Four-Dimensional Flow Magnetic Resonance Imaging for Cardiovascular Imaging: from Basic Concept to Clinical Application

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Magnetic resonance imaging (MRI) plays an important role in evaluation of the cardiovascular system. Two-dimensional phase-contrast MRI has been used to assess regional blood flow parameters such as flow velocity and volume and regurgitant fraction. Recently, four-dimensional (4D) flow MRI that acquires three-dimensional (3D) velocity and encodes volume coverage has been developed and applied to various clinical settings. 4D flow MRI allows retrospective flow measurement at any cross-section and 3D flow visualization through postprocessing. More advanced flow parameters based on fluid dynamics have been proposed and applied to 4D flow MRI to further understand flow mechanisms that might be related to the evolution and progression of cardiovascular diseases. The purpose of this review is to introduce the basics of 4D flow image acquisition and postprocessing, and its clinical application to selected cardiovascular diseases.

Key words Magnetic resonance imaging · Hemodynamics · Heart diseases · Vascular diseases · Pulmonary hypertension.

INTRODUCTION

Magnetic resonance imaging (MRI) has become an important diagnostic tool for evaluating the cardiovascular system. Various image acquisition protocols are conducted to diagnose cardiac and vascular diseases, measure volumes and functions, and assess the effects of medical, endovascular, and surgical interventions in routine clinical settings. Among them, phase-contrast (PC) MRI has been mainly used for two purposes since the early clinical application of MRI in the 1980s [1,2]. The first purpose is two-dimensional (2D)/three-dimensional (3D) PC magnetic resonance angiography (PC MRA) using its magnitude image. This technique has been applied to various fields from the cerebrovascular system to the lower peripheral arteries [3-6]. The second purpose is 2D PC MRI for flow quantification based on the direct relationship between the phase of MR signals and

flow velocity. The imaging plane is generally set orthogonal to the vascular axis, providing various flow-related parameters such as blood flow velocity, blood flow volume, and regurgitant fraction through the cross-sections to evaluate the hemodynamic state.

Recently, time-resolved PC MRI with velocity encoding along x-, y-, and z-directions and 3D volumetric anatomic coverage [also termed four-dimensional (4D) flow MRI] has been developed and applied for the evaluation of cardiovascular hemodynamics in multiple regions of the human body [7]. 4D flow MRI has several advantages over conventional 2D PC MRI, such as measuring velocity parameters on any plane placed retrospectively at postprocessing, 3D flow visualization, and advanced hemodynamic parameters using 3D velocity information.

The purpose of this review is to introduce the basic protocols, advantages and disadvantages, and postprocessing for image evaluation of 4D flow MRI. A selected clinical application of 4D flow MRI will also be illustrated and further potential applications of 4D flow MRI as a cardiovascular imaging modality

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ty will be discussed.

IMAGE ACQUISITION AND POSTPROCESSING

Blood flow velocity measurement on 2D PC MRI

On PC MRI, magnetic field gradients are used to encode the spatial movement of the spins. Sequence schemes are characterized by velocity encoded bipolar gradients consisting of two lobes of equal area (duration and amplitude) and opposite gradient polarity similar to the diffusion-weighted sequences [8,9]. The bipolar gradients generate phase shifts, resulting in net-zero shifts for stationary spins. However, moving spins gain a nonzero phase because the encoding magnetic field strength changes with the location of the moving spins. If the spins move along the direction of the gradient with a constant velocity, the change in the phase is proportional to the velocity of the moving spins. The velocity information can be obtained as a phase-difference image, which is created by subtraction of two phase images acquired by toggling the bipolar gradient (acquisition of all imaging parameters is the same except for the polarity of the bipolar gradient) or acquired with and without velocity encoding. For accurate velocity quantification, it is important to assess background phase errors caused by the eddy current, concomitant gradient field, and gradient non-linearity [10]. Generally, the 2D PC cross-sectional image is set perpendicular to the flow direction to obtain through-plane velocity [11]. Acquisition of data over multiple cardiac cycles generates a series of flow velocity (phase difference) and anatomical (magnitude) images reflecting the temporal changes in velocity and morphology in the target vessel [7].

One of the most important acquisition parameters in PC MRI is the velocity encoding setting [7]. Velocity encoding is defined as the speed (usually in centimeters per second) along the bipolar gradient that provides the phase difference of π (180°). A velocity encoding setting lower than the maximum flow velocity results in a large phase difference exceeding $\pm\pi$ and aliasing artifacts (between $\pi+\alpha$ and $-\pi+\alpha$) [11]. In contrast, a velocity encoding setting that is too high causes small phase differences and a low velocity-to-noise ratio. Therefore, it is ideal to set the velocity encoding as low as possible yet not below the maximum velocity [7]. Antialiasing correction (phase unwrapping) may be possible at postprocessing and implemented in some software. The suggested velocity encoding settings are 150–200 cm/s for the thoracic aorta, 250–400 cm/s for aortic valve stenosis and coarctation of the aorta, 100–150 cm/s for intracardiac blood flow, and 50–80 cm/s for other great arteries and veins [7].

Tracing vessel borders in magnitude images allows measurement of flow-related parameters during the cardiac cycle, such

as mean blood flow through the cardiac cycle, blood flow and velocity in each cardiac phase, ejection time, and acceleration time [12,13].

Data acquisition on 4D flow MRI

On 4D flow MRI, the abovementioned 2D PC MRI is expanded to 3D acquisition. Velocity encoding along the x-, y-, and z-directions with 3D volumetric coverage provides datasets containing 3D velocity vector in each voxel during cardiac cycles [14]. In the fields of the chest and abdomen, respiratory gating is implemented if necessary. Although the total scan time available for a clinical MRI examination is limited, sufficient spatial (>5 – 6 voxels across the vessel diameter) and temporal (<40 ms) resolutions have been recommended to achieve accurate flow quantification [11].

Magnitude images acquired using 4D flow MRI are termed 3D PC MRA images. The anatomical information of the vascular lumen plays an important role in vascular volume extraction and flow volume quantification in postprocessing of 4D flow MRI. Some postprocessing software can use other MRA images, such as balanced steady-state free precession (SSFP) images for vessel segmentation [15], although misalignment between the anatomical and velocity images may occur. The potential merits of balanced SSFP images include bright blood images with high signal-to-noise ratio (SNR) [16].

Use of gadolinium-based contrast media

Theoretically, 4D flow MRI does not require gadolinium-based contrast media because the signal intensity is dependent on flow velocity. In large vessels with large flow velocities, such as the aorta and its major branches, good SNR, velocity-to-noise ratio, and contrasts between the vessel and surrounding tissues can be acquired without using gadolinium-based contrast media [7]. However, contrast-enhanced 4D flow MRI can take advantage of enhanced SNR and contrasts, which enables visualization of the vessels even when they have a small size and/or slow blood flow velocity. Changes in the signal intensity during 4D flow scan depending on the timing after administration of contrast media may affect velocity data.

Four-dimensional flow MRI postprocessing and analysis

Two-dimensional flow analysis on any cross-section

One of the great advantages of 4D flow MRI over traditional 2D PC MRI is that the postprocessing allows analysis of any vascular cross-section in the acquired volume data. Therefore, it is easy to tweak the angular alignment along the vascular course or analyze multiple cross-sections without additional scans (Fig. 1). Studies that compared measured blood flow ve-

locities have demonstrated good agreement between 2D PC and 4D flow MRIs in various fields, such as the abdominal and intracranial arteries [17,18].

Visualization of 3D blood flow

On 4D flow MRI each voxel has information on the velocity vector. The process of connecting velocity vectors in adjacent voxels can generate 3D continuity of velocity vectors, which can be visualized using various methods such as instantaneous streamlines and flow vectors (Fig. 2) [7]. Calculating the paths of virtual massless particles provides path lines or particle traces. Various flow patterns in the target vessels, such as laminar flow, helical flow, and vortical flow, are demonstrated in the postprocessed 3D images (Figs. 1-6).

Flow analysis parameters

4D flow MRI can provide information on conventional flow analysis parameters on vascular cross-sections obtained using 2D PC MRI. These parameters include blood flow velocity, blood flow volume, antegrade and retrograde flows, regurgitant fraction, mean, minimal, and maximal flow velocities, and time-velocity curve. Furthermore, taking advantage of 3D velocity vector information, 4D flow MRI can be used to obtain more advanced parameters of hemodynamics such as wall shear stress (the tangential frictional force per unit area exerted by the flowing fluid on the luminal surface), oscillatory shear index (the directional change of wall shear stress during the cardiac cycle), kinetic energy (the mass of blood in the voxel multiplied by the square of the velocity in that voxel divided by

Fig. 1. Schematic illustration of 4D flow MRI. Schematic illustration of 4D flow MRI data acquisition and postprocessing. Four 3D raw datasets for each cardiac phase were collected consisting of magnitude images and three sets of velocity-encoded phase difference images to measure three-directional blood flow velocities (V_x , V_y , and V_z). The datasets were postprocessed using software. The postprocessing included several steps such as background phase correction, phase antialiasing, and segmentation of the target vessels. This method provided 3D flow visualization, retrospective flow quantification at any cross-section, and more advanced flow parameters. 4D flow MRI: four-dimensional flow magnetic resonance imaging, 3D: three-dimensional.

Fig. 2. Stanford type B aortic dissection. The flow velocity into the false lumen was accelerated at the entry site just distal to the ostium of the left subclavian artery. In the descending aorta, the flow velocity appeared to be faster in the true lumen than in the false lumen. (A) Flow velocity vector image in which vectors at multiple cross-sections were demonstrated by their three-dimensional direction, length, and color. The bottom graph demonstrates flow volumes together with cardiac phases at individual cross-sections. (B) Particle trace image in which the particles were seeded at the same locations as in (A). (C) Streamline image representing the trajectories that the particles take through a static vector field.

Table 1. Selected clinical applications of four-dimensional flow magnetic resonance imaging

Vascular territories	Clinical indications
Cerebral arteries	Extracranial-intracranial bypass [44] Arteriovenous malformations [45,46]
Aorta	Aortic dissection [23,28] Thoracic aortic aneurysm [29,30] Endoleak after endovascular aortic repair [31] Retrograde aortic flow as a potential source of embolic stroke [47] Bicuspid aortic valve [32,33,48] Coarctation of the aorta [49]
Pulmonary artery	Pulmonary hypertension [38-40,42]
Heart	Intracardiac flow visualization [50] Congenital heart disease [24,34-37]
Liver and portal vein	Cirrhosis [43] and portal hypertension [51]
Kidney	Renal artery stenosis [17]
Peripheral arteries	Peripheral arterial disease [88]

two), vorticity (rotating or swirling motion around an orthogonal axis to the vessel centerline), and helicity (rotational motion around the longitudinal axis of the vessel centerline) [19-22]. Studies have reported the clinical application of these advanced parameters using 4D flow MRI [23-27].

CLINICAL APPLICATION OF 4D FLOW MRI

Numerous past studies have reported the feasibility and clinical utilities of 4D flow MRI [23,24,28-51]. Table 1 summarizes the selected clinical applications of 4D flow MRI in various vascular fields. Past studies have also demonstrated hemodynamics of normal cohorts, various hemodynamic changes in cardiovascular diseases, and comparisons before and after interventions for cardiovascular diseases [26,41,52,53]. This article focuses on the clinical application of 4D flow MRI in the field of the great arteries, including aortic diseases, adult congenital heart diseases (CHDs), and pulmonary hypertension.

Fig. 3. Four-dimensional flow images of the thoracic aorta. The streamlines in a young subject with a bicuspid valve showed a significant helical flow in the ascending aorta (A) whereas those in a young healthy subject appeared straight (B).

Fig. 4. Repaired tetralogy of Fallot. (A) Maximum intensity projection image of gadolinium contrast-enhanced MR angiography demonstrating residual stenosis at the bifurcation of the pulmonary artery. (B) Particle trace image of 4D flow MRI in the systolic phase demonstrating accelerated flow at the bifurcation. (C) Particle trace image of 4D flow MRI in the diastolic phase demonstrating a regurgitant flow from the main pulmonary artery to the right ventricle and large vortex formation in the right ventricle. MR: magnetic resonance, 4D flow MRI: four-dimensional MR imaging.

Aortic diseases

Aortic dissection

Aortic dissection is a life-threatening emergency condition. A tear in the intimal layer that allows blood flow to propagate within the medial layer generates a false lumen. Any condition that increases intimal shear stress or decreases arterial wall strength is considered to be a risk factor [54]. In contrast to Stanford type A dissection, for which surgical intervention is indicated, medical management is widely accepted as the first-line treatment for uncomplicated type B dissection. However, it is important to perform a risk assessment at an early stage to determine the merits of the intervention [54].

CT is the most commonly used imaging modality for the di-

Fig. 5. Particle trace image of four-dimensional flow magnetic resonance imaging in total cavopulmonary connection (anterior view). Blood from both the superior vena cava (blue) and inferior vena cava (red) flowed to the bilateral pulmonary arteries.

agnosis and follow-up of aortic dissection because of its speed, widespread availability, and excellent diagnostic accuracy [55]. The diameter of the aorta and the amount of false lumen thrombosis are used to stratify and select patients for treatment [23]. Moreover, recent studies have revealed that hemodynamic parameters, such as flow pattern, flow volume, and velocity, play a role in false lumen expansion [23,56]. Although the emerging tool of computed flow dynamics can provide blood flow information, patient-specific inflow boundary conditions may be required to obtain meaningful hemodynamic measurements [57].

MRI has advantages of allowing actual hemodynamic measurements in patients with aortic dissection requiring careful follow-up. Müller-Eschner et al. [58] demonstrated 3D visualization of accelerated blood flow through the entry site towards the false lumen wall in chronic type B aortic dissection using 3D MR velocity mapping (Fig. 2). François et al. [28] used 4D flow MRI to investigate the differences in hemodynamic features between the true lumen and the false lumen in aortic dissection. Their study showed that blood flow was primarily laminar in the true lumen, whereas it appeared complex, abnormal, and non-laminar in the false lumen. Clough et al. [23] assessed whether 4D flow MRI can visualize and quantify the flow characteristics of 12 patients with aortic dissection and whether these features are related to the rate of aortic expansion. The stroke volume and velocity in the false lumen were positively associated with more rapid aortic expansion during follow-up. Four-dimensional flow MRI also demonstrated a helical flow in the false lumen in 8 out of 12 patients, which was associated with the rate of aortic expansion [23]. The new features obtained from 4D flow imaging may help provide better predictors for long-term follow-up, possible complications, and patient mortality and morbidity,

Fig. 6. A patient with chronic thromboembolic pulmonary hypertension underwent four-dimensional flow magnetic resonance imaging before and after BPA. The mean pulmonary artery pressure measured via right heart catheterization improved from 45 mm Hg to 24 mm Hg after BPA. (A) Particle traces in the end-systolic phase before BPA demonstrating a vortex flow in the distal main pulmonary artery. (B) Particle traces in the end-systolic phase after BPA demonstrating a reduced degree of vortex flow in the distal pulmonary artery. The flow velocity also improved. BPA: balloon pulmonary angioplasty.

although these associations are yet to be determined.

Aortic aneurysm

Aortic aneurysm is the second most frequent disease of the aorta after atherosclerosis [55]. Both thoracic aortic aneurysms (TAAs) and abdominal aortic aneurysms (AAAs) require surgical repair for patients with a maximum aortic diameter ≥ 55 mm [55]. However, recent data indicated that patients with an aortic size below 50 mm still have an incremental yearly risk of rupture dissection or death that is greater than 5% [59]. The current geometric figure datasets may not be fully adequate for preventing acute complications. Disease processes, such as aneurysm formation, are largely dependent on hemodynamic factors in the vascular system.

Past studies have compared the ascending aortic flow characteristics and clinical risk profile of proximal TAAs. Hope et al. [29] compared the flow pattern between healthy volunteers and patients with ascending aortic aneurysms; larger helices, vortex, and retrograde flows were found more often in the patients with aortic aneurysms than in the controls. Kari et al. [30] calculated the flow compression index as a fraction of the area of high-velocity mid-systolic flow over the complete cross-sectional ascending aortic aneurysm according to the ascending aortic aneurysm morphology. Eccentric aneurysm was associated with a high level of flow compression (low flow compression index) irrespective of the underlining aortic valve morphology and function. These findings may indicate the potential diagnostic value of 4D flow MRI in clinical risk evaluation of patients with TAAs [30].

Sakata et al. [31] used 4D flow MRI, computed tomography angiography (CTA), and duplex ultrasonography to identify endoleaks in patients after nitinol-based stent graft deployment for AAAs. Endoleaks were detected by 4D flow analysis in 18 of 31 (58.1%) patients, by CTA in 13 patients (41.9%), and by duplex ultrasonography in six patients (19.4%), demonstrating that 4D flow MRI is more sensitive for assessing endoleaks than CTA and ultrasonography. Furthermore, 4D flow MRI could differentiate type IIa endoleaks (to-and-fro biphasic flow pattern forming branch vessels) from type IIb endoleaks (monophasic flow pattern with a connection between the in-flow and outflow branches). Their study focused on 4D flow MRI based on its advantages, which enable evaluation of the flow direction as well as the entire view of the endoleaks after endovascular aortic repair.

Adult CHD

The incidence of CHD varies among studies. Early studies reported an incidence of CHD of approximately 4 to 5 per 1000 live births whereas a later study reported an increasing incidence of up to 12 to 14 per 1000 live births [60]. This differ-

ence in the incidence (lower in early studies and higher in later studies) reflects the fact that recent development of diagnostic tools such as imaging modalities has allowed the identification of early and mild CHDs, rather than only severe CHD. With great advancements in pediatric cardiology and cardiovascular surgery, most patients with CHD now survive to adulthood and the overall prevalence of adult CHD (ACHD) is estimated to be 3000 per million [61]. Consequently, increasing numbers of patients with ACHD need to be managed with medical, surgical, and endovascular interventions. Because of its noninvasiveness and easy access, transthoracic echocardiography (TTE) is the first-line modality for cardiovascular imaging in ACHD as well as other acquired heart diseases. However, the access window of TTE is limited, especially in the right heart system and pulmonary arteries, despite the importance of assessing right heart function in ACHD [62]. Conventional cardiac MR (CMR) has been used to evaluate complex morphology and function of the heart and cardiovascular hemodynamics. 4D flow MRI may offer a new additional window to evaluate the complex hemodynamics of ACHD. We introduce the current role of CMR and potential 4D flow application of selected ACHDs.

Bicuspid aortic valve

Bicuspid aortic valve (BAV) is the most common CHD with a reported prevalence of approximately 1% of all live births [60]. BAV is often identified by a fusion of the two aortic valve cusps with raphe in an area of fusion. Fusion of the left and right coronary cusps is the most common pattern and is reported in over 70% of BAV cases [63]. Patients with BAV develop valve dysfunctions of aortic stenosis and/or regurgitation and dilated ascending aorta over time. The ascending aorta of patients with BAV enlarges at a higher rate than that of matched controls with tricuspid aortic valves; dilatation of the ascending aorta then becomes a risk factor for aortic dissection and rupture, which are major causes of morbidity and mortality [64]. BAV aortopathy has been attributed to genetic and hemodynamic causes. Although the relative contribution of genetics and hemodynamics remains a subject of debate, both factors are probably contributing factors [65]. The abnormal valve morphology affects the aortic blood flow patterns and velocities, resulting in remodeling of the proximal segment of the aorta from the aortic root to the arch.

4D flow imaging is useful for noninvasive evaluation of the altered blood flow pattern and measuring the wall shear stress in the ascending aorta affected by the abnormal morphology and dysfunction of BAV. Past studies have reported an abnormal helical blood flow and significant elevation of the wall shear stress in the ascending aorta of patients with BAV compared with that of individuals with tricuspid valves. Even patients without valve dysfunction and aortic dilatation demon-

strated these hemodynamic alterations in the ascending aorta (Fig. 3) [32,33].

The pattern of aortic dilatation is dependent on the morphologic valve fusion patterns. Mahadevia et al. [66] reported that the presence and type of BAV fusion were associated with changes in the regional wall shear stress distribution, systolic flow eccentricity, and expression of BAV aortopathy. In the right and left cusp fusion patterns, a flow jet is directed toward the right anterior aortic wall and patients have dilatations in the tubular ascending aorta accompanied by varying degrees of aortic root dilatation. Conversely, in the pattern with fusion of the right and noncoronary cusps, the jet is directed toward the posterior wall of the aorta and dilatation of the aortic root only or involvement of the entire ascending aorta and arch is frequently found.

A recent study reported that valve-mediated hemodynamics are even correlated with the distal ascending aorta [67]. Four-dimensional flow MRI can identify the eccentric jet flow in patients with BAV and may help stratify the risk for development of ascending aortic aneurysms and aortic dissection. Moreover, a current study showed that an elevated aortic wall shear stress corresponded to more severe extracellular matrix dysregulation and elastic fiber degeneration compared with normal wall shear stress of adjacent regions in the same aorta [68]. This indicates that wall shear stress, as assessed using 4D flow MRI, may serve as a noninvasive biomarker of regional aortic disease in patients with BAV aortopathy.

The majority of patients with BAV will require aortic valve replacement using bioprosthetics or mechanical valves in their lifetime [69]. Recently, the hemodynamic change after aortic valve replacement was evaluated using 4D flow CMR. Bissell et al. [70] reported that abnormal flow hemodynamics tended to normalize after mechanical aortic valve replacement, in contrast to a remnant abnormal flow pattern after bioprosthetic aortic valve replacement. This indicated that the aortic growth rate after aortic valve replacement might depend on the type of the replaced valve.

Despite the limitation of time and spatial resolution, the parameters evaluated in 4D flow MRI may be novel biomarkers of BAV and might help to stratify the risk of cardiovascular events and predict the prognosis of patients. They may also improve surgical strategies and help develop clinical guidelines that allow individuals to achieve good clinical outcomes [71].

Repaired tetralogy of Fallot

Repaired tetralogy of Fallot (TOF) is the most common cyanotic CHD and involves four heart defects: a large ventricular septal defect, pulmonary stenosis, right ventricular (RV) hypertrophy, and an overriding aorta. In adults with surgically repaired TOF during childhood, important issues may arise such as en-

largement and dysfunction of the right ventricle, pulmonary regurgitation, and stenosis in the right and left pulmonary arteries [62]. A significant amount of pulmonary regurgitation is common after surgical removal of stenosis in the right ventricular outflow tract and pulmonary valve. Although the “free” pulmonary regurgitation can be asymptomatic and tolerated for a long time after the surgical repair, the volume overload results in dilatation of the right ventricle. When the ventricle becomes decompensated, excessive right ventricular dilatation with deteriorated function, arrhythmia, and premature death can be induced. CMR can be used to stratify the risk and surgical intervention of repaired TOF with right heart failure [52,72,73]. In clinical practice, the proposed indications of pulmonary valve replacement in asymptomatic patients based on CMR findings include RV end-diastolic volume index $>150 \text{ mL/m}^2$, RV end-systolic volume index $>80 \text{ mL/m}^2$, RV ejection fraction (EF) $<47\%$, and left ventricular (LV) EF $<55\%$ [73].

The application of 4D flow MRI for repaired TOF includes quantification of the flow volume (regurgitant flow volumes and fraction and flow distribution in the left and right pulmonary arteries and collaterals) and peak velocity and visualization of the flow directionality [11]. 3D visualization of hemodynamics in the entire heart and proximal great arteries provides a comprehensive overview of the flow pattern changes in patients with repaired TOF (Fig. 4) [34]. A study by Geiger et al. [34] comparing comprehensive hemodynamics between patients with repaired TOF and healthy subjects showed approximately 2.6 times higher blood flow in the right pulmonary artery than in the left pulmonary artery in patients with repaired TOF; in contrast, the flow ratio of the right pulmonary artery to the left pulmonary artery was 1.1 in the controls. The systolic peak velocity in the pulmonary trunk was approximately two times higher in the patients than in the controls. Although differential blood flow and regurgitation in the branched pulmonary arteries were discussed earlier for 2D PC MRI [35,74], 4D flow MRI covers the entire volume thus improving understanding of flow alterations in patients with repaired TOF. Hirtler et al. [24] assessed intracardiac flow and vorticity in patients with repaired TOF, and confirmed the advantage of 4D flow MRI over conventional 2D PC CMR. The right heart intra-arterial, intraventricular, and outflow tract flow patterns differed significantly between healthy volunteers and affected patients. The peak vorticity in both the right atrium and ventricle was significantly higher in the patients. Moreover, the degree of regurgitant flow in the pulmonary trunk was associated with higher vorticities in the right atrium and ventricle. Jeong et al. [36] assessed differences in ventricular kinetic energy between patients with repaired TOF and healthy volunteers. The peak systolic kinetic energy in both the right and left ventricles appeared to be higher in the patients with repaired TOF than in

the healthy subjects, although the difference was not significantly different. The ratio of the main pulmonary artery flow to the right ventricular kinetic energy and the ratio of the aortic flow to the left ventricular kinetic energy were both lower in the patients with repaired TOF than in the controls. These results indicate that a greater ventricular kinetic energy is necessary to generate blood flow in the pulmonary and systemic circulations in patients with repaired TOF than in healthy subjects.

4D flow MRI in repaired TOF visualizes abnormal flow dynamics and helps us understand and explore new parameters, such as flow energy loss, that may potentially be used as imaging biomarkers [37,75]. Comprehensive coverage of flow velocity data in 4D flow MRI may reveal interactions of functional and hemodynamic findings associated with right heart failure in repaired TOF. Future studies are warranted to assess whether such parameters derived from 4D flow MRI allow determination of surgical interventions or risk stratification.

Fontan circulation for functionally single ventricles

Various congenital complex cardiac defects are associated with only single functional ventricles, which have to maintain both the systemic and pulmonary blood circulations. In “Fontan circulation,” the systemic venous return is connected to the pulmonary arteries without the interposition of the ventricle to improve arterial desaturation and chronic volume overload [76]. One of the Fontan circulations is total cavopulmonary connection where the inferior vena cava is connected to the pulmonary artery, bypassing the right atrium through the extracardiac conduit, and the superior vena cava is directly connected to the pulmonary artery. Patients with single ventricle diseases are now mainly treated with total cavopulmonary connection and the survival rate of these patients has improved over the past decades. However, most patients develop a late complication such as pulmonary arteriovenous malformation, systemic ventricular dysfunction, or thromboembolism, due to the abnormal hemodynamics.

4D flow MRI can evaluate the eccentric blood flow, which is difficult to assess using echocardiography (Fig. 5). A recent study revealed asymmetric caval blood flow distribution to the right and left pulmonary arteries in patients with Fontan circulation [77]. 4D flow MRI is also used to quantify the kinetic energy in the intraventricular blood flow and might be a useful noninvasive method of monitoring patients with Fontan circulation and detecting signs of ventricular and circulatory dysfunctions [78].

Pulmonary hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) at rest of >25 mm Hg measured via invasive right heart catheterization. The clinical symptoms of pul-

monary hypertension include dyspnea upon exertion, fatigue, chest pain, and syncope that limits physical activities. Although these clinical symptoms are non-specific for pulmonary hypertension, their severity is associated with mortality and morbidity. TTE is widely used for the screening of pulmonary hypertension as a noninvasive imaging modality; however, its specificity for identifying pulmonary hypertension is limited [79]. Therefore, 4D flow MRI may have a promising potential to identify and evaluate the severity of pulmonary hypertension and subsequently monitor the therapeutic effects. Pulmonary hypertension is classified into five major groups, which share similar pathological and hemodynamic characteristics and therapeutic approaches [80].

An elevation in pulmonary arterial pressure and pulmonary vascular resistance alter the blood flow patterns in the major pulmonary arteries. Past studies have used several blood flow parameters in the main pulmonary artery to characterize pulmonary hypertension [38–40,81]. Reiter et al. [39] demonstrated the appearance of vortical flow in the main pulmonary artery on time-resolved 3D PC MRI in patients with pulmonary hypertension. The manifestations of pulmonary hypertension coincided with the appearance of vortical blood flow in the main pulmonary artery with high sensitivity and specificity. They also demonstrated that the duration of vortical blood flow (percentage of the cardiac phases with the vortex present, t_{vortex}) in the main pulmonary artery as observed on 3D PC MRI allowed estimation of elevated mPAPs and diagnosis of pulmonary hypertension [40]. When the cutoff value of t_{vortex} was set to 14.3%, the sensitivity and specificity to diagnose pulmonary hypertension were 97% and 96%, respectively [40]. The main pulmonary artery of patients with pulmonary hypertension shows secondary morphological changes including dilatation that may induce vortical formation of the blood flow. In a general population-based study using 4D flow MRI, abnormal vortices occurred in the main pulmonary artery in 3% of subjects with no history of pulmonary hypertension [41]. The geometry of the main pulmonary artery dividing into the bilateral pulmonary arteries may influence the formation of an abnormal vortical flow even in healthy subjects. Barker et al. [38] used 4D flow MRI to measure the diameter, peak systolic velocity, peak flow, stroke volume, and wall shear stress at the main, right, and left pulmonary arteries in 17 subjects with pulmonary arterial hypertension and 19 healthy subjects. The peak systolic velocity, peak flow, stroke volume, and wall shear stress at all locations were significantly lower in the patients with pulmonary arterial hypertension than in the healthy subjects. Similarly, other investigators reported vortex flow formation, early onset of retrograde flow, and low wall shear stress in the pulmonary artery observed using 4D flow MRI as characteristics of pulmonary hypertension [82].

Among the categories of pulmonary hypertension [80], chronic thromboembolic pulmonary hypertension (CTEPH) is unique in its potential for curative interventions. CTEPH develops in 0.1–8.8% of patients with acute pulmonary embolisms [83]. However, in the clinical setting we often encounter patients without a clear history of pulmonary embolism therefore the exact incidence of CTEPH has been difficult to estimate. Regarding the mechanism, organizing clot and secondary vascular remodeling in the pulmonary arteries induce elevation of pulmonary vascular resistance resulting in pulmonary hypertension [84]. According to guidelines [85,86], pulmonary thromboendarterectomy and newly developed balloon angioplasty combined with medications can be indicated to treat CTEPH. We evaluated the degree of vortex flow in the main pulmonary artery using the ratio of retrograde flow area to the arterial cross-sectional area where the maximum vortex flow was observed in the end-systolic phase. The ratio of the retrograde flow in the main pulmonary artery was moderately correlated with the mPAP in patients with CTEPH ($r=0.68$, $p<0.01$) [42]. Furthermore, the degree of vortex flow decreased after several balloon pulmonary angioplasty (BPA) sessions together with improvement of the mPAP (Fig. 6) [53]. This indicates that 4D flow MRI can potentially monitor the effects of treatment in patients with CTEPH who undergo BPA.

CURRENT LIMITATIONS AND FUTURE DIRECTIONS OF 4D FLOW MRI

Long scan time

As shown in Fig. 1, a long scan time is generally required to acquire a large amount of volume datasets. Therefore, the balance between acquisition volume, spatial resolution, and time resolution should be taken into account to complete clinical examinations within reasonable time slots. However, accelerated image acquisition has been improving due to the development of hardware and data acquisition algorithms; new technologies that can be implemented for 4D flow MRI include high-performance gradient system enabling shorter echo time and repetition time, phased-array coils, multi-channel receiving system, parallel imaging, compressed sensing, and radial sampling [43]. Respiratory motions should also be considered when imaging the thoracic and abdominal vascular systems and use of abdominal compression belts is a common method to minimize respiratory motions and thus increase the acceptance rate of respiratory gating during acquisition. Real-time respiratory self-gating is also possible for 4D flow imaging [87].

Postprocessing

Currently, several third-party vendors provide commercial software separate from the MR system manufacturers. Report-

ed studies have used in-house programs and commercial products for postprocessing. Accessibility is one of the key factors for widespread use of 4D flow MRI in the clinical setting. A cloud-based postprocessing system has been launched, which may accelerate the clinical application of 4D flow MRI. Although numerous studies have been conducted to demonstrate its utility in congenital and acquired cardiovascular diseases, accumulation of more evidence is required to establish the clinical role of 4D flow MRI as an emerging technique for patient management and risk stratification.

SUMMARY

4D flow MRI can be used to analyze 3D hemodynamics based on the velocity vector, with potential clinical application in various fields. The retrospective setting of analysis planes for blood flow evaluation is a large advantage of 4D flow MRI in the clinical setting. The 3D flow visualization offers comprehensive understanding of flow fields. Advanced flow parameters have been proposed for comprehensive analysis of flow dynamics. Although these parameters are currently mainly applied in research fields, they may play a role in revealing the mechanisms underlying the evolution and progression of cardiovascular diseases.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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