# A ANNUAL REVIEWS

# Annual Review of Biomedical Engineering 4D Flow with MRI

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Annu. Rev. Biomed. Eng. 2020. 22:103-26

First published as a Review in Advance on March 10, 2020

The Annual Review of Biomedical Engineering is online at bioeng.annualreviews.org

https://doi.org/10.1146/annurev-bioeng-100219-110055

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# **Keywords**

4D flow, magnetic resonance imaging, blood flow, hemodynamics

### Abstract

Magnetic resonance imaging (MRI) has become an important tool for the clinical evaluation of patients with cardiac and vascular diseases. Since its introduction in the late 1980s, quantitative flow imaging with MRI has become a routine part of standard-of-care cardiothoracic and vascular MRI for the assessment of pathological changes in blood flow in patients with cardiovascular disease. More recently, time-resolved flow imaging with velocity encoding along all three flow directions and three-dimensional (3D) anatomic coverage (4D flow MRI) has been developed and applied to enable comprehensive 3D visualization and quantification of hemodynamics throughout the human circulatory system. This article provides an overview of the use of 4D flow applications in different cardiac and vascular regions in the human circulatory system, with a focus on using 4D flow MRI in cardiothoracic and cerebrovascular diseases.

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# **1. INTRODUCTION**

Noninvasive cardiovascular evaluation with magnetic resonance imaging (MRI) is widely used to evaluate cardiovascular disease based on both morphological and functional information. Initial applications of MRI included the assessment of cardiovascular abnormalities, such as arterial stenosis, impaired global cardiac function, and myocardial fibrosis and scarring. The past decades have seen the rise of MRI-based blood flow quantification, including the integration of flow imaging with two-dimensional (2D) phase contrast (PC) MRI into clinical guidelines and algorithms (1). More recently, the use of time-resolved 3D PC MRI with three-directional flow velocity encoding, referred to as 4D flow MRI, allows for the comprehensive in vivo measurement of 3D blood flow dynamics in the heart and large vessels, with full volumetric coverage throughout the cardiac cycle. The resulting data (3D + time + 3 velocity directions) allow for the calculation of a multitude of derived fluid mechanics parameters, such as wall shear stress (WSS), kinetic energy, and pressure gradients. The opportunity to better understand and assess in vivo 3D blood flow dynamics has made both the acquisition methods and applications of 4D flow the subject of intense ongoing research in the cardiovascular imaging community.

In this review, we focus on the most recent technical advances, in terms of both optimization of MRI data acquisition and advanced post-processing. For a description of the more standard technical aspects, the reader is referred to two 2015 consensus papers (2, 3). In addition, this article provides an overview of the use of 4D flow applications in different cardiac and vascular regions in the human circulatory system, with a focus on using 4D flow MRI in cardiothoracic and cerebrovascular diseases.

# 2. TECHNICAL ASPECTS

# 2.1. Traditional 2D Flow Imaging with MRI

PC MRI (also termed flow-sensitive MRI or MR velocity mapping) was originally described in the 1980s (4–6) and takes advantage of the direct relationship between blood flow velocity and the phase of the MRI signal. To eliminate unwanted background phase effects, two acquisitions with different velocity-dependent signal phases are needed to encode (using bipolar magnetic field

gradients) and measure blood flow velocity along a single direction. The signal intensities in the resulting phase-difference images are directly related to the blood flow velocity and can thus be used to visualize and quantify blood flow.

For cardiovascular applications, the 2D PC data are collected over multiple cardiac cycles using ECG-gated imaging to measure time-resolved pulsatile blood flow. For a standard 2D PC MRI clinical protocol, data acquisition typically includes single-direction velocity measurement orthogonal to a 2D imaging slice (through-plane encoding) and is performed during a 10–20-s breath-hold period. Following image reconstruction, 2D PC MRI yields a series of anatomic (magnitude) and flow velocity (phase-difference) images that represent the temporal changes in morphology and blood flow during the cardiac cycle.

# 2.2. 4D Flow MRI: Data Acquisition

In 4D flow MRI (also termed 4D PC or 3D time-resolved PC with three-directional velocity encoding), velocity is encoded along all three spatial dimensions throughout the cardiac cycle, thus providing a time-resolved 3D velocity field. As shown in Figure 1a, three-directional velocity measurements can be efficiently achieved by using interleaved four-point velocity encoding (Venc), which acquires one reference image and three velocity-encoded images along three orthogonal (x, y, z) directions. Similar to 2D PC MRI, data acquisition is synchronized with the cardiac cycle, and data collection is distributed over multiple cardiac cycles using so-called k-space segmentation techniques (only a fraction of the entire 4D flow data is measured during each cardiac cycle, and the data are successively collected over multiple cardiac cycles). After completion of the 4D flow acquisition, four time-resolved 3D data sets are generated (these are magnitude data depicting anatomy and three flow data sets representing the velocities  $V_x$ ,  $V_y$ , and  $V_z$ ) (Figure 1b). The large amount of data collected over multiple RR intervals made 4D flow MRI incompatible with use in the clinical setting prior to developments in the 1990s and 2000s (i.e., the high amplitude magnetic field gradients, phased array coils with multireceiver channels, parallel imaging). Due to the large amount of data that has to be collected (three spatial dimensions, three velocity directions, time over the cardiac cycle), total 4D flow MRI scan times may still range between 5 and 15 min (depending on heart rate, spatiotemporal resolution, and anatomic coverage). Thus, for thoracic and abdominal applications, respiration control is needed to minimize breathing artifacts. Different strategies have been applied, including the use of respiratory bellows, navigator gating, and self-gating techniques (7-11).

**2.2.1. 4D** flow MRI: velocity sensitivity. Venc is an important, user-defined parameter, setting the maximum flow velocity that can be acquired without velocity aliasing. When the measured blood flow velocity exceeds the acquisition setting for Venc, velocity aliasing can occur, and this is visible as a sudden change from high to low velocity within a region of flow. Thus, accurate flow visualization and quantification may be compromised unless antialiasing correction can be successfully performed. It is important to note, however, that velocity noise is directly related to Venc. Therefore, selecting a high Venc value may alleviate the issue of velocity aliasing, but it will also increase the level of velocity noise in flow velocity images. As a result, Venc should ideally be selected to be as high as needed to avoid aliasing but as low as possible to reduce velocity noise (typical settings: Venc = 150-200 cm/s in the thoracic aorta, 250-400 cm/s in an aorta with aortic valve stenosis or coarctation, or 80-120 cm/s for cerebrovascular applications). If a large imaging volume with various vessels is examined, there may be no optimal Venc setting, so the value must be chosen in accordance with the clinical question.



C Fundamental data acquisition (k-space sampling) strategies

k<sub>v</sub>

**b** 4D flow MRI data



CartesianRadialSpiral $k_y$  $k_y$  $k_y$  $k_y$  $k_y$  $k_y$  $k_x$  $k_x$  $k_x$ 

**d** Imaging acceleration: k-space sparse sampling techniques



(Caption appears on following page)

#### Figure 1 (Figure appears on preceding page)

Data acquisition and imaging acceleration strategies used in 4D flow MRI. (*a*) Synchronization of 4D flow MRI data acquisition with cardiac motion and patient's breathing by ECG and respiratory gating. For each cardiac time frame, reference data and three velocity-sensitive scans are acquired to reconstruct four volumetric data sets. (*b*) Anatomic magnitude data and three data sets with blood flow velocities encoding along the  $V_x$ ,  $V_y$ , and  $V_z$  directions. (*c*) 4D flow data can be acquired using different segmented  $k_x$ - $k_y$ -space sampling strategies: standard Cartesian (two k-space lines collected for each cardiac cycle), radial, or spiral. (*d*) k-space undersampling techniques for 4D flow imaging acceleration. Each technique can be applied to the three sampling patterns in panel *c*. For standard parallel imaging (e.g., generalized autocalibrating partially parallel acquisition, or GRAPPA, and sensitivity encoding, or SENSE), the k-space center is fully sampled and the typically achievable acceleration factor is on the order of R = 2 to 3. k-t acceleration is based on sparse sampling along both the spatial and temporal dimensions, which results in higher acceleration factors, on the order of R = 4 to 8. 3D data are displayed for the  $k_z$ - $k_y$  space; sampling along the temporal dimension is represented by the small graphs (*green* and *black dots* represent acquired lines). Compressed sensing is based on randomly undersampled k-space data, and the image is reconstructed using iterative techniques.

2.2.2. Acceleration techniques: k-space sampling and sparsity exploitation. Long scan times on the order of 5–15 min have previously relegated 4D flow MRI to the realm of research. However, current implementation is quickly approaching clinically feasible scan times, on the order of 2-8 min. Parallel imaging takes advantage of multichannel receiver coils, with reconstruction either in the image domain using sensitivity encoding techniques (known as SENSE) or in the k-space domain using generalized autocalibrating partially parallel acquisition (known as GRAPPA). These techniques are commonly used in MRI applications, including 4D flow, allowing a two- or threefold acceleration (Figure 1d). Recently, more advanced methods such as the k-t broad-use linear acquisition speed-up technique (known as k-t BLAST) (12), k-t GRAPPA (13), k-t principal component analysis (known as k-t PCA) (14), and circular Cartesian undersampling (known as CIRCUS) (15) have allowed for even greater imaging acceleration factors (Figure 1d). Another promising technique to accelerate 4D flow MRI is compressed sensing in which data are acquired in a sparse and random manner, and this is followed by nonlinear recovery of the data (16). For example, it has recently been shown that aortic 4D flow MRI with compressed sensing can be performed with scan times on the order of 2-3 min without substantial degradation of image quality (10).

Alternative techniques that are increasingly used to accelerate 4D flow MRI exploit non-Cartesian data sampling strategies, such as vastly undersampled isotropic voxel radial projection imaging (known as PC-VIPR), which uses a 3D radial sampling pattern with angular undersampling (17) or spiral data acquisition (18). Radial sampling has two advantages over Cartesian read-outs: (*a*) Sparse sampling results in streak image artifacts instead of foldover artifacts, which allows for higher undersampling factors (17); and (*b*) the center of the k-space is continuously sampled, and this results in insensitivity to a patient's motion (20). As an alternative, spiral k-space sampling can cover the entire k space uniformly and rapidly, allowing for rapid measurements of 4D flow MRI velocity (9, 11, 21). However, both radial and spiral sampling are sensitive to eddy current effects, which require efficient correction strategies, and image reconstruction is more computationally demanding (11). An illustration of acceleration techniques is provided in **Figure 1***c*,*d*.

# 2.3. Pre- and Post-Processing for Standard Visualization and Quantification

4D flow MRI data are affected by systematic velocity encoding errors caused by magnetic field inhomogeneity, concomitant magnetic fields (Maxwell terms), and eddy currents. Thus, data preprocessing is an important part of any data analysis workflow to correct background phase-offset errors (3). In addition, denoising and velocity antialiasing may also be applied (22).



#### Figure 2

4D flow-based visualization of aortic hemodynamics. Example of systolic 3D streamlines, 3D wall shear stress, pressure mapping, viscous energy loss, and pulse wave velocity for a healthy aorta, all in sagittal oblique views. Abbreviations: AAo, ascending aorta; DAo, descending aorta.

After preprocessing, a 3D PC MR angiography based on a combination of magnitude and velocity data can be calculated to guide segmentation and flow visualization. Several 3D blood flow visualizing options can be employed to present the 4D flow data.

- Volumetric and maximum intensity projections of peak velocity can be used for easy volumetric identification of peak flow velocities.
- 3D streamlines represent the instantaneous blood-flow vector field for a single cardiac time frame and are used to visualize the spatial distribution and orientation of blood flow velocities. Color-coding by velocity magnitude facilitates the visual identification of regions with high systolic flow velocities (Figure 2).
- For visualization of the temporal evolution of 3D blood flow, time-resolved path lines can be used to display (in movie mode) the dynamic information and changes in blood flow during the cardiac cycle (3).

There are several pitfalls in 4D flow imaging that are related to the acquisition of data, the patient, and processing; **Table 1** summarizes the sources of errors and strategies for error mitigation.

# 2.4. Validation of Flow and Velocity Measurements

As for any novel quantitative imaging technique, validating the blood flow velocities measured by 4D flow is essential. Due to the lack of a gold standard measurement technique for the in vivo assessment of time-resolved 3D blood flow velocities inside the human body, a number of alternative approaches and surrogate validation metrics have been studied including:

- using dedicated pulsatile and steady in vitro flow phantoms (23–26)
- making comparisons with Doppler ultrasound (limited by 2D analysis planes and singledirection velocity) (27–29)

Source of error	Type of error	Consequences	Mitigation strategy
Acquisition related	Background phase offset	Inaccurate velocities and flow	Use stationary flow fit
	Low spatial and/or temporal resolution	Underestimation of peak flow and other quantitative parameters	Adapt to the region of interest, with at least 5–6 voxels across the vessel diameter
	Inadequate Venc	Aliasing or low SNR or VNR	Set Venc to 90% of expected velocity and use unaliasing post-processing
	Inadequate FOV	Too big: acquisition time too long, resolution too low Too small: region of interest not covered, spatial aliasing	Cover region of interest
	Acceleration parameters too high	Low SNR, blurring, spatial artifacts, underestimation of velocities	Adapt parameter to sampling technique, magnetic field, coils, contrast
	Intravoxel dephasing due to turbulence	Underestimation of velocities	Increase spatial resolution, reduce echo time
Patient related	Heart rate variability	Blur	Use arrhythmia rejection algorithm, prospective gating
	Respiratory motion	Respiration artifacts (ghosting, streaks, blurring)	Use respiratory gating, soft gating, averaging
	Other motion	Blur	Work with the patient; use a shorter scan time
	Overweight	Low SNR	Use contrast
Processing related	Inadequate volumetric segmentation	Loss of measurement accuracy	Complete a visual check; provide training
	2D retrospective slice placement non-orthogonal to flow	Underestimation of velocities and flow	Use automated placement or a dedicated tool; provide training
	Inter- and intraobserver variability	Reproducibility	Use automated segmentation; provide training to observer

# Table 1 Potential sources of errors in 4D flow MRI: types, consequences, and proposed mitigation strategies

Abbreviations: FOV, field of view; SNR, signal-to-noise ratio; Venc, velocity encoding; VNR, velocity-to-noise ratio.

- making comparisons with standard 2D PC MRI in healthy volunteers (30–34) or patients (35–37) (limited by two analysis planes and single-direction velocity encoding)
- using internal flow consistency, based on the principle of mass conservation—that is, flow
  must be the same between the input and the output or between a main vessel and the sum
  of the branching vessels (38–40)
- making comparisons with patient-specific computational fluid dynamics (CFD), which is comparable to 4D flow because it provides representation of multidirectional volumetric velocities; several relevant studies have shown good accuracy using this comparison to quantify WSS (even if it was underestimated) and energy-derived parameters (41–43).

Studies across different institutions and MR systems have demonstrated that 4D flow MRI permits flow volume quantification that is comparable to 2D PC MRI and has good scan–rescan repeatability. Further, 4D flow MRI measures velocity in all spatial directions, has superior spatial coverage, and has been shown to be better at capturing the peak velocity of a stenotic jet (44).

# 2.5. Advanced Post-Processing

4D flow MRI offers the opportunity to derive advanced hemodynamic measures, such as vorticity and helicity, WSS, pressure gradients, viscous energy loss, turbulent kinetic energy, and pulse wave velocity (PWV). A more detailed description of advanced metrics is provided in **Table 2**. Some of these advanced metrics have become available in commercial software (an example of 4D flow advanced post-processing in a healthy thoracic aorta is shown in **Figure 2**), whereas most are still relegated to academic research tools.

# **3. APPLICATIONS**

Initial applications of 4D flow MRI were focused on the heart and large vessels, such as the aorta and pulmonary arteries. Nonetheless, 4D flow MRI can be applied to other vascular territory throughout the human circulatory system, such as the cerebral large arteries and veins, carotid arteries, and abdominal (liver and renal arteries) and peripheral vessels. An overview of standard and advanced post-processing applications is provided in **Table 3** and examples are shown in **Figure 3**. In this review, we focus on the use of 4D flow MRI for the comprehensive assessment of thoracic aortic and intracranial hemodynamics.

# 3.1. Thoracic Aorta

Newly evolving MRI techniques such as 4D flow MRI, as well as the clinical need for continued improvements in patient diagnosis, risk stratification, and monitoring of surgical and medical treatment, have led to strong interest in applying advanced MRI techniques to diseases of the thoracic aorta. Trends in thoracic aorta MRI are moving beyond simple anatomic descriptions and aortic diameter measurements to better capture changes in aortic flow and functional impairment that result from aortic pathologies or aortic valve dysfunction.

3.1.1. Bicuspid aortic valve-related aortopathy. Bicuspid aortic valve (BAV) is a congenital fusion of the leaflets of the aortic valve affecting 1% to 2% of the general population, predominantly males. Patients with BAV have a higher risk of valve dysfunction or severe disease of the ascending aorta (dilatation, aneurysm, dissection), or both. However, the underlying mechanisms of the development of aortic disease are not fully understood, and there is ongoing debate regarding the relative contribution of genetic and hemodynamic abnormalities to BAV-associated aortopathy. 4D flow MRI-based in vivo analysis of BAV-mediated changes in aortic flow patterns has helped shed new light on the underlying mechanisms of aortopathy development in patients with BAV. 4D flow MRI studies have shown that BAV is associated with complex, disturbed blood flow dynamics when compared with those of participants with normal tricuspid aortic valves, even in the absence of aortic valve disease or aortic dilatation (45). An early 4D flow study contributed evidence that these flow alterations resulted in elevated WSS in the ascending aorta-that is, BAV patients experienced significant differences in hemodynamic forces implicated in vessel wall remodeling (46). Altered aortic WSS and flow patterns in BAV were confirmed by other studies (47, 48). Moreover, aortic WSS patterns differed based on BAV valve fusion type (49, 50) and were closely associated with the expression of different aortopathy phenotypes (51-53): Right-to-left coronary cusp fusion was associated with elevated WSS in the anterior wall, while right-to-noncoronary cusp fusion was associated with elevated WSS in the right posterior wall and aortic arch dilatation (Figure 4). In addition, there is a high level of evidence that WSS is mediated by valve function and is increased in cases of aortic valve stenosis (54, 55) or regurgitation (56).

Metric	Equation	Description
Vorticity ( <i>w</i> )	$\tilde{\omega} = \nabla \times \tilde{v}$	Beyond visualization of flow helix using streamlines; a quantitative approach is feasible
Helicity	$\tilde{v} \cdot \tilde{\omega}$	using these parameters (95–97)
Wall shear stress vectors (τី)	$\tilde{\tau} = \begin{bmatrix} \frac{\partial v_x}{\partial x} & \frac{1}{2} \left( \frac{\partial v_y}{\partial x} + \frac{\partial v_y}{\partial y} \right) & \frac{1}{2} \left( \frac{\partial v_z}{\partial x} + \frac{\partial v_x}{\partial z} \right) \\ \frac{1}{2} \left( \frac{\partial v_x}{\partial y} + \frac{\partial v_y}{\partial x} \right) & \frac{\partial v_y}{\partial y} & \frac{1}{2} \left( \frac{\partial v_z}{\partial y} + \frac{\partial v_y}{\partial z} \right) \\ \frac{1}{2} \left( \frac{\partial v_x}{\partial z} + \frac{\partial v_z}{\partial x} \right) & \frac{1}{2} \left( \frac{\partial v_y}{\partial z} + \frac{\partial v_z}{\partial y} \right) & \frac{\partial v_z}{\partial z} \end{bmatrix} \cdot \tilde{n}$	<ul> <li>WSS is the blood shear rate near the vessel wall, which is implicated in endothelial changes and vascular remodeling.</li> <li>In 4D flow MRI, WSS can be calculated from 2D analysis planes that are perpendicular to the vessel lumen (30, 98) or, as more recently demonstrated, with 3D techniques (99–101). The oscillatory shear index is the degree of WSS inversion over the cardiac cycle. An inherent limitation of 4D flow–based WSS quantification is related to underestimation due to the relatively low spatial and temporal resolutions of 4D flow MRI compared with numerical simulations (102). Nonetheless, information about WSS distribution and relative changes have been shown to be reproducible if the 4D flow data acquisition protocol is consistent (103, 104).</li> </ul>
Kinetic energy	$\mathrm{KE} = \frac{1}{2} \cdot \rho \cdot \mathrm{V} \cdot v(t)^2$	This equation for blood KE is derived from the Newtonian kinetic energy formula. The direction of the velocity is not considered in the calculation of blood KE (105).
Turbulent kinetic energy	$\text{TKE} = \frac{1}{2} \rho \sum_{i=1}^{3} \sigma_i^2$	TKE provides a direction-independent measure of flow turbulence intensity that is based on rapid velocity fluctuations within an individual imaging voxel (106).
Viscous energy loss from viscous dissipation $(\phi_v)$	$\phi_{v} = \frac{1}{2} \sum_{i} \sum_{j} \left[ \left( \frac{\partial v_{i}}{\partial x_{j}} + \frac{\partial v_{j}}{\partial x_{i}} - \frac{2}{3} (\nabla \cdot v) \delta_{ij} \right) \right]^{2},$ where $\delta_{ij} = 1$ for $i = j$ and $\delta_{ij} = 0$ for $i \neq j$ . EL = $\mu \sum_{i=1}^{\text{num voxels}} \phi_{v} V_{i}$	Viscous energy uses the concept of viscous dissipation and is based on a reformulation of the viscous portion of the Navier–Stokes energy equations (107).
Pressure drop	$\Delta \mathbf{P} = \frac{1}{2} \rho (v_2^2 - v_1^2) + \rho \int_1^2 \frac{\mathrm{d}v}{\mathrm{d}t} \cdot \mathrm{d}s$ $\Delta \mathbf{P}_{\text{simplified Bernoulli}} = 4v^2$	Pressure drop is a widely used clinical parameter to assess the severity of a stenosis, typically based on the simplified Bernoulli equation. In 4D flow, this concept can be expanded by taking advantage of the volumetric data set to improve estimation of the pressure drop: The extended Bernoulli equation is used to account for pressure recovery in valvular stenosis (108, 109), while the general Bernoulli equation increases the precision of pressure drop estimation (110).
Pressure mapping	$-\nabla p = \rho \left( \frac{\delta v}{\delta t} + v \cdot \nabla v - g \right) - \mu \nabla^2 v$	By assuming blood to be an incompressible laminar Newtonian fluid, pressure gradients can be calculated using the Navier–Stokes equations and displayed as 4D pressure difference maps. However, applications are challenging in cases of turbulent stenotic flow (73, 75).

# Table 2 Advanced 4D flow MRI hemodynamic metrics

(Continued)

Tabl	le 2	(Continued)
		· · · · · · · · · · · · · · · · · · ·

Metric	Equation	Description
Blood stasis	$r_{\rm stasis} = \frac{n_{\rm stasis}}{N_{\rm tot}}$	Several methods have been proposed to quantify blood stasis based on volumetric residence time or analysis of distance traveled, following the path of a virtual particle (111) or based on low-velocity analysis in a voxel through time, with threshold values depending on the anatomic region, as in the equation proposed here (112).
Pulse wave velocity	$PWV = \frac{\Delta d}{\Delta t}$	PWV is a marker of arterial stiffness independent of blood velocities. PWV quantification requires high temporal resolution (113, 114). Changes in the method used to estimate the time shift ( $\Delta t$ ) may induce changes in the absolute value of PWV (114).

Abbreviations:  $\Delta d$ , the distance traveled by the wave; EL, viscous energy loss; g, gravitational force; KE, kinetic energy;  $\mu$ , blood viscosity (3.2 × 10<sup>-3</sup> Pa);  $\tilde{n}$ , inward normal vector;  $n_{stasis}$ , the number of cardiac time frames in the cardiac cycle below a velocity threshold (e.g., 0.1 m/s); PWV, pulse wave velocity;  $\rho$ , blood density (assumed to be 1060 kg/m<sup>3</sup>);  $\sigma_i$ , velocity fluctuation intensity in three mutually perpendicular directions, i; TKE, turbulent kinetic energy; V, voxel volume;  $v_r$ , velocity magnitude for each voxel at each cardiac time frame; WSS, wall shear stress.

Recently, the application of the concept of an aorta atlas established confidence intervals for normal WSS based on results in a healthy control cohort (57, 58). This method was successfully applied to BAV patients to create WSS heat maps showing areas of increased or decreased WSS (i.e., occurring outside 95% of normal values) (59, 60) (**Figure 4**). In a prospective study with tissue collection from 20 BAV patients undergoing aortic surgery, Guzzardi et al. (61) showed a relationship between a heat map increase in WSS (>95% of normal values), extracellular matrix dysregulation (an increase in matrix metalloproteinase and transforming growth factor- $\beta$ ), and elastic fiber degeneration. This study demonstrated for the first time in BAV aortopathy a relationship between altered hemodynamics as assessed by 4D flow and histological wall damage. Moreover, in cases of aortic stenosis associated with BAV, elastic fiber thinning was also correlated with WSS (62).

Interestingly, a recent 4D flow MRI study found that relatives of patients with BAV who did not have aortic valve abnormalities presented with altered aortic shape and increased vortex flow (63). These results highlight the need for more data to better understand the link between the genetic disorder, the expression of the valvulopathy, and the alteration of aortic hemodynamics.

**3.1.2. Marfan syndrome.** Marfan syndrome is a genetic connective tissue disease with a high risk of aortic wall abnormalities that lead to aortic dilatation complicated by dissection or rupture. Disturbed blood flow patterns, such as local helix flow, have been described in the aortic root and in the proximal descending aorta (64). Circumferential WSS and peak systolic velocities were increased in patients with Marfan syndrome when compared with controls matched for degree of aortic dilatation (65). Segmental differences in WSS occurred at the inner curvature of the proximal part of the ascending aorta and in the anterior part of the more distal ascending aorta (65), while lower values were observed in the inner proximal descending aorta segment, correlating with a helix flow pattern (66). These results were confirmed in a pediatric cohort in which an inverse relationship was found between WSS and aortic dissection. These findings were highlighted by the case of a patient developing a type B aortic dissection at a region of low WSS that was identified

Anatomic region	Disease	Parameters	References
Great vessels		•	
Aorta	Bicuspid-related aortopathy	FV, vorticity quantification, WSS, PWV	45, 61, 69, 96
	Marfan disease	FV, WSS, PWV	64, 65, 69
	Aneurysm or dilatation (thoracic or	FQ, helicity quantification, EL, WSS,	69, 107, 111,
	abdominal)	PWV, stasis	115-117
	Dissection	FV, FQ	70, 71
	Coarctation	FV, pressure mapping, WSS	72,75
	Atherosclerosis, vascular ageing	FQ, WSS, TKE, PWV, pressure mapping	118–121
	Material-related changes (graft, TEVAR)	FV, FQ, WSS	76, 82, 117
Pulmonary artery	Pulmonary hypertension	FQ, vorticity quantification, WSS, KE, EL	122–124
Cardiac		•	1
Congenital heart	Univentricular heart treated by Fontan procedure	FV, FQ, KE, EL	125–127
	Tetralogy of Fallot	FV, FQ, vorticity quantification, KE, TKE, pressure drop	110, 128–130
	TGA treated by ASO	FV, FQ, pressure drop	110, 131
	Atrial or septal defects	FV, FQ	132, 133
Valves	Aortic stenosis	FQ, TKE, viscous energy loss, pressure drop, WSS	44, 106, 107, 134
	Aortic regurgitation	FV	135
	Mitral valve regurgitation	FV, FQ	136, 137
	Changes resulting from a valvular prosthesis	FV, WSS	138
Ventricles	Heart failure	FV, FQ, KE, TKE	139, 140
	НСМ	FV, FQ, pressure drop, energy loss	141, 142
Atria and appendages	Atrial fibrillation	FV, FQ, stasis	112, 143
Small vessels			
Intracranial	Aneurysm	FV, FQ, vorticity, WSS	90
	Stenosis	FV, FQ, pressure drop	84, 85
	Malformation	FV, FQ, pressure mapping	92, 93, 144
Carotid	Stenosis	FQ, WSS	145, 146
	Atherosclerosis	PWV, WSS	147, 148
Abdominal	Portal hypertension	FV, FQ	39
	Mesenteric stenosis	FQ, WSS	149
Peripheral arteries	Stenosis	FQ, WSS	150

# Table 3 Overview of applications of 4D flow-derived hemodynamic parameters

Abbreviations: ASO, arterial switch operation; EL, energy loss; FV, flow visualization including velocity maximum intensity projections, streamlines, and path lines to observed leakage, as well as helicity and disturbed flow; FQ, flow quantification including peak velocities, net flow, forward flow, and backward flow; HCM, hypertrophic cardiomyopathy; KE, kinetic energy; PWV, pulse wave velocity; TEVAR, thoracic endovascular aortic repair; TGA, transposition of great arteries; TKE, turbulent kinetic energy; WSS, wall shear stress.

# a Fontan circulation



**C** Atrial fibrillation



**b** Aortic valve stenosis



**d** Portal hypertension



#### Figure 3

Example of 4D flow MRI analysis in different vascular regions. (*a*) 3D path line visualization in a 14-year-old male patient with a univentricular heart treated by Fontan surgery showing flow originating from the superior vena cava (SVC; *blue*) and the inferior vena cava (IVC) through an extracardiac conduit (*yellow*). The path lines show the relative distribution of vena cava flow in the right pulmonary artery (RPA) and left pulmonary artery (LPA). (*b*) Mapping of systolic velocity maximum intensity projection (MIP) and viscous energy loss (EL) in a 79-year-old man with aortic valve stenosis, showing a maximal velocity of 4.8 m/s and a net energy loss of 55 mW. (*c*) Flow stasis map in a dilated left atrium (LA) (210 ml maximum volume) in a patient with atrial fibrillation, with a mean stasis of  $63 \pm 19\%$ . (*d*) 3D streamlines depicting liver hemodynamics and portal flow in a case of portal hypertension in a 58-year-old woman (RPV refers to the right portal vein and LPV to the left portal vein).

in a 4D flow study 3 years prior to the dissection event (68). Nonetheless, the predictive value of WSS alteration remains unclear, and further longitudinal studies are required. Another study reported increased aortic PWV (i.e., stiffness), in agreement with previous aortic distensibility studies (69).



#### Figure 4

Aortic 4D flow MRI in bicuspid aortic valve (BAV)–related aortopathy. Wall shear stress (WSS) heat map and 3D streamline blood flow visualization in two patients with different right-to-left coronary cusp and right-to-noncoronary cusp aortic valve fusion phenotypes. (*Top*) BAV patients with right-to-left leaflet (*left*) and right-to-noncoronary (*right*) aortic valve leaflet fusion morphology. 3D streamlines at peak systole show distinct, eccentric flow jet patterns for each BAV function phenotype. (*Bottom*) 3D WSS heat maps: Red indicates regions of high WSS; blue indicates low WSS; and gray indicates normal WSS (N WSS) as compared with a healthy age-and sex-matched control cohort.

**3.1.3. Aortic dissection.** Aortic dissection is a life-threatening aortic wall injury leading to the creation of both a true and a false lumen. Pilot 4D flow MRI studies have been used to quantify blood flow in true and false lumens (70) and demonstrated its utility in improving the detection of hemodynamically active dissection flap tears and flow reentry sites (71).

**3.1.4.** Aortic coarctation. Aortic coarctation is a congenital narrowing (stenosis) of the aorta, often addressed by surgical repair in childhood. However, even after successful repair, aortic arch shape is usually altered, with an angulated aortic arch leading to marked helical flow (35), and patients often develop hypertension during follow-up. In addition, coarctation patients present with increased overall WSS (72), probably linked to both vortical and accelerated flows, even in the absence of a significant stenosis.

To assess coarctation severity, peak flow velocities at the location of the vessel narrowing (e.g., measured by Doppler echocardiography) are used to estimate the local pressure gradient via the simplified Bernoulli equation (72). A more comprehensive evaluation of pressure change in the aorta can be achieved by 4D flow–based 3D pressure mapping (73, 74). This application was validated against cardiac catheterization in a small group of patients undergoing endovascular treatment, and further studies are needed to assess its contribution to guiding the management of coarctation (75).

**3.1.5.** Aortic surgical or endovascular treatment. Several studies have evaluated the impact of different types of aortic valve prostheses and aortic root surgery on postintervention aortic hemodynamics. Valve-sparing aortic root replacement, mechanical valve replacement, and the Ross procedure resulted in better restoration of normal physiological flow patterns compared with the use of a bioprosthetic valve and transaortic valve replacement (76–80). However, most studies included only small sample sizes and did not control for age or aortic shape (e.g., patients undergoing transaortic valve replacement were older than those receiving surgical bioprotheses).

Following endovascular repair, 4D flow MRI may be more sensitive than computed tomography for detecting endoleaks (i.e., persistent blood flow within the aneurysm sac) (81), even without contrast injection (82), and this could be useful for preventing complications in this patient population that frequently has impaired renal function.

#### **3.2. Intracranial Vessels**

Transcranial Doppler ultrasound is routinely used for cerebrovascular flow measurements, but the technique is limited by the acoustic windows of the head. As an alternative, 4D flow MRI can be used to measure 3D cerebrovascular blood flow dynamics. Emerging applications include the hemodynamic evaluation of intracranial aneurysms, arteriovenous malformations (AVMs), and intracranial atherosclerotic disease (**Figure 5**). Of note, cerebral blood flow is highly influenced by age, and age-matched control groups are essential in clinical studies (83).

**3.2.1.** Intracranial atherosclerotic stenosis and vein thrombosis. Intracranial atherosclerotic plaques can alter local and global hemodynamics, particularly proximal or distal to stenosed vessels. 4D flow can be useful to estimate intracranial artery stenosis and its impact on cerebrovascular hemodynamics (**Figure 5**). In a study that included 22 patients, Wu et al. (84) found that intracranial atherosclerotic lesions altered distal flow and also altered flow in the ipsilateral collateral arteries. Pressure gradient estimation (i.e., quantification of stenosis severity) is feasible using the modified Bernoulli equation, as recently presented by Vali et al. (85) in a study of 16 patients.

In a prospective longitudinal study with 6 months of follow-up, Schuchardt et al. (86) were able to detect flow changes related to cerebral venous thrombosis, showing stagnant flow, acceleration in nonocclusive thrombosis, and change in flow directions, as well as normalization when anticoagulation treatment achieved complete recanalization.

**3.2.2. Cerebral aneurysm.** A large number of studies investigating flow patterns in intracranial aneurysms were based on CFD techniques used in conjunction with participant-specific boundary conditions extracted from medical images. In addition, 4D flow studies have demonstrated the feasibility of computing WSS in intracranial aneurysms in comparisons with CFD (87–89) (**Figure 5**). These studies confirmed that aneurysm size and morphology were significantly correlated with aneurysm velocity distribution, vorticity, and WSS: Saccular aneurysms had higher peak velocity than did fusiform aneurysms, while both vorticity and WSS were higher in giant saccular aneurysms compared with small saccular and fusiform aneurysms (90).

In a study including 70 unruptured cerebral aneurysms, Futami et al. (91) demonstrated that the ratio of the aneurysm to the parent vessel size (a morphological predictor of rupture) was significantly associated with inflow rate and aneurysm jet flow patterns, highlighting the potential for flow dynamics to improve stratification for rupture risk.

**3.2.3.** Arteriovenous malformation and fistulas. In patients with cerebral AVMs, flow information is potentially valuable for gaining a better understanding of the impact of a focal AVM



# Figure 5

Intracranial 4D flow in arteriovenous malformation (AVM), intracranial artery stenosis, and aneurysm. (*a*) Spetzler–Martin grade 3 left frontal AVM in a 51-year-old male. (*Top*) 3D streamlines and (*bottom*) flow distribution network graph. (*b*) Images from a 76-year-old female with severe right intracranial carotid artery (ICA) stenosis (*white arrow*), displayed as (*top*) a velocity maximum intensity projection on coronal view and (*bottom*) axial view. Note that the maximum velocity is not seen due to a lack of temporospatial resolution even with an isotropic resolution of 1 mm<sup>3</sup>. (*c*) Image from a 68-year-old female with a small irregular aneurysm ( $6 \times 4 \times 11 \text{ mm}$ ) with a 6-mm neck at V4 of the left vertebral artery: (*top*) streamlines and (*bottom*) wall shear stress.

on flow redistribution in the brain and guiding planning for embolization treatment. Recent studies have demonstrated the potential of 4D flow MRI for evaluating global and regional AVM flow characteristics in arteries feeding the AVM as well as in contralateral arteries and draining veins. The findings showed that 4D flow MRI could assess treatment-induced changes in cerebrovascular flow distribution and demonstrated significant associations between 4D flow metrics, cerebral perfusion indices, and AVM risk factors, such as Spetzler–Martin grade (92). To derive a better understanding of these changes in regional circle of Willis flow dynamics induced by an AVM, a systematic quantitative analysis based on a flow network graph has recently been introduced (93) (**Figure 5**).

# **4. FUTURE DIRECTIONS**

Recent developments related to highly accelerated 4D flow MRI have resulted in increased flexibility in its application, with reduced scan times and increases in spatiotemporal resolution. These developments have led to the more widespread use of 4D flow MRI, but further improvements in spatial resolution are needed to reliably quantify vascular hemodynamics near the vessel wall or in small arteries. Developments have also shown that the image quality of 4D flow MRI and its dynamic velocity range (e.g., fast peak systolic forward flow and slow diastolic backward flow) can be further improved by dual- or multi-Venc flow encoding. By interleaving high and low Venc acquisitions and combining these with imaging acceleration techniques, dual-Venc 4D flow MRI has shown promise for making detailed velocity measurements in neurovascular and aortic applications (23, 94).

As described in this review, many useful 4D flow MRI applications have been demonstrated, but multicenter validation and standardization are needed. Furthermore, there is a lack of outcome studies for most of the 4D flow metrics. These studies are urgently needed to prove that it has added value in the clinical setting beyond standard Doppler ultrasound or 2D PC MRI techniques. In addition, the use of 4D flow imaging has substantially expanded, but its use is mostly still limited to large academic centers, and it needs to be better integrated into the clinical workflow. To this end, efforts should focus on distributing accelerated 4D flow MRI imaging protocols and developing more efficient data analysis solutions. Current and future efforts will be dedicated to identifying the most promising 4D flow metrics, and these will be applied increasingly widely.

# 5. CONCLUSIONS

4D flow MRI is a technique applicable for use throughout the body, allowing for the computation of multiple hemodynamic metrics derived from a wealth of data. And there is intense ongoing research into sequence optimization, the automation of data processing, the development of new flow metrics, and continuing to expand its application to an increasing number of cardiovascular pathologies.

# DISCLOSURE STATEMENT

M.M. has received research support from Siemens Healthineers, received research grants from Circle Cardiovascular Imaging and Cryolife Inc., and is a consultant for Circle Cardiovascular Imaging.

### ACKNOWLEDGMENTS

The authors thank Dr. Susanne Schnell, Maria Aristova, and Justin Baraboo for their help in preparing the figures. G.S. received grant support from the French College of Radiology Teachers (CERF) and French Radiology Society (SFR).

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