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Flow Imaging: Cardiac Applications of 3D Cine Phase-Contrast MRI

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Abstract

Global and regional blood flow dynamics are of pivotal importance to cardiac function. Fluid mechanical forces can affect hemolysis and platelet aggregation, as well as myocardial remodeling. In recent years, assessment of blood flow patterns based on time-resolved, three-dimensional, three-directional phase-contrast magnetic resonance imaging (3D cine PC MRI)(1) has become possible and rapidly gained popularity. Initially, this technique was mainly known for its intuitive and appealing visualizations of the cardiovascular blood flow. Most recently, the technique has begun to go beyond compelling images towards comprehensive and quantitative assessment of blood flow. In this article, cardiac applications of 3D cine PC MRI data are discussed, starting with a review of the acquisition and analysis techniques, and including descriptions of promising applications of cardiac 3D cine PC MRI for the clinical evaluation of myocardial, valvular and vascular disorders.

Introduction

Global and regional blood flow dynamics are of pivotal importance to cardiac function(2-4). Fluid mechanical forces can affect hemolysis, platelet activation and aggregation, as well as myocardial remodeling(2,5-9). In both normal and diseased hearts, blood flows in a highly complex manner through the cardiac chambers. This cannot be assessed by the diagnostic tools currently in use, as these are often limited to the measurement of peak velocity across a valve stenosis or the measurement of cardiac output. Given the lack of appropriate tools for the assessment of time-varying three-dimensional flows, it is not surprising that our understanding of intracardiac blood flow remains far from complete.

In recent years, assessment of blood flow patterns based on time-resolved three-dimensional three-directional phase-contrast magnetic resonance imaging (3D cine PC MRI)(1) has become possible and rapidly gained popularity. Initially, this technique was mainly known for its intuitive and appealing visualizations of the cardiovascular blood. Most recently, the technique has begun to go beyond compelling images towards comprehensive and quantitative assessment of blood flow. In this article, cardiac applications of 3D cine PC MRI data are discussed, starting with a review of the acquisition and analysis techniques.

Three-dimensional Cine Phase-Contrast MRI acquisition

Standard protocols for acquisition, processing and presentation of 3D cine PC MRI do not exist. Different research groups use their own approaches and adapt them for different applications (10-16). Differences exist in temporal coverage, spatial coverage, acquisition time, and data quality. The majority of the techniques are optimized for vascular applications. Real time three-dimensional PC MRI measurements are still not possible, which means that cardiac gating is necessary. Using cardiac gating, different parts of k-space acquired from different heart beats can be merged into a full dataset covering a part or a complete cardiac cycle. Different gating options exist, and can be divided into prospective and retrospective methods. In prospective gating the different parts of k-space are acquired at defined time points from the ECG trigger, until the 3D k-spaces at these defined times points are fully acquired. A limitation of prospective gating arises from the fact that the length of different heart cycles will differ. As full 3D datasets only can

be reconstructed for those times points where data is acquired from every heart beat, the last part of the heart cycle, late diastole, cannot normally not be adequately covered using prospective gating. In retrospective gating, the different parts of k-space, acquired at different heart beats, are retrospectively assembled into full 3D datasets at a number of cardiac phases. In order to do this, all heart cycles are linearly or non-linearly stretched to the same length, and full 3D datasets are reconstructed by interpolation of the required data parts at a number of heart phases. Large beat to beat variations will also in this gating technique affect the data quality, but occasional significantly longer or shorter heart beats can often be excluded. Retrospective gating, with its full coverage of the complete heart cycle, is therefore well suited to the study of intracardiac blood flow, which is seldom static and has important unique characteristics at each temporal phase.

Scan time is frequently an important factor in cardiac 3D cine PC MRI measurements. The scan time is largely defined by the spatial coverage and the temporal and spatial resolution of the data acquired. In 3D cine PC MRI, the temporal resolution is typically limited by the repetition time (TR) x 4 flow encoding segments, unless the flow encoding segments are acquired in consecutive cardiac cycles. Various methods are used in trade-off between spatiotemporal resolution and scan time. Segmented k-space techniques are commonly used, in which several k-space segments are acquired per cardiac cycle, which decreases the temporal resolution, but also the scan time. Minimizing the imaged field-of-view can further reduce the imaging time, such as focusing the acquisition on the left ventricle, but most cardiac applications require coverage of the complete left side or the whole heart(15,17-20). Other techniques can be used to further decrease the scan time, either by use of parallel imaging, data-driven sparse sampling, efficient non-cartesian k-space trajectories, or combinations of these(14,21-23). It is important to realize the cost associated with all of these trade-offs, in order to ensure sufficient data quality. In addition, recognized sources of error such as eddy currents(24), concomitant gradient fields(25), and gradient field distortions(26), have to be handled with care, in order to obtain sufficient data quality for reliable analysis. Quality control based on simulation studies(27), phantom experiments(19,28), and especially in-vivo validations(17,19), is therefore of major importance. Small changes in imaging settings, such as a longer echo time (TE), may sometimes result in significant gains in image quality, or conversely may degrade the

data. The optimal imaging settings are often system dependent, and need to be thoughtfully sought and defined.

In the literature, terminology regarding 3D cine phase-contrast MRI acquisition varies, unfortunately resulting in confusion. Initially, the term three-dimensional was used to describe a three-directional two-dimensional MRI acquisition(29). Later on, 3D cine PC MRI acquisitions have sometimes being referred to as 4D or 7D. Normally, the same terminology is used for acquisition using either prospective or retrospective gating. In this manuscript, 3D cine phase-contrast MRI (3D cine PC MRI) is used to describe a three-dimensional three-directional phase-contrast MRI acquisition with prospective or retrospective cardiac gating. The majority of the cardiac 3D cine PC MRI studies are, however, performed using retrospective cardiac gating.

Flow visualization and quantification techniques

The time-resolved 3D velocity data can be visualized using a range of different techniques, such as color mapping of speed, vector plotting, or particle tracing. Of these techniques, particle tracing has become most popular due to its intuitive and appealing appearance. In temporally varying flows, different kinds of particle traces can be computed, including streamlines, streaklines, and pathlines. Instantaneous streamlines are parallel to the velocity vector for a single instant in time at every point, but are inadequate descriptors of time varying flow, and may cause confusion. Long streamlines, computed from one time frame of a time-varying flow field, can be misinterpreted as representing more than one time frame, and should be used with care and clear communication, especially for visualization of the highly variable intracardiac blood flow. A pathline follows the path that an imaginary particle, or a tiny drop of dye, would take over time. Pathlines have become most popular for the visualization of intracardiac blood flow. Streaklines, comparable with the continuous injection of dye, have seldom been mentioned in combination with PC MRI data, but do in fact appear when continuous emission of pathlines is created over time. Initially, particle traces were emitted from interactively positioned points or 2D grids(28). Emitters could be positioned based on anatomical landmarks, obtained from the low contrast magnitude data from the 3D cine PC MRI acquisition or balanced steady-state free precession images, or previous visualization of the

flow field. Emitters could be refined to match a specific flow of interest by downstream filtering of traces at a desired flow route(18). Areas of interest can also be defined using automatic characterization of flow features, e.g. by using a pattern matching approach(30). Using this approach, flow structures of interest, such as vortices, swirling flow, diverging or converging flow, and parallel flow, can be defined. Recently, a semi-automatic pathlines based approach for the visualization and quantification of intracardiac blood flow was validated(17). In this approach, pathlines are emitted from a 3D volume covering a complete cardiac chamber and traced both forwards and backwards in time to cover a complete cardiac cycle,. For the left ventricle, a comprehensive assessment with low intra and inter-user variability was obtained by emitting pathlines at the time of isovolumic contraction from a segmented left ventricle. This approach allows for quantitative assessment of the left ventricular blood flow, in total or separated into different functional components.

It should be noted that particle trace visualizations can yield compelling images and animations even if the data quality is poor. An appealing feature of the pathlines analysis technique proposed by Eriksson et al(17) is that it allows for dataset specific quality control. In the study, the number of pathlines entering and leaving the left ventricle was well matched, suggesting that pathlines computed over a large part of the cardiac cycle could be accurately traced. The left ventricular outflow volumes, computed by multiplying the number of traces with the emitter density, correlated with estimates obtained by through-plane phase-contrast MRI and Doppler ultrasound. Comparison of the pathline based left ventricular inflow and outflow volumes creates a dataset-specific data quality assessment. When accurate volume flow assessment is the predominant aim, direct integration of the velocities in a 2D slice, through the 3D data is preferred(19). If retrospective valve tracking is used in this approach, volume flow can even be obtained through all four heart valves simultaneously(31,32).

Over the years, invasive measurements of pressure have played an important role in the assessment of cardiovascular hemodynamics. Non-invasively, the pressure difference over a stenosis estimated from the peak velocity using the simplified Bernoulli equation(33) has become an important clinical method for assessment of valvular stenoses. In principle, a similar approach could be based on 4D PC MRI. However,

the 4D nature of the data is better exploited by computation of the time-resolved 3D pressure field. In laminar flow, pressure gradients can be computed from the time-resolved 3D velocity field using the Navier-Stokes equations. These pressure gradients can be integrated along any line to obtain the pressure difference(34). Further, by solving the pressure Poisson equation, the complete 3D pressure field can be obtained throughout the heart(35,36). This technique has been applied to measurement of the pressure field in the normal human heart during early and late diastolic filling, as well as systole. Regional and shifting pressures could be visualized; even the relative low pressures in the center of the vortices were apparent. Even though this scalar representation of the flow field is intuitive and pressure is already an important clinical parameter, the technique has not yet been utilized to study the blood flow dynamics in the diseased heart, in part due to the unavailability of suitable software(36). Other important reasons are that the relative rather than the absolute pressure field is obtained and the pressure field can only be obtained in laminar flow. While this is likely adequate for normal hearts and some cardiac regions, many clinical applications may involve valvular stenoses or regurgitation which involve turbulent blood flow.

Traditionally, in 3D cine PC MRI only the phase of the MRI data is used to estimate the mean velocity within a voxel. Other MRI flow imaging techniques also allow assessment of the velocity distribution within the voxel. Recently, it has been shown that the PC MRI technique can be extended to the measurement of any moment of a velocity distribution, e.g. standard deviation or skew, within a voxel(37). Based on this theoretical framework, a method has been presented and validated that utilized the magnitude of a 3D cine PC MRI measurement to obtain the standard deviation of the intravoxel velocity distribution (38,39). Often one and the same acquisition can be used to obtain both the mean velocity and the intravoxel velocity standard deviation, but sometimes different velocity encoding ranges (VENC) are necessary in order to obtain accurate measurements. The standard deviation in one direction is directly related to the turbulent normal stress in that direction. The turbulent normal stresses in 3 orthogonal directions add up to the turbulent kinetic energy, which is a common measure of turbulence intensity(16). Turbulent blood flow in the heart causes viscous dissipation, which is the major cause of pressure drop over tight stenoses(40). Fluctuations in flow velocity and pressure impose fluid mechanical forces on its surroundings, which have been associated with hemolysis (5-9). In the heart, imaging of turbulence intensity appears very sensitive to

valvular abnormalities. While only low or negligible levels of turbulence intensity were observed in normal hearts, considerably elevated values were observed in valvular stenoses and regurgitation, as well as prosthetic heart valves(16).

Intracardiac blood flow in health and disease

Assessment of blood flow patterns based on 3D cine PC MRI has been used to study intracardiac flow in both normal and diseased hearts. The technique has been used to describe the blood flow patterns in the normal left atrium(41). Vortical blood flow was seen not only during ventricular systole, but also during diastolic diastasis when the mitral valve was open. The blood from the left pulmonary veins was predominantly incorporated in these vortices, while the blood from the right veins mainly streamed along the vortex periphery. These blood flow patterns may have beneficial effects in avoiding left atrial stasis in the normal subject in sinus rhythm. While the dominant systolic vortex in healthy volunteers was situated in proximity to the left sided pulmonary veins, in patients with mitral regurgitation the systolic vortex was instead located in proximity to the regurgitant jet(42). In these patients, elevated turbulent kinetic energy was observed in the left atrium. The average TKE per cardiac cycle was strongly related to the regurgitant volume.

In diastole, blood transiting the left atrium fills the left ventricle in early and late diastolic phases. However, the direction of the blood flow differs between these filling phases (18,43), probably related to a change in location and orientation of the mitral valve due to progressive LV filling and atrial contraction. Based on 3D cine PC MRI data, it was concluded that alignment and spatial offset are important sources of error in Doppler diastolic parameters(43). Blood entering the left ventricle at different time points is characterized by different pathways through the left ventricle. Pathlines emitted from the mitral annulus at peak early inflow continue to the apex before turning towards the aortic valve, while pathlines emitted at peak late inflow do not reach the left ventricular apex(18,43). The left ventricular inflow is surrounded by a (partial) ring vortex, which is strongest underneath the mitral valve leaflets. This ring vortex is initiated at early diastole, and reaccelerated at late diastole. In the normal left ventricle, the anterior part of the ring vortex is

strongest. Its strength diminishes with the onset of systole. This anterior vortex is even more pronounced in patients with dilated cardiomyopathy(3).

Using pathline based flow analysis technique proposed by Eriksson et al(17), the blood flow in the left ventricle can be divided into different components according to different patterns over the cardiac cycle. Bolger et al(18) defined 4 different flows: *direct inflow*, which enters and exits the LV in one heart beat, *retained inflow*, which enters the left ventricle but is not ejected with the next systole, *delayed ejection volume*, the volume that is already within the left ventricle at the onset of diastole but achieves ejection during the ensuing systole, and a *residual volume* that both starts and ends the cardiac cycle inside the left ventricle(18). In the normal heart, about two thirds of the blood entering the left ventricle in diastole leaves the left ventricle in the following systole(17,18); the *direct flow*. The *retained inflow*, and *delayed ejection volume* constitute one third of the inflow and outflow, respectively. The *direct flow* preserves a significant portion of its kinetic energy during its transit through the ventricle, compared to the *retained inflow*, which has lost the major part by end diastole. The relative amount of *direct flow* taking this efficient route through the left ventricle, has been shown to be considerably smaller in patients with congestive heart failure(3,18).

The systolic left ventricular outflow is characterized by elevated velocities through the aortic valve and vortices behind aortic valve leaflets, in the sinuses of Valsalva(44,45). Three-dimensional cine PC MRI has been used to investigate these vortices after different approaches to valve-sparing aortic root replacement(44,45). Aortic outflow abnormalities, such as valvular stenosis or subvalvular membrane, typically result in increased velocities and elevated values of turbulent intensity in the aortic root(16). In aortic valve regurgitation flow, high velocities and elevated values of turbulent intensity were seen in the left ventricle(16). The presence of a prosthetic aortic valve results in slightly elevated peak velocities, and considerably elevated turbulent intensity values compared to the normal aortic root(11,16). The effect of a prosthetic heart valve on the velocity field and turbulent intensity seems to be specific to the valve type(46).

Right heart flow is even more unexplored using 3D cine PC- MRI, but similar methods can be used for assessment of the right ventricle blood flow (see Figure 1). Prospectively gated 3D cine PC MRI has been used to map blood flow patterns in patients with congenital heart disease(20,47), where complex abnormalities in cardiac anatomy make hemodynamic evaluation particularly challenging.

Progress towards clinical applications

Over the years, 3D cine PC MRI has turned into a comprehensive technique for the assessment of blood flow in the cardiac chambers. This makes it a powerful method for research applications dealing with intracardiac blood flow. In its initial applications, 3D cine velocity MRI was mainly used to increase our understanding of the blood flow patterns in the normal heart. Time consuming acquisition and analysis, in combination with the complexity of the intracardiac blood flow patterns themselves, hampered studies of the diseased heart. Today, even though the intracardiac blood flow patterns in the normal heart are still far from completely understood, studies of the effect of different pathologies are now possible, and several of these have been reported or are underway. These studies can be expected to further increase our understanding of intracardiac blood flow patterns, bringing the technique closer to clinical application. The use of cardiac 3D cine PC MRI in large multicenter studies remains troublesome, however. Three dimensional cine PC MRI sequences have become available on many MRI systems, often as a commercial product. The majority of these techniques do not include the use of retrospective gating, however, which is necessary to cover the complete cardiac cycle and is vital in intracardiac blood flow assessment. An important obstacle in the clinical application of 3D cine PC MRI is also its long scan time. Typical acquisition times are currently too long to be added to a standard cardiac MRI protocol or to justify its use in clinical practice. The usage of parallel imaging, data-driven sparse sampling, or efficient non-cartesian k-space trajectories(14,21-23) can decrease the scan time, but at the cost of data quality. Even though recently important improvements in the analysis process have been reported, further studies are necessary in order to adapt the analyses method to the question at hand. With optimized analysis methods and a sufficiently decreased acquisition time, so that a 3D cine PC can be part of a standard cardiac MRI protocol, clinical investigations will accelerate.

Conclusion

The potential of cardiac 3D cine PC MRI for clinical evaluation of myocardial, valvular and vascular disorders appears great. A single 3D acquisition encompassing the entire heart and adjacent aorta can provide a wealth of information, which can be used to extract different clinically relevant parameters for each chamber and flow of interest. One 3D acquisition could replace several 2D quantitative flow acquisitions, saving expensive and time-consuming planning. Retrospective localization of slices would be especially helpful for complex anatomies such as congenital heart diseases, and would also allow for volume flow measurements that track the valve planes. Particle trace based visualization and quantification may add to the diagnosis and staging of heart diseases such as dilated as well as ischemic cardiomyopathy, while turbulence intensity mapping appears to be most promising for the detection and quantification of valvular disease. The role and incremental benefits of these measurements remain to be determined with future studies. Robust, efficient and widely available tools optimized for intracardiac blood flow studies will be the key to performing the large patient studies which will be crucial to refining our understanding of intracardiac blood flow patterns and developing novel clinical applications in the future.

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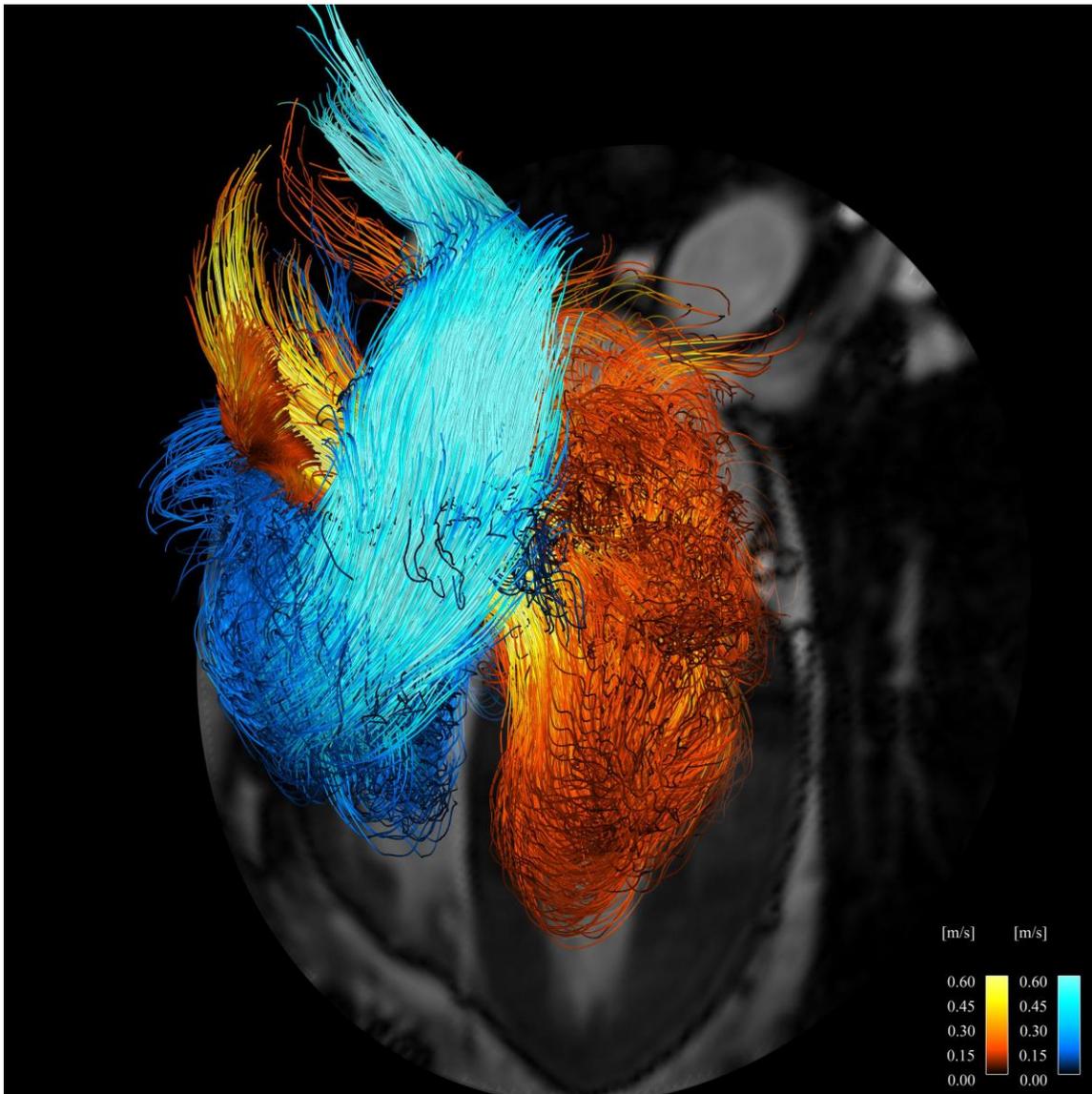
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This article describes a potential clinical application of cardiac 3D cine PC MRI; flow mapping and quantification in patients with Fontan circulation.

Figures



Pathline visualization of Direct intracardiac blood flow in the left (red-yellow) and right (blue-turquoise) side of the heart of a healthy, 54 year old male. Direct flow enters the ventricle during diastole and leaves the ventricle during systole in the analyzed heart beat(17). A separately acquired balanced steady-state free precession four chamber image provides anatomical orientation.