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**Title:** Atrioventricular septal defect : advanced imaging from early development to long-term follow-up
**Issue Date:** 2016-03-24
Part 3

Long-term follow-up after atrioventricular septal defect correction
Chapter 3.1

Cardiovascular function and flow by 4-dimensional magnetic resonance imaging techniques: new applications

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SUMMARY

Acquisition techniques related to 4D flow Magnetic Resonance Imaging (MRI) improved rapidly over the last three decades. Most importantly, a major improvement was the acceleration of the acquisition which resulted in a clinically feasible scan duration and led to more comprehensive use of 4D flow MRI in clinical research. This resulted in various new applications of 4D flow MRI for the evaluation of various physiologic and pathologic cardiovascular flow patterns. Visualization tools aim at displaying the direction and magnitude of blood flow velocity from 4D flow data, by using for instance a vector glyph or streamline representation or by constructing pathlines from particle tracing. Such tools are applied to provide insight in the temporal distribution of the three-dimensional flow velocity and enable the quantification of hemodynamic markers. These hemodynamic markers play an important role in the quantitation of abnormalities in cardiovascular blood flow patterns and the characterization of vascular and myocardial remodelling which can possibly be used to predict pathology such as heart failure, aortic dissection or aneurysm or thrombus formation. This review focuses on the clinical use of 4D flow MRI and presents an overview of new applications of visualisation and quantification tools to describe physiologic and pathologic cardiovascular blood flow.

INTRODUCTION

Over the last three decades, technology in cardiovascular magnetic resonance imaging (MRI) developed remarkably which contributed to the evolution of four-dimensional (4D) flow MRI from an imaging tool strictly limited to research environments into a clinically practical modality providing valuable disease-specific information. 4D flow acquisitions allow visualization and quantification of intra-cardiac blood flow and blood flow in the great arteries and veins, providing new insights in normal and pathologically altered blood flow patterns that were previously only suggested by computational fluid dynamics or in vitro simulations. In the current review, we will address important technical developments in cardiovascular MRI that contributed to the evolution of 4D flow, discuss the latest advances in acquisition tools and present an overview of current clinical applications in vascular, valvular and intra-cardiac blood flow visualization and quantification.

DEVELOPMENT OF FLOW ASSESSMENT WITH MRI: TOWARDS FAST AND ACCURATE 4D FLOW

After the commercial introduction of whole-body MRI scanners in the early 1980s, Moran was the first to describe in vivo two-dimensional (2D) imaging with one-directional velocity informa-
tion for each voxel [1], by adding velocity-sensitive and velocity-compensated gradients to a standard gradient-echo pulse sequence. Bryant et al. [2] and van Dijk [3] demonstrated the use of motion-induced phase shifts to encode the magnitude and direction of blood flow velocity. The principle of velocity-encoding or phase-contrast imaging relies on manipulating the phase signal of spins moving in the direction along a magnetic field gradient in contrast to the phase of stationary spins, in such a way that the difference in phase between moving and stationary spins is proportional to the velocity of those moving spins. A velocity-sensitive gradient induces a phase shift proportional to the velocity, but other factors than motion (i.e., magnetic field inhomogeneity, eddy currents, concomitant gradient effects) which depend on $B_0$ (i.e., the static magnetic field), induce additional phase shifts. By performing a subtraction of echoes from acquisitions using alternating velocity-sensitive and velocity-compensated gradient schemes, these additional phase shifts are eliminated and only phase shifts related to velocity remain. After image reconstruction, the accustomed phase images from phase-contrast MRI are obtained, in which the grey value is linearly related to the velocity of blood flow. Typically, imaging is performed in a time-resolved manner [4], resulting in multiple phases during one average cardiac cycle. Data collection extends over multiple cardiac cycles and is synchronized to the patient’s ECG signal using either prospective [5] or retrospective gating [6]. With prospective gating, a trigger signal starts off data acquisition and data is collected over multiple heart beats at predefined time points of the cardiac cycle. Prior to acquisition, the heart beat interval is set in the acquisition protocol, determining the start of each trigger. Variations in the true heart beat during the acquisition may result in inaccurate acquisition timing, leading to inaccuracies especially in late diastolic flow assessment, or even missing flow assessment in this part of the cardiac cycle. With retrospective gating, data collection is performed continuously throughout the cardiac cycle and stored with the trigger signal. During image reconstruction, this recorded trigger signal is used to retrospectively assign the collected data to subsequent timings in the cardiac cycle. Since velocity-encoded imaging is not real-time and velocity images are reconstructed from data acquired over multiple heart beats, therefore representing average velocities at specific time points in the cardiac cycle, alterations in the velocity over multiple heart beats cannot be picked up.

Nowadays, 2D cine MRI with one-directional through-plane velocity-encoding is widely used in clinical protocols to assess the function of cardiac chambers and heart valves by evaluation of trans-valvular blood flow [7,8]. Intra-cardiac blood flow, however, is a complex three-dimensional and highly-dynamically-changing phenomenon which requires multi-dimensional imaging. 4D flow MRI is the term used for time-resolved three-dimensional (3D) three-directional velocity-encoded MRI with data collected during several minutes but represented as one average heart-beat. From this acquisition, the blood flow velocity is acquired in a 3D volume (e.g., covering the heart or the great thoracic vessels) by encoding the three individual vector components consecutively [9]. Visualization tools are required to display the multi-dimensional data such as
the time-dependent velocity vector field and quantification algorithms have been developed for hemodynamic analysis.

The first 4D flow MRI protocols involved a long acquisition time, which is the major drawback for introducing this technique in clinical practice [10,11]. Several improvements led to acquisition protocols which can provide good quality data acquired in less than 10-15 minutes. Accelerated acquisition techniques using parallel imaging [12] or undersampling in k-t domain (k-t BLAST Broad-use Linear Speed-up Technique) [13] vastly reduced acquisition time. In contrast to conventional Cartesian read-out methods, algorithms for data read-out using Echo Planar Imaging (EPI) [14] or implementing radial [15] or spiral read-out trajectories [16] further contributed to the reduction of acquisition times towards a clinically acceptable scan duration. The introduction of radial undersampling, known as VIPR (vastly undersampled isotropic projection reconstruction) [15] revealed the advantage of a larger area coverage, higher spatial resolution and improvement of hemodynamic analysis.

Because scan time still exceeds a breath hold and respiratory motion may significantly degrade image quality, specific techniques have been developed to minimize breathing artefacts. Commonly used techniques are bellows reading [17], that corrects via registration of the excursion of the abdominal circumference, and navigator gating [18], based on diaphragm movement. In both cases, collected data are only included for image reconstruction when acquired during the time in the respiratory cycle when breathing motion is minimal. Rejection of data can be reduced to 20-40% with adaptive k-space recoding [19]. The drawbacks of these types of respiratory compensation are that these methods are based on abdominal or long-liver movement instead of relying on heart movement, and the inaccuracy caused by the time delay between signal and movement [20]. To overcome these disadvantages respiratory self-gating is introduced, where k-space data of the heart is used to provide information about its movement [21].

Due to mentioned developments, it is currently possible to acquire whole-heart 4D flow data in under 10-15 minutes, with echo time 2-4 ms, repetition time 5-7 ms, spatial resolution 2-3 mm and temporal resolution 30-40 ms [22]. The implementation of these acceleration techniques however, led to a negative trade-off: increasing inaccuracies in velocity quantitation. Most notably are local phase offset errors, caused by eddy currents [23], Maxwell terms [15] and gradient field nonlinearity [24]. 4D flow acquisition implies volume coverage with consequently a larger anatomical area included than for conventional 2D flow acquisitions. Therefore, measurements are performed in areas further from the iso-center of the magnet where they are more prone to offset errors. During pre-processing, the major source of these errors should be taken into account and additional background correction methods have been developed, either by a phantom correction [25] or by using a plane-fitting correction algorithm based on the phase signal sampled in areas inside the acquired 3D volume with no velocity, in order to correct the position-dependent velocity offset [26,27].
VISUALIZATION TECHNIQUES

4D flow data represents the pulsatile time-resolved three-directional velocity distribution inside a 3D volume (i.e., the heart or great arteries and veins). Several image processing techniques are available to present this multi-dimensional data for qualitative visual interpretation, usually projecting velocity or flow as animations onto anatomical images presented in cine mode. Figure 1 illustrates three available and often-used visualization methods. A glyph (graphic symbol) display of the velocity vector field represents the magnitude and direction of the velocity measured inside each voxel. Color coding or adjustment of the size of the vector glyph may be used to represent the velocity magnitude. Streamlines [28] are lines instantaneously tangent to the local velocity vector in each position at a specific time point and connected to all points along the direction of this line. Therefore, streamlines can be used to visualize the flow direction.

Figure 1. Three types of 4D flow visualization.

3-chamber orientation with velocity color coding (in cm/s). In panel A and D velocity vector glyph representation, in panel B and E streamline representation and in panel C and F pathline representation after forward (C) and backward (F) particle tracing. 4D flow MRI data was obtained with a 3T MRI scanner in a 9 year old healthy girl (informed consent was obtained from the parents) with a heart rate of 89 beats per minute. A-C represent the same mid-systolic phase (i.e., 136 ms after R-peak), D-F represent the same early diastolic phase (i.e., 409 ms after R-peak). In C and F, respectively forward and backward tracing was performed with particles being released in the left ventricle at end diastole. LV left ventricle, LA left atrium, Ao aorta.
only at this specific instant in time and do not represent the true pathlines of flow over time. Color coding can again be used to display the velocity magnitude [29].

Particle tracing is an often-used visualization tool to display the true pathline of flowing blood over time [30]. In particle tracing, virtual particles are positioned at a predefined position and time and subsequently released inside the 3D velocity field and then followed over time. The trajectory of the particles is calculated by either forward or backward tracing, by using the local velocity at each position and time point and calculating the next or previous position of this particle. Pathlines can be displayed over time with color coding either representing velocity magnitude or labelling the origin or destination of the particles in the flow field. The discretization in time and space in combination with the quality of data defines the accuracy of particle tracing. When uncorrected, a particle near a physical border may dissipate through this border if the local velocity at a specific time point directs this particle towards the border and the distance covered over the time step exceeds the distance to the border. To check the quality of particle tracing, agreement in the particle count entering and leaving a volume should be verified [31].

Another line representation that is used for displaying flow is the streakline [32]. This line is constructed similarly to a pathline, with a virtual particle being released from a seed point inside a flow field. With streaklines, however, particles will be released continuously over time from the same seed point. At an instant in time, the positions of all consecutively released particles from the same seed point are connected to construct the streakline. Since streaklines are not representatives of the true pathline or velocity of blood flow, this type of visualization has not found widespread use in physiological hemodynamics. Isosurfaces are used as a visualization tool to cluster and segment flow structures. For example, vortical or helical flow can be displayed with an isosurface, clustering blood with identical vorticity or helicity together inside the flow field [33].

**QUANTIFICATION TECHNIQUES**

Visualization techniques as described above aid in the qualitative interpretation of flow patterns in 4D flow data. In addition, quantification tools have been developed to assess hemodynamic markers from 4D flow data. Using particle tracing, a four-component evaluation of the intracardiac blood flow has been introduced [31]. According to the moment of passing the LV relative to the cardiac cycle, the blood volume inside the LV at end diastole can be subdivided into four functional components: 1. direct flow, which is the amount of blood that enters the LV during diastole and is subsequently ejected through the aorta in the next systole; 2. retained inflow, which is the amount of blood that enters the LV during diastole but is not ejected in the next systole; 3. delayed ejected flow, which is part of the blood already present inside the LV during diastole but leaves the LV during the next systole; 4. residual volume, which is the amount of
blood that was not part of the blood entering during diastole and is not ejected in the next systole, and therefore resides in the LV for more than two cardiac cycles. Using particle tracing and color coding, the four components in intra-cardiac blood flow are labelled and the distribution can be followed over time [31].

From local velocity and flow rate, the kinetic energy of flowing blood can be calculated. Stroke volume multiplied by the blood density represents the mass $m$ of flowing blood. The kinetic energy of this blood flow is then calculated by $0.5mv^2$, with $v$ being the mean velocity. Another parameter representing energy of blood flow that is often used is the turbulent kinetic energy [34]. Turbulence is characterized by incoherent flow and rapid fluctuations in velocity, which cannot be picked up by the magnitude of velocity encoding. However, the standard deviation of the velocity distribution within each voxel can be assessed and this parameter is related to the turbulent kinetic energy. Another hemodynamic marker that is of high interest is the wall shear stress (WSS), as this shear stress affects vascular remodelling through its act on endothelial cells. WSS can be quantified [35,36] based on the assumption that a laminar condition exist in the boundary layer of the blood vessel, in which WSS is calculated by the wall shear rate multiplied by the blood viscosity, with the wall shear rate being the derivative of local velocity at the vascular wall.

The aortic pulse wave velocity (PWV, i.e., the speed of the systolic pulse propagating through the aorta) is being used as a surrogate marker for aortic stiffness. PWV is calculated by measuring the transit time of wave propagation over a predefined segment of the aorta (Figure 2). Although temporal resolution in 4D flow is limited, global PWV assessment in the total aorta using 4D flow has been described [37]. High temporal resolution, required for accurate regional PWV assessment, can be achieved by combining multiple one-directional velocity-encodings [38].

Diastolic vortices are important phenomena in intra-ventricular blood flow patterns that can be evaluated with 4D flow (Figure 3). Vorticity describes the local rotation of fluid particles. A vortex represents a compact region of vorticity and forms when boundary layers separate, for instance distal to valve leaflets. Due to variance in speed in the shear layer, blood swirls and may separate from the boundaries, forming a compact vortex [39]. During early (E) and late (A) filling, a circular vortex ring is formed from the tips of the mitral and tricuspid valve leaflets, causing minimal loss in kinetic energy [40]. The vortex ring formed in the left ventricle is suggested to form a channel that prevents spreading of the inflow jet and loss of momentum to convective deceleration [41]. Additionally, the vortex ring contributes to the redirection of flow towards the aorta and possibly aids mitral valve closure [42] and prevents thrombus formation [43]. Various parameters have been suggested to characterize vortices and their association with systolic and diastolic function. With Echocardiographic studies (using contrast or vector flow mapping) found a relation between abnormal left ventricular function and vortex size, intensity and position [44,45]. The vortex formation time (VFT), introduced by Gharib et al. [46], is a parameter computed from the equations for trans-mitral flow and ejection fraction and has been proposed as an indicator for cardiac health and diastolic function with suggested prognostic value in
predicting heart failure [47]. In contrast, Stewart et al. demonstrated no association between VFT and diastolic function [48]; they postulated that the vortex pinches off the mitral valve already before E-peak, leading to an abrupt deceleration of the velocity propagation. Since VFT is based on the assumption that the vortex is only completely formed at E-peak, they concluded that VFT is not useful as an indicator for cardiac function.

Figure 2. Regional aortic pulse wave velocity assessment.

![Figure 2](image1.jpg)

Two combined high-temporal one-directional in-plane velocity-encoded MRI acquisitions, performed with 3T MRI scanner in a 44 year old healthy male volunteer (informed consent was obtained). In A, in-plane velocity is displayed in a mid-systolic phase of a double-oblique sagittal view of the aorta, using a velocity vector glyph representation with color coding (cm/s). In B, velocity-time curves are displayed, sampled at 200 equidistantly-spaced positions along the 40 cm long centerline of the aorta, starting from the aortic valve to the abdominal aorta. From these velocity-time curves, the relation between sampling position and the transit-time for velocity wave propagation can be obtained, which defines the regional pulse wave velocity.

Figure 3. Visualization of the diastolic vortex in the left ventricle distal to the mitral valve.

![Figure 3](image2.jpg)

Obtained with a 1.5T MRI scanner in a 45 year old male patient with ischemic cardiomyopathy (informed consent was obtained). In A, a 4-chamber orientation with streamline representation and velocity color coding (in cm/s) is presented and in B, a vorticity isosurface display, segmenting the ring-like structure of the vortex. LV left ventricle, LA left atrium, RV right ventricle, RA right atrium.
Figure 4. Streamline visualization of left ventricular inflow.

Velocity color coding (in cm/s) of 4D flow MRI data, displaying the early diastolic inflow in a 4-chamber orientation, obtained with a 3T MRI scanner in a 33 year old healthy male volunteer (A) and a 30 year old female patient with a corrected atrioventricular septum defect (B) (informed consent was obtained in both subjects). The dotted line represents the anatomical annulus of the left atrioventricular valve. In A, an apically-directed inflow is visualized, in contrast to the laterally-directed inflow (B) in the patient, due to restricted opening of the valve. Peak inflow velocity is visualized 1-2 cm distal to the anatomical annulus, at the location of the valve leaflets. LV left ventricle, LA left atrium, RV right ventricle, RA right atrium.

Figure 5. Streamline representation of atrioventricular regurgitation.

Velocity color coding (in cm/s) of 4D flow MRI data in a 4-chamber orientation, obtained with a 3T MRI scanner in a 16 year old female patient with a corrected atrioventricular septum defect and recurrent regurgitation in both left and right atrioventricular valves (solid arrows) during follow-up (informed consent was obtained from the patient and parents). A represents an early systolic phase (i.e., 34 ms after R-peak at heart rate of 61 beats per minute) and B represents mid-systolic phase (i.e., 201 ms after R-peak). Note the dynamically-changing direction of the regurgitant jets, illustrating the need for dynamical adaptation of measurement planes to the flow direction throughout the cardiac cycle. Due to turbulence at the regurgitant orifice, intra-voxel spin coherence is absent leading to dispersion of phase signal, especially notable at early systole at the left atrioventricular valve (A, dotted arrow). Therefore, quantification of regurgitant flow is usually performed 1.5 – 2 cm proximal to the valve, inside the atrium. Retrospective valve tracking at left and right atrioventricular valve resulted in an assessment of mean effective forward flow volume of 95 ml per cardiac cycle, and regurgitant fractions of 11% at the left atrioventricular valve and 15% at the right atrioventricular valve. LV left ventricle, LA left atrium, RV right ventricle, RA right atrium.
From intra-cardiac blood flow, transvalvular stroke volumes and regurgitation can be assessed, describing valve and chamber function. Retrospective valve tracking was introduced to transvalvular velocity mapping, with the measurement plane following the valve plane and the angulation adapting to the blood flow direction, to accurately quantify blood flow through any of the four heart valves obtained from one single 4D flow acquisition [49,50]. The high velocity regurgitation jet is usually analyzed in a plane inside the atrium distal to the valve plane, in order to avoid underestimation of regurgitation velocity due to phase dispersion from turbulent flow. This 4D flow approach with retrospective valve tracking was proven to be more accurate for transvalvular velocity mapping than conventional 2D one-directional velocity-encoded (VE) MRI using a fixed acquisition plane [49,50]. From transvalvular velocity mapping, parameters such as cardiac output, ejection fraction, the effective forward flow volume, peak flow rate, peak velocity, retrograde flow and regurgitation fraction can be assessed.

Besides quantification of flow volume, the trans-atrioventricular flow rate graph allows assessment of diastolic function analysis. From the flow rate graph, usually the following diastolic function parameters are determined: early (E) and late or atrial (A) filling rates, E/A ratio, E-peak acceleration and E-peak deceleration duration. When 4D flow data extents to the left atrium, wave form analysis of pulmonary venous inflow, another indicator for diastolic function, may be assessed when velocity sensitivity and temporal resolution allow [51]. Kumar et al. defined the fractional propagation parameter as the ratio between the longest jet stream of early diastole to the length of the entire ventricle [52]. The flow propagation velocity \( V_{\text{prop}} \) is another marker used for classifying diastolic function; \( V_{\text{prop}} \) describes the speed of the early filling wave propagation, which is driven by a pressure gradient between atrium and apex [53]. From the intra-ventricular inflow in combination with streamline visualization, the inflow propagation can be evaluated [54], albeit no 4D flow approach has been able to provide sufficiently high temporal resolution, required for assessing the transit time of blood flow waves over a relatively short propagation distance inside the left ventricle.

Moreover, retrospective positioning of measurement planes in a 4D flow dataset of thoracic vessels allows accurate flow quantification, giving access to various hemodynamic parameters such as, antegrade and retrograde flow, peak velocity, wall shear stress and kinetic energy. With this approach, the pressure drop over a valve stenosis can be estimated using the equation of Bernoulli and accurate peak velocity assessment at both sides of the valve. However, accurate velocity depiction in a high-grade stenosis might be difficult, as phase dispersion due to turbulent flow makes assessment of high peak velocities impossible. Furthermore, pressure gradients can be estimated from the intra-cardiac velocity field when using the Navier-Stokes equation. In this approach, it is assumed blood to be an incompressible Newtonian fluid and velocity to have zero variation (i.e., no turbulence) [55].
Applications

In the following section, we will review the current status of 4D flow applications in clinical research and discuss promising results already obtained by applying the visualization and quantification tools that were described above. We will review first applications of 4D flow for evaluating intra-cardiac flow patterns in the atria and ventricles, followed by blood flow quantification across atrioventricular valves and finally, in the thoracic vessels.

Flow patterns in the atria

The left atrium is a conduit and reservoir which directs the inflow of blood from the four pulmonary veins towards the mitral valve during diastole and collects blood during systole. Visualization of 4D flow data revealed vortical flow in the left atrium during systole and diastole. This vortical flow is mainly formed from blood coming from the left pulmonary veins, while the blood from the right pulmonary veins passes along the vortex [56]. In the right atrium, a vortex is formed, rotating in an anti-clockwise direction [57]. In healthy volunteers, more and longer vortices and higher velocities were found in younger than in older individuals [58], which could be related to a decreased atrial compliance and late active (A-peak) filling becoming more dominant with ageing. The increased risk factor for thrombosis and systemic embolisms in patients with atrial fibrillation might partly be caused by disturbed flow. Preliminary results from Fluckiger et al. using 4D flow showed that patients with atrial fibrillation have lower atrial flow velocities and patients after treatment may reach similar velocities compared with age-matched controls [59]. In patients with mitral regurgitation, atrial vortices did not originate from the inflow through the (left) pulmonary vein, but from the regurgitation jet. Furthermore, a relation between mitral regurgitation fraction and left atrium turbulent kinetic energy loss was found [60].

Flow patterns in the left ventricle

Visualization techniques such as particle tracing have contributed to knowledge on the pathway of blood entering the ventricle through the atrioventricular valve and exiting through the aorta [57]. This pathway is assumed to be energy efficient and depends on multiple factors such as chamber shape, LV pressure, myocardial function and valve function. Changes in the cardiac flow pathway may influence cardiac function. Using computational fluid dynamics, simulated changes in flow direction have shown to reduce the heart pumping efficiency by 10% [40]. Moreover, it is suggested that changed hemodynamic forces act upon cardiac adaption through epigenetic mechanisms [61]. In an early study by Mohiaddin and colleagues, 4D flow was used to describe altered flow patterns in patients with dilated left ventricles. In normal subjects, the diastolic inflow through the mitral valve is directed towards the apex while in patients with dilated left ventricles, the inflow is directed towards the lateral wall, giving rise to a well-developed circular flow pattern [62]. Another study using 4D flow to describe LV inflow in patients with diastolic dysfunction showed that the high velocity inflow did not reach as far into the ventricle.
4DFlow MRI techniques

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as in healthy controls [52]. Figure 4 shows a laterally directed inflow in a patient who underwent correction for atrioventricular septum defect at early age, compared with a healthy control. The four-component evaluation of the intra-cardiac blood flow (i.e., direct flow, retained flow, delayed ejected flow and residual volume) in combination with particle tracing has provided unique insight in altered systolic and diastolic flow in patients with heart failure [63]. In patients with compensated heart failure, not only a decreased amount direct flow was observed, but also the kinetic energy of direct flow at end diastole was reduced. Furthermore, in a patient with a dilated cardiomyopathy, increased retained flow was described and related to increased kinetic energy loss of the retained flow [64]. The amount of residual volume potentially may predict intra-chamber thrombus formation.

Despite the high potential of 4D flow for evaluating intra-cardiac flow patterns, not much has been reported yet on vortex analysis in left ventricular flow patterns using 4D flow MRI. Foll et al. [58] used 4D flow with particle tracing and velocity vector fields to semi-quantitatively calculate vortex numbers and measure vortex duration and area based on the 2- and 4-chamber view and they observed smaller vortices in the base of the LV in women compared with men. Furthermore, Toger et al. quantified vortex volume [65] extracted from 4D flow and described smaller volumes in patients with ischemic cardiomyopathy. Further studies using 4D flow are required to standardize vortex description and quantification and detect clinical relevant parameters.

Flow patterns in the right ventricle

Despite the increasing interest in the right ventricular function, particularly in congenital heart disease, little is known about right ventricular (RV) fluid dynamics. This is mainly due its complex anatomy and function and difficulties to visualize the RV in 3D with echocardiography. Only recently, a computational fluid dynamics model was suggested to simulate right ventricular flow [66]. Fredriksson et al. [67] used 4D flow in combination with particle tracing and four-component evaluation to describe differences in LV and RV blood flow distribution and kinetic energy in healthy volunteers. Diastolic characterization of RV vortices has been so far only reported in vivo using echocardiography in dogs [68]. Kheradvar and Pedrizetti [39] depicted the complexity of the vortex in the right ventricle. In patients with a corrected Tetralogy of Fallot (TOF), more, and pathological vortices were observed in the right atrium and ventricle using 4D flow [69,70].

Transvalvular flow quantification

As was described above, 4D flow allows reliable and reproducible transvalvular flow assessment at each of the four heart valves when retrospective valve tracking is implemented [50]. Accurate quantification of valve regurgitation is clinically important as the regurgitation fraction is an indicator for morbidity and mortality and therefore a determinant for surgical decision making. Assessment of regurgitation with 2D one-directional through-plane VE MR is still routine clinical practice, however, correlation between flow volumes at consecutive valves is lacking. With a 4D flow approach, conservation of mass has been described between the inlet and outlet
of cardiac chambers, a requirement for accurate quantitation of regurgitant volumes [71,72]. Several studies applied 4D flow with retrospective valve tracking in various patient groups, such as patients with functional mitral [73,74] or aortic valve insufficiency [75], patients with ischemic cardiomyopathy [76] and patients after correction of TOF [71]. These studies compared their flow results either with Doppler echocardiography or MRI planimetry, and concluded that 4D flow with retrospective valve tracking was superior to conventional 2D one-directional VE MRI for assessment of valve patency, regurgitation fraction and effective forward flow. Especially, quantification of eccentric jets is challenging with echocardiography [77]. Figure 5 shows an example of a 16 year old patient, corrected for atrioventricular septum defect at early age, who underwent a 4D flow evaluation as a part of follow-up cardiovascular MRI examination. Streamline visualization revealed multiple eccentric regurgitant jets over the atrioventricular valve, dynamically changing its orientation during systole. With 4D flow, multiple measurement planes were adjusted perpendicular to the regurgitation jet(s) throughout systole allowing reliable quantification of the regurgitation fraction.

While the gold standard in detecting intra-cardiac shunt remains echocardiography, a new visualization technique (i.e., volume-rendered stereoscopic velocity fusion visualization) based on 4D flow showed improvement of detection of shunts with MRI [78]. Moreover, volumes of shunts can be more accurately estimated when using 4D retrospective valve tracking approach in describing the forward flow through the cardiac chambers.

Classification of diastolic filling parameters obtained from trans-atrioventricular flow rate graphs in patients with ischemic heart failure using 4D flow showed excellent agreement with Doppler echocardiography, superior to conventional 2D one-directional VE MRI [79]. It should be taken into account that temporal resolution (0.8 ms) used in echocardiography is vastly superior to MRI. This might interfere with accurate assessment of peak velocity. Furthermore, with MRI, flow rate graphs are usually used for diastolic function testing in contrast to the velocity-time graphs with echocardiography. Also, with echocardiography, diastolic parameters are assessed at the tip of atrioventricular valves and measurement performed at annulus level, as done in MRI calculations, are known to result in changes in E/A ratio [80]. Therefore, new reference values for classifying various types of diastolic dysfunction should be defined and applied when using 4D flow.

**Flow patterns in the thoracic vessels**

Early 4D flow MRI studies have contributed to understanding blood flow in the aorta [81,82]. During systole, the normal blood flow in the aorta forms an anti-clockwise helix in the ascending aorta and clockwise helix in the aortic arch. Quantification of helicity is possible by combining velocity vectors with vorticity [83]. The highest velocity is found in the ascending aorta. During diastole, mild retrograde flow is visualized, which is important for perfusion of the coronary arteries. Regional differences of wall shear stress and oscillatory shear index are found in the healthy aorta, which might explain why specific locations are vulnerable for atherosclerotic
3.1 plaque formation or for dissection [84]. Several studies using 4D flow MRI revealed pathological blood flow in diseased aortas, such as coarctation of the aorta [85] or dissection (Figure 6). Furthermore, 4D flow can be used to describe pathology and hemodynamics within the abnormal vessel due to valvular pathology. Patients with bicuspid aortic valves, who frequently develop aortic aneurysms, show aberrant helical flow patterns in the ascending aorta [83]. Whether this abnormal flow leads to aneurysm formation or whether the abnormal flow is a consequence of abnormal aorta wall structure and luminal size remains a debate. Other studies on aberrant helical flow in aortic aneurysms suggest additional value of 4D flow in prediction and prevention of aneurysms [86, 87]. Sigovan et al. found a correlation between eccentric flow jets in patients with aortic valve diseases and local increased wall shear stress and aortic dilatation [88]. Figure 7 gives an example of a patient with aortic valve stenosis leading to an eccentric outflow jet, helical flow and aberrant laminar velocity and wall shear stress. Furthermore, in patients with aortic stenosis, the turbulent kinetic energy is high at the site of the stenosis and can be related with irreversible pressure loss [89]. When the stiffness of the aorta increases due to atherosclerosis, hypertension or connective tissue disorder such as the Marfan syndrome, an increased pulse wave velocity has been described as a precursor of aortic disease and related to end-organ damage [90, 91]. Abnormal flow with altered wall shear stress has been described in these patients at relatively early stages of disease [92]. In patients with Marfan syndrome, multi-directional velocity-encoding has been proposed for accurate PWV assessment regionally in the aorta [38], relating lumen dilatation to increased PWV [93]. Another application for 4D flow of the aorta is the evaluation of abnormal retrograde flow, which can lead to retrograde embolization into the branches of the

Figure 6. 4D flow visualization of a type A aortic dissection in a 50 year old male patient with Marfan syndrome.

Obtained with 1.5T MRI. In A, a double-oblique sagittal maximal intensity projection of a contrast-enhanced magnetic resonance angiogram of the aorta is presented (i.e., first-pass imaging of 25 mL contrast bolus Dotarem (Guerbet, Gorinchem, the Netherlands) with a molarity of 0.5 mmol/mL, intravenously injected at an infusion rate of 2 mL/s). The dissection is visualized from the aortic arch to the abdominal aorta. In B, 4D flow MRI data of a mid-systolic phase is presented with velocity color coding (in cm/s) in velocity vector glyph representation. In the descending aorta, the true lumen is displayed with high flow velocity and the false lumen with low velocity. Through-plane velocity mapping is performed at ascending (labeled by 1) and proximal descending aorta (labeled by 2 and 3) at the level of the pulmonary trunk (in C and E) and at the abdominal aorta (labeled by 4 and 5 in D and F). The true lumen (labeled by 2 and 4) presents high pulsatile flow while the false lumen (labeled by 3 and 5) presents low flow.
aorta causing embolic stroke [94]. Early detection of retrograde flow might become a prognostic factor for embolization.

Using 4D flow, the normal blood flow pattern in the pulmonary circulation revealed two counter rotating helices in the left and right pulmonary artery [95]. In contrast, this helical flow was not found in a patient with corrected transposition of the great arteries and aberrant in a patient with correction of abnormal venous return. From 4D flow data obtained in patients after correction of a Tetralogy of Fallot, an increased peak systolic velocity in the pulmonary trunk and abnormal vertical flow in the main pulmonary artery were revealed [70,71]. A recent 4D flow study presented a patient with pulmonary regurgitation and pulmonary artery stenosis, who had a larger pressure drop and energy loss in the pulmonary artery branches [96]. Although some retrograde pulmonary flow is normal, increased backward flow has been described in pulmonary hypertension. Furthermore, presence of vorticity in the pulmonary flow pattern was

![Image](image_url)

**Figure 7.** 4D flow visualization of the aortic outflow with different visualization techniques.

Velocity color coding (in cm/s) of the aortic outflow, by a velocity vector glyph representation (A and E), streamline representation (B and F) and pathline representation after forward particle tracing (C and G). 4D flow MRI data was obtained with a 3T MRI scanner in a 23 year old healthy female volunteer (A-C) (informed consent was obtained) and a 56 year old male patient with aortic valve stenosis and dilated aortic root, clinically referred for MRI. In the patient, 4D flow visualization revealed an eccentric aortic outflow jet distal to the valve stenosis (E-G) with an area of recirculating flow in the ascending aorta. Particle tracing revealed a strong helical flow pattern in the ascending aorta (G). The through-plane velocity profile was retrospectively reformatted at the level of the sinotubular junction (dotted line in A and E), and presented for a mid-systolic phase in panels D (volunteer) and H (patient). For the volunteer in D, an approximately laminar velocity profile was obtained, presenting a skewed parabolic profile with the maximal velocity shifted towards the inner curve (i.e., the left wall). The wall shear rate at the left wall was calculated at 37 s⁻¹ and at the right wall 80 s⁻¹. For the patient, backward flow was visualized in the dilated ascending aorta at the left wall, with a calculated wall shear rate of −144 s⁻¹ and at the right wall of 241 s⁻¹. LV left ventricle, Ao aorta.
correlated with pulmonary hypertension and the duration of this abnormal pattern has been correlated with mean pulmonary artery pressure [97].

A unique patient group for the clinical application of 4D flow MRI constitute patients with a Fontan palliation of their congenital heart defect. The Fontan procedure is the treatment for patients with a univentricular heart where biventricular repair is not possible. Several surgical approaches have been developed to create the connection of the superior and inferior vena cava with the right and left pulmonary artery: the total cavopulmonary connection (TCPC). However, late complications frequently occur. Etiology and risk factors for complications, including protein losing entropathy (PLE), development of pulmonary arteriovenous malformations (PAVMs), thrombosis, stenosis and aneurysms, are largely unknown. Understanding of flow patterns in the Fontan circulation might advance knowledge in the etiology of these risk factors and contribute to improvement of surgical techniques. Recent work has successfully employed 4D flow for visualizing and quantifying the distribution of caval flow towards the right and left pulmonary artery [98,99]. An unequal distribution of blood flow is associated with pulmonary arteriovenous malformations [100]. Moreover, it is possible to demonstrate kinetic energy loss due to helical flow formation in the pulmonary arteries. As can be seen in Figure 8, altered flow patterns with

Figure 8. 4D flow streamline visualization of the Fontan circulation.

Two patients who underwent surgery at the age of 5, during which a total cavopulmonary connection with an extra cardiac conduit (TCPC-EC) was made to connect the inferior (IVC) and superior vena cava (SVC) to both the left (LPA) and right pulmonary artery (RPA). In A, a 13 year old female patient is presented, with normal distribution of blood flow through the conduit without loss of kinetic energy. Stroke volumes and kinetic energy per heart beat: SVC 12 ml and 0.12 mJ, IVC 18 ml and 0.09 mJ, LPA 16 ml and 0.10 mJ, RPA 15 ml and 0.12 mJ. Total volume at the inlet of the connection was 30 ml with a kinetic energy of 0.21 mJ, and the total volume at outlet was 31 ml with kinetic energy of 0.22 mJ. In B, a 15 year old female patient is presented, with an area of recirculating flow present in the connection, proximal to the LPA, resulting in significant kinetic energy loss. Stroke volumes and kinetic energy per heart beat: SVC 21 ml and 0.25 mJ, IVC 34 ml and 2.0 mJ, LPA 26 ml and 0.41 mJ, RPA 29 ml and 0.18 mJ. Total volume at the inlet was 55 ml with kinetic energy of 2.25 mJ, total volume at outlet was 55 ml with kinetic energy of 0.59 mJ, resulting in a total kinetic energy loss of 1.66 mJ. Prior to MRI, informed consent was obtained from the patients and their parents.
related kinetic energy loss can be observed in patients with a similar extra cardial TCPC, possibly due to differences in geometry of the connection of the conduit to the pulmonary arteries.

CONCLUSION AND FUTURE PROSPECTIVE

4D flow MRI acquisition techniques improved rapidly over the last three decades. Shorter scan duration made 4D flow applicable for clinical use. The concomitant development of visualization tools such as streamlines and particle tracing enriched knowledge on blood flow hemodynamics. Intra-cardiac blood flow patterns (e.g., vortices) may possibly add to the diagnosis of diastolic dysfunction. Moreover, as increasing evidence arises that hemodynamics play an important role in vascular and myocardial remodelling, altered blood flow patterns can possibly be used to predict pathology such as aneurysm or thrombus formation and early therapy can be aimed at prevention of these pathologies. Besides qualitative interpretation of 4D flow data by visualization techniques, quantitative tools are increasingly used. Further studies are required to evaluate which hemodynamic markers will be clinically relevant and in what way 4D flow can help to improve early detection of pathology and identify response to treatment.

ACKNOWLEDGEMENTS

We would like to thank Pieter J. van den Boogaard, BSc, Mohammed El Baz, MSc., and Patrick J.H. de Koning, MSc., for their help in providing MRI data and images and Gerrit Kracht for his help with image design.
REFERENCES


4DFlow MRI techniques

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