Clinical Application of 4D Flow MR Imaging to Pulmonary Hypertension

Hideki Ota¹,²*, Hiroki Kamada¹, Satoshi Higuchi¹, and Kei Takase¹,²

Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure (PAP). Although right-heart catheterization is the gold standard method for the diagnosis of PH by definition, various less-invasive imaging tests have been used for screening, detection of underlying diseases-causing PH, and monitoring of diseases. Among them, 4D flow MRI is an emerging and unique imaging test that allows for comprehensive visualization of blood flow in the right heart and proximal pulmonary arteries. The characteristic blood flow pattern observed in patients with PH is vortical flow formation in the main pulmonary artery. Recent studies have proposed the use of these findings to determine not only the presence of PH but also estimate the mean PAP. Other applications of 4D flow MRI for PH include measurement of wall shear stress, helicity, and 3D flow balance in the pulmonary arteries. It is worth noting that 4D flow has also the potential for longitudinal follow-ups. In this review, the clinical definition of PH, summary of conventional imaging tests, characteristics of pulmonary arterial flow as shown by 4D flow MRI, and clinical application of 4D flow MRI in the management of patients with PH will be discussed.

Keywords: magnetic resonance imaging, 4D flow, pulmonary artery, pulmonary hypertension, velocity

Introduction

Pulmonary hypertension (PH) is characterized by elevated pulmonary arterial pressure (PAP). The etiology of PH may be idiopathic or related to a variety of diseases. In the current clinical practice, image examination plays a critical role in the diagnosis and management of patients with PH. In cases of suspected PH, transthoracic echocardiography and chest X-ray examinations are the most commonly used and appropriate imaging tests.¹ Cardiac magnetic resonance (CMR) imaging, which has been used for work-up purposes due to its accessibility and long examination time, can provide a comprehensive evaluation of cardiac function, tissue characteristics, and flow dynamics with no risk of radiation exposure. Moreover, some features including evaluation of flow dynamics require no contrast enhancement.

Since its introduction in the 1980s, 2D cine phase-contrast (PC) MRI has been widely used for the quantitative evaluation of regional hemodynamics in the cardiovascular system.²⁻⁴ 4D flow MRI, which is time-resolved PC MRI with velocity encoding along the x-, y-, and z-directions and 3D volumetric anatomic coverage, has been recently developed; it can be used for the evaluation of cardiovascular hemodynamics in various regions.⁵ This technique (4D flow MRI) can evaluate pulmonary arterial blood flow and may further enhance the diagnostic value of CMR imaging in PH. In this review, the clinical definition of PH, summary of conventional imaging tests, characteristics of pulmonary arterial flow as shown by 4D flow MRI, and clinical application of 4D flow MRI in the management of patients with PH have been discussed.

Clinical Definition and Classification of PH

In the field of PH, definitions, scientific and clinical progress, and future needs have been discussed at the World Symposium on Pulmonary Hypertension (WSPH), which has begun in 1973 and is held every 5 years in recent times. In the past, PH was defined as a mean pulmonary artery pressure $\geq 25$ mmHg on right-heart catheterization (RHC); the mean pulmonary artery $\leq 20$ mmHg was considered normal, and 21–24 mmHg was considered as borderline PH.⁶⁻⁷ At the 6th WSPH held in Nice in 2018, it was proposed that pulmonary vascular resistance (PVR) $\geq 3$ WU among borderline cases should be included in pre-capillary PH.⁸

The clinical classification of PH can be divided into five major groups according to similar clinical presentation,
pathophysiological characteristics, and treatment strategy (Table 1). In clinical practice, the pathogenesis of PH might be complex, as there may be cases in which the etiology could be multifactorial. The clinical manifestations of PH include dyspnea on exertion and limitation of activity due to fatigue, chest pain, and fainting. The World Health Organization functional class (Class I, the mildest form - IV, the most severe form) is widely used to describe the severity of patients with PH. The severity of symptoms is associated with prognosis, although it is not highly disease-specific. Prolonged and persistent PH, irrespective of the etiology, results in irreversible remodeling of the pulmonary vasculature with elevated PVR; mortality is attributed to right-heart failure, resulting from the increase in the afterload secondary to the elevated PAP. Early diagnosis and appropriate intervention according to the etiology will improve the quality of life and prognosis of patients with PH.

Among the etiologies of PH, chronic thromboembolic pulmonary hypertension (CTEPH), classified as group IV, has drawn attention in both research and clinical settings. CTEPH is caused by pulmonary artery stenosis and occlusion due to an organic thrombus and secondary vascular remodeling. Episodes of acute pulmonary embolism occur in approximately 0.1%–8.8% of patients, and many patients have no clear history. In the past, surgical endarterectomy was the only intervention method other than drug therapy. However, the efficacy of balloon pulmonary angioplasty (BPA) for patients with inoperable CTEPH has been actively reported in Japan, and the prognosis has been improving. Such patients require long-term management; thus, the role of imaging tests along with the treatment effects during follow-up is needs to be elucidated.

**Imaging tests for PH**

The definitive diagnosis of PH was made using RHC as the reference standard to measure PAP. However, owing to its invasive nature, several steps before conducting RHC should be considered. Various imaging modalities are helpful in the diagnosis and classification of PH (Figs. 1 and 2). When PH is suspected, transthoracic Doppler echocardiography in the resting state is commonly performed as a screening test following chest radiography (Fig. 1). Doppler echocardiography demonstrates a sensitivity of 70%–100% and specificity of 68%–98% in detecting moderate PH. The peak tricuspid regurgitation velocity as measured by Doppler echocardiography is used to estimate the probability of PH. Echocardiography also allows for the detection of other abnormal findings that can be associated with PH, such as intracardiac shunts and dilatations of the right ventricle and pulmonary arteries. However, limitations of echocardiography include its operator-dependent technique and limited windows to assess the functions of right heart that are influenced by factors altering the position of the heart in relationship to the echo probe, such as obesity and hyperinflated lungs. Regarding quantitative assessment of right

### Table 1 Updated clinical classification of PH

| 1 PAH                                                                 |
|-----------------------------------------------------------------------|
| 1.1 Idiopathic PAH                                                     |
| 1.2 Heritable PAH                                                      |
| 1.3 Drug- and toxin-induced PAH                                        |
| 1.4 PAH associated with:                                               |
| 1.4.1 Connective tissue disease                                        |
| 1.4.2 HIV infection                                                    |
| 1.4.3 Portal hypertension                                              |
| 1.4.4 Congenital heart disease                                         |
| 1.4.5 Schistosomiasis                                                  |
| 1.5 PAH long-term responders to calcium channel blockers               |
| 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement|
| 1.7 Persistent PH of the newborn syndrome                              |
| 2 PH due to left-heart disease                                         |
| 2.1 PH due to heart failure with preserved LVEF                        |
| 2.2 PH due to heart failure with reduced LVEF                          |
| 2.3 Valvular heart disease                                             |
| 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH |
| 3 PH due to lung diseases and/or hypoxia                               |
| 3.1 Obstructive lung disease                                           |
| 3.2 Restrictive lung disease                                           |
| 3.3 Other lung disease with mixed restrictive/obstructive pattern      |
| 3.4 Hypoxia without lung disease                                       |
| 3.5 Developmental lung disorders                                       |
| 4 PH due to pulmonary artery obstructions                              |
| 4.1 Chronic thromboembolic PH                                          |
| 4.2 Other pulmonary artery obstructions                                |
| 4.2.1 Sarcoma or angiosarcoma                                          |
| 4.2.2 Other malignant tumors                                           |
| 4.2.3 Non-malignant tumors                                             |
| 4.2.4 Arteritis without connective tissue disease                      |
| 4.2.5 Congenital pulmonary artery stenosis                             |
| 4.2.6 Parasites Hydatidosis                                            |
| 5 PH with unclear and/or multifactorial mechanisms                     |
| 5.1 Hematological disorders                                            |
| 5.2 Systemic and metabolic disorders                                   |
| 5.3 Others                                                            |
| 5.4 Complex congenital heart disease                                   |

HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease.
ventricular (RV) systolic function, several echocardiographic parameters have been studied; however, each method has its limitation. A recent study by Sato et al. demonstrated that tricuspid annular plane systolic excursion (TAPSE) as measured by M-mode echocardiography significantly predicted CMR imaging-derived RV ejection fraction as the reference standard. A ventilation and perfusion (V/Q) lung scan is performed to diagnose CTEPH (Fig. 2a). A V/Q lung scan demonstrates a sensitivity of 90%–100% and specificity of 94%–100% for differentiating between idiopathic pulmonary arterial hypertension (PAH) and CTEPH. CT is a very useful tool in the diagnosis and work-up of PH, providing comprehensive anatomical information about the heart, pulmonary vasculature, and parenchyma (Fig. 2b). Using modern multi-detector CT scanners, Ley et al. reported that pulmonary angiography demonstrated sensitivities and specificities of 99%–100% and 100%, respectively, in the detection of CTEPH. Lung parenchymal images help to identify various underlying lung conditions, such as interstitial lung disease, chronic obstructive pulmonary disease (COPD), and pulmonary venous occlusive diseases that may lead to PH. The role of CMR imaging will be detailed in the next subsection.

**CMR imaging in PH**

The role of CMR imaging in the management of PH is shown in Table 2. CMR imaging is the gold standard method for the evaluation of the function and morphology of the right heart and has the advantages of being non-invasive, reproducible, and free of blind spots. A recent statement on imaging and PH also recommends the use of CMR imaging to monitor RV function.

In PH, cine MRI reveals flattening and paradoxical motion of the interventricular septum with D-shaped left ventricle, dilatation of the RV chamber, thickening of the RV wall, and rounding of the RV (Fig. 2c). The end-diastolic and end-systolic volume index, ejection fraction, cardiac index, and ventricular mass index are parameters that can reflect the severity and prognosis of PH. A recent meta-analysis including 22 studies with a total of 1938 participants reported the use of cine MRI parameters to determine the prognosis of pulmonary arterial hypertension. According to the pooled hazard ratios, every 1% decrease in the RV ejection fraction was associated with a 4.9% increase in the risk of clinical deterioration and 2.1% increase in the risk of death. An increase in the RV end-systolic volume index and RV end-diastolic volume index was also associated with clinical deterioration and the risk of death. Another meta-analysis also demonstrated that the RV ejection fraction was the strongest predictor of all-cause mortality, followed by the RV mass index, RV end-diastolic volume index, and RV end-systolic volume. A study by Johns et al. assessed the interventricular septal (IVS) angle in the identification of combined pre- and post-capillary PH in patients with PH due to left-sided heart disease. The systolic IVS angle was elevated in patients with combined pre- and post-capillary PH. It was also predictive of all-cause mortality (hazard ratio, 1.615).

In late gadolinium-enhanced MRI, enhancement of the RV insertion point is frequently observed in patients with PH. This is thought to be due to fibrosis and inflammation caused by increased mechanical stress at the RV junction, as well as myocardial fiber disarray. It is also associated with early systolic paradoxical IVS motion.
Fig. 2 Multiple imaging tests of a woman in her 70s with chronic thromboembolic pulmonary hypertension. (a) Multiple segmental perfusion defects with right-side dominance are observed in lung perfusion scintigraphy. (b) Multiple stenocclusive lesions with right-side dominance and dilatations of the central pulmonary arteries are demonstrated in the volume-rendering image of CT pulmonary angiography (light blue, pulmonary arteries, red, pulmonary veins). (c and d) Cine MRI in the late diastolic (c) and late systolic (d) phases demonstrates dilatation and wall thickening of the right ventricle. Leftward intraventricular septal bowing and D-shaped left ventricle are appreciated in the late systolic phase (d). (e) Lung perfusion MRI demonstrates right-side dominant perfusion defects (arrows) in the lung parenchyma, similar to the lung perfusion scintigraphy (a). (f and g) 4D flow MRI before and after BPA. Vortical flow in the main pulmonary artery and right-dominant reduced blood flow is observed before BPA (f). The findings were improved after BPA (g). BPA, balloon pulmonary angioplasty.
Table 2  Role of CMR for pulmonary hypertension

| Method                          | Parameters                                                                 |
|--------------------------------|-----------------------------------------------------------------------------|
| Cine MRI                        | Morphology and function                                                     |
|                                 | - right ventricular (RV) hypertrophy, RV dilatation, tricuspid valve deformation, flattening of the interventricular septum (IVS), paradoxical motion of the IVS, proximal pulmonary arterial dilation, pericardial and pleural effusion, visual assessment of the blood flow, regional wall motion by feature-tracking strain analysis. |
|                                | Myocardial strain imaging                                                  |
|                                 | - fast strain-encoded imaging, cine MRI with feature-tracking method       |
|                                | - biventricular regional function assessment                              |
| Late gadolinium enhancement/T1 map | positive enhancement at the right ventricular insertion point, prolonged T1 in the myocardium, extracellular volume. |
| Myocardial tissue characteristics | Area-adjusted septal native T1 values that consisted of the mean T1 values and areas measured for the interventricular septum and the upper and lower RV insertion points. |
| 2D phase-contrast MRI           | Blood flow parameters                                                      |
|                                 | - Blood flow velocity, regurgitant fraction, Qp/Qs,                        |
|                                 | Distensibility of the pulmonary artery                                    |
| 4D flow MRI                     | 3D blood flow visualization                                                |
|                                 | - flow pattern, vortical flow                                              |
|                                 | Conventional blood flow parameters                                        |
|                                 | Parameters obtained by 2D phase-contrast MRI                              |
|                                 | Advanced hemodynamic parameters                                            |
|                                 | - wall shear stress, energy loss, helicity                                 |
|                                 | MR angiography and perfusion                                               |
|                                 | Evaluation of pulmonary vasculature                                        |
|                                 | Heterogeneous perfusion in the lung parenchyma for CTEPH                   |

CMR, cardiac magnetic resonance; CTEPH, chronic thromboembolic pulmonary hypertension; IVS, interventricular septum; RV, right ventricular.

enhancement may also extend from the RV junction to the ventricular septum. However, the value of late gadolinium enhancement (LGE) for the prediction of patients with PH is controversial. Previous studies have demonstrated a potential association between positive LGE at RV insertion points and RV dysfunction with a poor prognosis. On the contrary, other studies suggested no significant association between those two variables. Further large studies may be warranted to determine the value of LGE in the management of patients with PH.

Recent advancements in technology allow the quantification of myocardial T1 and the extracellular volume (ECV) in the clinical setting. Myocardial T1 mapping is a pixel-wise demonstration of longitudinal relaxation times. An ECV map is generated from pre- and post-contrast T1 maps corrected for the hematocrit level. Some past studies used T1 mapping and explored its value for PH. These studies evaluated T1 values in RV insertion points, IVS, and LV free wall. A large study consisting of 490 consecutive patients with PH demonstrated that elevated myocardial native T1 in the RV insertion point was found to a similar extent in patient subgroups and was independently associated with increased IVS angle. However, native T1 metrics did not contribute to the prediction of overall mortality. In a longitudinal study involving patients with CTEPH, Roller et al. calculated area-adjusted septal native T1 values that consisted of the mean T1 values and areas measured for the interventricular septum and the upper and lower RV insertion points. Area-adjusted septal T1 values were correlated with the mean PAP (mPAP) and PVR, and the T1 values significantly decreased after BPA. The study indicates a potential role of T1 mapping in monitoring the treatment effect of patients with CTEPH.

In PC MRI, it is known that the mean pulmonary artery blood flow velocity correlates with the mPAP, and when the cutoff value for the mean pulmonary artery blood flow velocity is set at 11.7 cm/s, the sensitivity and specificity for an mPAP > 25 mmHg are reported to be 93% and 82%, respectively. It has also been reported that pulmonary artery distensibility (change in pulmonary artery cross-sectional area during the cardiac cycle) measured using PC MRI is correlated with PVR and exercise tolerance.

MR angiography evaluates the anatomy of pulmonary vessels in a manner similar to CT angiography. In PH, the pulmonary arteries are generally dilated on the central side and narrowed on the peripheral side. In addition, CTEPH patients have characteristic angiographic findings, and these findings can be visualized to some extent, although the spatial resolution is limited. MR angiography and dynamic contrast-enhanced perfusion MRI are established in the clinical assessment of patients, particularly with PH and thromboembolic disease (Fig. 2e). A study by Johns included 74 patients with suspected CTEPH and demonstrated that dynamic contrast-enhanced lung perfusion MRI showed increased sensitivity when compared with perfusion scintigraphy when screening for CTEPH.

4D flow MRI in PH

In recent studies of 4D flow MRI in the pulmonary vasculature, most reports evaluated the central segments from the pulmonary artery trunk to the right and left main pulmonary
arteries (Figs. 2e, 2f, and 3). Application of 4D flow MRI for the chest and abdomen inhere a trade-off between spatial resolution and information that requires respiratory synchronization or increasing the number of excitations. A spatial resolution of < 2.5 x 2.5 x 2.5 mm^3 for the aorta or pulmonary artery is recommended in the consensus statement. Therefore, using current 4D flow MRI, it is difficult to evaluate the peripheral pulmonary vascular bed, where lesions causing most cases of PH are located. On the contrary, remodeling also occurs in the central pulmonary artery due to increased PAP and PVR, resulting in dilatation and stiffening.

Advantages of 4D flow MRI include not only providing retrospective quantification of blood flow but also advanced hemodynamic parameters, such as vorticity, helicity, wall shear stress (WSS), and energy loss.

Vortical flow formation in PH
In normal cases, laminar and undisturbed stream lines were observed on 4D flow MRI (Fig. 3). In contrast, as the mPAP increased, vortical flow formed in the pulmonary artery trunk and became distinct. Reiter et al. recruited 145 patients with suspected PH and demonstrated that the percentage of cardiac phases with vortex present (t_vortex) correlated with the degree of mPAP (r^2 = 0.95). The area under the curve for the t_vortex-based diagnosis of PH was 0.99, and the calculated cut-off value (t_vortex = 14.3%) for the presence of PH resulted in a sensitivity of 0.97 and specificity of 0.96. Vortical blood flow with a t_vortex < 14.3% was specific for borderline PH. In another study by Ramos et al., the vortex duration assessed by CMR imaging had a higher diagnostic yield for detecting elevated PAP compared to the peak systolic tricuspid regurgitation pressure gradient measured by Doppler echocardiography, potentially due to the low sensitivity of echocardiography. The duration of vortical flow can be followed longitudinally. Reiter et al. also reported that MR-driven mPAP, as calculated by the change in the duration of vortical flow, was correlated with the change in RHC-driven mPAP. A secondary morphological change in PH, the dilation of the pulmonary arterial trunk, may have influenced the formation of vortex flow. However, in a study of normal subjects, vortical flow formation was reported to occur in approximately 3% of subjects without a history of PH. In normal subjects, the geometry of the pulmonary arterial trunk, which bifurcates to the left and right, may affect the formation of vortical flow.

Hemodynamic characterization in Group III PH
A limitation exists for determining the presence of PH using pulmonary vascular measurements of imaging tests in patients with lung diseases, such as interstitial lung disease and COPD (group III PH), although some studies reported promising results. Different approaches for estimating the degree of PH are possible using 4D flow MRI. Oganesyan et al. evaluated the pulmonary arterial stiffness, vorticity, and helicity of blood flow in COPD patients and controls. Vorticity is a vector describing local flow rotation rate at any time point of the cardiac cycle at defined anatomical location. Helicity is a scalar describing the relationship between flow strength and the amount of local rotation in flow; it is mathematically defined as the scalar dot product between velocity and vorticity vector fields integrated over a defined anatomic space. In their study, COPD patients had decreased maximum systolic helicity in the main pulmonary artery, and helicity was associated with increased pulmonary arterial stiffness and RV function. This technique, 4D flow MRI, may have diagnostic potential for hemodynamic characterization in patients with cardiopulmonary disease.

Hemodynamic effects of percutaneous intervention for group IV PH
Percutaneous stent intervention of branches of pulmonary arteries can be performed in patients with congenital heart diseases and large vessel vasculitis. CMR imaging, including 4D flow MRI, can be used for comprehensive evaluations of the target vessels in the proximal segments, as well as the ventricular function. In a study conducted on a swine, Pewowaruk et al. used CMR imaging to evaluate the RV strain and 4D flow MRI findings before and after stent intervention for proximal pulmonary artery stenosis and found that inefficient RV and left ventricular flow patterns, as defined by vorticity in the chambers, were dominant in the stenosis group compared with the sham group, and ventricular functions were improved along with reduced vorticity after stenting. The authors revealed the impact of pulmonary artery stenosis and subsequent stent treatment on ventricular function. Kamada et al. reported that stent treatment for unilateral pulmonary artery stenosis in large-vessel vasculitis resulted in an increase in overall pulmonary blood flow and improved blood flow balance between the right and left pulmonary arteries. In CTEPH patients, 4D flow MRI allows for the demonstration of drastic changes in pulmonary blood flow after pulmonary thromboendarterectomy and BPA (Fig. 2e and 2f).

WSS in PH
It is worth noting that 4D flow MRI can obtain not only the blood flow patterns but also the blood flow velocity profile in the central pulmonary artery to analyze the WSS (Fig. 4). The WSS is a dynamic frictional force induced by blood flow along the surface of the vascular walls. Such mechanical stimulation by blood flow is thought to be involved in vascular wall remodeling. The WSS affects the vascular smooth muscle, leading to changes in tissue properties, and, ultimately, to the remodeling of the vascular geometry. Time-resolved WSS parameters can be obtained along with systolic, diastolic, and average WSS in cardiac phases. In addition, depending on studies, WSS parameters may be obtained at cross-sections or 3D vascular segments. Studies indicated that low WSS in the pulmonary arterial trunk may become
characteristic findings of PH. Barker et al. performed 4D flow MRI on 19 healthy subjects and 17 subjects with PH to measure the pulmonary artery diameter, peak systolic velocity (Vmax), peak flow (Qmax), stroke volume, and WSS in the pulmonary artery trunk and the right and left main pulmonary arteries. At all locations, the Vmax, Qmax, stroke volume, and WSS were lower in the PH group than in the healthy group. Odagiri et al. also reported vortex formation in the pulmonary artery trunk, backward blood flow in the pulmonary artery trunk during systole, and a decreased WSS in PH. Terada et al. evaluated WSS parameters at the pulmonary arterial trunk of 17 consecutive patients with respiratory diseases (5, PAH; 12, non-PAH). Systolic WSS and mean WSS of the PAH group were significantly lower than those of the non-PAH group; moreover, systolic, diastolic, and mean WSS were negatively correlated with mPAP. Ikoma et al. used 4D flow MRI to evaluate the pulmonary artery hemodynamics in systemic sclerosis (SSc) patients; the WSS at the peak systolic phase was significantly lower, whereas the oscillatory shear index was greater in patients with SSc without manifest PAH than in controls. The hemodynamic changes detected by 4D flow MRI may help patient management even at stages that precede manifest PAH in patients with SSc.

**Conclusion**

The clinical application of CMR imaging, including 4D flow MRI in PH, was discussed based on recent clinical studies. In addition to established evidence of CMR imaging, 4D flow MRI, an emerging technique, has the potential to provide a clinical value for the management of patients with PH, including diagnosis, severity assessment, treatment monitoring, and prognosis determination.
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Conflicts of Interest
The authors declare that they have no conflicts of interest.

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