Diagnosis and Management of Pulmonary Arterial Hypertension using MR Imaging

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Pulmonary arterial hypertension (PAH) is a syndrome that results from restricted blood flow through the pulmonary arterial circulation, which leads to a pathological increase in pulmonary vascular resistance (PVR) and ultimately to right heart failure. The prognosis of patients with PAH has improved with the recent development of new medications. The need for new noninvasive diagnostic tools is increasing. Magnetic resonance (MR) imaging is the gold standard for assessing the right ventricle (RV). Its high degree of reproducibility makes it ideal for monitoring changes in RV parameters in response to therapy. MR imaging can also provide both anatomical and functional information about pulmonary hemodynamics. This article reviews the current status of MR imaging of the right side of the heart and pulmonary circulation in patients with PAH and other associated pulmonary diseases.

Keywords: lung, MRI, pulmonary hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by a pathological increase in resistance of the pulmonary circulation (PVR) that leads to right ventricular dysfunction, exertional impairment, and premature death.¹ There is currently no cure, but several treatments that have become available in recent years have improved the prognosis of patients with this devastating disease.¹² Three classes of drugs developed and approved for the treatment of PAH—prostanoids, endothelin-1 receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors—have been shown to improve various hemodynamic parameters as well as functional capacity and exercise tolerance.² Thus, quantitative assessment of the pulmonary circulation is indispensable to the management of patients with PAH.

This article reviews magnetic resonance (MR) imaging-based techniques to assess the pulmonary circulation. MR imaging has evolved in the last decade as one of the most attractive modalities for this imaging. Traditionally, the diagnostic imaging evaluation of PAH has consisted primarily of echocardiography, invasive right heart catheterization, and ventilation/perfusion scintigraphy. MR imaging has a good balance of high spatial, temporal, and contrast resolution, requires no radiation exposure, is highly accurate and reproducible, and provides both anatomic and functional information. Discussion of analysis of right ventricular (RV) function precedes discussion of the MR imaging-based method for assessing pulmonary circulation, which emphasizes PAH.

Evaluation of the Right Ventricle

PAH, a mean pulmonary arterial pressure (mPAP) of 25 mmHg at rest or 30 mmHg with exercise, is defined at cardiac catheterization.¹ Its severity does not strongly correlate with symptoms or survival, but RV mass and size and right atrial (RA) pressure, which reflect functional status, are strong predictors of survival in patients with PAH.³⁴ Thus, evaluation of RV morphology and function is especially important in the management of patients with PAH.

MR imaging is the gold standard for quantifying
RV volume and ejection fraction, and fast steady-state free precession (SSFP) sequence with breath holding has become widely available for cardiac imaging in the last decade. In this sequence, contrast depends on the T2-to-T1 ratio of tissues and is largely independent of blood flow, which allows clear demonstration of the endocardial border and precise measurement of RV volume. Simpson's method is most commonly applied to a stack of contiguous short-axis cine loops acquired from base to apex. This approach is highly accurate and does not rely on geometrical assumptions, and its good reproducibility highlights the role of MR imaging in the serial follow-up of patients for such purpose as evaluating the effect of therapy.

PAH affects the right heart and results in RV hypertrophy and dilation and RA enlargement. The extent of RV dilatation, hypertrophy, and systolic dysfunction are directly proportional to the severity of PAH. As an example, a ratio of RV to left ventricular (LV) mass that exceeds 0.6 detects PAH with a sensitivity of 84% and specificity of 71%, and is reported more specific than Doppler echocardiography. Importantly, quantification of RV functional parameters appears to add prognostic information; in a study of patients with idiopathic PAH, end-diastolic volume index ≥ 84 mL/m² for the RV and ≤ 40 mL/m² for the LV were independent predictors of one-year mortality. More sophisticated analyses of RV performance can be obtained with simultaneous quantification of pressures with MR imaging-compatible catheters to derive RV volume/pressure loops.

In severe PAH, the RV assumes a spherical shape with greater cross-sectional area than the LV, which results in abnormal septal function that impairs LV performance. The interventricular septum (IVS) is flat when RV and LV pressures are equal, but paradoxical IVS bowing occurs when RV pressure increases (Fig. 1). A linear relationship between trans-septal pressure and curvature of the septum is expected based on Laplace's law. Several methods have been proposed to assess this septal curvature. Dellegrottaglie and associates reported the accuracy and reproducibility of the curvature ratio of the LV septum to the free wall in predicting RV systolic pressure in patients clinically known to have or suspected of having PAH, with same-day right heart catheterization as the reference standard. Roeleveld and colleagues reported that systolic pulmonary artery pressure (PAP) was proportional to septal curvature, with a regression coefficient (r) of 0.77 (P < 0.001), and demonstrated reduced leftward ventricular septal bowing after treatment with a vasodilator (epoprostenol).

MR imaging can also identify damage to the RV myocardium. In patients with severe pulmonary hypertension, Blyth's group showed delayed gadolinium (Gd) enhancement concentrated at the RV insertion points and in the IVS, the extent of which correlated with RV function and pulmonary hemodynamics. The diagnostic capability and clinical utility of delayed enhancement of the RV insertion points is still unclear.

Evaluation of Pulmonary Circulation using Phase-contrast Cine Imaging

Phase-contrast (or velocity-encoded) cine MR imaging (Fig. 2), another important tool, allows
Fig. 2. (a, b) Double-oblique steady-state free precession cine magnetic resonance (MR) images of the pulmonary trunk. (c, d) Double-oblique segmented gradient-echo phase-contrast MR images perpendicular to the pulmonary trunk (repetition time [TR], 13.77 ms; echo time [TE], 9.5 ms; flip angle, 30°; matrix size, 179 x 256; rectangular field of view, 240 x 27.2 mm; and thickness 6 mm). (e) Magnitude and (d) phase images were reconstructed from the same acquisition. In cine-encoding imaging, it is important that the imaging plane is positioned orthogonal to the main direction of flow. Two images (a, b) presenting the longitudinal plane of the target vessel are used simultaneously to plan the orientation of the phase-contrast plane. White lines show the imaging planes of (c) and (d).

Fig. 3. Time-velocity curves of the pulmonary trunk and right and left pulmonary arteries in a normal volunteer.

direct correlation of phase shift with the velocity of flowing spins in the blood vessels and calculation of the velocity from the phase shift. Flow volume can also be obtained by measuring the area of the vessels. This principle has been known since the 1960s, and a breath-hold version of 2-dimensional (2D) phase contrast imaging has been developed and widely used clinically during the past decade. Recently, 3-dimensional (3D) acquisition of phase-contrast images (referred to as 4D-PC MRI) has been proposed, which is expected to allow comprehensive assessment of cardiovascular function.

Two-dimensional phase contrast flow measurement is widely used for noninvasive assessment of blood flow in the heart and great vessels in the assessment of PAH. Stroke volume (SV), a useful measure for PAH, can be calculated with pulmonary arterial flow. Long-term follow-up suggests that a 10-mL change in SV is clinically important in patients with PAH.

Phase-contrast cine MR imaging can provide time-velocity curves of the pulmonary artery, which include valuable information about pulmonary hemodynamics. The time-velocity curve of the main pulmonary trunk, which changes smoothly with the cardiac cycle in normal subjects (Fig. 3), is steep in patients with PAH (Fig. 4). Several parameters, including acceleration time, acceleration volume, ratio, and average velocity, have been proposed for quantitative analysis of the time-velocity curve.

Sanz and colleagues assessed the diagnostic value of these parameters in PAH in 59 subjects and found that average velocity correlated best with mPAP. PAH was correctly diagnosed with average velocity above the cutoff value of 11.7 cm/s (measured in expiration), with sensitivity of 92.9% (39/42) and specificity of 82.4% (14/17). On the other hand, diagnostic sensitivity for the minimum area of pulmonary artery (cutoff value, 6.6 cm²) was 92.9% (39/42), and specificity was 88.2% (15/17). We measured the average velocity in 25 patients with PAH or suspected PAH and found that the average velocity correlated significantly with mPAP. Compared with right ventricular systolic pressure (RVSP) measured on ultrasonography, the r value was smaller (Fig. 5). The average velocity determined by MR imaging (cutoff value, 7 cm/s, measured in inspiration) was better than that by ultrasonography, with sensitivity of 90.9% and specificity of 92.9%. Sensitivity was 100% and specificity was 57.1% for RVSP measured on ultrasonography (cutoff value >35 mmHg).

Nogami and associates used cine-encoding im-
Fig. 4. (a) Chest radiograph, (b) planar anterior-posterior image of perfusion scintigraphy, and (c) time-velocity curves of the pulmonary arteries derived from magnetic resonance (MR) imaging in a patient with primary pulmonary hypertension. (a) Chest radiograph demonstrates enlargement of the proximal pulmonary arteries with tapering of the peripheral vasculature. (b) Perfusion scintigraphy shows heterogeneous mottled perfusion pattern. (c) Time-intensity curve shows higher peak velocity and shorter time to peak velocity compared with the values of normal subjects (Fig. 3).

ages to evaluate the regurgitant jet of the tricuspid valve and calculated pulmonary arterial systolic pressure using Bernoulli’s equation in a manner similar to that used in ultrasonography. They reported better correlation for systolic pulmonary arterial pressure between phase-contrast MR imaging and catheterization ($r = 0.94$) than between cardiac ultrasonography and catheterization ($r = 0.86$).

In addition, phase-contrast cine MR imaging can be used to evaluate dynamic changes in arterial cross-section and, therefore, pulmonary artery stiffness. A change in pulmonary artery (PA) cross-sectional area of less than 16% during the cardiac cycle was identified recently as a predictor of mortality in PAH. In addition, alterations in PA elasticity can be detected before development of overt PAH and may aid early detection of abnormal circulatory physiology. Phase-contrast cine MR imaging can be applied to evaluate the right and left pulmonary arteries and allow measurement of stroke volume into each lung. Saouti and coworkers measured flow, resistance, and compliance of each lung using MR imaging and right heart catheterization in patients with chronic thromboembolic pulmonary hypertension. They found low flow and high resistance in the more affected lung.

Phase-contrast imaging can be obtained with either breath-holding or respiratory gating. Breath-hold image acquisition allows easy alignment of the perpendicular plane to the vessels, but respiratory gating offers better temporal resolution. In addition, blood flow measured with breath-hold MR imaging may differ from physiological blood flow during normal breathing because breath-holding can change intrathoracic pressure and thereby considerably influence systemic venous return to the heart. Sanz’s group obtained phase-contrast images during end-expiratory breath holds preceded by brief hyperventilation.
Fig. 5. Relationship between mean pulmonary artery pressure (mPAP) measured on right heart catheterization and (a) average velocity (AV) of the pulmonary trunk by magnetic resonance (MR) imaging and (b) right ventricular systolic pressure (RVSP) measured on echocardiography (n = 24). The correlation was significant for mPAP-average velocity (r = -0.574, P = 0.003) and mPAP-RVSP (r = 0.799, P < 0.001).

Gadolinium (Gd)-enhanced Pulmonary Perfusion Imaging

Ideal perfusion imaging would delineate blood flow at a capillary level. MR imaging of the lung, however, is extremely challenging for several reasons. Intrinsic low proton density and the multiple air-tissue interfaces cause very short T2* of the lung parenchyma. Respiratory and cardiac motion and pulmonary blood flow also reduce signal. Thus, short echo time (TE), short repetition time (TR) and another fast imaging technique, such as parallel imaging, are necessary to obtain signal from the lung parenchyma. Hatabu and coworkers were the first to describe 2D dynamic contrast-enhanced perfusion imaging of the lung using ultra-short TE imaging. Furthermore, Ohno and associates proposed Gd-enhanced time-resolved MR angiography to assess pulmonary perfusion whereby T1-weighted 3D images of the whole lung are obtained with short TR and TE following rapid injection (4 to 5 mL in one second) of a small amount of contrast material (Fig. 6). This method allows simultaneous assessments; quantitative assessment of regional abnormalities in pulmonary perfusion in the entire lung and assessment of disease severity according to PVR and mPAP using a 1.5T MR unit.

Time-resolved MR angiography can clearly demonstrate perfusion defect in pulmonary arterial thromboembolism (PTE) (Fig. 7), and Ohno’s group confirmed its utility for diagnosing PTE. By vascular zone, sensitivity of MR angiography was 83%, and specificity, 97%; by patient, sensitivity was 92% and specificity, 94%. Still, the diagnostic capability of perfusion MR imaging is less than that of CT for detecting subtle subsegmental PTE. For example, Kluge and associates reported 92% sensitivity of perfusion MR imaging and specificity of subsegmental PTE limited to 75%. They reported the misdiagnosis of emphysema as PTE using MR perfusion imaging because of the difficulty diagnosing emphysema by loss of signal on nonenhanced MR imaging. Thus, Gd-enhanced perfusion MR imaging is generally not yet the method of choice for PTE.

On the other hand, Gd-enhanced MR imaging can provide useful information about pulmonary hemodynamics. Using short-axis images of the RV and LV of 43 patients with scleroderma obtained after bolus Gd injection using a 3T MR unit, Skrok and colleagues measured pulmonary transit time (PTT) and other parameters in time intensity curves of the RV and LV and found PTT longer in patients with PAH (median, 8.2 s) than those without (median, 6.5 s). Furthermore, PTT correlated significantly with mPAP measured by right heart catheterization (r = 0.56, P < 0.002). PTT is a useful measure in assessing PAH but is also prolonged in patients with coronary artery disease, LV hypertrophy, and LV dysfunction.

In particular, analysis of MR angiographic signal intensity curves of the lung could yield parameters of vascular physiologic relevance, including mean transit time (MTT), pulmonary blood flow (PBF), and pulmonary blood volume (PBV). Ohno’s
Fig. 6. Gadolinium (Gd)-enhanced magnetic resonance (MR) imaging. These images were obtained with a 1.5T MR unit and 32-channel phased-array coil. Acquisition parameters were: repetition time (TR), 2.35 ms; echo time (TE), 0.8 ms; flip angle, 25°; matrix size, 132×208; rectangular field of view, 430×430 mm; and 12 slabs covering the whole lung (thickness, 12 mm). Temporal resolution was 1.0 s for each 3-dimensional dataset. Signal intensity of the lung parenchyma is very low (left image), increases with enhancement of the pulmonary arteries (middle image), and decreases with enhancement of the aorta (right image).

Fig. 7. A 45-year-old female patient with acute pulmonary embolism. (a) Fusion images with computed tomography (CT) and perfusion scintigraphy demonstrated multiple segmental perfusion defects. (b) Quantitative pulmonary blood flow (PBF) maps derived from gadolinium (Gd)-enhanced magnetic resonance (MR) imaging demonstrated segments with markedly reduced PBF in both lungs, which corresponded with perfusion defect on scintigraphy.

group applied this method to patients with PPH and found low PBF and prolonged MTT in these patients. They also described good negative correlation between PBF and PVR (r = −0.79, r² = 0.62, P < 0.001), and moderately positive correlation between MTT and PVR (r = 0.60, r² = 0.36, P = 0.022). In acute pulmonary thromboembolism (APTE), PBF is the most reliable parameter for distinguish-
Fig. 8. A 75-year-old female patient with pulmonary fibrosis (nonspecific interstitial pneumonia). (a) Coronal computed tomographic (CT) image shows fibrosis in the bases of both lungs. (b) Segmentation map of CT image using the original system. Light purple area, normal lung; light blue area, fibrosis. (c) Quantitative maps of mean transit time (MTT) derived from gadolinium (Gd)-enhanced magnetic resonance (MR) imaging demonstrate markedly prolonged MTT (red area) in the left and right lung bases, which corresponds with fibrosis on CT. Light green on MTT map represents areas with normal MTT.

PAH and Pulmonary Fibrosis

PAH is an unfavorable complication in idiopathic or secondary pulmonary fibrosis that occurs with high frequency in patients with combined pulmonary fibrosis and emphysema (CPFE), which is emphysema in the upper lung zone and pulmonary fibrosis in the lung base. Sergiacomi’s group showed that MTT derived from dynamic MR images of the RV correlated with mPAP on right heart catheterization in patients with CPFE. PAH is also associated with collagen vascular disease. In particular, PAH occurs in 10 to 33% of patients with systemic sclerosis and, along with pulmonary fibrosis, is the most common cause of death in these patients. Ohno and associates demonstrated good correlations between the mean values of PBF, PBV, and MTT derived from time-resolved MR imaging and systolic PAP on right heart catheterization in patients with pulmonary fibrosis of collagen vascular disease.

It is interesting that MR imaging parameters for PAH correlate with extent of fibrosis on CT images. Previously, we developed a system to measure disease extent automatically on CT images. We compared such quantitative CT images with a map of MTT derived from the original system and found regional prolongation of MTT, which corresponded with fibrosis on CT, in patients with idiopathic pulmonary fibrosis (Fig. 8). These results call for the consideration of CT and MR imaging as complementary investigative tools in such conditions. A combined CT and MR imaging approach should provide valuable information about pulmonary hemodynamics.

Conclusion

Several imaging modalities can be combined to evaluate the right heart and pulmonary circulation. In particular, advances in echocardiography, CT, and MR imaging have contributed to a progressive shift to a noninvasive approach in the diagnosis and management of PAH. MR imaging provides information on cardiac function and dynamic information regarding regional lung perfusion without irradiation. MR imaging is destined to become the gold standard for imaging the right heart. Though MR imaging is not widely available at present for the evaluation of PAH, further technological advances in MR imaging promise to improve detection of early disease stages or evaluate the mechanisms of action and efficacy of novel therapeutic interventions.

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References


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