Clinical intra-cardiac 4D flow CMR: acquisition, analysis, and clinical applications

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Identification of flow patterns within the heart has long been recognized as a potential contribution to the understanding of physiological and pathophysiological processes of cardiovascular diseases. Although the pulsatile flow itself is multi-dimensional and multi-directional, current available non-invasive imaging modalities in clinical practice provide calculation of flow in only 1-direction and lack 3-dimensional volumetric velocity information. Four-dimensional flow cardiovascular magnetic resonance imaging (4D flow CMR) has emerged as a novel tool that enables comprehensive and critical assessment of flow through encoding velocity in all 3 directions in a volume of interest resolved over time. Following technical developments, 4D flow CMR is not only capable of visualization and quantification of conventional flow parameters such as mean/peak velocity and stroke volume but also provides new hemodynamic parameters such as kinetic energy. As a result, 4D flow CMR is being extensively exploited in clinical research aiming to improve understanding of the impact of cardiovascular disease on flow and vice versa. Of note, the analysis of 4D flow data is still complex and accurate analysis tools that deliver comparable quantification of 4D flow values are a necessity for a more widespread adoption in clinic. In this article, the acquisition and analysis processes are summarized and clinical applications of 4D flow CMR on the heart including conventional and novel hemodynamic parameters are discussed. Finally, clinical potential of other emerging intra-cardiac 4D flow imaging modalities is explored and a near-future perspective on 4D flow CMR is provided.

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Introduction

Reliable analysis of blood flow carries a great importance for the accurate interpretation and management of cardiovascular diseases. Available non-invasive imaging modalities in clinical practice allow for calculation of velocity in only 1-direction and lack 3-dimensional (3D) volumetric velocity information. This prohibits a critical assessment of blood flow in cardiac cavities and great vessels, since the flow is multi-dimensional and multi-directional.1

Four-dimensional flow cardiovascular magnetic resonance imaging (4D flow CMR) has been introduced as a novel tool for visualization and quantification of flow within the heart and major blood vessels.2 This technique allows for simultaneous velocity encoding in all three directions and provides 3D volumetric information resolved over time (4D = 3 spatial dimensions + time). Initial 4D flow CMR clinical and research applications mainly focused on major blood vessels due to straightforward morphology and relatively low amount of dynamic deformation over the cardiac cycle. Of note, recent technical improvements in the technique have led to significant improvements in dynamic cardiac chamber segmentation over the cardiac cycle. As a result, a large amount of data have been recently mounted in the literature regarding intra-cardiac 4D flow CMR applications. In particular, in addition to intra-cardiac flow examination with conventional flow parameters such as mean/peak velocity and stroke volume,7 an increasing number of 4D flow data derived novel hemodynamic parameters [e.g. kinetic energy (KE)] have been recently introduced.4,5 These novel parameters have provided valuable insights particularly into cardiac energetics. Moreover, a large variety of analysis tools became available for 4D flow data analysis. However, a standard post-processing approach is missing, which impacts interpretation and limits clinical adoption.

The aim of this review is to serve as a guide for clinicians who consider using intra-cardiac 4D flow CMR in clinical practice and for research. In the first part, the 4D flow acquisition and analysis processes are briefly discussed. In the second part, clinical applications of 4D flow CMR regarding cardiac diseases are discussed with emphasis on novel hemodynamic parameters. Finally, 4D flow imaging potential of other modalities (e.g. echocardiography) is reviewed and a near-future perspective on 4D flow CMR is provided.

Acquisition

Data acquisition

The 4D flow CMR data acquisition is based on the ECG-gated phase-contrast (PC) technique including time-resolved spoiled gradient echo pulse sequences.6 The retrospective ECG-gating is preferable, as the prospective-gating does not integrate the entire cardiac cycle and consequently, the evaluations of the late-diastolic mitral flow and diastolic function are compromised. Motion suppression is essential,
since the image quality is significantly reduced with respiratory motion.\textsuperscript{7} Compensation for respiratory motion-related artefacts can be achieved by using bellows reading, navigator gating of the diaphragm motion, or recently introduced self-gating techniques which provide the unique advantage of using the raw k-space data itself.\textsuperscript{8} The 4D flow CMR data acquisition may be performed after contrast administration. Although this procedure presents the advantage of increased signal-to-noise ratio (SNR), the influence of contrast agents on data acquisition may vary according to the duration from contrast administration.

**Duration of acquisition**

Despite application of acceleration techniques, 4D flow image acquisition is still time consuming (up to 15 min). Important acceleration approaches include parallel imaging,\textsuperscript{9} compressed sensing,\textsuperscript{10} and non-Cartesian trajectory techniques.\textsuperscript{11} However, acceleration of the image acquisition impacts essential scan parameters such as SNR, spatial and temporal resolution. For this reason, a 4D flow CMR consensus report introduced reference acquisition and reconstruction values such as <40 ms for temporal resolution and 3.0 \times 3.0 \text{ mm}^3 for spatial resolution.\textsuperscript{1} More recently, recommended values regarding use of 4D flow CMR in congenital heart disease (CHD) were reported.\textsuperscript{12} Although a combination of acceleration techniques may provide effectively reduced scanning time, one should be cautious since such techniques may impact the efficiency of the other one. The performances of the acceleration techniques may vary in terms of susceptibility to artefacts, image quality, and consistency of intra-cardiac flow quantifications. Nonetheless, recent research reported feasible error ratios (<8%) for commonly applied acceleration techniques compared to phantom models.\textsuperscript{13} Finally, to compensate the loss in SNR due to the use of accelerated acquisition techniques, high field strength magnetic resonance imaging (MRI) systems (e.g. 3 Tesla) can be employed.\textsuperscript{14} yet the field strength may affect the quantification of the parameters including novel hemodynamic parameters.

**Sources of errors**

Several sources of error impact the quality and accuracy of 4D flow data and require correction prior to flow visualization and quantification. Similar to other types of PC CMR methods, the major sources of errors comprise concomitant gradient field effects (Maxwell terms), gradient field non-linearity, Eddy current effects, and phase wraps. It is important to note that correction methods for background phase offsets may vary according to MRI systems, sequences, protocol, and region of interest. While some MRI vendors provide correction for concomitant gradient field effects during standard reconstruction, additional correction is often required to improve analysis.

**Velocity encoding**

Similar to 2D PC-CMR, the sensitivity of velocity encoding (Venc) should be set by the operator prior to the image acquisition as \(\sim 10\%\) higher than the maximum expected velocity. If the Venc is set too high, this causes a decreased SNR, while too low Venc leads to aliasing artefacts. Since the prediction of the maximum velocity is not feasible for every case, regular use of an anti-aliasing algorithm is recommended, as well.\textsuperscript{1} A 2D velocity sensitivity scout can also be helpful to avoid velocity aliasing. For cardiovascular conditions featuring a wide range of flow velocities such as valvular diseases associated with stenotic/regurgitant flow, setting multiple Vencs may help to assess the whole velocity spectrum.\textsuperscript{15} However, this approach is not very practical due to a significant increase in acquisition time (e.g. 15 min).

**Visualization**

3D phase-contrast MR angiography can be derived from 4D flow CMR data for orientation and visualization.\textsuperscript{16} 4D flow CMR visualization can also be fused with balanced steady-state free precession cine images to guide anatomic orientation. The most commonly used 4D flow visualization techniques are streamlines and pathlines.\textsuperscript{1} The magnitude of velocity can be represented by colour-coding or adjustment of the vector size, or both. Streamlines are instantaneous traces tangent to the local velocity vectors demonstrating the blood flow directions at specific time points,\textsuperscript{17} as shown in Figure 1 and Supplementary data online, Video S1a–f. Time-resolved pathlines represent a path followed by a virtual massless particle over time\textsuperscript{18} and thus visualize the temporal course of flow over time. Using pathline visualization, separate components of left ventricular inflow (e.g. inflow leaves the ventricle within one cardiac cycle) were demonstrated.\textsuperscript{19} Pathlines in combination with streamlines allow identification of through-plane placements for quantification in complex flow patterns.\textsuperscript{20}

**Analysis tools**

Today, 4D flow CMR acquisition sequences are available across all major vendors (i.e. Siemens, GE, Philips). Recently, a wide range of comprehensive analysis tools emerged providing visualization and quantification of the various parameters. The non-standardized structure of these analysis tools appears as an important problem slowing down transition towards regular clinical use. We provide detailed information regarding the variability, citation frequency, and current functionality of the available analysis tools based on clinical intra-cardiac 4D flow CMR studies, in a supplemental file. The majority of the analysis tools offer a dedicated 4D flow CMR data visualization and analysis [e.g. Segment-Medviso, Mass, GTFlow (gyrotools), Arterys, CAAS MR (Pie Medical Imaging), cvi42 (Circle Cardiovascular Imaging, MEVISFlow)]. It should be noted that provided analysis regions (e.g. vascular, intra-cardiac) and properties substantially differ between the packages. For instance, a package may not offer aortic evaluation, while another lacks valvular flow quantification. Furthermore, some platforms are involved in 4D flow CMR data analysis through in-house programming (e.g. Matlab, EnSight, Mimics-Materialize, Paraview, ITK-SNAP, R-Tech, FourFlow). These analysis tools are generally implemented for correction of the technical artefacts such as background phase offset errors, visualization, and segmentation of the region of interest. Figure 2 summarizes the visual and quantitative analysis process of 4D flow CMR in a conceptual manner.

**Clinical relevance of 4D flow CMR in intra-cardiac diseases**

**Atrial flow characteristics in patients with atrial fibrillation**

Thromboembolic events in atrial fibrillation (AF) are mainly attributed to embolism of the thrombus originating from the left atrium.
Detailed evaluation of flow in the atria may help to understand the mechanism of thrombus formation. Using capabilities of 4D flow CMR, vortical flow in the LA during systole and diastole was reported (Figure 3 and Supplementary data online, Video S2a–c). Duration and frequency of vortices correlated inversely with increase in age and it was reported that patients with vortex
formation in the LA have a smaller LA volume and higher peak flow velocity. Therefore, it is postulated that formation of vortices within atria may have a role in avoiding atrial blood flow stasis.

4D flow CMR has the ability to provide global quantification of flow metrics within the heart. Patients with persistent AF demonstrated lower mean blood flow velocity within the LA compared to patients in sinus rhythm. A larger study including 40 patients revealed that LA blood flow velocities are remarkably reduced in patients in sinus rhythm with a history of AF.3 In the same study, a significant inverse correlation was found between mean/peak LA velocity and CHA2DS2-VASc score, which is the recommended risk model to estimate the stroke risk in patients with AF, indicating that LA flow metrics acquired by 4D flow CMR may add value for risk stratification of stroke. Markl et al. compared the flow dynamics between LA and left atrial appendage (LAA) in healthy controls and patients with AF. Interestingly, there was no significant difference for mean and peak flow velocities between LA and LAA. These findings suggest that AF distorts flow dynamics not merely in the LAA, but in the entire LA. Finally, multi-centre studies exploring multiple factors predicting stroke in patients with AF including fibrosis, geometry, shape, and flow characteristics are awaited.

Valvular heart diseases
Accurate quantification of valvular regurgitation is of great importance for the clinical management. Using 4D flow CMR, analysis planes can be modified according to the location and angulation of moving valvular structures for quantification of valvular regurgitation. Besides, implementation of retrospective valve tracking allows reproducible and robust trans-valvular flow assessment at each of the four heart valves (Figure 4). Using retrospective valve tracking, the planes of flow quantification follow the valve plane over the cardiac cycle and can be adjusted according to the blood flow direction. 4D flow CMR with retrospective valve tracking was reported to be superior than conventional 2D 1-directional velocity mapping in patients with mitral and tricuspid valve regurgitations. Yet, the manual placement and tracking of multiplanar reformating planes in every cardiac phase is time consuming. Using an automated valve tracking method, the analysis time to quantify flow across four valves is considerably shortened compared to manual tracking (i.e. 14 vs. 25 min). Recently, it has been shown that aligning the analysis plane with the velocity jet rather than the valve further improved quantification of regurgitation.

4D flow CMR could allow robust peak velocity quantification of stenotic jets, although phase dispersion due to highly turbulent flow may compromise the accuracy. It has been shown that 4D flow CMR exhibited higher peak velocities than 2D flow CMR both for aortic and pulmonary valves. Possibly, this may be explained by accurate detection of the site with the highest velocity using streamlines and the advantage of 3-directional flow velocity information. Another recent study has reported that transthoracic echocardiography (TTE) slightly underestimates peak velocities for aortic stenosis compared to 4D flow CMR suggesting that 4D flow CMR may be the preferred option especially for eccentric and multiple jets.

A novel hemodynamic parameter derived from 4D flow data is wall shear stress (WSS). Although this measure is referring to frictional shear stress on the aorta and the true WSS is not directly accessible due to insufficient spatial resolution, it provided significant insights regarding clinical consequences of bicuspid aortic valve (BAV) and aortic valve stenosis. It has been argued that a BAV may have an asymmetrical orifice and thus an increased eccentric flow angle which leads to increased WSS and dilation of the ascending aorta. Furthermore, BAV with stenosis yielded an even larger
extent of increased WSS in the ascending aorta than without stenosis.\textsuperscript{35} Evaluation of WSS in the aorta is promising to be used in the management of aortic valve disease and valve replacement strategies.\textsuperscript{36}

**Congenital heart diseases**

CHD frequently results in important alterations in cardiovascular flow dynamics, which may have clinical consequences. Accurate quantification of flow parameters in this patient group is therefore essential for optimal patient management. Careful planning of 2D flow CMR with the use of several imaging planes leads to long acquisition times and potential misalignment of planes may underestimate velocity measurements. Easy planning of a single 3D volume in 4D flow CMR may provide faster scanning than 2D flow CMR. Moreover, 4D flow CMR permits retrospectively placement of analysis planes at any arbitrary location within the acquisition volume. It has been shown that flow quantification with 4D flow CMR may provide improved and time-efficient flow quantification compared to 2D flow CMR in CHD.\textsuperscript{37} However, small shunt flow volumes may still be underestimated by 4D flow CMR due to insufficient spatial resolution. In these particular cases, evaluation of pulmonary vs. systemic flow volume can be performed using 4D flow CMR to ensure the accuracy of the results.\textsuperscript{38} Finally, visualization of abnormal flow patterns within the heart may contribute to understanding the interaction between surgically changed heart structures and hemodynamics in CHD.\textsuperscript{39}

**Investigational clinical applications of 4D flow CMR-derived hemodynamic parameters**

**Kinetic energy**

An important part of the total work of the heart transfers into KE of blood and KE is directly involved in the movement of blood.\textsuperscript{40} Recent
developments of 4D flow CMR enable quantification and mapping of KE of blood flow within the heart (Figure 5 and Supplementary data online, Video S3a–c). For every voxel, KE is computed by multiplying 0.5 times the density of blood with the voxel volume, and velocity magnitude squared. The KE of the region of interest can then be computed by summing the KE of each voxel at a certain time frame.

Evaluation of intra-cardiac energy profiles integrated over a complete cardiac chamber may provide more comprehensive clinical data than only planar measurements can offer. Eriksson et al. reported that heart failure patients with mild left ventricle (LV) remodelling exhibited impaired preservation of inflow KE compared to healthy individuals despite equivalent stroke volumes. In particular, the total direct flow KE at end-diastole was lower in heart failure patients which may closely affect diastolic–systolic coupling. Furthermore, it was documented that myocardial infarction resulted in a decrease of the average LV KE over the whole cardiac cycle. Although these studies provide insight into altered energy levels in patients with LV dysfunction, study settings and results are not coherent enough to draw clear clinical conclusions.

Assessment of LV energetics may provide a consistent classification for impaired LV filling. In healthy individuals, LV KE during E and A waves presented a stronger relation with increasing age than 2D mitral inflow measurements. Another study investigated right and left atrial KE in healthy volunteers and demonstrated three peaks in KE time profiles in both atria: during ventricular systole, early ventricular diastole, and atrial contraction. Early diastolic KE of the LA was correlated with LV mass, whereas the same situation was not observed in the right chambers. Presumably, LV mass plays a determinant role in increasing the pressure gradient within the LV during diastole.

Finally, following mitral valve intervention for mitral valve insufficiency, a decrease of mean systolic and early-diastolic KE peaks was observed. However, late-diastolic KE peak remained close to pre-operative high levels suggesting that physiological flow patterns within the LV may not be fully restored after surgery.

**Turbulent kinetic energy**

While standard cardiovascular blood flow is predominantly laminar, it can transitionally become turbulent with high-velocity fluctuations due to conditions such as valvular stenosis. Part of the energy content of turbulent flow dissipates as heat and is irreversibly lost from the blood flow. Turbulent kinetic energy (TKE) provides a measure of this energy loss and can be estimated by 4D flow CMR based on intra-voxel velocity distribution and its relation with the MR signal. Significance of turbulence within the normal heart has long been investigated, but no agreement has been reached, yet. Using 4D flow CMR, TKE values were found similar for LA and LV ranging from...
0 to 5 mj in healthy subjects. \(^{47,48}\) Besides, LV TKE values were compared between healthy subjects and individuals with dilated cardiomyopathy (DCM). \(^{47}\) Although early diastolic LV TKE did not differ between groups, late diastolic LV TKE was significantly higher in DCM patients, suggesting that inefficient flow is particularly occurring during late diastole. In another study in patients with clinically significant mitral regurgitation, average LA TKE per cardiac cycle was associated with the regurgitant volume indicating the severity of mitral valve regurgitation. \(^{48}\) Furthermore, patients with aortic valve stenosis demonstrated higher TKE in the ascending aorta compared to healthy individuals. \(^{49,50}\) TKE may serve as a complementary tool to echocardiography to tailor the management of aortic stenosis. Finally, patients with repaired Tetralogy of Fallot with a high level of pulmonary regurgitation demonstrated higher TKE levels in the right ventricle (RV) compared to ones with a low pulmonary regurgitation, \(^{51}\) and a strong relationship was observed between TKE levels and the RV end-diastolic volume index.

### Viscous energy loss

Another form of energy loss within blood flow is called viscous energy loss (EL) and this does not necessarily require any pathological situation such as TKE. The EL arises as a result of frictional forces between blood flow elements due to the variability of flow velocities within a vessel. \(^{52}\) 4D flow CMR allows quantification of EL by providing the 3-directional flow velocity field and using the Navier–Stokes equations. \(^{53}\)

Using 4D flow CMR, the association between EL and altered flow dynamics within the LV was investigated in patients with corrected atrioventricular septal defect. It was found that EL was higher during diastole in this patient group compared to healthy individuals. \(^{52}\) Presumably, new positioning of the left atrioventricular valve created a more laterally directed inflow pattern and altered LV filling dynamics. Moreover, it was demonstrated that in patients after surgical correction of the pulmonary circulation according to the Fontan procedure, intraventricular EL is increased compared to healthy subjects. \(^{52}\) In another recent study, hemodynamic stress response on intraventricular EL, KE, and vorticity were shown to be inversely related to maximal exercise capacity in Fontan patients. \(^{54}\) Since it is unclear how the heart reacts to elevated levels of EL in the LV, further studies investigating the clinical relevance of EL are warranted.

### Pressure difference

4D flow CMR offers the quantification of pressure gradients throughout the cardiovascular system based on either the simplified Bernoulli equation (pressure gradient = 4\(V_{peak}^2\)) or the Navier–Stokes equation. 4D flow CMR allows for the estimation of spatial and temporal information of flow-related pressure differences, \(^{55}\) not absolute pressure values.

Relative pressure maps can be employed to assess intra-cardiac pressure differences (Figure 6). \(^{56,57}\) Furthermore, intra-cardiac hemodynamic forces which are closely related to pressure variations could be quantified in three directions. \(^{58}\) Importantly, it was reported that hemodynamic forces significantly differ between patients with left ventricular dysynchrony and healthy controls including loss of longitudinal forces in diastole. \(^{59}\) This new approach of quantification of left ventricular dysynchrony may play a potential role in improving cardiac synchronization therapy outcomes.

### 4D flow CMR vs. 4D colour Doppler echocardiography and 4D flow CT

The expected clinical benefits of cardiac flow imaging in its complete dimensionality are prompting clinicians to have such option in clinical practice through a robust modality. In this regard, 4D application of colour Doppler echocardiography has undergone extensive clinical research, as well. For consistent use of nomenclature, we will use the term of 4D (3D + time) colour Doppler echocardiography throughout the manuscript. A summary of comparison of typical features between 4D flow CMR and 4D colour Doppler echocardiography is provided in Table 1.

An important and highly clinically relevant advantage of both 4D flow CMR and 4D colour Doppler echocardiography is that they enable retrospective flow assessment. Although 4D colour Doppler echocardiography can evaluate flow in 3D and against time, this can only be done in a single direction, whereas 4D flow CMR offers simultaneous 3-directional \(V_{enc}\), which provides assessment of flow in any direction in the acquired volume of interest. Advanced 3D flow visualization tools of 4D flow CMR assist in identification of complex flow patterns and only 4D flow CMR can offer a full quantification of flow at an arbitrary location within the acquired volume of interest, which precludes the missing region of interests for flow quantification. Importantly, these applications can be benefitted during post-processing with the employment of specific software and naturally are time consuming. Colour flow imaging with 4D echocardiography allows the advantage of fast viewing of flow during acquisition, yet the quality of images can significantly be affected due to low spatial and temporal resolution. Notably, the implication of 4D colour Doppler echocardiography can allow improved atrioventricular valve regurgitation grading through proximal iso-velocity surface area (PISA) and vena contracta (Figure 7 and Supplementary data online, Video S4a and b). Transesophageal echocardiography (TEE)-derived 3D integrated PISA was found more accurate than TTE-derived 3D integrated PISA and 2D echocardiography PISA approaches for mitral regurgitation quantification in a study validated against CMR. \(^{60}\) The superiority of TEE-derived 3D approach may be primarily due to no geometric assumption as a result of 3D imaging and increased proximity to the valve with TEE imaging. Importantly, no grading cut-off values have been established yet regarding 4D echocardiography colour Doppler indexes.

Of note, 4D flow CMR exceptionally permits generation of several novel hemodynamic parameters such as KE which may lead to enhanced clinical management for cardiac diseases (e.g. heart failure). \(^{72}\) Furthermore, in addition to 4D flow imaging, CMR can provide a comprehensive whole-heart imaging experience in a single scan including gold standard quantification of volume and function, evaluation of myocardial edema and myocardial fibrosis. Therefore, CMR can be considered as a reasonable modality in terms of cost-effectiveness, although CMR stands intrinsically as an expensive modality.

Alternatively, intra-cardiac 4D flow evaluation with computed tomography has been recently explored in a feasibility study. \(^{61}\) This application is simply based on combination of computational fluid dynamics with conventional coronary CT angiography data. Although
having the advantage of submillimeter spatial resolution, the requirement of retrospective gating for the entire cardiac cycle data prevents the application of this technique in clinical practice, as prospective gating is the accepted approach at present with the aim of reduced radiation. In addition, the lengthy and complex computational process remains another fundamental drawback.

Clinical perspective and future directions

Optimal severity grading values for cardiac valvular diseases should still be established for 4D flow CMR; existing severity classifications are based on echocardiographic and 2D flow assessment. For congenital cases requiring follow-up, an important advantage of the use of 4D flow CMR is that comprehensive accurate hemodynamic data can readily be obtained without using radiation. The novel hemodynamic parameters reveal underlying mechanisms of cardiac diseases and hold promise for employment in clinical practice, albeit they remain research parameters yet. Recent research documented a consistent relationship between left-heart diastolic novel hemodynamic quantities (e.g. KE, vorticity) and healthy ageing.22,62 Besides, gender-related significant differences were observed for LV and LA 3D vortex flow.22,62 Advancing these investigations may provide a deeper understanding regarding the physiological effects of age and gender differences on the intra-cardiac flow. Notably, there is a fundamental need for multi-center longitudinal studies to test the clinical validity of these and other preliminary findings.

The acquisition process of 4D flow CMR although time consuming is relatively straightforward, whilst analysis of the data is still quite complex. In contrast to the previous decade, options of analysis tools became diverse presenting a non-standardized structure in terms of provided analysis region, ancillary tools such as valvular tracking and application methodology. Further development and establishment of a standardized analysis process that allows for a uniform workflow will generate reproducible and comparable quantification.

In addition, 4D flow CMR datasets are intrinsically of large volume and therefore integration of artificial intelligent approaches such as machine learning can allow much more rapid acquisition and analysis processes. Reconstruction duration can be significantly shortened as less amount of sampling will be needed and automation of segmentation will extremely decrease analysis time. Moreover, further improvement in image quality of 4D flow magnitude data in terms of signal intensity and contrast will enable a much more effective and fast segmentation and improved feature tracking. Considering the current rate of respective technological developments and expanding

Figure 6 Flow and pressure gradient assessment in the left ventricle. Demonstration of flow and pressure quantifications in the left ventricle at basal, mid, and apical levels in a 12-year-old healthy male. On the left side, determination of the levels on the long-axis and segmentation on the short-axis views, in the middle-right, flow curves and the relevant flow and pressure gradient results are displayed. On the far-right side, 3-dimensional appearances of the levels on a 2-dimensional multi-planar view are shown and the pressure differences between basal and apical levels are temporally plotted over the cardiac cycle.
Table 1  Comparison of characteristics between 4D flow CMR and 4D colour Doppler echocardiography

|                       | 4D flow CMR                                                                 | 4D colour Doppler echocardiography                                      |
|-----------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Acquisition           | ECG-gated, phase contrast, segmented cine acquisition                        | Real time, single or multi-beat acquisition                              |
| Respiration control   | Free breathing, navigator gating, bellows reading, self-gating               | Breath hold                                                             |
| Velocity encoding     | 3D, full 3D velocity vector field                                            | Single direction (in the direction of ultrasound beam)                  |
| Spatial resolution    | $1.5 \times 1.5 \times 3.0 \times 3.0 \times 3.0 \text{ mm}^3$              | Variable$^a$                                                           |
| Temporal resolution   | 30–40 ms                                                                    | 10–25 frame rate per second (40–100 ms) for zoomed/full volume single-beat acquisitions |
| Flow visualization    | 3D (streamlines, pathlines)                                                 | 3D velocity profiles                                                   |
| Flow quantification   | Retrospective globally or planar analysis at any location in 3D acquisition volume of interest | Semi-quantification (vena contracta, PISA of atrioventricular valves) |
| Total scan time       | 5–20 minutes (dependent on heart rate, efficiency of respiration control, type of parallel imaging) | 10–20 s per 3D view with colour flow imaging                           |
| Flow data analysis    | Full quantification, large variety of analysis tools, time consuming         | Semi-quantification, large variety of analysis tools                    |
| Requirement of expertise | Experienced CMR team is needed                                             | Experienced echo team is needed                                          |
| Derivation of hemodynamic parameters | KE, TKE, EL, pressure difference, vortex flow, haemodynamic forces | –                                                                       |
| Clinical applications | Valvular disease, congenital heart disease                                   | Valvular disease, congenital heart disease                              |
| Cost effectiveness    | Relatively expensive                                                        | TTE: inexpensive                                                        |
| Prosthetic valve flow | Not ideal, high level of metallic artefacts                                 | TEE: relatively inexpensive                                              |

$^a$Dependent on several factors, but it is considered significantly lower than 4D flow CMR.

Figure 7  Valvular flow quantification with 4D flow CMR and 4D colour Doppler echocardiography. On the left side, valvular flow visualization and quantification of 4D flow CMR is displayed in a 12-year-old healthy male. 3D blood flow on multi-planar views during systole for aortic valve and during diastole for mitral valve is visualized. The segmentations were done using an artificial intelligence approach. Furthermore, aortic and mitral valve flows are temporally plotted over the cardiac cycle and valvular flow measurements are provided. On the right side, measurement of 3D vena contracta area of functional mitral regurgitation with 4D colour Doppler transesophageal echocardiography in a 51-year-old male is shown. Volume rendering view (top left), two perpendicular long-axis views of mitral regurgitation jet and one short-axis view (bottom right) at the level of coaptation defect are visualized. Vena contracta area was measured as 0.6 cm$^2$ and circumference of the jet as 3.3 cm.
incorporation of artificial intelligence in 4D imaging, it is of the high likelihood that 4D flow CMR will be an essential clinical tool within the upcoming 5–10 years and massively enhance the understanding of flow within the heart.

To conclude, 4D (3 dimensions + time) flow CMR is a novel, powerful tool to study the impact of cardiovascular disease on flow and vice versa. Multiple advanced hemodynamic parameters can retrospectively be derived from the 4D flow CMR datasets. While offering clear advantages over other imaging modalities including 4D colour Doppler echocardiography and 4D flow CT, the lack of analysis tools that allow for standardized quantification of 4D flow values prevents a rapid widespread adoption for routine clinical use.

Supplementary Data
Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

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