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Four-dimensional phase contrast magnetic resonance angiography: Potential clinical applications

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Abstract

Unlike other magnetic resonance angiographic techniques, phase contrast imaging (PC-MRI) offers co-registered morphologic images and velocity data within a single acquisition. While the basic principle of PC-MRI dates back almost 3 decades, novel time-resolved three-dimensional PC-MRI (4D PC-MRI) approaches have become increasingly researched over the past years. So-called 4D PC-MRI includes three-directional velocity encoding in a three-dimensional imaging volume over time, thereby providing the opportunity to comprehensively analyze human hemodynamics *in-vivo*. Moreover, its large volume coverage offers the option to study systemic hemodynamic effects. Additionally, this offers the possibility to re-visit flow in any location of interest without being limited to predetermined two-dimensional slices.

The attention hemodynamic research has received is partially based on flow-based theories of atherogenesis and arterial remodeling. 4D PC-MRI can be used to calculate flow-related vessel wall parameters and may hence serve as a diagnostic tool in preemptive medicine. Furthermore, technical improvements including the availability of sufficient computing power, data storage capabilities, and optimized acceleration schemes for data acquisition as well as comprehensive image processing algorithms have largely facilitated recent research progresses.

We will present an overview of the potential of this relatively young imaging paradigm. After acquisition and processing the data in morphological and phase difference images, various visualization strategies permit the qualitative analysis of hemodynamics. A multitude of quantitative parameters such as pulse wave velocities and estimates of wall shear stress which might serve as future biomarkers can be extracted. Thereby, exciting new opportunities for vascular imaging and diagnosis are available.

Keywords

phase contrast MRI; blood flow; hemodynamics; 4D flow; flow-sensitive MR; aneurysm; atherosclerosis; PC VIPR; PC HYPR Flow

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Introduction

Notice of a diagnostic ‘one-stop-shop’ is often made when promising new techniques are first presented, referring to the fact that a single acquisition can be exploited for different diagnostic goals. A good example is the ECG-synchronized high-resolution computed tomography angiography (CTA) of the chest. In a single examination, it potentially allows for the diagnosis of coronary artery disease, pulmonary embolism, and aortic dissection – the “triple-rule-out” examination¹. In addition, ECG-gated CTA can be used to extract dynamic information about the heart.

4D phase contrast (PC) imaging, i.e., time-resolved 3-dimensional phase contrast imaging with velocity sensitivity in all three spatial directions, is in, some respects, a ‘one-stop-shop’ MRI technique. However, it is not yet as well researched and embedded in clinical imaging protocols as “triple-rule-out” CTA. However, since both morphologic and dynamic information are simultaneously available, these 4D PC techniques are especially interesting for cardiovascular diseases, neurovascular imaging, and organ hemodynamics where complex flows are present and systemic and localized changes interact. Furthermore, the opportunity to simultaneously obtain morphological and functional results in a reasonable scan time without the restraints of ionization radiation is particularly interesting in pediatric imaging, congenital heart disease in particular.

It is the main objective of this review to present an insight into the potential that this young technique undisputedly has. Since there are different vascular territories to be investigated and different analysis options at hand, we will cover the different analytical aspects within various vascular territories 4D PC-MRI has been applied to so far. The section on neurovascular imaging will mirror the adaptation to time-resolved contrast-enhanced and high spatial resolution imaging with sophisticated undersampling and projection reconstruction schemes for signal recovery. Qualitative hemodynamic analyses will be discussed using clinical examples from organs systems such as the heart and the liver. For the discussion of flow, pressure, and derived vessel wall quantification derived from the acquired velocity fields, aortic imaging will be the main focus. There is a multitude of potential applications of this technique and not all of them can be discussed. And although certain applications and hemodynamic parameters are discussed in a specific vascular territory, the presented imaging and analysis principles are transferable to different vascular territories.

Basic technical considerations

Phase contrast imaging

Fully three-dimensional phase contrast imaging with three-directional velocity-sensitivity was first introduced by Wigstrom et al. in 1996². Its roots, however, date back to the proposal to use phase shifts for signal generation by Paul Moran in 1982³. It is interesting to note that before contrast-enhanced MR angiography was introduced, phase contrast imaging was primarily considered as an alternative to time-of-flight for the generation of MR angiographic studies.

Currently, there are multiple encoding schemes by which phase contrast can be used as a method to detect and measure velocity and, in the context of this overview, the motion of blood flow in particular. In its simplest form, initial flow compensation is followed by two opposing gradients that are played out in succession. While stationary tissue experiences no resulting net magnetization (the magnetization by opposing gradients cancels out), spins of moving tissue are confronted with non-matching magnetic field gradients. This results in a remaining net magnetization which can be picked up in form of a small residual phase.

Subtraction of data from before and after gradient reversal thereby enables the determination of the 'phase difference', which is directly proportional to the velocity of the underlying motion (figure 1 A and B).

Such basic one-directional velocity encoding strategies are nowadays implemented on all clinical MR scanners. Phase contrast imaging in form of two-dimensional (2D) slices with one-directional flow encoding has become a basic tool for routine qualitative and quantitative cardiovascular flow analysis. For example, 2D PC-MRI is used regularly in clinical practice for determination of the Q_P/Q_S ratio in congenital heart disease by measuring the flow through the main pulmonary artery (Q_P) and the ascending aorta (Q_S). Also, it is a basic instrument in testing of cardiac valve function, for the determination of the severity of vessel stenoses, and for the qualitative analysis of shunts.

From 2D to 3D phase contrast imaging

The subsequent introduction of 3D imaging phase contrast with multidirectional motion-encoding schemes was the logical consequence of two overt advantages: First, three-dimensional (3D) imaging in general is increasingly used to exploit the inherent high signal. Second, 3D imaging avoids potential error arising at the non-ideal borders of multiple 2D slabs that could be joined to a 3D data volume. In 3D phase contrast imaging, however, six acquisitions are theoretically required for three-directional velocity encoding (taking into account that simple motion encoding uses two acquisitions to detect unidirectional flow). To render such acquisitions more time-efficient and suitable for clinical purposes, Pelc et al. have proposed using simple or balanced Hadamard-type four-point encoding schemes (figure 1 C)4.

In addition, modified encoding schemes are used to allow a time-efficient adaptation of the velocity sensitivity to a reasonable large range of velocities. Cautious choice of the velocity encoding sensitivity adapted to the expected velocities is mandatory to maximize the sensitivity to slow flow velocities while avoiding aliasing and, hence, erroneous data5. Johnson and Markl introduced a five-point encoding principle that offers increased sensitivity towards a larger range of velocities despite a reasonable small acquisition time penalty in comparison to dual- or multiple-vec encoding6.

Emerging technologies: acceleration and image processing

Several emerging technologies including novel image processing algorithms and acceleration schemes have been proposed to further overcome acquisition time restraints. They will likely contribute to the next generation of techniques by providing flow information in addition to highly detailed displays of anatomy. So far, their predominant implementation is neurovascular MR angiographic imaging. Their transfer to other vascular territories is mostly pending. The main innovations include 1) the acceleration of image acquisition by using radial undersampling strategies7, and 2) the application of highly constrained projection local reconstruction (HYPR LR) to contrast-enhanced whole brain MR scans8. By doing so, time-resolved whole brain imaging during the first passage of the contrast bolus with high spatial resolution and simultaneous phase contrast velocity information becomes available for different vascular territories and clinical questions. In our preliminary clinical experience, these techniques have produced images with high spatial and temporal resolution; features that are essential for the evaluation of the neurovascular system and may be transferred to other vascular territories.

Radial undersampling: an example of an acceleration technique—Undersampled acquisitions using radial readout trajectories were initially introduced with the radial acquisition obtained in the X-Y plane and phase encoding in the Z direction (Stack-of-Stars,

SOS)9. This approach reduces scan time while maintaining excellent spatial resolution. Similarly, steady state free precession SOS imaging is currently used for cardiac exams10-11. Furthermore, radial imaging can also be performed as a 3D volume (vastly undersampled isotropic voxel radial projection imaging – VIPR) producing a spherical acquisition with the highly desirable feature of encompassing a large volume, and in a neurovascular context, whole brain coverage12-13. The 3D radial acquisition is fast and multiple scans can be acquired during the passage of the contrast bolus (multi-echo VIPR)14. Also, velocity encoding gradients can be added to the 3D acquisition, simultaneously providing quantitative velocity information and phase contrast based vascular morphology15. Phase contrast VIPR (PC VIPR) also allows covering the whole thorax or abdomen in a single experiment.

PC HYPR Flow algorithm—Time-efficient sampling such as radial undersampling suffers a SNR penalty proportional to the square root of their acceleration factor. To recover SNR, post-processing algorithms can be applied16. When a dynamic contrast-enhanced series is obtained, highly constrained projection local reconstruction (HYPR LR) can be used to improve the spatial resolution and image quality of the contrast-enhanced dynamics series 17-18. Conceptually, each frame of an imaging time series is multiplied by a constraining (or composite) image to improve the signal-to-noise and spatial resolution of each frame. One approach is to use a 4D PC MRI acquisition as the composite image for the reconstruction of serial images. This strategy is termed PC HYPR Flow and is diagrammed in figure 2.

The PC HYPR Flow exam has two components, first a series of undersampled whole brain 3D radial scans is obtained during the first pass of a contrast bolus (CE VIPR). Each whole brain 3D CE VIPR scan is acquired in approximately one second. Following the dynamic phase of the acquisition, the second component is a radial 3D five-point velocity encoded phase contrast scan (5pt PC VIPR). Each frame in the CE VIPR series is then multiplied times the PC VIPR constraining data producing a new time series with nearly the signal to noise ratio and resolution of the 3D PC MRA exam. (HYPR reconstruction) In addition, the phase contrast velocity data are reconstructed to provide fully co-registered speed images and quantitative velocity information7.

Visualization options for phase contrast data

Angiography and basic use of velocity information

The acquired data volume in 4D PC MRI with its 3-directional velocity encoding is enormous. Visualization with grey scale values encoding for direction and velocity as performed in clinical routine for 2D PC-MRI becomes tedious when all three velocity directions are to be evaluated. Therefore, different visualization approaches, some even home-built, have been investigated and applied.

For depiction of the morphology, the image magnitude is usually used. Depending on the underlying pulse sequence, this magnitude is of varying quality. To overcome this limitation, research efforts applying steady state free precession pulse sequences or contrast agents, including intravascular contrast agents, are under investigation 19-20.

To illustrate the vasculature, either complex differences or velocity-weighted angiograms are routinely used. In general, both allow for vascular imaging and 3D isosurface rendering depending on the achieved signal-to-noise-ratio (SNR) during the experiment 19- 21-22.

Visualization of hemodynamics

Next to combined image processing algorithms, the velocity information from 3D PC-MRI needs to be assessed. In order to evaluate the hemodynamics qualitatively, various visualization principles are used. We will discuss the most commonly used principles although there are more available options.

Three basic visualization tools can be commonly found in medical literature, with slight differences in their terminology²³. Vector graphs are the most basic form of visualization. Each velocity vector is displayed at the location of acquisition (see also fig. 10 C). If more vector graphs are displayed than the actual spatial (or temporal) resolution permits, interpolation has been performed. Subsequently, the vectors can be color coded to display the magnitude and direction of flow. Such encoding can be implemented with a variety of derived parameters, e.g. general direction of flow, pressure differences, or other blood flow characteristics.

Some assumptions are made with two alternative visualization options that usually attract more attention. Sometimes, they are summarized under the term ‘particle paths’. Time-resolved particle traces resemble virtual particles that are released into the data volume from a user-defined seed point or plane and follow the acquired velocity field over time. In contrast, streamlines are virtual tangents to the velocity vectors through the data volume at a chosen point in time. Both can also be color-coded. An especially interesting aspect of color-coding that could prove to be useful in the future application of 4D PC-MRI is a feature called “connectivity mapping”. Connectivity mapping uses back- and forward tracking of streamlines to connect their origin with the location of interest. By doing so, the contribution of vascular regions to the blood flow region of interest can be analyzed. For example, the contribution of the superior or inferior vena cava can be tracked through the right atrium into the ventricle, or shunt volumes can be tracked.

Although streamlines and the particle traces are powerful visualization tools they are limited by the accuracy of the velocity measurements. Particle traces, in particular, are dependent on the error of each acquired velocity vector over time and space. By tracing the particle through the vector field, these errors tend to accumulate²⁴.

Clinical applications

Neurovascular application of 4D PC-MRI—Magnetic resonance angiography (MRA) plays a major role in the evaluation of patients with suspected vascular disease or other diseases that affect the vascular system. MRA is of particular importance in a multitude of neurological disorders.

Currently, most patients presenting with symptoms of stroke are examined using a combination of contrast enhanced MRA for the extra cranial arterial system and 3D TOF for the intracranial vasculature. The combination of MR angiography and MR imaging generates a comprehensive diagnostic approach with the ability to assess the impact of the vascular pathology on the surrounding parenchyma. This is most apparent when diffusion weighted and perfusion weighted imaging are combined with morphologic cross-sectional imaging and MRA. It is now well recognized that this combination of MR methods is an important tool in the evaluation of patients with acute and chronic brain ischemia and infarction²⁵.

Serial neurovascular imaging—Serial vascular imaging in general has played an important role in the evaluation of cerebrovascular disease since the introduction of catheter angiography in the 1930’s²⁶. The sequential filling of vessels and the delayed filling in

regions of arterial of stenosis provides qualitative assessment of vascular compromise. Time-resolved MRA of the extra-cranial arteries has shown great utility in identifying nearly concluded internal carotid arteries and altered or slow flow within the vertebrobasilar system²⁷. PC HYPR Flow is a recently introduced time-resolved approach that provides several advantages in comparison to other MRA techniques:

1. It results in a temporal resolution of 1 frame per second, generating a series of 3D whole brain images of the arterial and venous system. The time-resolved images allow for a qualitative evaluation of the relative speed of filling of the intracranial vessels. Such contrast arrival information is complemented by the simultaneous availability of quantitative velocity measurements within large and medium-size vessels. Previous reports have shown that PC HYPR Flow provides images of diagnostic quality²⁸ and that the velocity measurements are consistent with previous 2D phase contrast MRA techniques²⁹. An example of a PC HYPR Flow examination is demonstrated in figures 2 and 3. Note that each frame of the dynamic phase acquisition is a complete 3D volume encompassing the entire intracranial vascular system.
2. The use of the phase contrast data is especially advantageous when used as the composite image for HYPR LR reconstruction. Since most of the vascular signal is derived from the PC VIPR exam, only a small volume of contrast material is needed for the serial imaging³⁰. By reducing the volume of contrast material the contrast bolus can be shortened, improving the arterial-to-venous separation. This is particularly important in the cerebrovascular system, where the arterial venous transit time is fast and recirculation of the contrast bolus can occur quickly. Typically, 2-4 mL of contrast, followed by a sufficiently large saline flush to ensure prompt delivery to the central circulation, are adequate to obtain the time-resolved information.

PC HYPR Flow in arteriovenous malformation—To further illustrate the power of the PC HYPR Flow approach, we have studied patients with arteriovenous malformations (AVM) of the brain. AVMs of the brain are characterized by rapid flow with shunting through the nidus and dilated venous drainage both deep and superficial. Pathologic changes within the vascular structures include flow induced aneurysms, AV fistulas and varices. In Figure 3, we demonstrate a thalamic AVM imaged using PC HYPR Flow. The sagittal serial images demonstrate the hypertrophied posterior choroidal artery supplying the AVM, the nidus and the rapid shunting into the dilated venous system. These are all important features, allowing for excellent characterization of the AVM using classification systems such as the Spetzler Martin grading³¹. When combined with cross-sectional imaging, the relationship of the AVM to eloquent brain structures can be well appreciated³²⁻³³.

PC HYPR Flow in intracranial aneurysms—PC HYPR Flow can also be used to evaluate intracranial aneurysms. Two approaches have been clinically implemented. PC HYPR Flow stack-of-stars (SOS) uses radial readout in the XY plane and phase encoding in the Z direction. Using the PC HYPR Flow SOS approach the voxel size can be reduced to isotropic 0.45 mm hence improving the detection and hemodynamic characterization of small intracranial aneurysms. The higher spatial resolution is particularly important in the evaluation of intracranial aneurysms where a vascular loop or infundibulum can mimic an aneurysm. Here, the simultaneously available velocity information obtained with higher resolution enables us to obtain better velocity data in and around the orifice of the aneurysm and within the aneurysm sac itself. PC HYPR Flow using VIPR provides isotropic spatial resolution of 0.68mm and is also useful for evaluating aneurysms 3 to 4 mm in size.

Thereby, the flow into and around the aneurysm can be visualized and characterized (figure 4).

PC HYPR Flow in the venous system—An area that is particularly interesting and has yet to be completely explored is the assessment of the venous system using PC HYPR Flow. There are a number of pathologic conditions such as idiopathic intracranial hypertension that are occasionally associated with stenosis of the dural sinuses³⁴. So far, the relationship between idiopathic and trail hypertension and stenosis of the dural sinuses is entirely unclear. There are reports that treatment of the stenosis within the venous outflow can improve intracranial hypertension^{35–36}. Using PC HYPR Flow, it is possible to assess the filling dynamics of the venous structures as well as to measure venous flow velocity and pressure gradients related to stenosis in the transverse sinus³⁷. Patients could be stratified based on the degree of venous compromise and pressure gradients within the dural sinuses. In this respect, figure 5 shows an area of stenosis in the transverse sinus illustrating the potential of PC HYPR Flow to help in the study of patients with venous outflow obstruction.

Non-neurovascular clinical applications of qualitative 4D PC-MRI analyses

Clinically, there are multiple potential clinical applications for qualitative analyses of visualizing 4D PC–MRI hemodynamics. The present literature contains a good amount of experience with flow patterns that are considered normal or abnormal^{38–39}. Especially the presence of vortices, a secondary flow pattern consisting of recirculating flow within a vessel⁴⁰, has been considered abnormal and associated with altered distribution of the kinetic energy and modified shear forces on the vessel wall. In this respect, qualitative hemodynamic analyses could be used in situations when the vascular geometry is changed such as in determination of progression of aneurysms or after vascular surgery. There have already been approaches to use such qualitative analysis for the evaluation^{41–42} and optimization of surgical approaches⁴³. The latter holds the promise of a patient-centered medicine with tailoring of surgical measures to the individual needs.

Also, connectivity mapping could prove useful in situations with complex shunts. Especially congenital cardiovascular disease and its follow-up usually raise questions with regards to the hemodynamic conditions. A few reports have now been able to visualize, the hemodynamics in coarctation^{44–46}, in extracardiac total cavopulmonary connection (TCPC), one of the more common procedures in children with a single ventricle, or persistent ductus arteriosus^{47–48}. Little is known about the predisposing factors that lead to the clinical deterioration of those patients. The hemodynamic analysis in these diseases could add valuable information to the discussion.

Similarly, the large-volume coverage as achieved with PC VIPR has, to the experience of the authors, contributed to clinical diagnostics in patients with liver cirrhosis. The hepatic blood supply is unique in that there is a dual blood supply to the liver (hepatic artery, portal vein). In addition to standard morphological imaging, a volumetric velocity field acquisition allows for the analysis of a large vascular territory with a wide range of velocities, such as that encountered in the splanchnic arterial and portal venous system. Pioneered with 4D PC-MRI using a limited field of view by Stankovic and coworkers⁴⁹, the information from multiple imaging modalities and Doppler ultrasound measurements can now be achieved in a single acquisition applying PC- VIPR⁵⁰ (see figure 6).

While the previous two applications are under investigation, tremendous success has been reported in the evaluation of qualitative aortic hemodynamics. Hope et al. have succeeded in identifying different flow patterns in the ascending aorta of patients with bicuspid aortic valves. Their results add to the discussion to what extent hemodynamic and tissue factors contribute to the aneurysm development in this patient collective. Similarly, Harloff et al.

were able to prove a so far unidentified source of cerebral insults in patients with cryptogenic stroke. In their analysis, retrograde flow pathways originating from large atherosclerotic plaque in the descending aorta were followed into the supra-aortic arteries and correlated with the laterality of stroke.

Such results will most likely have an impact on diagnostic thinking and clinical management of patients. In figure 7, we outline an exemplary basic post-processing pathway for cardiac flows although approaches not relying on the placement of emitter planes are also available. Noticeably, the patient data contained a tricuspid regurgitation and largely altered flows in the right ventricular outflow tract.

Future directions concerning the visualization include the transfer to the heart with its complex hemodynamics. The ability to analyze the flow paths through the heart, derive different aspects of energy distribution such as the kinetic energy, and pressure differences is interesting not only in heart failure or congenital heart disease 51-52. Furthermore, translational research has already succeeded in high-detailed motion analyses that exceed the potential of tagging 53-55. Tissue phase mapping (TPM) of the heart used in combination with cardiac flow analyses is an interesting asset worth researching, especially in order to derive all aspects from a single acquisition.

Quantification of 4D PC MRI data

Quantification options

In addition to flow volumes (the temporal integral of the acquired velocities and the vessel area), various other quantitative parameters can principally be extracted from the 3D velocity field (figure 8). Since an entire 3D volume is seamlessly covered, any desired location within the data volume can be evaluated. This could also become of value in the workflow of the MR examination. Especially in complex anatomical conditions when the placement of multiple 2D slices can be strenuous 4D PC-MRI could help to overcome such limitations. In this context, the 3D approach offers the *a posteriori* analysis of locations which were not of primary interest and might not have been covered by 2D measurements. In the anecdotal experience of the authors, 4D acquisitions have already become an important backup for complex cardiovascular cases in clinical routine in cases when additional information is needed or 2D plane placement was suboptimal. Furthermore, the fact that 3D velocity fields are available may help to overcome limitations of the simplified Bernoulli equation for pressure estimation by solving the Navier-Stokes equation.

Potential clinical applications

Pulse wave velocity—Among the parameters that can be calculated using multiple 2D slices is the pulse wave velocity (figure 9). While multiple slices have to be acquired and co-registered using the 2D approach, 4D PC-MRI offers all necessary information from a single acquisition. The term pulse wave velocity (PWV) characterizes the velocity by which the pulse wave propagates through the vessel or system of interest. Although PWV usually receives little attention during clinical diagnosis, it is a well established parameter that is frequently used in research studies of vascular pathology. The PWV has been shown to correlate well with vascular stiffness and risk for coronary artery disease and stroke as shown in the Rotterdam Study and by others 56-57. Therefore, it could be valuable in preemptive diagnostic settings or in the follow-up of therapy, e.g., in lipid-lowering attempts in diabetic children with already increased aortic wall stiffness 58. In addition, the PWV is a better marker in hypercholesteremic children than the intima-media thickness 59.

Markl and coworkers have shown that the global aortic PWV can be estimated from 4D PC-MRI datasets. They were able to show the expected PWV changes between young volunteers ($4.39 \pm 0.32\text{m/s}$) and older subjects with cardiovascular disease ($7.03 \pm 0.24\text{m/s}$; $p < 0.001$) despite a suboptimal temporal resolution. They also analyzed the different quantitative approaches including two arrival time methods (see also figure 9) and cross correlation⁶⁰.

With improved spatiotemporal resolution, the analysis of regional PWV changes could become an interesting application in clinical diagnostics. Especially locations prone to stenosing arteriosclerosis such as the aortic arch, the carotid arteries, and the renal arteries qualify for this assessment. The analysis of PWV could also be transferred to other vascular territories such as the pulmonary arteries in pulmonary artery hypertension or altered pulmonary flow physiology. Thereby, entirely new information could be interesting additional biomarkers for the severity of disease⁶¹.

Wall shear stress and oscillatory shear index—The endothelial surface is the part of the vessel where a lot of physiological vascular processes are regulated. In addition to the blood pressure that acts as a perpendicular force on the endothelium, the blood flow creates a frictional force, the so-called wall shear stress WSS⁶². WSS acts locally by inducing the secretion of nitric oxide (NO) and prostacyclin resulting in vessel dilatation, hindrance of platelet activation, and attenuation of smooth muscle cell proliferation. It also directly interacts with endothelial gene expression and maintains an atheroprotective phenotype in high and elevated WSS levels. In conditions where WSS is low and the directional changes of the WSS, expressed by the oscillatory shear index (OSI), are high, atherosclerotic lesions develop⁶³. Initially proposed by Caro et al., this theory has now been widely accepted⁶⁴. The observation of high atherosclerotic burden at the inner curvature of vessel bends and at the outer parts of vessel bifurcation has been experimentally confirmed by numerous studies.

The sparsity of non-invasive methods to measure WSS and OSI in humans has largely prevented this research in the past. Only a few studies using 2D PC-MRI have aimed at analyzing these forces *in-vivo*^{65–66}. In principal, the data provided by phase contrast imaging contains most information necessary for WSS computations (figure 10). The vessel radius (r) can be derived from the magnitude information, the blood flow (Q) from the phase difference information. Only the blood flow viscosity (μ) has to be accepted as a constant with relative narrow inter- and intra-individual changes.

Initially, computational fluid dynamics (CFD) has been used for the investigation of the relationships between WSS and OSI on vascular diseases. CFD can use realistic vascular geometries and *in-vivo* acquired inflow conditions to model blood flow to calculate the WSS.

4D PC-MRI may enable for novel *in-vivo* WSS research and transfer of insights to pre-emptive medicine. Limited by its spatial resolution and the assumption, that flow at the border to the vessel wall is known, 4D PC MRI allows for consistent WSS and OSI estimations⁶⁷. In comparison to CFD that relies on numerous assumptions, 4D PC-MRI is mainly restricted in its estimations by a spatial resolution between 1.4 and 2.4mm. While PC-MRI currently underestimates the WSS from CFD by an order of magnitude it can provide such data *in-vivo* and within a diagnostic time frame suitable for most patients and disease-related questions.

The recently presented *in-vivo* data are consistent with previous CFD computations and the expected rheology. In healthy subjects our own work revealed that WSS acquired *in-vivo* is lower at the inner curvature of the aortic arch and the branches of the supra-aortic vessels⁶⁸.

These results match the localization of atherosclerotic burden in daily routine and gross necroscopy. In a study by Harloff et al., we transferred the diagnostic approach to stroke patients. Despite some limitations and controversial findings in the ascending aorta, we were able to correlate critical WSS and OSI values with severe atherosclerotic plaque⁶⁹.

The calculation of WSS and OSI could also provide vital information in non-atherosclerotic diseases. Conditions such as aneurysm formation, whether of degenerative nature, associated with connective tissue disorders, or following surgery such as in coarctation, have been speculated to be at least associated with if not triggered by hemodynamics. So far, CFD is the dominant approach to derive vessel wall parameters in such conditions. However, initial 4D PC-MRI results in coarctation and coarctation repair have been presented and are promising for future follow-up results ^{44, 70-71}.

Pressure differences: solving the Navier-Stokes equation—Currently, the simplified Bernoulli equation $\Delta P_{peak} \approx 4v_{max}^2$ is a generally accepted way of calculating pressure differences (ΔP) from the detected velocity (v) in a stenosis. While this approach is part of clinical routine, it relies on various assumptions, one being the presence of steady flow. Shortcomings associated with those assumptions could be overcome with a method that comprises an entire 3D velocity field such as 4D PC-MRI.

An early proposal to solve the Navier Stokes equation on the basis of a MR-derived data volume was presented in 1996 by Yang et al.⁷². In brief, the Navier-Stokes equation is an application of Newton's second law of conservation of motion to fluid motion. To derive a pressure gradient, the viscosity (μ), density (ρ), gravity, and velocity derivatives of the fluid are needed. Since velocity derivatives such as convective acceleration can be obtained from 4D PC-MRI, the Navier-Stokes equation can be solved for pressure gradients (ΔP).

Initial applications to MR have been presented by Tyszka for aortic flow and Thompson for intracardiac pressure gradients^{37, 73}. In 2007, Lum and colleagues evaluated pressure gradient determination with PC VIPR compared to invasive pressure measurements in an animal model of carotid, iliac, and renal lesions. Their results showed excellent correlation for iliac and carotid stenoses ($r = 0.952$, $p < 0.001$) but a poor correlation for renal stenoses⁷⁴. Improved compensation for breathing motion significantly improved pressure gradient quantification in porcine renal artery stenosis ($r=0.977$; $p < 0.001$)⁷⁵.

For clinical use, Bock et al. transferred the technique to a cohort of patients with coarctation⁷⁶ (see figure 11). Results in comparison to pressure gradients as estimated by clinical echocardiography are under submission (personal communication). With such a method at hand, diagnostic decision making especially in the preoperative workup could change from invasive pressure acquisitions during catheterization to a mainly MR-based protocol.

Summary

To the belief of the authors, there are already numerous obvious advantages to 4D PC-MRI. First, it provides comprehensive insights into physiology. The amount of data that can be achieved with this approach is overwhelming. Extracted parameters range from basic physiologic measures, over clinical useful pressure differences, to the analysis of complex properties of rheology including the wall shear stress (see figure 8). Admittedly, some of the introduced properties do not have a clinical meaning yet and can only be considered to be of academic interest. However, especially pre-emptive medical research efforts are currently exploring the main parameters WSS and PWV.

Second, 4D PC-MRI offers a deepened understanding of the interaction between morphology and function. Despite previous model simulations, unprecedented insights into blood flow physiology and morphodynamic interactions are now available in-vivo. They encourage the scientific creativity to explore the new possibilities and determine its application in medicine.

Third, the prescription of a single data volume that can be exploited for information of various different localizations is especially practical in complex morphological conditions. When applied with post processing algorithms such as PC HYPR Flow, even demanding pathologies such as intracranial AVMs can be investigated in high spatiotemporal detail with perfect co-registration of morphology and dynamic information. And without the need for exact placement of multiple slices, 4D PC-MRI not only avoids tedious repetitions and potential misregistration at neighboring slices, but allows for the evaluation of locations that were not in the primary focus.

Finally, MR is advantageous over other imaging methods that provide simultaneous registration of morphology and function in various aspects. Most importantly, MR allows to freely applying a large volume acquisition due to its lack of ionizing radiation. Thereby, 4D PC-MRI seems optimally suited for comprehensive cardiovascular imaging of the pediatric patient and physiologic studies with provocation tests such as administration of drugs that, e.g., alter the heart rate or influence organ perfusion.

Limitations and future directions

Future technical developments will have to help to overcome some of the basic limitations inherent in this technique. Without going into detail, short echo times (TE) and improved spatial and, to a lesser extent, temporal resolution could greatly improve the quantitative analysis. The introduction of parallel imaging and view sharing methods in both spatial and temporal domain is lagging behind. However, both the sequence programming effort and the post-processing are non-trivial. Similarly, any improvement to the signal-to-noise and contrast-to-noise ratio in the magnitude image, for example by using steady state free precession pulses or contrast agents with increased blood-pool persistence would be beneficial to the clinical applicability [19–20].

Noticeably, most quantification processes are MatLab-based, in any case home-built, and research-site specific solutions. Similarly, there are multiple commercial software solutions for blood flow visualization. None of these have been designed for diagnostic purposes or offer a particularly appealing graphical user interface. Moreover, similar to differing clinical greyscales among vendors in clinical 2D PC-MRI, there are no conventions regarding color-coding, use of visualization strategies, or acquisition standards.

Some of the described applications are, to date, of experimental nature and need further clinical validation. Although the applied phase contrast sequences are validated, there are ongoing research efforts regarding the post-processing strategies and their optimization. We are optimistic that with the increased attention this young imaging approach receives, most vendors will start to implement such 4D PC-MRI sequences as investigational devices and more clinical applications and validation will become available.

In conclusion, we have shown that there is great inherent clinical potential in 4D PC-MRI. So far, most implementations are research applications and are available for investigational use at specific sites only. Despite technical advances, 4D PC-MRI has had only limited impact on clinical routine imaging so far. The main explanation is its restricted availability in some specialized centers and for investigational purposes only. An additional reason is that future clinical applications need to be further characterized and thoroughly researched

in large patient collectives. In light of a missing non-invasive reference standard this lack of a reference standard presents the main impediment for a faster distribution of 4D PC-MRI research so far. Also, the comprehensive postprocessing of data with the need for considerable user interaction remains challenging despite improved computing powers. However, with the increasing interest in such analyses, vendors are likely to commit to an implementation of hemodynamic analyses and render such an approach and support in sequence maintenance and post-processing software more widely available. By doing so, an entire new diagnostic approach to vascular and cardiac disease and preventive medicine could become reality.

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Fig. 1.

Principle of phase contrast MRI. (A) Stationary (static) tissue experiences no net magnetization after exact reversal of magnetic field gradients. Moving spins, however, will experience different field gradients which will not cancel out. The remaining magnetization can be detected in form of a small net phase. (B) Subtraction of phase information before and after gradient reversal thus results in a phase difference proportional to the velocity of the underlying motion. In (C) the transfer to 3-directional velocity encoding, as commonly performed in 3-dimensional imaging, is outlined. Note, however, that multiple multidirectional encoding schemes are available 4, 6.

Fig. 2.

Flow chart describing the components of a PC HYPR Flow processing chain for cranial imaging. The strength of this imaging and post-processing approach is the combination of advantages each technique has. The high temporal resolution of the whole volume time-resolved contrast-enhanced MRA (tr CE-MRA) using radial undersampling (VIPR) is complemented by the high spatial resolution of the undersampled phase contrast data (PCVIPR). Note that principally a different high spatial resolution constrained image could be used. The simultaneously acquired phase contrast velocity data can be used to display flow patterns applying streamlines and particle traces, to calculate volume flow, and to estimate derived vessel wall parameters. In our clinical routine we achieve serial images with a spatial resolution of $0.68 \times 0.68 \times 0.68\text{mm}$ and a sub-second temporal update rate. PC HYPR Flow Imaging courtesy of Yijing Wu, PhD; hemodynamic visualization courtesy of Ben Landgraf, BS, University of Wisconsin.

Fig. 3.

Detailed view of a thalamic arteriovenous malformation (AVM) visualized with PC HYPR Flow (same patient as in figure 2). In (A) the whole brain CE-MRA with sub-second temporal resolution is displayed. (B) is the simultaneously available high-resolution PC angiogram (PC VIPR). Procession with HYPR results in a high spatial and temporal resolution (C) with the simultaneous option to perform hemodynamic analyses (D). In (D), visualization (EnSight, CEI, Apex, NC) with streamlines was color-coded enhancing the flow from and to the AVM. Angiographic images courtesy of Yijing Wu, PhD; hemodynamic visualization courtesy of Ben Landgraf, BS, University of Wisconsin.

Fig. 4.

(A) 3D angiographic reconstruction from PC VIPR data and (B) streamline visualization of a 4 mm paraclinoid aneurysm. Streamlines are displayed during early diastole. The visualization is based on the velocity information derived from a PC HYPR Flow acquisition. ICA = internal carotid artery, MCA – middle cerebral artery, LT – left, Rt = right. Visualization courtesy of Steve Kecskemeti and Ben Landgraf, BS, University of Wisconsin - Madison.

Fig. 5.

Stenosis of the transverse sinus (white arrows). (A) shows a 3D angiographic view based on the PC VIPR data performed with MIMICS Innovation Suite (Materialise, Ann Arbor, MI; blue = venous, red = arterial). For hemodynamic analyses, color-coding was achieved based on pressure differences (B) and velocity information (C). All data was derived from a singular PC HYPR Flow acquisition. A marked drop in pressure across the stenotic segment and elevated velocities with the stenosis can be appreciated. Visualization courtesy of Ben Landgraf, BS, University of Wisconsin – Madison.

Fig. 6.

(A) Visualization of a color-coded PC angiogram of the upper abdomen (diaphragm to renal arteries) performed with MIMICS Innovation Suite (Materialise, Ann Arbor, MI). The venous system is coded in blue, the arteries in red, and the portal vein in yellow. For the latter, a streamline visualization using EnSight (CEI, Apex, NC) can be appreciated in (B). Clearly, the potential of large volume coverage and the feasibility to analyze singular vessels of interest or multiple structures and their interdependencies can be appreciated. Visualization courtesy of Ben Landgraf, BS, and Eric Niespodzany, MS, University of Wisconsin - Madison.

Fig 7.

A typical visualization pathway of 4D PC- VIPR can include (A) the creation of an isosurface and placement of cutplanes that serve as either emitter planes for visualization options or as analysis planes for quantification. Vascular territories such as the aorta (B) or the pulmonary artery (C; early RV diastole) can be appreciated in singular views or at the same time (D-F). (D) – (F) shows the temporal evolution of flow patterns from the superior and inferior vena cava (SVC, IVC, respectively) and the right ventricular outflow tract (RVOT) during selected RV systolic (D, E) and diastolic (F) time points. Note the regurgitant flow volume (TR) through the tricuspid valve and the flow vortex in the right ventricular outflow tract (white arrowheads). Ao = aorta; DAo = descending aorta; RA = right atrium. Visualization courtesy of Michal Markl, PhD, University Hospital Freiburg, Germany.

Fig 8.

Schematic overview over the quantitative results that can potentially be extracted from 4D PC-MRI (based on previously published results, not complete).

Fig. 9. Schematic illustration of a transit time method to analyze the pulse wave velocity (PWV) based on waveform characteristics. Here, the time to foot (TTF) is used by fitting a line to the upslope of the waveform. The point the fitted line creates crossing the baseline is used to analyze the time shift between the locations of the two analysis planes. The distance between those slices and the time between waveform characteristics is used for calculation of the PWV. Obviously, a high spatial resolution of the acquired flow information allows for a better fit. Similarly, a large distance between slice A and B provides a more accurate PWV estimation. Note that 3 acquisitions are needed for a 2D approach (slice A, slice B, sagittal plane of the aorta) whereas a 4D PC-MRI data volume contains all necessary information in a perfectly co-registered way.

Fig. 10.

Wall shear stress (WSS) can be calculated from the acquired 4D PC-MRI data. For each acquired voxel, three-directional velocity information is available. In a 2D plane with velocity encoding in a single direction, Poiseuille's law can be applied to estimate the shear stress magnitude at the vessel wall (WSS magnitude symbolized by arrows 1 and 2).

Following Poiseuille's law, WSS is proportional to the blood flow Q (area times velocity), viscosity (μ), and inversely proportional to the radius (r) of the vessel. Since 4D-PC MRI encodes for all three directions of blood flow, not only the magnitude but also contributing circumferential and through-plane fractions to the WSS magnitude can be analyzed 44- 67. Hemodynamic visualization courtesy of Ben Landgraf, BS, and Eric Niespodzany, MS, University of Madison.

Fig. 11.

Pressure difference map in a patient after surgery for coarctation. The pressure gradient can be visually appreciated by the color swap (left). On the top right, pressures over time (yellow line) as derived from the acquired 4D velocity field are plotted against pressure gradients derived from the simplified Bernoulli equation. The difference between MR and echocardiography can be related to both, an underestimation of velocity by MR due to volume averaging and to overestimation by echocardiography since maximum values in the center are measured. Image courtesy of Dipl.-Ing. Jelena Bock, University Hospital Freiburg, Germany.