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# Four-Dimensional Flow Magnetic Resonance Imaging and Applications in Cardiology

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## Abstract

Blood flow through the heart and great vessels moves in three dimensions (3D) throughout time. However, the assessment of its 3D nature has been limited in the human body. Recent advances in magnetic resonance imaging (MRI) allow for the comprehensive visualization and quantification of in-vivo flow dynamics using four-dimensional (4D) flow MRI. In addition, this technique provides the opportunity to obtain advanced hemodynamic biomarkers such as vorticity, helicity, wall shear stress (WSS), pressure gradients, viscous energy loss (EL), and turbulent kinetic energy (TKE). This chapter will introduce 4D flow MRI which is currently used for blood flow visualization and advanced quantification of cardiac hemodynamic biomarkers. We will discuss its advantages relative to other in-vivo flow imaging techniques and describe its potential clinical applications in cardiology.

**Keywords:** Cardiac flow, 4D flow MRI, hemodynamic biomarkers, and flow quantification

## 1. Introduction

Imaging and quantifying various characteristics of blood flow throughout the heart is essential in modern-day cardiology. Measuring blood velocities, pressure gradients, regurgitation, stasis (and much more) is one of the most important tools physicians have for diagnosing cardiovascular pathology, stratifying severity, evaluating disease progression, and determining the most effective treatment strategies. Improving the accuracy and depth of such hemodynamic measurements is an ongoing process that continues to enhance clinical success. Two-dimensional phase-contrast magnetic resonance imaging (2D PC-MRI) and Doppler echocardiography are currently the most widely used techniques for measuring cardiovascular blood flow in-vivo [1]. However, while these modalities provide immense value in clinical practice, they have their limitations. Velocity can only be measured in one direction; in Doppler echocardiography following the direction of the ultrasound beam and in 2D PC-MRI following the encoding direction assigned by the user. This can cause errors in flow measurements, depending on whether the beam/plane is placed at the exact location of interest and/or orthogonal to the direction of flow [2, 3].

These 2D measurements often rely heavily on mathematical assumptions that are not always valid [2]. For example, 2D calculations of pressure gradients are known to underestimate pressure recovery downstream of stenosis [4]. In addition, some techniques provide limited viewpoints of the thoracic cavity, such as trans-thoracic echocardiography and trans-esophageal echocardiography [1, 5]. It is also possible to acquire the in-plane velocities (X and Y directions) over time (two velocities + time) or the three plane velocities (X, Y, and Z directions) over time (three velocities + time).

Time-resolved three-dimensional (3D) phase-contrast magnetic resonance imaging (i.e. 4D flow MRI) is a novel non-invasive, non-ionizing imaging technique that provides accurate qualitative and quantitative assessment of blood velocity in all three principle directions [6, 7]. This allows for enhanced accuracy of previously measurable parameters obtained routinely by Doppler echocardiography, such as velocity and reverse flow, as well as the calculation of new parameters, such as wall shear stress (WSS), 3D pressure gradients, and turbulent kinetic energy (TKE). These parameters can be retrospectively visualized and quantified in volumes (rather than cross sections), over the course of a cardiac cycle, and in unlimited viewpoints. Authors can refer to 2D, 3D, 4D, 5D or 7D flow depending on the acquisition scheme used to encode the velocity directions over time. Thus, it is important to understand how the velocity acquisition is defined. In this chapter, 4D flow MRI measures 3 velocity encoded directions in a stack of planes along the cardiac cycle. As such, the ongoing development of 4D flow MRI provides great promise in improving the clinical management of cardiovascular disease.

## **2. Data acquisition and pre-processing**

### **2.1 Safety and preparation**

There are safety measures and recommendations that should be considered for subjects undergoing 4D flow MRI [6, 8]. Patients can fill out pre-imaging safety questionnaires that consider items that can cause a hazard or interfere with the MRI examination. The safety information may become frequently updated because of continuous and rapid changes in the MRI technology. Before starting any cardiac MRI study, compatible electrocardiogram (ECG) leads should be placed on the subject's chest properly. The accurate synchronization of data acquisition with phases of the cardiac cycle, including different stages of contraction and relaxation, is one of the essential requirements for efficacious cardiac MRI exam. This technique is called ECG-gating. A phased-array receiver coil is required to capture the electromagnetic signals needed to create an image. Thus, it is important that receiver coils are positioned appropriately to cover the regions of interest. The use of contrast agents is optional in 4D flow MRI, but they can help increase the signal-to-noise ratio, and therefore improve the image quality.

### **2.2 Data acquisition**

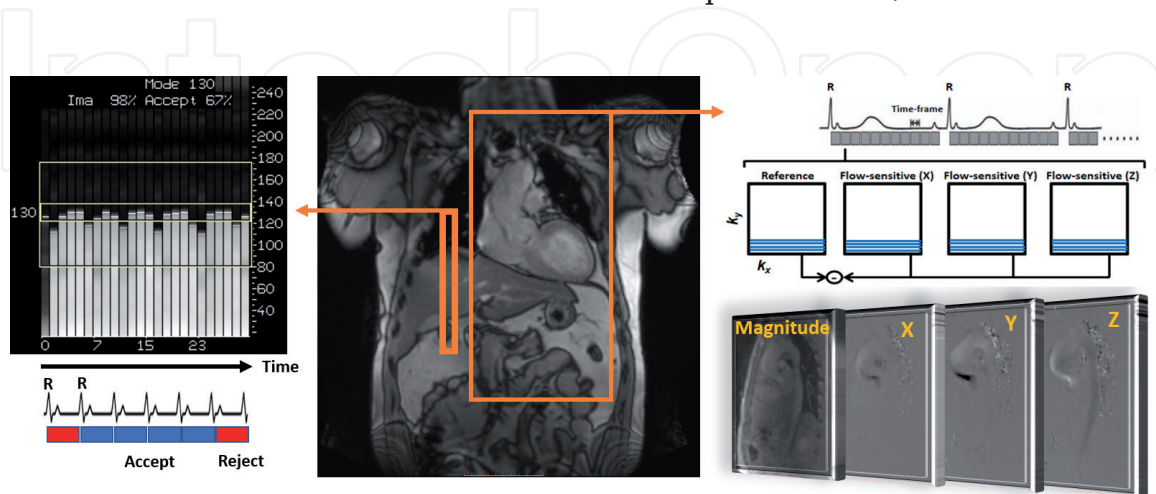
In 4D flow MRI, acquisition parameters (ex: spatial resolution, temporal resolution, field of view, etc.) are optimized and programmed into the scan protocol to provide the best possible imaging accuracy. Setting major scan parameters is primarily a fine balance between adequate temporal/spatial resolution and minimized scan time. Imaging accuracy can also be affected by artifacts (i.e., distortions in the image that are not present in reality), of which velocity encoding (Venc) is an important contributor. Velocity encoding is a user-defined parameter that sets

the upper and lower limits of blood velocity which can be appropriately imaged for within the scan protocol. If the patient's blood velocities fall above the Venc limit, aliasing will corrupt the image with artifacts in those locations. However, if the Venc range is set too high, the image can be populated with noise [9]. Furthermore, artifacts can arise from movement due to cardiac motion and breathing. As shown in **Figure 1**, ECG-gating compensates for cardiac motion to determine when the heart is most still, at which point images are acquired [10]. Simultaneously, diaphragmatic navigator gating compensates for breathing artifacts by similarly tracking movement of the patient's diaphragm and acquiring images at the point of least movement [11]. This allows the patient to breath freely during the scan without creating breathing-related artifacts. These approaches are applied to provide the clearest possible images of 3D global and local blood flow characteristics. Four types of images are produced after acquisition: one magnitude image (shows anatomical structures) and three phase images (shows blood velocity along the Venc directions, often x, y, and z axes).

The most important limiting factor for adding 4D flow to a routine clinical cardiac MRI exam is long scan times associated with multidimensional imaging over the entire cardiac cycle. In 1990s, the total scan time was roughly 40–80 minutes which made difficult its routine application in clinical settings. In recent years, scan times have been further reduced due to ongoing progress in advanced imaging techniques. Nowadays, different reconstruction techniques (parallel imaging, radial and Cartesian sampling, compressed sensing, etc.), in addition to enhanced computing power, have reduced the scan time to 3–10 minutes [12–14]. The latter is facilitating its penetration as a diagnostic tool. Finally, all acquired data are saved in the Digital Imaging and Communications in Medicine standard format in the MRI system database.

### 2.3 Pre-processing and correction

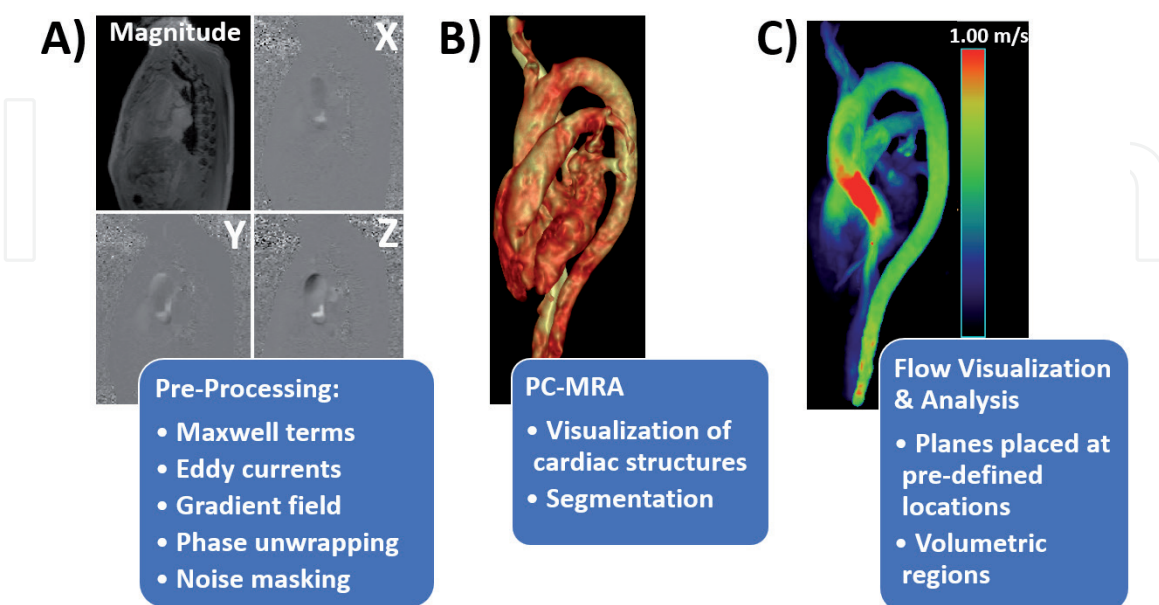
Due to a range of errors, image quality can be damaged by various factors including noise, eddy current effects, concomitant gradient field effects (Maxell terms), velocity aliasing, and gradient field nonlinearity. Data pre-processing is applied to rectify these potential errors using several correction strategies to make 4D flow MRI a reliable source of 3D flow visualization and quantification, as illustrated in



**Figure 1.** Data acquisition for 4D flow MRI. Data acquisition covering the whole heart (large orange rectangle) is acquired using electrocardiogram-gating and respiratory control (small orange rectangle). Three-dimensional velocity-encoding (right side) is used to obtain velocity-sensitive phase images which are subtracted from reference images to calculate blood flow velocities along all three spatial dimensions (X, Y, Z) and averaged magnitude visualizing anatomy over the cardiac cycle.

**Figure 2** [15]. Three-dimensional phase-contrast magnetic resonance angiography (3D PC-MRA) can be obtained at this stage based on acquired data from 4D flow MRI by several presented strategies without the need for further MRI acquisition. A 3D PC-MRA can display complex vascular structures and geometries of interest without requiring a contrast agent. It is vastly helpful in some situations, such as patients with contrast agent contraindication. In addition, 3D PC-MRA allows the user to retrospectively isolate specific volumes of interest for analysis.

However, 4D flow MRI images present difficulties for segmentation algorithms due to extensive variability in cardiovascular structure, geometric intricacy, low resolution, high background noise and motion artifacts. For that reason, manual segmentation remains a widely used method, but manual segmentation takes a long time to perform and is prone to observer variability [16]. There are some established semi-automatic segmentation methods [17–19] which are faster than manual segmentation, nevertheless they are still operator dependent. Recent machine learning and artificial intelligence strategies have shown great ability to solve 4D flow MRI segmentation problems [20]. Machine learning algorithms are powerful techniques that train a machine (i.e. computer) to perform a specific task. Convolutional neural networks (CNNs), which is one of the deep learning techniques, forms the foundation of image segmentation. U-Net is a CNN that was developed specifically for medical image segmentation [21]. Several recent studies that focused on advancing imaging segmentation techniques. Berhane et al. developed a CNN model to segment the aorta from 4D flow MRI images [22]. The performance in this study was compared with manual segmentations, and they reported good agreement across flow and diameter along the aorta. Segmentation speed was <1 second per case, while manual segmentation required at least 360 seconds. Bratt et al. suggested a network based on the U-net and residual modules [23]. They reported similar segmentation performance, < 0.6 seconds per case, however the manual segmentation required 238 seconds per case. Wu et al. developed a combinatorial network for segmenting the left ventricle (LV) [24]. They claimed that combining networks can increase the accuracy of the segmentation.



**Figure 2.**

**Data pre-processing.** Acquired 4D flow images are pre-processed applying multiple corrections (panel A). A phase-contrast angiogram (PC-MRA) is calculated to visualize the cardiac structures and can be used for individual segmentation of vessels, panel B. the generated PC-MRA and/or segmentation can be used to mask the velocity field for appropriate visualization and analysis using planes or volumetric regions of interest, panel C. In this example a 58-year-old control volunteer is presented.

## 2.4 Flow visualization and quantification

Before flow visualization and quantification, general data quality control, including visual inspection and quantitative quality control, is recommended to ensure internal data is consistent and accurate. Dedicated visualization and quantification software can be used for obtaining streamlines, pathlines, volume rendering, and/or maximum intensity projection (MIP). Streamlines represent a blood particle's instantaneous path tangential to the velocity vector at a particular point of time, such as at peak systole. Pathlines represent a blood particle's path over time (i.e. trajectory). Volume rendering allows us to represent voxel-by-voxel values in a dynamic spatial manner, given access to the entire field of view. A MIP is a single-plane image representing the maximum values through a given direction of the volume, similar to an X-ray image. Taken together, these flow visualization techniques reveal a wealth of information about blood flow abnormalities and cardiovascular disease progression. One of the most significant advantages 4D flow MRI is the ability to retrospectively quantify cardiac flow parameters within specified regions of interest. Flow can be analyzed within a specific volume that has been isolated via segmentation, or via a 2D cross-sectional analysis plane placed within a volume of interest. These analysis planes can be flexibly placed at any anatomical location to quantify general and advanced blood flow parameters. Some of these visualization and quantification methods will be illustrated in the following section.

## 3. Applications in cardiology

### 3.1 Congenital heart disease

Eight out of every 1000 infants are born with congenital heart disease (CHD), which encompasses all structural heart defects present at birth, including the great vessels and cardiac valves [25]. Individuals with CHD may develop many cardiac complications, even after surgical correction of the abnormality, including valve insufficiency, arrhythmias, and heart failure [25]. Tetralogy of Fallot is one of the most common forms of cyanotic ("blue baby") CHD, accounting for about 10% of all CHD [26]. Tetralogy of Fallot involves a combination of four defects including right ventricular hypertrophy, aortic override, pulmonary stenosis, and a ventricular septal defect. These patients undergo multiple repeat surgeries and procedures over their lifetime but the hemodynamic factors contributing to the optimal quality of life and outcomes are understudied and poorly understood. Congenital heart disease can benefit from 4D flow MRI via the calculation of advanced hemodynamic parameters, such as WSS, TKE, 3D pressure mapping, and energy loss [5]. For demonstration, we primarily focus on pressure mapping, but **Table 1** provides an overview of 4D flow MRI hemodynamics in CHD.

Fluid pressure measured within the cardiovascular system is widely used in CHD diagnosis, such as coarctation of the aorta, pulmonary hypertension, or atrio-ventricular septal defects. The pressure difference across structural abnormalities (ex: stenosis or ventricular septal defect) or within the LV can reveal much about the severity of the disease. Pressure mapping, based on the measured 3D blood flow velocity field, can be calculated by solving the Navier–Stokes equation, which describes the time-varying flow of a viscous, incompressible Newtonian fluid [33, 34]. This method allows for the estimation of temporally and spatially distributed pressure gradients and across a large vessel segment or cardiac chamber, **Figure 3**. Overall, 3D pressure mapping allows us to gain a better understanding of

Region	CHD type	Conventional flow parameters	Advanced flow parameters	References
Venous return	Fontan/single Ventricle	Collateral flow volume, peak velocity, valvular flow volume	KE, EL, flow connectivity distribution	[5, 8, 27, 28]
	Tetralogy of Fallot	Right heart (RA, RV, PA) systolic peak velocity, net flow, retrograde flow	WSS, vorticity, KE, EL, TKE, pressure drop	[5, 7, 8, 27–29]
Heart wall	Atrial Ventricular Septal Defects	Flow volume, shunt flow volume, shunt ratio	Vorticity, KE, EL, WSS	[5, 8]
Aortic valve	Bicuspid Aortic Valve	Net flow, regurgitation volume, peak velocity	WSS, turbulence, EL, pressure mapping, helicity, flow eccentricity, PWV	[5, 7, 8, 27, 28, 30]
	Marfan Syndrome	AV Peak flow, AV flow volumes	WSS, helical flow, PWV, pressure mapping	[8, 30, 31]
Outflow tracts	Dextro Transposition of the Great Arteries	Net flow volumes, flow ratio, peak velocity	WSS, helical flow	[5, 8]
	Aortic Coarctation	Collateral flow volume, peak velocity across stenosis	Pressure mapping, EL, WSS, helical flow	[5, 8, 27, 30, 32]

*CHD: congenital heart disease; AV: aortic valve; RA: right atrium; RV: right ventricle; PA: pulmonary artery; EL: viscous energy loss; KE: kinetic energy; PWV: pulse wave velocity; TKE: turbulent kinetic energy; WSS: wall shear stress.*

**Table 1.**

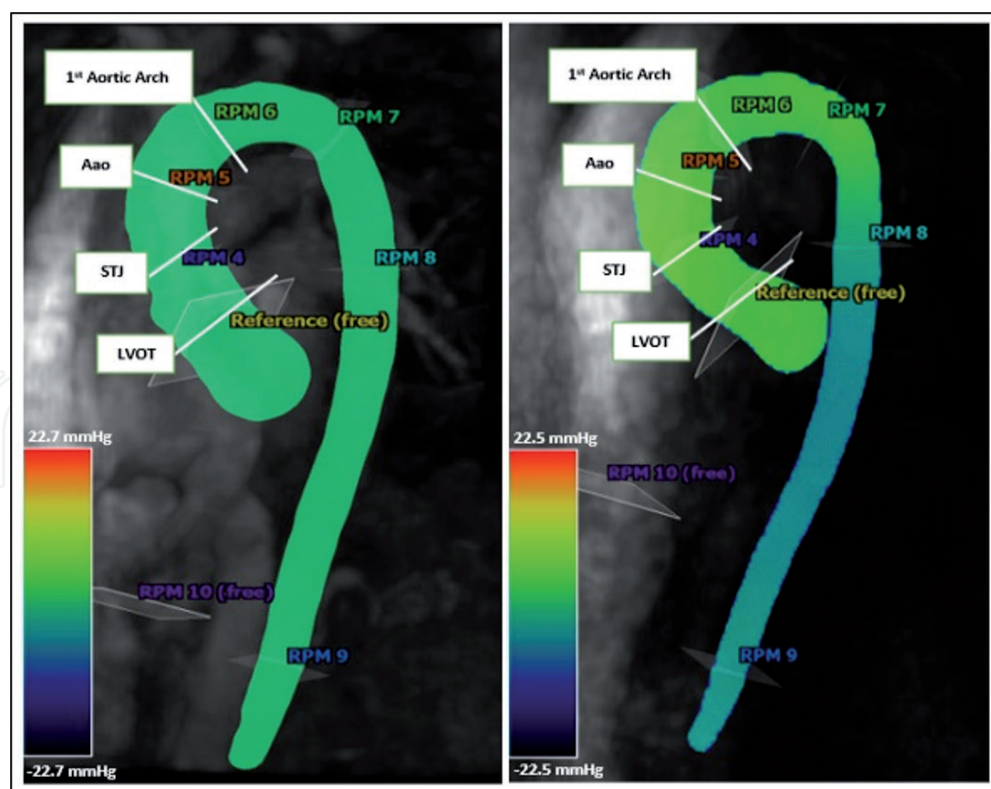
Overview of research on conventional and advanced 4D flow–derived hemodynamic parameters in CHD.

the basic determinants of time-varying flow in healthy and diseased hearts, which has the potential to improve our methods for diagnosing, treating, and surgically correcting CHD [35, 36].

### 3.2 Mitral regurgitation

Approximately 10% of the general population will develop mitral regurgitation (MR) throughout their lifetime [37]. Mitral regurgitation is defined as systolic retrograde flow from the LV into the left atrium (LA). The main causes are classified as primary (structural or degenerative abnormality of mitral valve apparatus) or secondary (a disease of the LV interferes with function and integrity of mitral valve apparatus) [38]. This disorder generally progresses insidiously, as the heart compensates for increasing regurgitant volume via LA enlargement that partially relieves LV overload. Long-standing regurgitation yields poor outcomes as it may lead to progressively more severe regurgitation, LV failure, pulmonary hypertension, atrial fibrillation (AF), stroke, and death [39]. If MR is severe, surgery is the recommended treatment to prevent heart failure [1]. Thus, early detection and assessment is crucial, especially in elderly patients who are often ineligible for surgical intervention.

Doppler echocardiography is the most widely used tool for the assessment of MR. The commonly considered parameters when classifying MR severity are jet area, width of vena contracta, effective regurgitant orifice area, regurgitant volume,

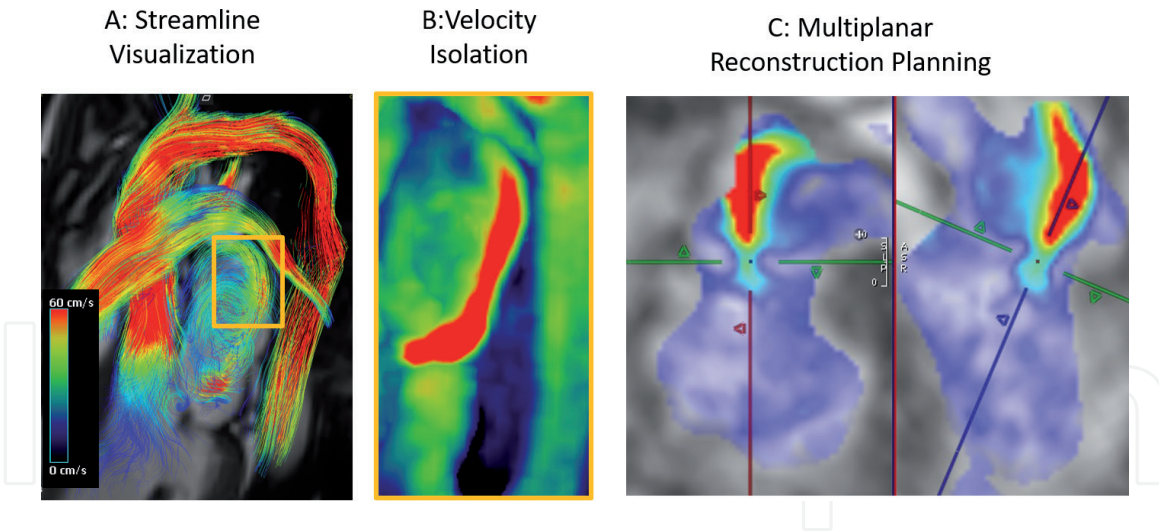


**Figure 3.**  
*Pressure mapping.* Volume rendering maps of a control (left) and a patient with repaired tetralogy of Fallot (right). Several analysis planes, including location reference. Reference plane for pressure is in yellow. RPM indicates analysis plane. LVOT: Left ventricular outflow tract; STJ: Sinotubular junction; AAO: Ascending aorta.

and regurgitant fraction. However, the accuracy of standard approaches used to quantify these parameters can be influenced by the mechanism of regurgitation, direction of the jet, jet momentum, LV loading condition, LA size, and the patient's blood pressure [40, 41]. It is also important to keep in mind that these standard-of-care diagnostic tools do not permit a comprehensive in-vivo assessment of 3D blood flow which is critical to the study of complex 3D hemodynamics surrounding MR. Cardiac MRI has recently been reported as a more accurate tool for quantification of MR flow characteristics and severity grading [42, 43]. Advanced measures of vortex formation, helical flow patterns, EL, pressure mapping, and WSS have shown usefulness for assessment of valve-related disease using 4D flow MRI [44]. The shape of vortex cores have been shown to closely resemble the valve shape, while the vortex's orientation is related to the LV inflow direction [45]. In demonstrating how to extract vortex information from 4D flow MRI, Krauter et al. showed that vortex shape, vorticity and kinetic energy (KE) strongly correlate with transmitral peak velocities [46]. Helical grade was also associated with systolic anterior motion of the mitral valve. Lastly, as shown in **Figure 4**, MR disturbs organized flow, resulting in a reduced contribution of left pulmonary veins to the vortical flow, potentially leading to less efficient ventricular filling and stasis [47].

It is important to note, however, that flow-based biomarkers still require further exploration before they can be reliably applied to daily clinical practice. The construction of 'atlases' that depict physiologically normal blood flow patterns through the LA shows great promise in helping identify the clinical utility of certain hemodynamic parameters and personalizing diagnoses. Normally, MR treatment is primarily based on chamber dimensions and qualitative regurgitation severity grading [48], but it is well recognized that these measures may be insufficient to guide treatment strategies and require multi-modality integration. Four-dimensional flow





**Figure 4.** *Mitral regurgitation.* The presented case has mitral thickening with evidence of cleft in the anterior mitral leaflet. Panel A shows a whole heart streamline visualization used to locate mitral regurgitation (orange box). Panel B shows the velocity volume rendering of the velocity field. The mitral regurgitant jet was highly eccentric into the atrial wall. Panel C illustrates the multiplanar reconstruction of the velocity field which allows multiple views of the regurgitant jet. Evaluation led to a mild regurgitation grading with a regurgitant fraction of 15%.

MRI has provided the ability to construct time-averaged 3D hemodynamic maps (i.e. atlases) from healthy subjects, which can then be used as a reference when evaluating a patient's MR severity. For example, Goffic et al. recently developed strategies for the generation of KE and helicity atlases [49]. Their preliminary data suggest that these atlases may provide insight into hemodynamic influence on LV dysfunction progression and, thus, could have implications on personalized assessment of MR. Such atlases can be created for any hemodynamic parameter of interest and will be further elaborated on in the aortic diseases section of this chapter.

### 3.3 Atrial fibrillation

Atrial fibrillation is an abnormally fast heart rhythm with uncoordinated atrial activation and ineffective atrial contraction [50, 51]. Multiple simultaneous electrical signals firing within the atria lead to irregular ECG patterns and atrial activity, loss of coordinated atrial contractions, and inadequate ventricular filling. It is classified according to the duration of episodes. At an early stage, an episode of AF terminates within 7 days of onset and sinus rhythm is restored (paroxysmal AF). However, as severity progresses, the AF episode may last beyond one week (persistent AF) or does not terminate (permanent AF). The most common complication of AF is thromboembolic events such as stroke [50, 51]. Reduced LA function increases the risk of blood stasis and clot formation in the LA, especially the left atrial appendage (LAA) which is a small extension of the LA. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score (accounts for patient history of: Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke, Vascular disease, Age between 65 and 74 years, and Sex) is currently recommended for stroke risk stratification for AF patients, based on clinical factors such as age, gender, and disease history [50–52]. This risk score is used to recommend the use of anticoagulants and further therapy. However, the score does not contain other individual physiologic factors, so prediction power is limited.

There have been efforts to improve diagnosis and evaluation of disease and risk-assessment of AF through analysis based on 4D flow measurements (**Table 2**). Although some contradictory reports exist, most of the recent studies characterizing AF blood flow with relatively large cohorts agree that there is a significant decrease of LA flow velocity in both persistent and paroxysmal AF patients

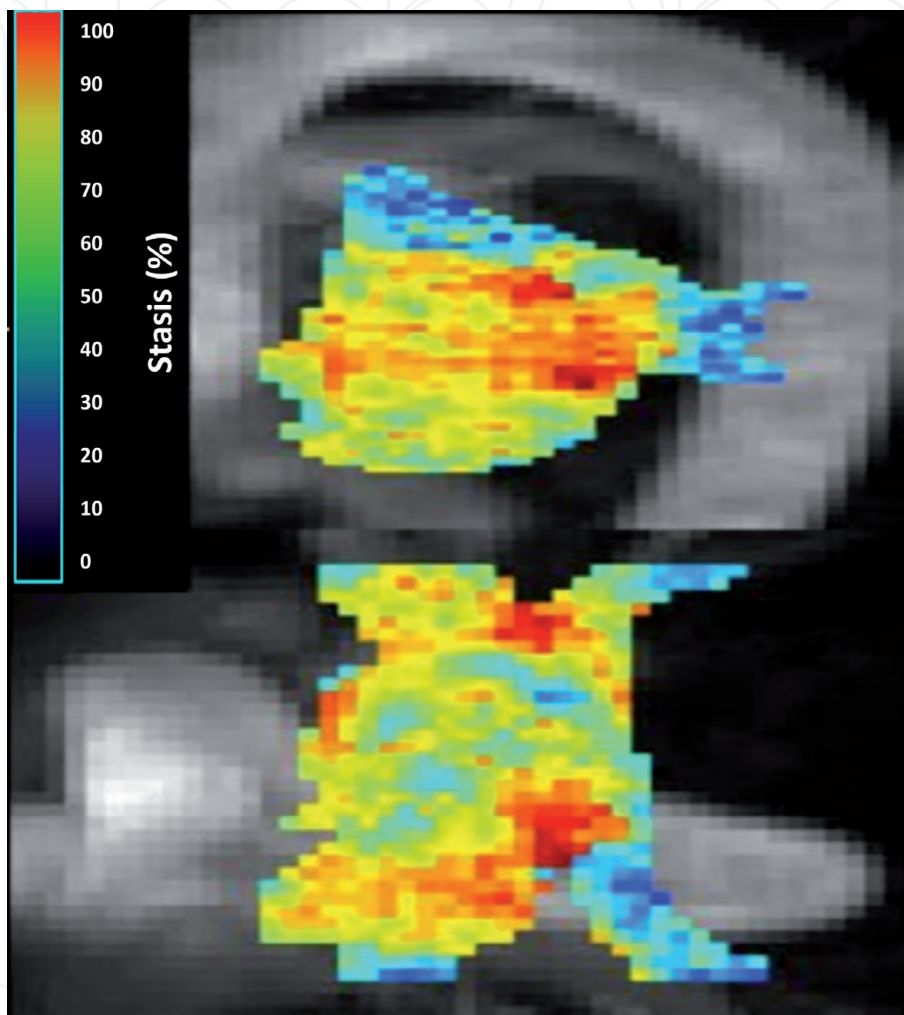
Study	Cohorts (n)	LA Flow parameters	Main Findings
Fluckiger et al. (2013) [53]	PAF (6) Persistent AF (4) Controls (19)	Mean velocity	Mean velocity ↓ in persistent AF cohort
Markl et al. (2016) [54]	AF-sinus (42) AF-afib (39) Young controls (10) Controls (20)	Peak velocity, time-to-peak velocity, stasis	1. Peak velocity ↓ in AF-afib 2. Stasis ↑ in AF-sinus and AF-afib
Lee et al. (2016) [55]	AF (40) Young controls (24) Controls (20)	Velocity (mean, median, and peak)	1. Velocity ↓ (mean and median showed most significant difference) 2. CHA <sub>2</sub> DS <sub>2</sub> -VASc score inversely correlated with mean, median, and peak velocity
Markl et al. (2016) [56]	AF-sinus (30) AF-afib (30) Controls (15)	Velocity (mean and peak), Stasis (in LA and LAA)	1. Individual variability of flow patterns in AF patients, despite the same CHA <sub>2</sub> DS <sub>2</sub> -VASc score 2. CHA <sub>2</sub> DS <sub>2</sub> -VASc correlated positively with stasis, but negatively with velocity
Garcia et al. (2020) [57]	PAF (45) Controls (15)	LA velocity (mean, median, and peak), pulmonary vein peak velocity, stasis, vortex size	1. Mean and median LA velocity ↓, pulmonary vein peak velocity ↓ 2. Stasis ↑ 3. Vortex size ↑ and correlated with CHA <sub>2</sub> DS <sub>2</sub> -VASc
Kim et al. (2020) [58]	PAF (28) Controls (10)	Peak velocity, delayed ejection, residual volume, regurgitation	1. Residual volume ↓ 2. Delayed ejection ↑
Demirkiran et al. (2021) [59]	PAF (10) Controls (5)	Velocity (mean and peak), stasis (in LA and LAA), KE (mean and peak)	1. Mean/peak velocities ↓ 2. LA and LAA stasis ↑ 3. Mean and peak KE ↓
Spartera et al. (2021) [60]	AF-afib (22) AF-sinus (64)	Velocity (mean and peak), stasis, vorticity, vortex volume	Peak velocity and vorticity are reproducible, stable, and exhibit similar interval-scan variability between cohorts

LA: left atrium; LAA: left atrial appendage; PAF: paroxysmal atrial fibrillation; AF: atrial fibrillation; AF-sinus: previous history of AF, but in sinus rhythm at time of imaging; AF-afib: in AF at time of imaging; KE: kinetic energy; CHA<sub>2</sub>DS<sub>2</sub>-VASc: stroke risk stratification system that accounts for patient history of congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke, vascular disease, age between 64 and 75 years, and sex.

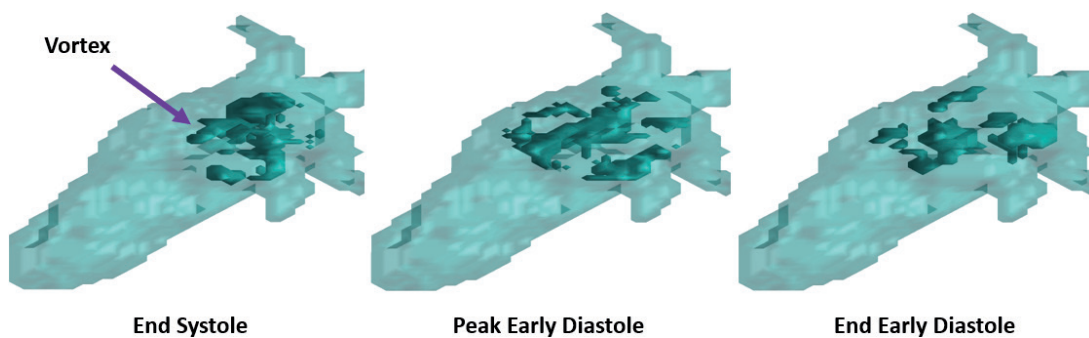
**Table 2.**  
 Summary of 4D flow studies in AF.

[54–57, 59]. Most notably, the increase of CHA<sub>2</sub>DS<sub>2</sub>-VASc score has been associated with reduced mean LA velocity [55, 56], which suggests 4D flow measurement may be able to improve risk assessment. Kinetic energy, which is proportional to the mean square of velocity, was also found to be markedly lower in AF patients than in controls [59]. Left atrial flow stasis is defined by Markl et al. [54] as the relative number of time frames, for each voxel, with flow velocity less than 0.1 m/s. Flow stasis has been confirmed by several studies to be elevated in AF patients [6, 8–10]. An example of a MIP for flow stasis is displayed in **Figure 5**. Also, flow patterns through the pulmonary vein into the LA have been studied [57].

In AF patients, fragmentation of LA inflow and vortex formation in the LA was characterized, see **Figure 6**. This study demonstrated that vortex size increased in paroxysmal AF and was associated with a greater risk score. Similar findings of decreased velocity and increased stasis have also been found in the LAA specifically [56, 59]. However, the limited spatial resolution of 4D flow MRI may not satisfy the minimum number of voxels needed to segment the LAA accurately and reliably in a certain number of cases [6]. In a recent study, reliability and reproducibility of 4D flow parameters in AF patients were reported [60]. Left atrial peak velocity



**Figure 5.** *Left atrial stasis maps. Maximum intensity projections of stasis using a sagittal-view (top) and a top-view (bottom).*



**Figure 6.** *Atrial vortex dynamics in atrial fibrillation.*

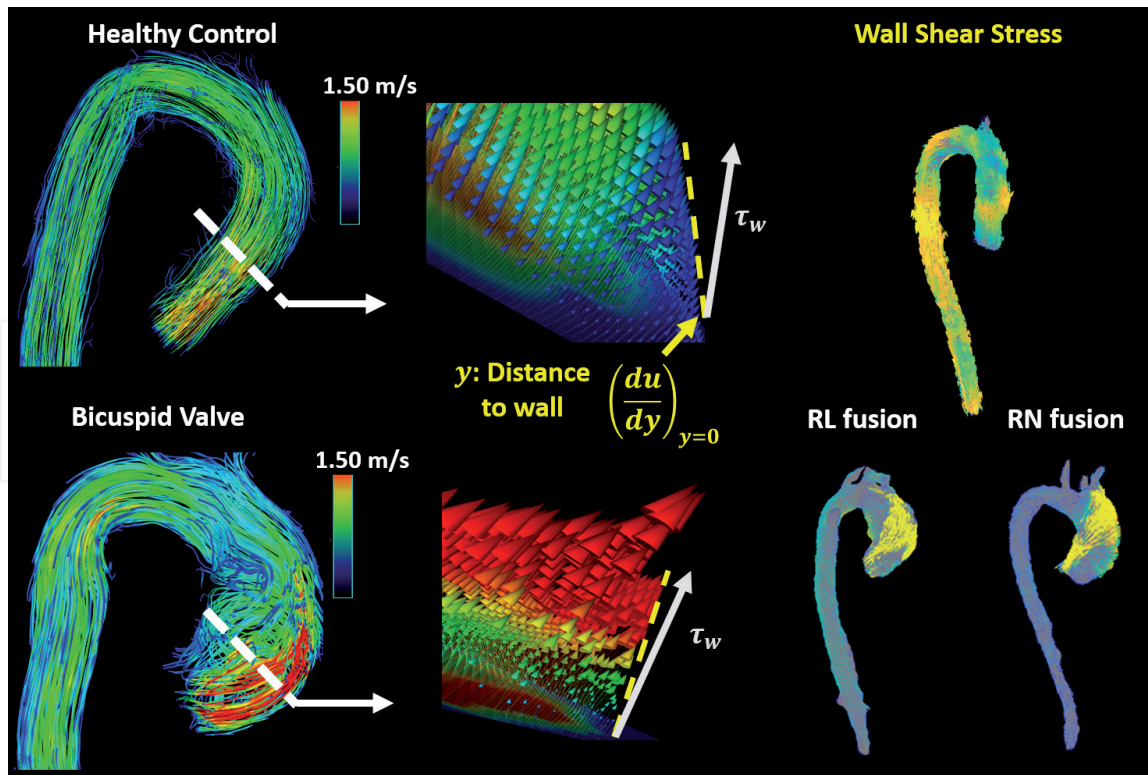
and vorticity were found to be more reproducible and independent of physiological factors than mean velocity, vortex volume and stasis.

### 3.4 Bicuspid aortic valve disease and Aortopathy

Bicuspid aortic valve (BAV) disease is the most common congenital valve disease, affecting 0.5–1.4% of the general population [61–63]. While an aortic valve normally contains three functional leaflets (i.e. tricuspid), a BAV contains only two. There are different sub-types of BAV: valves that developed with only two leaflets (Type 0) and valves that developed with three leaflets containing a fusion between any adjacent pair (Type 1) [64]. Type 1 phenotypes are further subdivided depending on what leaflet pair is fused. Despite being a valvular malformation, BAV disease is closely associated with aortic dilation (BAV aortopathy) that increases patients' risk of aortic aneurysms and dissections [65]. Traditionally, aortic diameters and growth rates have been used to stratify BAV patients at risk for aortic dissection, but these measures alone have been shown to possess limited prognostic value [66]. As well, uncertainties still exist regarding the exact pathophysiology of BAV aortopathy and the most effective timing of surgical intervention [67]. Thus, it is important to study new biomarkers that may enhance our understanding of BAV disease progression. Four-dimensional flow MRI has allowed the study of several new and promising biomarkers, such as abnormal flow patterns, WSS, and energy loss.

Eccentric flow jets and helicity are two characteristics of abnormal flow patterns that have shown strong connections with aortic dilation in BAV patients. A tricuspid aortic valve typically produces a centered systolic jet and bulk flow that is parallel to the ascending aorta, while BAVs tend to produce off-centered systolic jets (eccentric flow jets) that lead to circumferential flow and vortices (helicity). Each BAV phenotype has been shown to produce its own general pattern of jet eccentricity and helicity, and the direction and orientation of these abnormal flow patterns has been associated with patterns of aortic dilation [68–71]. For example, patients with right–left coronary leaflet fusion (Type 1 RL) are more likely to produce a flow jet aimed to the right-anterior wall that associates with dilation focused at the mid-ascending aorta, while right-non coronary leaflet fusion patients (Type 1 RN) tend to produce right-posterior flow jets that associate with diffuse dilation extending to the aortic root and/or arch as well, **Figure 7** [69, 70, 72]. Furthermore, Bissel et al. showed that BAV patients with normal flow jets and non-helical flow patterns tended to have similar aortic diameters to healthy volunteers [73]. While more longitudinal studies are needed to confirm causation, these studies seem to collectively suggest that abnormal flow patterns are connected to aortic dilation in BAV patients.

Wall shear stress, a measure of force exerted on the vessel wall by flowing blood, has consistently shown to be elevated in the ascending aorta of BAV patients [69, 74, 75]. The abnormal flow patterns created by a BAV are likely responsible for these increased WSS forces, and WSS itself has also been associated with regions of aortic dilation (**Figure 7**) [68, 69, 71, 73]. Seminal studies conducted by Bollache et al. and Guzzardi et al. demonstrated a possible physiologic mechanism behind WSS-associated aortic dilation, showing that elevated WSS levels may trigger maladaptive metalloproteinase activity which leads to medial elastin fiber degeneration and overall weaker connective tissue in the aortic wall [76]. Thus, it is thought that elevated WSS, driven by abnormal flow patterns, may be a direct mediator of aortopathy in BAV patients. This ability of 4D flow MRI to visualize flow patterns and quantify WSS may provide future clinical utility in the risk-stratification of BAV patients and identifying appropriate timing for aortic surgery.



**Figure 7.**

*Flow patterns and wall shear stress in a control and bicuspid valve phenotype. The white dashed lines represent the location where the sample velocity profile was obtained. These flow profiles can estimate the shear stress rate, blood flow spatial deformation. Since no flow occurs through the vessel wall, the speed of the blood flow at the vessel boundary is zero. The near wall region is the boundary layer where the wall shear stress (WSS) forces occur. The WSS expresses the force per unit area exerted in the fluid direction on the local vessel tangent ( $\tau_w$ ). Yellow dashed lines illustrate the flow profile slope near the wall. On the top, a healthy control illustrates normal flow in the proximal ascending aorta. On the bottom, samples of right-left (RL) fusion and right-non coronary (RN) fusion illustrate abnormal flow.*

### 3.5 Aortic stenosis

Aortic stenosis (AS) refers to the narrowing of the aortic valve opening, which restricts blood flow from the LV to the aorta. It is the most prevalent valvular disease in developed countries, affecting 2.4% of those >75 years of age [77]. It is commonly a result of BAV disease, chronic calcification, or rheumatic fever (in developing countries). Aortic stenosis often leads to complications such as LV dysfunction, heart failure, and aortic dilation, aneurysm and dissection [78]. Surgical repair or valve replacement are the only known definitive treatments and accurate diagnosis and staging are critical for surgical decision-making [79]. The most widely used parameters in assessing valve function include transvalvular pressure gradient, peak velocity, and valve area. However, up to 40% of AS patients present with discordant findings (ex: abnormally small valve area, but normal pressure gradient) that require additional imaging, and the heterogeneous nature of onset of secondary complications (ex: different dilation patterns, different rates of progression, etc.) is not well understood [80]. Four-dimensional flow MRI research continues to enhance our understanding these issues through the novel measurement of 3D peak velocity, 3D pressure gradients, and fluid energy losses.

Peak velocity and pressure gradients across the aortic valve are key components in AS severity grading [79]. However, as previously mentioned, echocardiography and 2D PC-MRI measurements often underestimate peak velocity, due to inaccurate

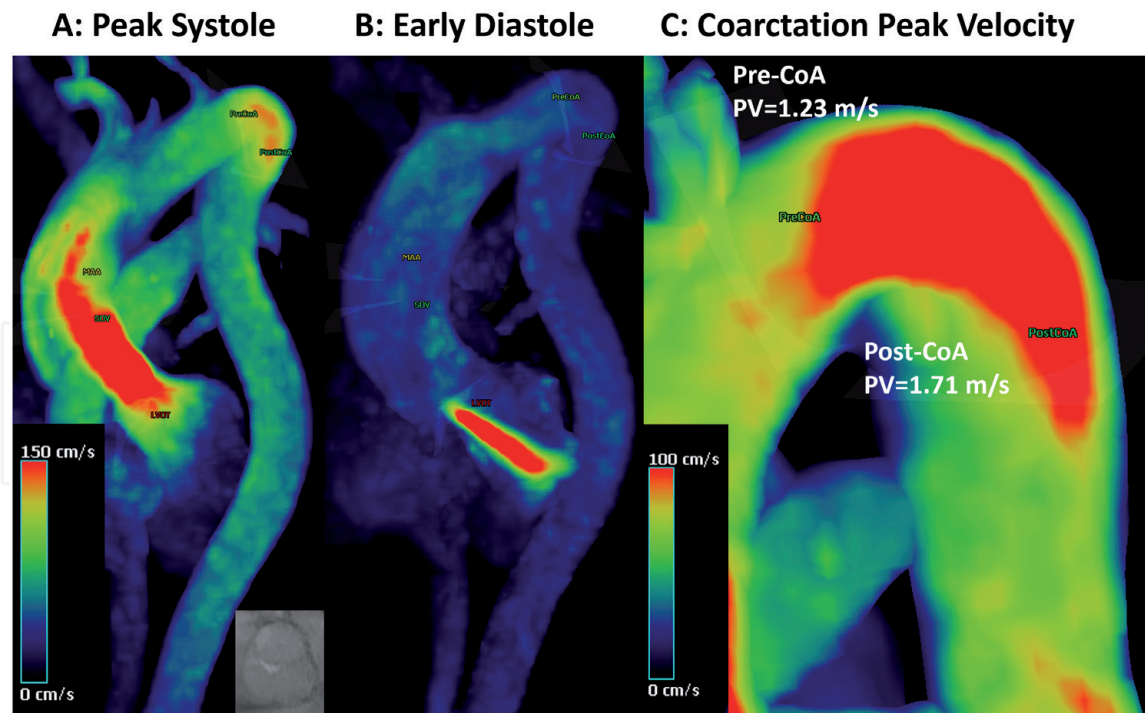
2D analysis plane placement, and overestimate pressure gradients, due to exclusion of downstream pressure recovery in calculations. The 3D visualization of these parameters using 4D flow MRI allows for more accurate identification of true peak velocity and a comprehensive calculation of pressure gradients that accounts for pressure recovery in the thoracic aorta. Due to this, 4D flow MRI may be a more accurate imaging modality for AS severity grading and surgical decision-making. Although, it should be noted that 3D pressure gradient calculations assume laminar flow, which may lead to inaccuracies when measuring severely stenotic flow where turbulence exists [33].

Fluid energy loss is an advanced hemodynamic parameter that provides information regarding LV workload. There are two types of mutually exclusive fluid energy loss measurements: viscous energy loss (EL; energy lost due to friction between adjacent fluid layers with different velocities) and TKE (energy lost to turbulence) [81]. Both measurements reflect LV output lost to abnormal flow patterns and, ultimately, a greater cardiac afterload. Larger fluid energy losses place greater workloads on the LV, which can lead to LV dysfunction and heart failure. Several studies have shown the presence of significantly elevated fluid energy losses in AS patients and explored the role of TKE in improved characterization of AS severity [82, 83]. Specifically, Binter et al. found TKE to be greater in AS patients compared to controls and demonstrated TKE to be influenced by aortic and valvular morphology [83]. Taken together, this body of research suggests that fluid energy loss may provide novel AS severity measurements that are complimentary to traditional evaluation techniques. Lastly, it should be noted that jet eccentricity, helicity, and WSS measurements may serve the same purpose in the study of AS as they do in the study of BAV disease. These parameters have shown close associations with aortic dilation, a common complication in AS patients [68, 69, 73, 84, 85]. Most studies exploring these associations use BAV patient cohorts, since AS is a common finding in BAV disease.

### **3.6 Aortic Coarctation**

Aortic coarctation (CoA) refers to a congenital narrowing of the thoracic aortic lumen, most often in the arch or descending portion, and accounts for approximately 6–8% of all congenital heart defects [86]. It often accompanies other congenital malformations, such as BAV (60%), aortic arch hypoplasia (18%), ventricular septal defect (13%), and sub AS (6%) [87]. Similar to AS, CoA causes an upstream increase in pressure, which may lead to LV dysfunction, aortic aneurysm and dissection, upper body hypertension, and stroke. Current diagnostics include computed tomographic angiography to image aortic structure and echocardiography to measure peak velocities and pressure gradients across the stenotic region. Due to the limitations of echocardiography, 4D flow MRI may provide added utility in characterizing CoA via 3D measurement of peak velocity profiles and pressure gradients.

The application of 4D flow MRI in generating 3D peak velocity profiles and pressure gradients serves the same benefits as previously mentioned in other cardiovascular disease. That is, it allows the visualization of temporally and spatially resolved flow patterns so that analysis planes may be placed in the most applicable locations and pressure recovery can be accounted for when measuring pressure drop across the CoA (**Figure 8**). Several studies to-date have found benefit in the use of 4D flow MRI for characterizing CoA flow patterns and evaluating post-repair hemodynamics in CoA patients [88–90].



**Figure 8.**

**Evaluation of a coarctation of the aorta.** Flow is visualized at peak systole (A) and early diastole (B). (C) Peak flow velocity (PV) across coarctation. This patient (male, 53 years old) has a type 1 LR BAV with severe aortic insufficiency (regurgitant fraction 56%), mild stenosis, coarctation measuring 21 mm, and moderate dilatation of the proximal ascending aorta (46 mm). LR: Left – Right coronary leaflet fusion; BAV: Bicuspid aortic valve.

## 4. Conclusion

In conclusion, 4D flow MRI is a powerful technique which can be used for calculating important clinical parameters. This chapter intended to introduce and summarize the usefulness of 4D flow for assessing cardiovascular diseases. Thanks to recent technical advances, 4D flow MRI has increased its use in cardiac MRI sites worldwide and it is in a ready-to-go state-of-art stage for clinical practicality.

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## Conflict of interest

Authors have no conflict of interest to declare in the context of this chapter.

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