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Imaging (Q Truong, Section Editor)

Clinical Applications of MRA 4D-Flow

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Keywords MRA · 4D-Flow · 4D · Flow · CMR · Magnetic resonance · Phase contrast · Blood flow · Aorta

Abstract

Purpose of review Four-dimensional (4D)-Flow cardiovascular magnetic resonance (CMR) is three-dimensional, time-resolved, three-directional velocity-encoded magnetic resonance that provides flow velocity data within a volumetric region across the cardiac cycle (CC). The goals of this paper are to review the current clinical applications of this technique; provide an overview of the general physics; discuss key points from the expert consensus document; and present recent advances in the field. The advantages and disadvantages of 4D-Flow CMR in comparison with the standard and gold standard methods are summarized.
Recent findings 4D-Flow CMR offers unique insights into cardiac and circulatory physiology with an ability to quantify advanced hemodynamic parameters in a variety of pathologic entities including aortic and pulmonary artery diseases, valvular heart disease, complex congenital heart disease, and extra-thoracic cardiovascular diseases. Recent large cohort studies highlight how it provides information that has clinical impact beyond a better understanding of the disease and that will permit better and more timely management and prognosis.
Summary 4D-Flow CMR provides unique qualitative and quantitative flow dynamics information and its impact on cardiac chambers, vessel walls, and myocardium. As scan acquisition and post-processing of 4D-Flow CMR become faster and simpler, the investigational and clinical opportunities will expand dramatically.

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Introduction

Blood flow (BF) through the chambers of the heart and great vessels is multidimensional and multidirectional. To assess multidirectional flow within the cardiovascular system, including complex geometries and flow features, one-dimensional and two-dimensional flow imaging is inadequate. As a result, three-dimensional (3D), three-directional flow sensitive cardiovascular magnetic resonance (4D-Flow CMR) was developed [1••, 2, 3]. 4D-Flow CMR includes information to make measurements of flow in all directions and within the imaged volume [1••].

What is it?

Magnetic resonance angiography (MRA) is a technique for vessel visualization that can be performed with or without the use of exogenous contrast (EC) agents for vascular enhancement. One of the methods of visualizing the vasculature without contrast takes advantage of phase differences in the magnetic resonance (MR) signal, called phase-contrast MRA (PC-MRA) [4•, 5, 6]. 3D PC-MRA is typically performed during free-breathing without cardiac gating [4•] and is commonly used to assess the abdominal vasculature without the need of EC administration. Including the temporal information, with respect to the cardiac cycle (CC), results are multiple 3D PC-MRA series that provide the data for 4D-Flow CMR [1••, 4•]. Since 4D-Flow CMR is gated to the CC, it reveals the BF in the area of interest, including the cardiac chambers (CCh) and the great vessels [7]. Taking the average velocity data, from all of the CCs from a 4D-Flow CMR acquisition, results in an angiogram that is analogous to that obtained from 3D PC-MRA [1••, 8, 9].

As with all PC-MRA acquisitions, 3D PC-MRA and 4D-Flow CMR provide two sets of images: magnitude images that depict the morphology in the imaging volume and phase images that include the velocity information from areas that are moving through and within the imaging volume. The signal intensity (SI) on the phase images is proportional to the velocity of that which is moving. Slower velocities result in lower SI and higher velocities result in higher SI. Grayscale or color-coded images can depict the velocity information. There are multiple different means of displaying the 3D, 3-directional velocity information from 4D-Flow CMR, each with their own advantages and disadvantages [4•].

In addition to the various color flow visualizations, a variety of flow parameters can be quantified from the 4D-Flow CMR data, including flow volumes and velocities, which we quantify using conventional two-dimensional (2D) PC. Taking advantage of the 3D, 3-directional velocity data available with 4D-Flow CMR, it is also possible to calculate a multitude of additional advanced hemodynamic parameters, including wall shear stress (WSS), pulse wave velocity (PWV), pressure gradients, helicity, vorticity, turbulence, and kinetic energy (KE), among others [1••].

Post-processing the 4D-Flow CMR data requires specialized software that allows correction of background errors and vascular segmentation prior to flow visualization and quantification [10, 11•, 12]. Accurate vascular segmentation is particularly important for WSS estimation [13].

When to use it?

The strength of 4D-Flow CMR lies in its ability to provide volumetric flow quantification throughout the imaging volume. Common applications for 2D-PC CMR include quantification of regurgitant flows and fractions, peak velocities and gradients from diseased valves, to quantitate shunts (Qp/Qs) and collateral flows in congenital heart disease (CHD) [14•], among others (Table 1). 4D-Flow CMR can obtain the same calculations. Several studies have shown that 4D-Flow CMR has less error and variation in these measurements than 2D-PC CMR, irrespective of scanner strength [18]. The reproducibility of these measurements is excellent [19–27].

A major advantage of 4D-Flow CMR is the ability to evaluate BF in many different locations from a single acquisition. For example, the same 4D-Flow CMR scan can quantify flow through all of the valves, the aorta and pulmonary arteries and veins, and the vena cava. 4D-Flow CMR has also been applied to flow quantification in other cardiovascular territories [1••].

The time-resolved visualization of BF allows the identification of flow directionality and areas of flow acceleration, which could be particularly clinically important in patients with previous multiple surgical repairs of CHD [14•, 28], and mostly relevant in complex CHD to assess the flow directionality, the patency of repairs, or remaining defects [7, 27, 29•, 30, 31, 32•]. In patients with aortic aneurysms and aortic valve disease, including bicuspid aortic valves, altered flow patterns (FP) through the aortic valve and within the ascending aorta (AA) frequently result in eccentric flow emanating from the aortic valve and targeting the AA wall. This has been shown to change the mechanical effects on the aortic wall and is thought to be linked to changes in vessel wall mechanical properties [33–36]. Table 1 shows basic flow visualizations and parameters used in routine clinical practice. More advanced hemodynamic parameters can be calculated [1••], but their utility in routine clinical CMR remains unknown.

Aortic valve disease

4D-Flow CMR has also the ability of characterized local morphological and hemodynamic differences between tricuspid and bicuspid aortic valves even when having similar aorta dimensions. Studies using 4D-Flow CMR have shown that the maximal aorta diameter is associated with not only age and peak velocity but the degree of flow displacement [15••, 16••]. Emerging evidence suggest that the altered hemodynamics in patients with aortic stenosis causes the abnormal FP in the AA that associate with its wall remodeling and degeneration into aortopathy with the further dilatation [37••].

Aorta disease

The role of 4D-Flow CMR is very important in the aorta evaluation of aortic aneurysms and coarctation. Numerous studies in patients with aortic disease have shown the wide variation in hemodynamic information provided by 4D-Flow CMR including changes in BF velocities and volumes, variability in flow symmetry and directionality [15••, 16••], and alterations in hemodynamic stresses on the vessel wall. In

Table 1. Basic applications of 4D-Flow CMR [1••, 14•, 15••, 16••, 17]. *ASD* atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *Qp/Qs* pulmonary flow/systemic flow, *MIP* maximum intensity projection, *PSAP* pulmonary artery systolic pressure, *PAH* pulmonary artery hypertension, *CHD* congenital heart disease

Pathology		Parameter	Quantification	Equivalent with 2D-PC CMR
Basic applications				
Valvular heart disease	Stenosis	Stenotic jet using pathlines and streamlines	Flow volume	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
		Peak velocity by systolic streamlines or MIPs of speed images	Peak velocity	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
		Maximum and mean transvalvular gradients	Estimated pressure gradients with modified Bernoulli equation	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
		Outflow patterns using streamlines	Flow pattern	No
		Time course of flow curve	Time course of flow	No
	Regurgitation	Regurgitant jet using pathlines and streamlines	Flow volume and fraction	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
	BAV	Aortic root morphology and diameters, flow direction, symmetry, and displacement	Diameters, centerline displacement, flow displacement, direction, and symmetry	Yes, for morphology and with limitations for direction and symmetry depending on flow direction, proper acquisition, and visualization.

Table 1. (Continued)

Pathology		Parameter	Quantification	Equivalent with 2D-PC CMR
Shunts and collateral vessels	ASD, VSD, PDA, fistulae, etc.	Identification of shunt flow and its directionality using pathlines	Flow volume (shunt flow volume and Qp/Qs)	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
Aortic disease	Aneurysm, coarctation, dissection, flaps, etc.	Peak velocity location by systolic streamlines or MIPs of speed images	Flow volume	Yes, with limitations depending on flow direction, proper acquisition, and visualization.
		Identification of flow in false lumen and potential entry and/or exit sites	Flow pattern, flow volumes, fractions, relative flow in true and false lumen	Yes, challenging, just qualitatively and depending on proper acquisition and visualization.
	Tortuous aorta	Identification of highly disrupted flow patterns	Reduce forward flow and peak velocity.	Yes, just qualitatively and with limitations depending on flow direction, proper acquisition, and visualization.
Pulmonary artery disease	PAH Complex CHD, CHD status post-repair	Color-coded streamlines, time-resolved particle traces, vector graphs, blood flow trace patterns and their temporal behavior, peak velocity, and estimated pressure gradients with modified Bernoulli equation	Visual flow differentiation, acquired velocity fields, early retrograde flow, detection of the vortex flow, quantitative estimation of pulmonic pressure gradients, average velocities, minimum vessel areas.	Yes, for the estimation of PSAP with modified Bernoulli equation and with limitations for morphological evaluation of proximal arteries.
Congenital heart disease	Simple (ASD, VSD, PDA) Complex (single ventricle physiology, Fontan circulation, Fallot's tetralogy, post-operative status, etc.)	Identification of flow (directionality, shunts, collaterally, connectivity, and distribution) using pathlines and peak velocity location	Flow pattern, flow volume, regurgitant and high-velocity volumes and fractions, flow distribution. Qp/Qs. Peak velocity.	Yes, with limitations depending on flow direction, proper acquisition, and visualization.

patients with aortic coarctation, 4D-Flow CMR can measure the degree of collateral flow around the coarctation [17].

Interestingly, the observed hemodynamic changes in patients with aortic disease correlate with postoperative complications such as rupture and aneurysm formation [17, 38, 39], and the flow eccentricity correlates with focal increase of WSS and further dilatation [33, 40–42].

Figure 1 shows two examples of patients with bicuspid aortic valve and very distinct FP within the AA, even though the AAs are of similar size [16••, 17]. This is a promising use of the technique since the increasing information will help in understanding the pathophysiological mechanism of the diseases and could influence in target the individual treatment by stratifying the risk of the patient and guiding the timing of the surgery to improve results and prognosis.

A few recent studies have investigated the potential role for 4D-Flow CMR in assessing patients with aortic dissection. A recent paper by Allen et al. demonstrated that 4D-Flow CMR is capable of detecting small flap fenestrations in patients with type B aortic dissection [43••].

Aortic atherosclerosis as source of stroke

There is growing evidence highlighting the important role of distal aortic arch atherosclerosis in embolic stroke. 4D-Flow CMR has shown that retrograde flow from the distal aortic arch during diastole can lead to cerebrovascular embolism. Atherosclerotic aortas have increased stiffness due to the atherosclerosis itself, which increases the PWV and the earlier wave reflection from the peripheral vasculature, resulting in significant retrograde descending aortic flow, even without the coexistence of aortic valve insufficiency [17, 44–46]. The recommended protocol includes 3D aortic plaque detection, retrograde embolization, and diastolic retrograde flow in the aortic arch; this application is mainly important in the cryptogenic stroke etiology where complex descending aortic plaques play a role even in absence of aortic valve insufficiency [17].

Pulmonary arteries

4D-Flow CMR plays a very important role in the post-repair patients with complex CHD [14•], since it is able to differentiate flow from the right and from the left sides [47]. Pulmonary hypertension (PH) is an emerging area of interest for 4D-Flow CMR. The assessment of right ventricular (RV)-pulmonary artery (PA) interactions in patients with PH is enriched by the visual assessment of changes in the FP within the main pulmonary artery (MPA) [17]. In addition, quantifications of the changes in FP within the MPA correlate strongly with invasive measurements of peak systolic PA pressures [16••, 48]. The demonstration of early retrograde flow in the proximal pulmonary arteries [49] and the detection of the vortex flow in the MPA are surrogate markers of PH severity [17, 49].

Some dynamic parameters including the visual and quantitative estimation of pulmonic pressure gradients [17], like average velocities, and minimum PA areas have demonstrated the best diagnostic accuracy [50]. The estimation of the pulmonary artery systolic pressure relies in the same approach as in 2D-PC CMR that already has good correlation with Echo and invasive measurement when there is tricuspid regurgitation [17], but 4D-Flow is increasing in evidence that it will be possible to accurately measure directly the pressure differences using the Navier-Stokes equation [51], which is still work in progress for the

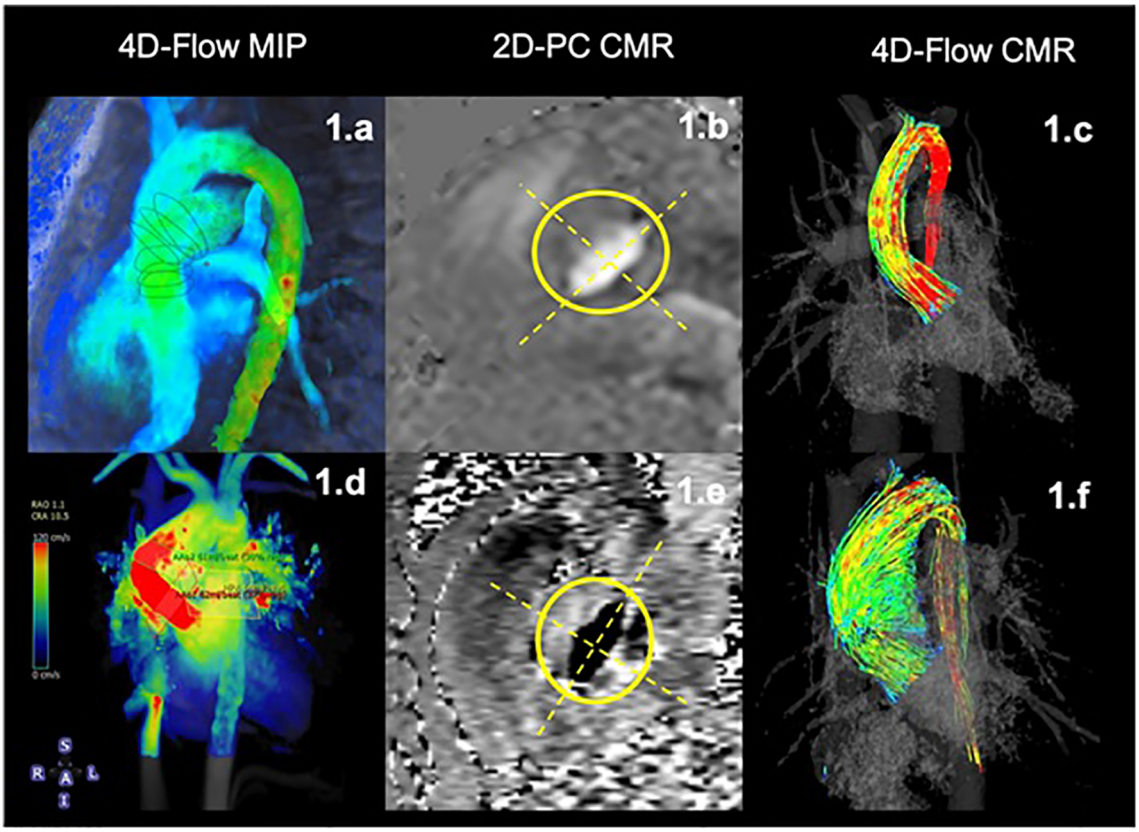

Fig. 1. Two examples of patients with bicuspid aortic valve, similar ascending aorta size but very distinct flow patterns within the ascending aorta. This figure shows two patients with bicuspid aortic valve, with similar aortic size but completely different blood flow in the ascending aorta, and the valve with a non-eccentric opening is shown in the bottom panel (1e) which has a less turbulent flow pattern in the ascending aorta in comparison with the upper panel where the opening of the valve is eccentric (1b) exhibiting a turbulent flow pattern in the ascending aorta. (1a) and (1d) show the 4D-Flow MIP images. (1b) and (1e) show 2D-PC CMR of the bicuspid's aortic valves. (1c) and (1f) show the 4D-Flow CMR images. MIP maximum intensity projection, CMR cardiovascular magnetic resonance, PC phase contrast.

PAH [17]. Considering comparable severity of pulmonary vascular resistance index, pathological flow hemodynamics seems to be more consistent in adult patients and more variable in children [52••].

Heart disease

4D-Flow CMR is used to investigate normal and abnormal FP (filling, ejection, and shunt patterns) between cavities (interatrial, atrioventricular, and intraventricular). For example, in normal physiology, the direction of the inertial recoil away from the ejected blood enhances the ventriculo-atrial coupling as a physiological change to exertion [17], and the FP within the ventricles shows asymmetric, regionally constrained ring vortices close to auriculo-ventricular valves (mitral and tricuspid) during diastolic inflow [53]. The visual assessments of the pathlines by 4D-Flow CMR on 3D time-resolved acquisitions show that the normal inflow which leaves the left ventricle (LV) in one heartbeat, the direct flow, is only 33% of its end-diastolic volume [54, 55]. In patients

with dilated cardiomyopathy, this direct flow is reduced along with the location, extent, and incidence of the vortex flow in LV cavity [17, 55, 56].

It is feasible to obtain a whole heart data set with this technique [17]. Early versions of this sequence required relatively long scan times of approximately 20 min [20, 57]. With newer, commercially available acceleration methods, whole heart 4D-Flow CMR can routinely be performed in 4–6 min. Clinically, 4D-Flow CMR is especially useful for the comprehensive analysis of the hemodynamics of repaired complex CHD [14•, 16••, 32•, 47, 58].

Quantification of RV diastolic function is also feasible with this technique; however, a recent meta-analysis showed that large, multicenter studies are required to validate the proposed method, to assess its reproducibility and clinical applicability [59•].

Cardiac valves

A well-known limitation of the 2D-PC CMR is the evaluation of valvular heart disease (VHD). 4D-Flow CMR, with retrospective valve tracking, is a more accurate method for assessing valvular function [3, 60, 61], especially true in patients with multiple diseased valves. 4D-Flow CMR can accurately measure the high velocity jet flow and the elevated turbulent intensity values [62].

Other relevant application of this technique is the status post-repair of VHD, specifically in valve-sparing aortic root replacements, to understand the hemodynamics of the spared valve and the vortex FP in the sinuses of Valsalva [63, 64]. 4D-Flow CMR has the ability to help us understand the impact of these valve prostheses on flow within the aorta [7].

Mitral regurgitation has been recently evaluated with 4D-Flow CMR allowing an accurate and faster than the conventional 2D-PC CMR approach, with strong correlation between the severity assessed by 4D-Flow CMR and the postsurgical LV remodeling [65•].

Other vascular applications—abdomen

Other vascular territories outside the heart and the great vessels have been well studied with 4D-Flow CMR. Areas in which 4D-Flow CMR has been studied the most extensively include the hepatic and portal venous system in patients with liver cirrhosis, portosystemic shunts, and portal hypertension. 4D-Flow CMR is well adapted to visualize and quantify FP within the hepatic and portal venous vasculature in patients with a highly variable anatomy [17, 66, 67].

Renal arteries are an interesting territory for the cardiovascular medicine since renovascular disease is a frequent cause of secondary systemic hypertension and of a progressive renal insufficiency. However, their evaluation is challenging due to their small size. 2D-PC CMR has limited value in measuring renal artery flow given the variable anatomy. For patients in which EC administration is contraindicated, 4D-Flow CMR is a viable alternative for non-contrast-enhanced MRA [28, 68].

Other vascular applications—neurovascular

Carotid arteries are a vascular territory that has received great attention due to importance in risk stratification of cardiovascular disease (CVD) and for its role in stroke. In diseased carotid arteries with atherosclerotic high-risk plaques, the

altered filling patterns, helix formations [69], abnormal flow deceleration or recirculation, low absolute WSS, and high oscillatory shear index have been observed with 4D-Flow CMR [70, 71].

The analysis of the intracranial vessels has its main application on characterization of brain aneurysms where the complex and vortical flow are commonly present [72, 73]. Interestingly, each aneurysm has different spatial and temporal evolution of vortical FP depending on the neck size [17]. The WSS is reduced relative to the parent artery, supporting the theory that low WSS may promote aneurysm growth. Initial results show good agreement in estimated WSS values with computational fluid dynamics (CFD) [74].

Other vascular applications—peripheral

Finally, the peripheral vessels have been analyzed qualitatively and quantitatively [75], but it has limited resolution with the current 4D-Flow CMR approaches and it is not routinely used [17].

Is it possible to do 4D-Flow CMR with all MRI scanners available?

It is possible to perform 4D-Flow CMR with current 1.5- and 3-T scanners of all main commercial brands. However, expertise of the operator and the readers is required for it to be performed in a reliable routine clinical practice. The state-of-the-art SCMR consensus about 4D-Flow CMR [1••] proposes the following scan acquisition parameters that could be used on any scanner: field of view to cover the region of interest (ideally maximum); spatial resolution of $< 2.5 \times 2.5 \times 2.5$ mm^3 for aorta or PA, $< 3.0 \times 3.0 \times 3.0$ mm^3 for whole heart and greater vessels (ideally maximum, at least 5–6 voxels across vessel diameter of interest isotropic resolution); velocity encoding (Venc) timing (beat- vs. TR-interleaved) of TR-interleaved; *k*-space segmentation factor of 2 (ideally 1), TR of < 40 ms (ideally maximum); retrospective ECG synchronization, if available; respiratory motion compensation, if available, using leading or trailing MR navigator on the liver/diaphragm interface, 6 mm window size, typically resulting in 50% acceptance rate (ideally 100% acceptance, motion correction); partial *k*-space coverage in phase- and slice-encoding directions, if available; elliptical *k*-space (ideally full *k*-space coverage); flip angle of Ernst angle ($\alpha = a\cos(e^{-TR/T1})$); parallel imaging of $R = 2–3$ depending on the number of channels in coil array (ideally no parallel imaging), *k-t* undersampling if available of $R = 4–5$ (ideally no *k-t* undersampling); single Venc, 10% higher than maximum expected velocity (ideally maximum expected velocity, multiple Vencs). The proposed postprocessing parameters include correction of Maxwell, Eddy current, and phase unwrapping, gradient non-linearity errors [1••].

The total scan time of this 3D volume acquisition is approximately 5 to 8 min [1••], but if it is crucial to reduce time, the following modifications to the above protocol would help acquire free-breathing without respiratory gating, which will increase scan efficiency with reasonably accurate flow volume quantification [20, 24]; reduce TR by increasing the *k*-space segmentation factor to 3, and this modification will reduce TR to 40–60 ms, the accuracy of peak velocity, and flow volume quantification; and finally, reduce spatial resolution and signal to noise ratio (SNR) by acquiring 65% × 65% of k_y and k_z phase encoding lines. As expected, this modifications will require additional quality

control (QC) since those are deviations from a validated standard protocol [1••].

A QC system should be implemented in all protocols that intend to use this sequence. The SCMR consensus also recommends a general data approach as follows: visual inspection of source images, quantitative QC that targets the parameter of interest (an excellent option is the conservation of mass principle), and if this matches the analysis parameter of interest, the study is good for clinical use; if not, the performing additional visual inspection of source images and of pathlines emitted from static tissue are recommended [1••].

Is it superior to the regular MRA and/or PC images?

It is well known that 2D-PC CMR has certain artifacts related to background phase offsets which translates into error in inflow volume measurements. 4D-Flow CMR has the same limitation and there are some measurements to compensate those [1••]. Flow volume quantifications with 4D-Flow CMR have several advantages to the conventional 2D-PC CMR. With 4D-Flow CMR, it is very straightforward to check the internal consistency of the data by employing the principle of conservation of mass that allows research and data quality assurance [1••, 20, 21, 76, 77]. It is possible to place analysis planes retrospectively at any location within the acquired 3D volume and calculate BF through any planes of interest despite. Another advantage of 4D-Flow CMR is that it only requires the acquisition of one 3D volume compared to the some predetermine and accurately locate relevant planes of 2D acquisitions. This is particularly important when multiple 2D-PC CMR acquisitions are needed [25]. In this scenario, 4D-Flow CMR is faster due to the single acquisition (ESM 1). As mentioned above, valve tracking with 4D-Flow CMR (ESM 2) improves assessment of VHD [61]. 4D-Flow CMR allows velocity measures in all spatial direction and coverage with better chances to capture the peak velocity of a stenotic jet [26]. A disadvantage of this technique is the lower TR, in the range of 50–55 ms, compared to the traditional 2D-PC CMR. This could result in lower peak flow rate and even smaller net flow volumes at even lower TRs, around 46 ms. [18, 78] This is an area where the future research will improve for different applications.

How accurate and reproducible is it?

There are different methods and equations proposed for 4D-Flow CMR that generate 3D PC-MRA. All average and combine the velocity and magnitude information obtained during the CC [4•, 7, 9, 79, 80]. This technique has the same limitation of 3D PC-MRA in that the motion of the cardiovascular structures throughout the CC are averaged. For many of the calculations performed, this is not an issue. The averaging of motion throughout the CC has a greater impact on parameters that are calculated at the edges of the moving structures. This is especially true for estimation of WSS at the aortic wall due to its inherited elastic properties causing distension and recoil motion of the aorta over the CC [81].

A recent multicenter trial compared 2D-PC CMR to 4D-Flow CMR which demonstrated faster and more comprehensive evaluation and quantification of BF volumes in CHD and with greater internal consistency of measurements.

Both CMR techniques showed significant agreement in measurements for MPA and its main branches flows and for Qp/Qs, but not for AA, superior vena cava and descending aorta flow [82••]. More research and validation in multicenter trial are needed to establish its reproducibility.

Recently, in animal comparisons, the flow in the aorta showed that can be accurately measured by 4D-Flow CMR compared to simultaneously measured invasive flow, helping to validate the quantitative reliability of this technique [83•].

Sedation in young children and infants?

In young children and infants, the considerations for the use of sedation or general anesthesia 4D-Flow CMR can be an advantage relative to other CMR sequences. 4D-Flow CMR is acquired during free-breathing. As long as the patient remains still, the acquisition can be performed successfully. In neonates, this can be done with the feed-and-swaddle technique and does not require any sedation. In infants that cannot be swaddled, CMR is generally performed with sedation or anesthesia to avoid patient motion during the scan. In contrast to many of the other traditional CMR sequences, 4D-Flow CMR does not require breath holding to obtain the highest quality images.

Advanced parameters

Advanced hemodynamic parameters that 4D-Flow CMR can calculate include WSS, which represents the viscous shear forces that the BF produces tangentially to the wall (vessel or myocardium). WSS could be used as an indicator of the consequences of abnormal BF to the endothelial cells and/or interstitial space or to the endocardium and its effects in the remodeling processes of the wall. PWV is the propagation speed of systolic pressure pulse in the arterial tree and can be use clinically as marker of stiffness and as a predictor factor of CVD [1••, 84–86]. Turbulent kinetic energy (TKE) represents the energy within the turbulent flow and can be used to estimate the impact of turbulent flow on blood components and the wall [1••, 62, 87–89]. Relative pressure field (RPF) measures the differences in pressure [1••, 90, 91]. KE of ventricular flow components or compartments represent momentum of blood flowing through the CCh and could serve as an indicator of ventricular dysfunction with potential risk stratification value and to assist in the individual treatment optimization [1••, 54, 55, 92].

Is this technique ready for prime time?

This field is rapidly evolving with improvements in imaging acquisition methods, data processing, and analysis techniques. There are several limitations of 4D-Flow CMR that still need to be addressed before it becomes a routine part of clinical CMR. First of all, it is important to understand its accuracy and precision, including acquisition sequences, reconstruction methods, and analysis parameters. The assessment of spatiotemporal fidelity and noise propagation mainly for a multi-purpose flow analysis where a combination of high and low

velocities flow coexists in the same patient; since those can alter the certainty of measurements [93], but research is working in sequences that permit the use of some Vencs at the same time [41, 94]. The presence of systematic errors that consists in unwanted bias of the measured velocity field which are related to gradient-induced Eddy currents, gradient non-linearity, and gradient fields are other limitations [95, 96], its prediction almost impossible; therefore, its correction methods need to be applied retrospectively during the image post-processing.

In vivo validation against gold standard methods is lacking for many areas of 4D-Flow CMR, but this technique can potentially become the new gold standard. Up-to-date, a pulsatile flow phantom could serve as reference standard for those areas where a gold standard is missing, and it is recommended to evaluate for precision including sensitivity especially to spatiotemporal resolution and SNR.

For the advanced applications, in the case of WSS, the longitudinal data is limited on its predictive value for risk stratification, and more research is needed in this area. In the case of PWV, it requires high temporal resolution and it is sensitive to artifacts. When TKE is low, it is affected by variations in intravoxel mean velocity. In stenotic flows, RPF does not take turbulence effects into account therefore; does not reflect turbulence-related pressure losses. The pathlines used to map the transit of blood through CCh keep accumulating errors that inversely affect the quality of velocity data in KE of ventricular flow [1••]. Unfortunately, up-to-date, the low worldwide availability and the relatively long acquisition times limit more applicability; [97•]; however, its advantages, the unique information obtained has motivated the constant research and advances in hardware and pulse sequences, along with the publication of the consensus statement guidelines [1••], wich resulted in a progressive increase in the use of this technique for the main cardiovascular applications (see above) [7].

Takeaway messages

The main purpose of this technique is to understand how the abnormal flow can promote and worsen heart and/or vascular disease in different ways in each patient with the same pathological entity.

This progressively evolve technique permits to study the interactions between circulating BF, CCh, and myocardial dynamics in vivo in the same study, allowing the refinement of all related previously described experimental cardiac and circulating physiology and those derived from the complex CFD. Additional investigation is needed to place this technique in the routine clinical management of patients.

Recent research

LV blood flow KE parameters measured by 4D-Flow CMR show stronger and independent correlations to age than standard diastolic metrics since it is associated with physiological factors [98•] that other MR or Echo techniques are not.

Recently, atrial fibrillation was investigated with 4D-Flow CMR which proved that it is feasible and accurate, and that there is overall impaired but

individually variable flow dynamics in left atrium and left atrial appendage, and that the atrial BF is in the normal range despite elevated CHADS2-VASC score [52••].

A comprehensive 3D evaluation of the fetal hemodynamics has been challenging due to technical difficulties such as the small size of the structures of interest, the movement of the fetus during the scan acquisition, and the difficulty to reconstruct data without cardiac gating until recently, since animal research successfully found that 4D-Flow CMR is feasible and enables characterization and quantification of complex FP in utero, offering more information about normal physiology and opening the door to the potential of this technique to qualitatively characterize the FP of the complex CHD supporting future new interventions to help improving results in this field [99•].

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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