Unravelling cardiovascular disease using four dimensional flow cardiovascular magnetic resonance

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Abstract Knowledge of normal and abnormal flow patterns in the human cardiovascular system increases our understanding of normal physiology and may help unravel the complex pathophysiological mechanisms leading to cardiovascular disease. Four-dimensional (4D) flow cardiovascular magnetic resonance (CMR) has emerged as a suitable technique that enables visualization of in vivo blood flow patterns and quantification of parameters that could potentially be of prognostic value in the disease process. In this review, current imaging processing tools that are used for comprehensive visualization and quantification of blood flow and energy distribution in the heart and great vessels will be discussed. Also, imaging biomarkers extracted from 4D flow CMR will be reviewed that have been shown to distinguish between normal and abnormal flow patterns. Furthermore, current applications of 4D flow CMR in the heart and great vessels will be discussed, showing its potential as an additional diagnostic modality which could aid in disease management and timing of surgical intervention.

Keywords 4-Dimensional flow · Cardiovascular magnetic resonance · Blood flow · Velocity

Introduction

In normal cardiovascular physiology, blood flow in the heart and great vessels shows complex and dynamic three-dimensional (3D) flow patterns, leading to efficient ejection of the blood into the pulmonary and systemic circulation [1]. Congenital or acquired heart disease causes alterations in these blood flow patterns resulting in increased energy loss [2] and reduction of the efficiency of the heart pump by over 10% [1]. Moreover, altered blood flow patterns induce changes to the endothelium, which may increase the risk for cardiovascular incidents later in life [3, 4]. Knowledge of these flow patterns increases our understanding of normal physiology and may help unravel the complex pathophysiological mechanisms leading to cardiovascular disease [1, 5]. However, these complex 3D flow patterns remain challenging to visualize and characterize. Four-dimensional (4D) flow cardiovascular magnetic resonance (CMR) has emerged as a suitable technique for comprehensive visualization and quantification of blood flow and energy distribution in the heart and great vessels in healthy subjects as well as in patients with cardiovascular disease [6].

The influence of altered aortic flow patterns on pathophysiology has been investigated most intensely in patients with a bicuspid aortic valve (BAV) [3, 7, 8] and in patients with Marfan syndrome [9–13]. For example, in patients with Marfan syndrome, flow parameters have been linked to an increased aortic size, as shown by 4D flow CMR [9–13]. Because of the complexity of the heart’s atria and ventricles, assessment of intra-cardiac blood flow characteristics is more challenging, but knowledge of such blood flow is of utmost importance in diseases like ischemic heart disease, dilated cardiomyopathy, congenital heart defects (CHD) and pulmonary hypertension.
In this review, the challenges in the application of 4D flow CMR to study hemodynamics in the cardiovascular system are discussed, as well as the visualization and quantification methods. Furthermore, current insights in normal flow patterns, flow disturbances due to cardiovascular disease and its consequences, as assessed with 4D flow CMR, will be addressed.

State of the art

Four-dimensional flow CMR, phase-contrast (PC) CMR with velocity-encoding in all three spatial directions, resolved relative to all dimensions of space and the dimension of time along the cardiac cycle, represents all directions and spatial regions of flow within the boundaries of the defined volume [14, 15].

Acquisition parameters

Recently, a consensus statement was published, stating the clinical and scientific significance of 4D flow CMR and providing recommendations for its use [15]. In this consensus statement, a list of acquisition parameter settings as a baseline 4D flow CMR protocol is proposed against which alternative protocols can be compared. Optimized parameter choices are recommended for special populations (e.g. children) or analysis of advanced flow parameters [15]. An important parameter is the Venc, which represents the maximum flow velocity that can be acquired without having to correct for phase wrapping. If the Venc is set too low, velocity aliasing will occur, however when the Venc is set too high, the level of velocity noise will increase [14]. A Venc that is set 10% higher than the maximal expected velocity is recommended [15].

Evaluation of flow patterns in the cardiac chambers requires a spatial resolution of <3.0×3.0×3.0 mm³ and <2.5×2.5×2.5 mm³ for the aorta or pulmonary artery. In order to extract feature information (i.e., stroke volume, peak velocity, peak flow rate, etc.) of flow (velocity) curves from the velocity field, a high temporal resolution is required. This resolution is defined by the repetition time, the number of velocity encodings and, in case of segmented acquisition, the number of segments. Since 4D flow CMR is to be applied to these large anatomical regions in the human body with adequate spatial and temporal resolution and potentially with some form of respiratory motion compensation, the acquisition time required to collect all this flow information is typically long (i.e., 10–25 min) and may be too demanding on patients or on the clinical workflow.

Three-directional encoding without any acceleration technique would be the most accurate approach, with the best signal-to-noise ratio (SNR) and the least amount of phase offset errors [15]. However, this is generally not feasible in a clinical setting. Therefore, to make 4D flow CMR applicable for clinical use, several methods are available to reduce acquisition time. Such accelerating techniques include parallel imaging using multi-element phased array coils (SENsitiviy Encoding, SENSE) [16] or k-t under-sampling methods like k-t BLAST (Broad-use Linear Acquisition Speed-up Technique) [17]. Acquiring read-outs of multiple k-lines per RF excitation may accelerate the acquisition as well, however, at the penalty of reducing temporal resolution and/or signal-to-noise. Furthermore, different acquisition strategies apart from the standard Cartesian k-space read-out, like echo planar imaging (EPI) [18], spiral [19] or radial [20] (e.g., PC-VIPR, vastly under-sampled isotropic projection reconstruction) read-out methods can further reduce acquisition time.

Another way to accelerate the acquisition is to acquire free-breathing 4D flow CMR with sophisticated respiratory gating or even without any respiratory motion control. Compensation of respiratory motion, which is used to reduce motion artifacts and improve accuracy, is usually difficult to achieve without significantly increasing scan duration. The most commonly used method for this motion suppression is respiratory gating by a navigator, however this increases acquisition duration substantially. Respiratory self-gating methods allow sampling of 4D flow data over the entire cardiac cycle, usually using center K₀ point, center K₀ profiles or low-resolution images to derive the breathing motion and then to adjust the acquisition scheme in real-time to reacquire motion-corrupted data, allowing free breathing while acquiring 4D flow data within clinically acceptable acquisition time [21, 22]. However, recently it was shown that 4D flow CMR without any respiratory gating may be performed while preserving accurate quantitative results from stroke volume assessment in the great vessels [23] and in whole-heart 4D flow [24].

Sources of error

Several sources of error can affect the 4D flow data and should be corrected for. Major sources of error are: eddy current effects, concomitant gradient field effects, gradient field non-linearity and phase wraps [15]. Inhomogeneities in the magnetic field and eddy current effects in the receive coil will result in background phase distortion [25]. Concomitant gradient fields are a result of Maxwell’s equations for the divergence and curl of the magnetic field and lead to background offsets [26]. Furthermore, a non-linear gradient field can induce deviations from the nominal gradient strength and orientation causing deviations in velocity quantification [27]. Some of these errors are partially corrected by reconstruction algorithms implemented on the
Magnetic Resonance Imaging (MRI) scanner software. Background phase offset errors are usually corrected by either performing a phantom velocity-encoded scan simulating static tissue and using this data set as a reference for background subtraction, or by the approach of fitting a multi-order polynomial through areas identified as static tissue, for correcting the local phase signal [28].

Finally, velocity aliasing, or phase-wrapping, will occur when blood flow velocities exceed the a priori set Venc value. The use of a phase-unwrapping algorithm is recommended prior to image analysis. Identification of abrupt phase shifts in the temporal and/or spatial domain is a common way to identify areas with phase wrapping [29]. Aliasing correction should be performed in the original source images of each individual encoding direction.

Visualization and quantification

Several tools are developed to help visualize velocity vector fields of blood flow in the heart and vessels which makes qualitative assessment of flow patterns possible. Visualization is needed in order to characterize blood flow parameters.

Most common visualization types are the vector glyph representation, or the use of streamlines or pathlines (Fig. 1). A vector glyph represents the magnitude and direction of the velocity measured from each voxel. However, a cine representation of vector data may be difficult to interpret, as data may quickly become cluttered.

Streamlines are curves which are tangent to the velocity direction at a particular point in time, representing the blood flow direction at an instant of time [30, 31]. Streamline visualization can be used for visualization of inflow and outflow direction, regurgitant jets and circulating flow patterns at specific time points in the cardiac cycle [32, 33]. In the aorta, streamline visualization is often used to show helical flow patterns [34]. Streamline visualization in combination with retrospective valve tracking allows for accurate quantification of net flow volumes through each of the four heart valves (Fig. 2) [35, 36]. Retrospective valve tracking is a method in which the scanned 3D volume is retrospectively reformatted into two-dimensional (2D) measurement planes with through-plane velocity encoding to allow for transvalvular flow quantification [35, 36]. Measurement planes can be adjusted per individual phase, following the valve position, inflow direction and the dynamically changing
Optimized positioning of these planes should be based on the direction of the peak velocity visualized by streamlines [37].

Different from streamlines, pathlines show the path a particle (i.e., a voxel) has followed over time [30]. Particle paths or pathlines are generated by backward/forward particle tracing using integration methods to calculate displacement from the velocity data [30]. For intra-cardiac blood flow, typically, at end diastole, each voxel inside the LV is considered to represent a seed point (i.e., a particle). Pathlines are then calculated by integration over time: backward tracing over the diastole and forward tracing over systole. Pathlines are also frequently used to evaluate complex flow patterns, such as helical flow patterns in the aorta and pulmonary artery [34, 38].

Another unique feature of particle tracing in intra-cardiac blood flow is the possibility to discriminate different parts of blood flow with some specific functional property based on where the seed points are flowing towards and where they came from. Different components in the blood flow organization in the left ventricle (LV) [39] and the right ventricle (RV) [40] can be discriminated, such as the 4-component evaluation (Fig. 3) as introduced by Bolger et al. [41] for the LV:

1. **Direct flow** blood that enters the LV through the mitral valve during diastole and is ejected from the LV into the aorta during the subsequent systole in the analysed heartbeat;
2. **Retained inflow** blood that enters the LV during diastole but is not ejected during the subsequent systole in the analysed heartbeat;
3. **Delayed ejection flow** blood that starts and remains inside the LV during diastole but is ejected during the subsequent systole;
4. **Residual volume** blood that remains within the LV for at least two subsequent cardiac cycles.

A fifth component can be added, **Regurgitation** blood that leaves the LV through the mitral valve into the atrium during systole [42]. It should be taken into account that particle tracing analysis requires high temporal resolution and adequate signal-to-noise, as results coming from an integration procedure on noisy data and over large time steps may not be reliable.

From the 3D flow velocity field, helical and vortical flow patterns can be identified in normal and pathological blood flow. An important intra-cardiac flow pattern is vortex flow: a group of fluid particles swirling around a common axis. Two methods have been used to analyze and visualize intra-cardiac vortex flow patterns: Lagrangian and Eulerian. Lagrangian coherent structures (LCS) can be used to quantify and visualize the total amount of flow that entrains into a vortex ring flow structure over a period of time [43]. Eulerian vortex core analysis allows quantitative characterization of instantaneous 3D vortical flow patterns and its intra-cardiac evolution over time [44]. Altered intra-cardiac 3D vortex flow properties have been identified in
the presence of abnormal valvular morphology and were associated with adverse blood flow efficiency [2, 44, 45].

Four-dimensional flow CMR is also used for studying energetics in the blood flow. The kinetic energy (KE) of a moving particle with a certain mass \( m \) (particle volume multiplied by the blood density) and velocity \( v \), can be calculated with the formula \( \frac{1}{2}mv^2 \). The KE at a specific time point can then be calculated by summing the KE of each voxel within a specified anatomical region. Viscous energy loss (EL) is the kinetic energy that is lost due to frictional forces among blood particles and surrounding structures in the ventricle, induced by the blood viscosity. EL can be calculated from the Navier–Stokes energy equations [2]. Turbulent kinetic energy (TKE) is another frequently used energy parameter used to quantify the energy lost due to turbulent flow and is calculated from dedicated reconstructions of the intravoxel distribution of spin velocities [46].

Wall shear stress (WSS) is a quantitative value for the shear forces of the blood flow acting on the vessel wall [47]. It can be used to quantify the impact of flow on the vessel wall and it has been shown to correlate with changes in the extracellular matrix (ECM) and endothelial cells [3]. Higher blood flow velocity will increase WSS [48].

Aortic wall elasticity, an important mechanical property of the vascular wall, can be measured with traditional 2D one-directional velocity-encoded CMR. [49] but also by multi-directional velocity-encoding or 4D flow CMR, [50] by measuring the propagation speed of the systolic wave front along the course of the aorta. This biomarker for arterial stiffness is called the pulse wave velocity (PWV) [51]. A shorter propagation time, thus higher PWV, is indicative of a stiffer aorta and presence of atherosclerosis [52].

Applications

In the following section normal and abnormal blood flow characteristics as assessed with 4D flow CMR will be reviewed. We will describe the use of 4D flow CMR in assessing normal intra-cardiac and intravascular flow patterns, as well as applications in acquired and congenital cardiovascular disease.
Atrial flow patterns

In the normal human heart, blood flow in the left atrium (LA) follows specific paths from the pulmonary veins to the mitral valve. The occurrence of atrial vortices has been shown, which may be beneficial in avoiding atrial stasis [53]. In the LA, inflow from the right pulmonary veins follows the atrial wall from its inlet near the interatrial septum toward the mitral annulus, while inflow from the left pulmonary veins suddenly shifts towards the mitral valve after entry through the lateral left atrial wall, as was shown with particle tracing analysis [53]. In the right atrium (RA), blood flow from the inferior vena cava (IVC) and superior vena cava (SVC) turns anterior after entering the atrium, which causes a forward rotating movement of the anterior part of the right atrial blood volume towards the inlet of the tricuspid valve [54].

Assessment of atrial flow patterns and blood flow velocity is important in patients with atrial fibrillation (AF), since AF is associated with an increased risk of embolic stroke due to thrombus formation in the LA [55]. Patients with AF show global and regional changes in atrial flow dynamics, such as decreased blood flow velocities and increased stasis, which can be evaluated with 4D flow CMR and could be a helpful indicator in risk assessment for thrombogenesis in these patients [56–58].

In patients with mitral regurgitation, severely disturbed flow patterns in the LA with elevated values of TKE develop, related to the severity of regurgitation [59]. These atrial flow effects of mitral regurgitation assessed by 4D flow CMR could potentially be used in risk assessment for the onset of decompensated heart failure in patients with prior asymptomatic mitral regurgitation [59]. The amount and severity of mitral valve regurgitation (i.e., the regurgitant flow volume and the regurgitant flow fraction) can accurately be assessed with the use of 4D flow CMR with retrospective valve tracking [35, 36].

In corrected atrioventricular septal defect (AVSD) patients, regurgitation of the left atrioventricular valve (LAVV) is common [60]. In these patients, the regurgitant jets are dynamic and eccentric (Fig. 2) and have a non-circular cross-sectional shape, which makes them challenging to quantify with echocardiography [61]. However, the regurgitant fraction and the volume of the complex regurgitant jets can be quantified accurately with the use of 4D flow CMR with retrospective valve tracking [33]. Furthermore, 4D flow CMR can also be applied to investigate intra-cardiac baffle constructions for leakage and obstruction, for instance after double switch operation for congenitally corrected transposition of the great arteries [62].

Flow patterns in the left ventricle

The complex geometry of the normal left ventricle (LV) causes asymmetric blood flow, which promotes efficient ejection of blood in the systemic circulation and minimizes the energy dissipation [1, 54]. In the normal LV, 30–35% of the LV end diastolic volume represents blood flow that enters the LV during diastole and is ejected into the aorta during systole in the subsequent heartbeat (i.e. direct flow) [39, 42]. Using 4D flow CMR, vortical flow patterns have been described that form distal to the mitral valve, with a close relation to the motion of the anterior mitral leaflet and the shape of mitral inflow [43, 44, 63]. During diastole, a pair of counter rotating vortices has been consistently reported to form distal to the mitral valve. In three-dimensions, this pair of vortices extend to form a ring-like vortex shape. 4D Flow CMR has enabled the characterization of the instantaneous time-evolution of 3D vortex ring flow within the LV over the complete diastole [44]. Formation of vortex ring flow has been suggested to help efficient MV closure and diastolic filling, minimize kinetic energy loss and prevent thrombus formation [1, 54, 64, 65]. Vortex flow patterns can change due to age, gender, blood pressure, ventricular geometry and mitral/atrioventricular valve abnormalities [45, 66].

In patients after AVSD correction, the LV inflow over the trans-left atrioventricular valve (LAVV) is altered (i.e., a more lateral inflow was shown by streamline visualization) (Fig. 2) [32]. 4D flow CMR with particle tracking showed that this altered inflow after AVSD correction also affected the intra-cardiac flow organization, which presented as reduced direct flow and increased retained inflow in the apical and lateral region of the LV cavity [42]. Despite that global cardiac function parameters (including ejection fraction, end diastolic volume, stroke volume and cardiac output) were within the normal range in these patients, significantly altered vortex ring flow properties were found and associated with a 2–4 fold increase in viscous energy loss levels compared to healthy volunteers [2, 45]. This might indicate that properties of vortex ring flow within LV blood flow could be a subclinical marker of cardiac (dys)function preceding decline in global functional parameters [2].

In patients with systolic or diastolic dysfunction, flow disturbances can be evaluated with 4D flow CMR imaging. LV diastolic dysfunction in patients with normal systolic LV function is a risk factor for mortality [67]. LV diastolic function parameters, such as early (E) and late (A) filling rates, E/A ratio, and E-peak acceleration and deceleration duration, can be assessed accurately with the use of 4D flow CMR with retrospective valve tracking [68]. Furthermore, a study using 4D flow CMR with color vector visualization showed that in patients with various stages of
diastolic dysfunction, LV diastolic flow only extends a short
distance in the LV and stops in the middle of the LV cav-
ity due to decreased flow acceleration [69]. Patients with
dilated cardiomyopathy showed a smaller direct flow vol-
ume and greater end-diastolic KE distribution in the resid-
ual volume, despite normal LV stroke volume, as shown by
particle tracing analysis with the 4-component model [70].
Whereas, in patients with ischemic dilated cardiomyopathy,
altered flow patterns were related to complex and asymmet-
ric vortex rings and decreased vortex volume [43].

Patients who have had a Fontan operation, a palliative
treatment for patients with single-ventricle physiology,
have complex and heterogeneous underlying ventricu-
lar morphologies which makes studying the intra-cardiac
blood flow in these patients challenging. However, the
dynamic and 3D nature of the blood flow in these patients
makes 4D flow CMR particularly suitable for the assess-
ment and quantification of these flow patterns. Recently,
various blood flow patterns were shown in these patients
with 4D flow CMR with streamline visualization and
inflow volumes were quantified with retrospective valve
tracking [37]. Assessment of the caval blood flow in these
complex patients will be addressed in the section on intra-
vascular blood flow patterns.

Flow patterns in the right ventricle

Visualization of flow in the right ventricle (RV) remains
challenging because of the complex 3D shape of this ven-
tricular cavity. In vivo and in vitro studies showed that in
the normal RV, blood flow rearranges along the converging
outflow tract during systole to form helical circulating
flow towards the pulmonary orifice [5, 40, 54]. Particle
tracing analysis in the RV showed that 44% of the blood is
direct flow, which moves from the RA into the RV during
diastole and moves towards the RV outflow tract, rounding
the infundibular septum and contributing to vortical forma-
tion that extends in the outflow tract [40]. Compared to the
other flow components, this direct flow possesses a larger
presystolic KE, which may benefit the efficiency of systolic
ejection [40].

Extensive knowledge of the RV flow and function is
of interest in many types of heart defects, especially in
patients with CHD, as lesions affecting the RV are an inde-
pendent risk factor for early attrition [71]. For example,
patients with Tetralogy of Fallot (ToF) have altered RV
flow patterns resulting in increased vortical flow patterns in
the RA and RV during diastole [72]. Accurate assessment
of forward flow and regurgitation fraction over the tricuspid
and pulmonary valve in these ToF patients after corrective
surgery, which is important in the assessment of RV dias-
tolic functional impairment, can be performed using 4D
flow CMR with retrospective valve tracking [73].

In patients with pulmonary hypertension (PH), RV dias-
tolic dysfunction (RVDD) is an important prognostic factor
[74]. Recently, it was shown by 4D flow CMR that patients
with RVDD due to PH have altered vorticity in the RV at
peak E- and A-diastolic filling. The presence of altered RV
vorticity could be a valuable marker to evaluate the risk of
RVDD development, as it was shown to have a clear rela-
tionship [75]. Furthermore, 4D flow CMR showed that PH
is related to altered KE RV work density (i.e., a measure of
the amount of work the RV has produce to transport blood
from RA to the pulmonary artery) and viscous energy loss
in the blood flow in the pulmonary artery,[76] which is also
shown to be related to increased vorticity in the blood flow
in the pulmonary artery [77].

In patients with ischemic heart disease, 4D flow CMR
could be used to detect impairment of RV function, as
shown by changes in flow distribution and KE, which could
potentially have prognostic implications [78].

Flow patterns in the great vessels

Aorta

Normal aortic flow patterns include right-handed heli-
cal outflow and late systolic retrograde flow (blood flow-
ing counter to the main forward stream), as shown by 4D
flow CMR [34, 79]. This helical and retrograde flow results
from the curvature of the arch, the pulsatility of the blood
flow and the compliance of the aortic wall [79]. Aging has
been shown to influence flow patterns in several ways;
direction of the helical flow may change from right-handed
to left-handed, [80, 81] the aortic velocity distribution may
change, resulting in changing WSS maps [82–84] and PWV
values along the aorta increase [85, 86]. Therefore, age has
to be taken into account when evaluating aortic flow pat-
terns in healthy subjects and patients with cardiovascular
disease.

The application of 4D flow CMR in patients with aor-
tic disease is promising as it can help gain knowledge of
the disease progression, it can aid the prediction of adverse
aortic events and can be useful in the optimization of indi-
vidualized management strategies. Most extensive aortic
4D flow research has been done in patients with BAV [3, 7,
8] and Marfan syndrome [9–13].

Patients with BAV frequently develop aortic valve dys-
function, ascending aortic aneurysms, and aortic dissec-
tion. For many years, aortic dilatation in these patients has
been attributed to the genetic susceptibility resulting in a
concomitant abnormal development of the ascending aorta
and BAV. 4D flow CMR shed another light on this hypo-
thesis by identifying different abnormal outflow patterns in
the ascending aorta (Fig. 4) that might predispose to this
aortopathy [7, 8]. Recently, it has been shown that different
fusion patterns of the aortic valve will lead to different impingement flow jets on the ascending aortic wall [3, 8]. Fusion of right and left leaflets causes right-handed helical flow and right-anterior flow jets, while right and non-coronary leaflet fusion causes left-handed helical flow with left-posterior flow jets [8]. These regions of altered flow patterns show elevated WSS which correlates well with extracellular matrix changes in that aortic region [3]. This suggests a hemodynamic contribution to the aortopathy.

In patients with Marfan syndrome, an inherited connective tissue disease at risk for thoracic aortic dilatation, local helix flow in the ascending aorta as well as abnormal regional WSS has been linked to increased aortic size [9–11]. Furthermore, in young patients with Marfan syndrome, hemodynamic differences in WSS were found at specific regions along the thoracic aorta that correspond to the locations where aortic dissection and aortic rupture often originate in these patients, i.e., the proximal ascending aorta and proximal descending aorta [13]. These data, together with the report of a single Marfan syndrome case in which prior to an aortic dissection type B, formation of abnormal flow patterns and altered WSS in the proximal descending aorta was observed, suggest that hemodynamic factors may play a predictive role in the onset of adverse events [12].

In patients with coarctation of the aorta (CoA), a short segment of narrowing of the proximal descending aorta just beyond the origin of the arteries that supply the head and arms, 4D flow CMR is an accurate method for the evaluation of collateral flow, which is related to hemodynamic significant coarctation [87]. Also, altered flow patterns and increased WSS can be found in patients with CoA in the entire aorta, before and after repair (Fig. 5) [88]. Other promising applications of aortic 4D flow CMR are related to noninvasive investigation of trans-stenotic pressure gradients in the presence of stenosis in vascular diseases such as aortic CoA [89, 90]. Today, severity of stenosis in CoA is estimated by ultrasonography but the pressure gradients are often overestimated compared to the actual measurements in vivo per catheter. This potentially leads to unnecessary early interventions, with its risk for the need of more complex and increased amount of re-interventions per patient. Thus, predicting the need and timing of intervention for aortic CoA non-invasively can be optimized with 4D flow CMR. Furthermore, energy losses that appears in these turbulent flow conditions can be quantified and maps for dissipation of kinetic energy can be created [91, 92]. These applications make it possible to simulate with advanced post-processing software (by virtual interventions) which intervention preserves the natural thoracic aortic function the most, prior to the intervention [93].

**Pulmonary artery**

In normal pulmonary physiology, two counter-rotating helical flow structures in the main pulmonary artery (PA) were shown with 4D flow CMR, which both contribute mainly to the flow in the right pulmonary artery (RPA) [94]. In early
systole, blood flow from the right side of the PA is distributed to the RPA and blood flow from the left side of the PA is distributed to the left pulmonary artery (LPA), while later in systole blood flow from the left posterior side of the PA is distributed to the RPA as shown by streamline visualization [94]. Changes in the pulmonary blood flow are age dependent, which may be helpful in future studies in understanding pathological blood flow in patients with pulmonary disease [95].

Patients with pulmonary hypertension (PH) are currently diagnosed when mean pulmonary artery pressure (mPAP), measured invasively by right heart catheterization, exceeds 25 mmHg [96]. 4D flow CMR with streamline visualization showed abnormal vortical flow in the main PA of these patients. The presence, and in particular the duration of vortical flow presence, could become a useful noninvasive diagnostic marker as it has been shown to correlate well with mPAP [77]. Also, a decrease in vorticity in the main PA and RPA as assessed by 4D flow CMR was recently associated with an increase in pulmonary vascular resistance (PVR) in patients with PH [97].

Altered flow patterns have also been described with 4D flow CMR in the PA of patients with repaired ToF [72]. The increase of these abnormal flow patterns, specifically helical and vortical flow, could be related to the size of the pulmonary arteries or increased PVR and elevated PAP [72].

In patients with a Fontan circulation, blood flows passively from the IVC and SVC to the pulmonary arteries without passing through a ventricle. As expected, this results in altered pulmonary and caval blood flow patterns [38]. As these patients require lifelong follow-up, accurate visualization and quantification of flow patterns is crucial. Several 4D flow CMR studies have shown that blood flow from the SVC favors the right pulmonary artery (RPA), while most of the IVC blood flows to the left pulmonary artery (LPA), as shown by particle tracing analysis [98, 99]. Recently it was shown that the cross-sectional area of the pulmonary arteries in these patients is related to altered flow distribution [99]. The study of caval blood flow distribution could help to identify the patients at risk for Fontan failure or the development of pulmonary arteriovenous malformations, an important complication in these patients leading to systemic oxygen desaturation [100].

Conclusions and future application/advances

In the recent years, 4D flow CMR has emerged as a suitable technique for research use and several studies have shown its clinical value in patients with congenital and acquired heart disease. Shorter acquisition duration has made application feasible in the clinic. However, dedicated studies investigating the reproducibility and reliability of some of the 4D flow CMR parameters are still warranted before 4D flow CMR can be applied in daily clinical practice. In this review, we showed the different advantages and possibilities of 4D flow CMR, intra-cardiac as well as intravascular. Knowledge of normal and abnormal blood flow has increased the understanding of normal physiology and is necessary for the distinction between cardiovascular health and disease. 4D flow CMR is a promising additional diagnostic tool that could aid in management of cardiovascular disease and timing of surgical intervention. Furthermore, 4D flow CMR gives the opportunity to further unravel the influence of different surgical reconstruction methods on the cardiac and vascular function. However, longitudinal follow-up studies are needed to clarify the clinical value of 4D flow CMR-derived hemodynamic factors for risk stratification. Other future applications include the use of 4D flow CMR in the assessment of blood flow patterns in coronary arteries, which is currently still too challenging because of demands regarding the high spatial resolution needed for such small vessels and stringent necessity of cardiac motion correction. However, this application might become feasible when further improvements in hardware and imaging at high field strength become available.
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Compliance with ethical standards

Conflict of interest We have no conflicts of interest to disclose.

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References

1. Pedrizzetti G, Domenichini F (2005) Nature optimizes the swirling flow in the human left ventricle. Phys Rev Lett 95(10):108101. doi:10.1103/PhysRevLett.95.108101
2. Elbaz MS, van der Geest RJ, Calkoen EE, de Roos A, Lelieveldt BP, Roest AA, Westenberg JJ (2016) Assessment of viscous energy loss and the association with three-dimensional vortex ring formation in left ventricular inflow: in vivo evaluation using four-dimensional flow MRI. Magn Reson Med. doi:10.1002/mrm.26129
3. Guzzi DG, Barker AJ, van Ooij P, Malaisrie SC, Puthuman JJ, Belke DD, Mewhort HE, Svystonyuk DA, Kang S, Verma S, Collins J, Carr J, Bonow RO, Markl M, Thomas JD, McCarthy PM, Fedak PW (2015) Valve-related hemodynamics mediate human bicuspid aortopathy: insights from wall shear stress mapping. J Am Coll Cardiol 66(8):892–900. doi:10.1016/j.jacc.2015.06.1310
4. Sby HJ, Hsieh HJ, Usami S, Chien S (1994) Fluid shear stress induces a biphasic response of human monocyte chemotactic protein 1 gene expression in vascular endothelium. Proc Natl Acad Sci USA 91(11):4678–4682
5. Manjoo JG, Domenichini F, Pedrizzetti G (2012) Describing the highly three dimensional right ventricle flow. Ann Biomed Eng 40(8):1790–1801. doi:10.1007/s10439-012-0540-5
6. Markl M, Chan FP, Alley MT, Wedding KL, Draney MT, Elkins CJ, Parker DW, Wicker R, Taylor CA, Herfkens RJ, Pelc NJ (2003) Time-resolved three-dimensional phase-contrast MRI. J Magn Reson Imaging 17(4):499–506. doi:10.1002/jmri.10727
7. Barker AJ, Markl M, Burkh J, Lorenz R, Bock J, Bauer S, Schulz-Menger J, von Knobelsdorff-Brenkenhoff F (2012) Bicuspid aortic valve is associated with altered wall shear stress in the ascending aorta. Circ Cardiovasc Imaging 5(4):457–466. doi:10.1161/CIRCIMAGING.112.973370
8. Hope MD, Hope TA, Meadows AK, Ordovas KG, Urbach TH, Alley MT, Higgins CB (2010) Bicuspid aortic valve: four-dimensional MR evaluation of ascending aortic systolic flow patterns. Radiology 255(1):53–61. doi:10.1148/radiol.09091437
9. Geiger J, Markl M, Herzer L, Hirtler D, Loeffelbein F, Stiller B, Langer M, Arnold R (2012) Aortic flow patterns in patients with Marfan syndrome assessed by flow-sensitive four-dimensional MRI. J Magn Reson Imaging 35(3):594–600. doi:10.1002/jmri.23500
10. Kroner ES, Scholte AJ, de Koning PJ, van den Boogaard PJ, Kroft LJ, van der Geest RJ, Hilhorst-Hofstee Y, Lamb HJ, Siebelink HM, Mulder BJ, Groenink M, Radonic T, van der Wall EE, de Roos A, Reiber JH, Westenberg JJ (2013) MRI assessed regional pulse wave velocity for predicting absence of regional aorta luminal growth in marfan syndrome. Int J Cardiol 167(6):2977–2982. doi:10.1016/j.ijcard.2012.08.057
11. Wang HH, Chiu HH, Tseng WY, Peng HH (2016) Does altered aortic flow in marfan syndrome relate to aortic root dilatation? J Magn Reson Imaging 44(2):500–508. doi:10.1002/jmri.25174
12. Hope TA, Kvitting JP, Hope MD, Miller DC, Markl M, Herfkens RJ (2013) Evaluation of Marfan patients status post valve-sparing aortic root replacement with 4D flow. Magn Reson Imaging 31(9):1479–1484. doi:10.1016/j.mri.2013.04.003
13. Geiger J, Arnold R, Herzer L, Hirtler D, Stankovic Z, Russe M, Langer M, Markl M (2013) Aortic wall shear stress in Marfan syndrome. Magn Reson Med 70(4):1137–1144. doi:10.1002/mrm.24562
14. Pelc NJ, Herfkens RJ, Shimakawa A, Enzmann DR (1991) Phase contrast cine magnetic resonance imaging. Magn Reson Q 7(4):229–254
15. Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carthall CJ, Ebbers T, Francis CJ, Frualychowicz A, Geiger J, Giese D, Hope MD, Kilner PJ, Kozerke S, Myerson S, Neubauer S, Wiesen O, Markl M (2015) 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson 17:72. doi:10.1186/s12968-015-0174-5
16. Thunberg P, Karlsson S, Wigstrom L (2003) Accuracy and reproducibility in phase contrast imaging using SENSE. Magn Reson Med 50(5):1061–1068. doi:10.1002/mrm.10634
17. Baltes C, Kozerke S, Hansen MS, Pruessmann KP, Taso J, Boesiger P (2005) Accelerating cine phase-contrast flow measurements using k-t BLAST and k-t SENSE. Magn Reson Med 54(6):1430–1438. doi:10.1002/mrm.20730
18. Firmin DN, Klipstein RH, Hounsfield GL, Paley MP, Longmore DB (1989) Echo-planar high-resolution flow velocity mapping. Magn Reson Med 12(3):316–327
19. Sigfridsson A, Petersson S, Carthall CJ, Ebbers T (2012) Four-dimensional flow MRI using spiral acquisition. Magn Reson Med 68(4):1065–1073. doi:10.1002/mrm.22397
20. Gru T, Koroce, P. R., Fawcett, W. R., Baid, J., Turk Q, Lum D, Zhou Y, Grist TM, Haughton V, Mistretta CA (2005) PC VIPR: a high-speed 3D phase-contrast method for flow quantification and high-resolution angiography. AJNR Am J Neuroradiol 26(4):743–749
21. Uribi S, Beeraum P, Sorensen TS, Rasmusson A, Razavi R, Schaefter T (2009) Four-dimensional (4D) flow of the whole heart and great vessels using real-time respiratory self-gating. Magn Reson Med 62(4):984–992. doi:10.1002/mrm.22090
22. Uribi S, Muthurangu V, Boubertakh R, Schaefter T, Razavi R, Hill DL, Hansen MS (2007) Whole-heart cine MRI using real-time respiratory self-gating. Magn Reson Med 57(3):606–613. doi:10.1002/mrm.21156
23. Nordmeyer S, Riesenkampff E, Crelier G, Khasheei A, Schnackenburg B, Berger F, Kuehne T (2010) Flow-sensitive four-dimensional cine magnetic resonance imaging for offline blood flow quantification in multiple vessels: a validation study. J Magn Reson Imaging 32(3):677–683. doi:10.1002/jmri.22280
24. Kanski M, Toger J, Steding-Ehrenborg K, Xanthis C, Bloch KM, Heiberg E, Carlsson M, Arheden H (2015) Whole-heart four-dimensional flow can be acquired with preserved quality without respiratory gating, facilitating clinical use: a head-to-head comparison. BMC Med Imaging 15:20. doi:10.1186/s12880-015-0061-4

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25. Walker PG, Cranney GB, Scheidegger MB, Waseleski G, Pohost GM, Yogananthan AP (1993) Semiautomated method for noise reduction and background phase error correction in MR phase velocity data. J Magn Reson Imaging 3(3):521–530
26. Bernstein MA, Zhou XJ, Polzin JA, King LF, Ganin A, Pelc NJ, Glover GH (1998) Concomitant gradient terms in phase contrast MR: analysis and correction. Magnetic Reson Med 39(2):300–308
27. Markl M, Bammer R, Alley MT, Enckis J, Draney MT, Barnett A, Moseley ME, Glover GH, Pelc NJ (2003) Generalized reconstruction of phase contrast MRI: analysis and correction of the effect of gradient field distortions. Magnetic Reson Med 50(4):791–801. doi:10.1002/mrm.10582
28. Gatehouse PD, Rolf MP, Graves MJ, Hofman MB, Totman J, Werner B, Quest RA, Liu Y, von Spiczak J, Dieringer M, Firmin DN, van Rossum A, Lombardi M, Schwitter J, Schulz-Menger J, Kilner PJ (2010) Flow measurement by cardiovascular magnetic resonance: a multi-centre multi-vendor study of background phase offset errors that can compromise the accuracy of derived regurgitant or shunt flow measurements. J Cardiovasc Magn Reson 12:5. doi:10.1186/1532-429X-12-5
29. Lotz J, Meier C, Leppert A, Galanski M (2002) Cardiovascular flow measurement with phase-contrast MR imaging: basic facts and implementation. Radiographics 22(3):651–671. doi:10.1148/radiographics.22.3.g02ma11651
30. Buonocore MH (1998) Visualizing blood flow patterns using streamlines, arrows, and particle paths. Magnetic Reson Med 40(2):210–226
31. Napel S, Lee DH, Frayne R, Rutt BK (1992) Visualizing three-dimensional flow with simulated streamlines and three-dimensional phase-contrast MR imaging. J Magn Reson Imaging 2(2):143–153
32. Calkoen EE, Roest AA, Kroft LJ, van der Geest RJ, Jongbloed MR, van den Boogaard PJ, Blom NA, Hazeekamp MG, de Roos A, Westenberg JG (2015) Characterization and improved quantification of left ventricular inflow using streamline visualization with 4DFlow MRI in healthy controls and patients after atrioventricular septal defect correction. J Magn Reson Imaging 41(6):1512–1520. doi:10.1002/jmri.24735
33. Calkoen EE, Westenberg JG, Kroft LJ, Blom NA, Hazeekamp MG, Rijlaardsdam ME, Jongbloed MR, de Roos A, Roest AA (2015) Characterization and quantification of dynamic eccentric regurgitation of the left atrioventricular valve after atrioventricular septal defect correction with 4D Flow cardiovascular magnetic resonance and retrospective valve tracking. J Cardiovasc Magn Reson 17:18. doi:10.1186/s12968-015-0122-4
34. Markl M, Draney MT, Hope MD, Levin JM, Chan FP, Alley MT, Pelc NJ, Herfkens RJ (2004) Time-resolved 3-dimensional velocity mapping in the thoracic aorta: visualization of 3-directional blood flow patterns in healthy volunteers and patients. J Comput Assist Tomogr 28(4):459–468
35. Roes SD, Hammer S, van der Geest RJ, Marsan NA, Bax JJ, Lamb HJ, Reiber JH, de Roos A, Westenberg JG (2009) Flow assessment through four heart valves simultaneously using 3-dimensional 3-directional velocity-encoded magnetic resonance imaging with retrospective valve tracking in healthy volunteers and patients with valvular regurgitation. Invest Radiol 44(10):669–675. doi:10.1097/RLI.0b013e3181ae99b5
36. Westenberg JG, Roes SD, Ajmone Marsan N, Binnendijk NM, Doornbos I, Bax JJ, Reiber JH, de Roos A, van der Geest RJ (2008) Mitral valve and tricuspid valve blood flow: accurate quantification with 3D velocity-encoded MR imaging with retrospective valve tracking. Radiology 249(3):792–800. doi:10.1148/radiol.2492080146
37. She HL, Roest AA, Calkoen EE, van den Boogaard PJ, van der Geest RJ, Hazeekamp MG, de Roos A, Westenberg JJ (2016) Comparative evaluation of flow quantification across the atrioventricular valve in patients with functional univentricular heart after Fontan’s surgery and healthy controls: measurement by 4D flow magnetic resonance imaging and streamline visualization. Congenital Heart Dis. doi:10.1111/chd.12397
38. Houtzager JH, Westenberg JJ, de Koning PJ, Hazeekamp MG, Roest AA (2014) Helical flow pattern in the right pulmonary artery after Fontan palliation. Eur Heart J Cardiovasc Imaging 15(10):1183. doi:10.1093/ehjci/jet096
39. Eriksson J, Carlhall CJ, Dyverfeldt P, Engvall J, Bolger AF, Ebbets T (2010) Semi-automatic quantification of 4D left ventricular blood flow. J Cardiovasc Magn Reson 12:9. doi:10.1186/1532-429X-12-9
40. Fredriksson AG, Zajac J, Eriksson J, Dyverfeldt P, Bolger AF, Ebbets T, Carlhall CJ (2011) 4-D blood flow in the human right ventricle. Am J Physiol Heart Circ Physiol 301(6):H2344–H2350. doi:10.1152/ajpheart.00622.2011
41. Bolger AF, Heiberg E, Karlsson M, Wigstrom L, Engvall J, Sigfridsson A, Ebbets T, Kvitving JP, Carlhall CJ, Wranne B (2007) Transit of blood flow through the human left ventricle mapped by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 9(5):741–747. doi:10.1089/jmri.2007.0748
42. Calkoen EE, de Koning PJ, Blom NA, Kroft LJ, de Roos A, Wolterbeek R, Roest AA, Westenberg JG (2015) Disturbed intracardiac flow organization after atrioventricular septal defect correction as assessed with 4D flow magnetic resonance imaging and quantitative particle tracing. Invest Radiol 50(12):850–857. doi:10.1097/RLI.0000000000000194
43. Toger J, Kanski M, Carlsson M, Kovacs SJ, Soderlind G, Arheden H, Heiberg E (2012) Vortex ring formation in the left ventricle of the heart: analysis by 4D flow MRI and Lagrangian coherent structures. Ann Biomed Eng 40(12):2652–2662. doi:10.1007/s10439-012-0615-3
44. Elbaz MS, Calkoen EE, Westenberg JJ, Lelièvelld BP, Roest AA, van der Geest RJ (2014) Vortex flow during early and late left ventricular filling in normal subjects: quantitative characterization using retrospectively-gated 4D flow cardiovascular magnetic resonance and three-dimensional vortex core analysis. J Cardiovasc Magn Reson 16:78. doi:10.1186/s12968-014-0078-9
45. Calkoen EE, Elbaz MS, Westenberg JJ, Kroft LJ, Hazeekamp MG, Roest AA, van der Geest RJ (2015) Altered left ventricular vortex ring formation by 4-dimensional flow magnetic resonance imaging after repair of atrioventricular septal defects. J Thorac Cardiovasc Surg. doi:10.1016/j.jtcvs.2015.07.048
46. Dyverfeldt P, Kvitving JP, Sigfridsson A, Engvall J, Bolger AF, Ebbets T (2008) Assessment of fluctuating velocities in disturbed cardiovascular blood flow: in vivo feasibility of generalized phase-contrast MRI. J Magn Reson Imaging 28(3):655–663. doi:10.1002/jmri.21475
47. Frydrychowicz A, Stalder AF, Russe MF, Bock J, Bauer S, Harloff A, Berger A, Langer M, Hennig J, Markl M (2009) Three-dimensional analysis of segmental wall shear stress in the aorta by flow-sensitive four-dimensional-MRI. J Magn Reson Imaging 30(1):77–84. doi:10.1002/jmri.21790
48. Burk J, Blanke P, Stankovic Z, Barker A, Russe M, Geiger J, Frydrychowicz A, Langer M, Markl M (2012) Evaluation of 3D blood flow patterns and wall shear stress in the normal and dilated thoracic aorta using flow-sensitive 4D CMR. J Cardiovasc Magn Reson 14:84. doi:10.1186/1532-429X-14-84
49. Grotenhuis HB, Westenberg JJ, Steendijk P, van der Geest RJ, Ottenkamp J, Bax JJ, Jukema JW, de Roos A (2009) Validation and reproducibility of aortic pulse wave velocity as assessed with velocity-encoded MRI. J Magn Reson Imaging 30(3):521–526. doi:10.1002/jmri.21886
50. Westenberg JJ, de Roos A, Grotenhuis HB, Steendijk P, Hendriksen D, van den Boogaard PJ, van der Geest RJ, Bax JJ, Jukema JW, Reiber JH (2010) Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. J Magn Reson Imaging 32(5):1086–1094. doi:10.1007/s00239-010-1050-y

51. Markl M, Wallis W, Brendecke S, Simon J, Frydrychowicz A, Harloff A (2010) Estimation of global aortic pulse wave velocity by flow-sensitive 4D MRI. Magnetic Reson Med 63(6):1575–1582. doi:10.1002/mrm.22353

52. Blacher J, Asmar R, Djane S, Simon J, Frydrychowicz A, Harloff A (2010) Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. J Magn Reson Imaging 32(5):1086–1094. doi:10.1007/s00239-010-1050-y

53. Markl M, Wallis W, Brendecke S, Simon J, Frydrychowicz A, Harloff A (2010) Estimation of global aortic pulse wave velocity by flow-sensitive 4D MRI. Magnetic Reson Med 63(6):1575–1582. doi:10.1002/mrm.22353

54. Blacher J, Asmar R, Djane S, Simon J, Frydrychowicz A, Harloff A (2010) Improved aortic pulse wave velocity assessment from multislice two-directional in-plane velocity-encoded magnetic resonance imaging. J Magn Reson Imaging 32(5):1086–1094. doi:10.1007/s00239-010-1050-y
pulmonary artery as a marker of pulmonary hypertension and a measure of elevated mean pulmonary arterial pressure. Circu Cardiovasc Imaging 1(1):23–30. doi:10.1161/CIRCIMAGING.108.780247

78. Fredriksson AG, Svalbring E, Eriksson J, Dyverfeldt P, Allehagen U, Engvall J, Ebbers T, Carlhall CJ (2016) 4D flow MRI can detect subtle right ventricular dysfunction in primary left ventricular disease. J Magn Reson Imaging 43(3):558–565. doi:10.1002/jmri.25015

79. Kilner PJ, Yang GZ, Mohiaddin RH, Firmin DN, Longmore DB (1993) Helical and retrograde secondary flow patterns in the aortic arch studied by three-directional magnetic resonance velocity mapping. Circulation 88(5 Pt 1):2235–2247

80. Frydrychowicz A, Berger A, Munoz Del Rio A, Russe MF, Bock J, Harloff A, Markl M (2012) Interdependencies of aortic arch secondary flow patterns, geometry, and age analysed by 4-dimensional phase contrast magnetic resonance imaging at 3T. Eur Radiol 22(5):1122–1130. doi:10.1007/s00330-011-2353-6

81. Bogren HG, Buonocore MH (1999) 4D magnetic resonance velocity mapping of blood flow patterns in the aorta in young vs. elderly normal subjects. J Magn Reson Imaging 10(5):861–869

82. Mohiaddin RH, Firmin DN, Longmore DB (1993) Age-related changes of human aortic flow wave velocity measured non-invasively by magnetic resonance imaging. J Appl Physiol 74(1):492–497

83. van Ooij P, Garcia J, Potters WV, Malaisrie SC, Collins JD, Carr JC, Markl M, Barker AJ (2016) Age-related changes in aortic 3D blood flow velocities and wall shear stress: Implications for the identification of altered hemodynamics in patients with aortic valve disease. J Magn Reson Imaging 43(5):1239–1249. doi:10.1002/jmri.25081

84. Yoges I, Jerosch-Herold M, Hedderich J, Pardun E, Hart C, Gabbert DD, Hansen JH, Petko C, Kramer HH, Rickers C (2012) Normal values of aortic dimensions, distensibility, and pulse wave velocity in children and young adults: a cross-sectional study. J Cardiovasc Magn Reson 14:77. doi:10.1186/1532-4299-14-77

85. Segers P, Rietzschel ER, De Buyzere ML, Vermeersch SJ, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR, Asklepios i (2007) Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. Hypertension 49(6):1248–1255. doi:10.1161/HYPERTENSIONAHA.106.085480

86. Smulyan H, Asmar RG, Rudnicky A, London GM, Safar ME (2001) Comparative effects of aging in men and women on the properties of the arterial tree. J Am Coll Cardiol 37(5):1374–1380

87. Hope MD, Meadows AK, Hope TA, Ordovas KG, Saloner D, Reddy GP, Alley MT, Higgins CB (2010) Clinical evaluation of aortic coarctation with 4D flow MR imaging. J Magn Reson Imaging 31(3):711–718. doi:10.1002/jmri.22083

88. Frydrychowicz A, Markl M, Hirtler D, Harloff A, Schlen- sak C, Geiger J, Stiller B, Arnold R (2011) Aortic hemodynamics in patients with and without repair of aortic coarctation: in vivo analysis by 4D flow-sensitive magnetic resonance imaging. Invest Radiol 46(5):317–325. doi:10.1097/RLI.0b013e3182034fc2

89. Rengier F, Delles M, Eichhorn J, Azad YJ, von Tengg-Kobligk H, Ley-Zaporoizhan J, Dillmann R, Kauczor HU, Underhinninghofen R, Ley S (2015) Noninvasive 4D pressure difference mapping derived from 4D flow MRI in patients with repaired aortic coarctation: comparison with young healthy volunteers. Int J Cardiovasc Imaging 31(4):823–830. doi:10.1007/s10554-015-0604-3

90. Rengier F, Delles M, Eichhorn J, Azad YJ, von Tengg-Kobligk H, Ley-Zaporoizhan J, Dillmann R, Kauczor HU, Underhinninghofen R, Ley S (2014) Noninvasive pressure difference mapping derived from 4D flow MRI in patients with un repaired and repaired aortic coarctation. Cardiovasc Diagn Ther 4(2):97–103. doi:10.3978/j.issn.2223-3652.2014.03.03

91. Dyverfeldt P, Hope MD, Tseng EE, Saloner D (2013) Magnetic resonance measurement of turbulent kinetic energy for the estimation of irreversible pressure loss in aortic stenosis. JACC Cardiovasc Imaging 6(1):64–71. doi:10.1016/j.jcmg.2012.07.017

92. Lantz J, Ebbers T, Engvall J, Karlsson M (2013) Numerical and experimental assessment of turbulent kinetic energy in an aortic coarctation. J Biomech 46(11):1851–1858. doi:10.1016/j.jbiomech.2013.04.028

93. Andersson M, Lantz J, Ebbers T, Karlsson M (2015) Quantitative assessment of turbulence and flow eccentricity in an aortic coarctation: impact of virtual interventions. Cardiovasc Eng Technol 6(3):281–293. doi:10.1007/s12339-015-0218-x

94. Bachler P, Pиноchet N, Sotelo J, Crelier G, Irrazaval P, Tejos C, Uribe S (2013) Assessment of normal flow patterns in the pulmonary circulation by using 4D magnetic resonance velocity mapping. Magn Reson Imaging 31(2):178–188. doi:10.1016/j.mri.2012.06.036

95. Wehrum T, Hagenlocher P, Lodemann T, Vach W, Dragoumis I, Hennemann A, von zur Muhlen C, Stuplich J, Ngo BT, Harloff A (2016) Age dependence of pulmonary artery blood flow measured by 4D flow cardiovascular magnetic resonance: results of a population-based study. J Cardiovasc Magn Reson 18(1):31. doi:10.1186/s12968-016-0252-3

96. Galie N, Torbicki A, Barat D, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J, Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoepner M, Humbert M, Naeije R, Pepke-Zaba J, Task F (2004) Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The task force on diagnosis and treatment of pulmonary arterial hypertension of the European society of cardiology. Eur Heart J 25(24):2243–2278. doi:10.1016/ej.2004.09.014

97. Kheyfets VO, Schafer M, Podgorski CA, Schroeder JD, Browning J, Hertzberg J, Buckner JK, Hunter KS, Shandas R, Fensterbach BE (2016) 4D magnetic resonance image flow imaging for estimating pulmonary vascular resistance in pulmonary hypertension. J Magn Reson Imaging. doi:10.1002/jmri.25251

98. Bachler P, Valverde I, Pinochet N, Nordmeyer S, Kuehne T, Crelier G, T Crelier G, Irrazaval P, Beerbaum P, Uribe S (2013) Caval blood flow distribution in patients with Fontan circulation: quantification by using particle traces from 4D flow MR imaging. Radiology 267(1):67–75. doi:10.1148/ radiol.12120778

99. Jarvis K, Schnell S, Barker AJ, Garcia J, Lorenz R, Rose M, Chowdhary V, Carr J, Robinson JD, Rigsby CK, Markl M (2016) Evaluation of blood flow distribution asymmetry and vascular geometry in patients with Fontan circulation using 4-D flow MRI. Pediatric Radiol. doi:10.1007/s00247-016-3654-3

100. Dasi LP, Whitehead K, Pekkan K, de Zelicourt D, Sundareswaran K, Canter K, Fogel MA, Yogananth AP (2011) Pulmonary hypertensive flow distribution in total cavopulmonary connections: extracardiac versus intracardiac. J Thorac Cardiovasc Surg 141(1):207–214. doi:10.1016/j.jtcvs.2010.06.009