for a new era of imaging in PH patients. These imaging

modalities complement echocardiography and invasive hemodynamic testing, and they may be useful as surrogate endpoints for early phase PH clinical trials. Even though the costs of MRI and CT continue to come down, it is important to recognize that a high volume of imaging tests is not appropriate, and the transition from volume-based to value-based imaging is on the horizon. By understanding the optimal techniques and indications for MRI and CT in PH, health care providers will be able to judiciously use these imaging tests, thereby increasing value and decreasing overall costs.

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