

4D Flow MRI – an Update

Michael Markl, Ph.D.^{1,2}; James Carr, M.D.¹; Michael Rose, B.S.³; Cynthia K. Rigsby, M.D.^{1,3,4}; Julia Geiger, M.D.¹

¹ Department of Radiology, Feinberg School of Medicine, Northwestern University, Chicago, USA

² Department Biomedical Engineering, McCormick School of Engineering, Northwestern University, Chicago, USA

³ Department of Medical Imaging, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, USA

⁴ Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, USA

Introduction

MRI techniques provide non-invasive and non-ionizing methods for the accurate anatomic depiction of the cardiovascular system. In addition, the intrinsic sensitivity of MRI to motion offers the unique ability to acquire blood flow simultaneously with anatomical data within a single measurement (phase contrast (PC) principle). The characterization of the dynamic components of blood flow with MRI has achieved considerable progress in recent years including new methodological advances such as 4D Flow MRI for the comprehensive *in-vivo* analysis of complex time-resolved 3D blood flow characteristics [1-7].

Standard clinically employed 2D CINE PC MRI takes advantage of the direct relationship between blood flow velocity and the MR signal to measure blood flow velocity along a single direction, similar to Doppler echocardiography [8]. Typical clinical imaging protocols measure blood flow in 2D imaging slices positioned orthogonal to the vessel which usually includes single-direction velocity measurement (through-plane encoding) and is performed during

a 10-15 second breath-hold period. The resulting images are used to quantify flow parameters such as peak velocity, net flow, or regurgitant fraction at the site of the imaging plane.

In 4D Flow MRI¹, velocity is encoded along all three spatial dimensions throughout the cardiac cycle, thus providing a time-resolved 3D velocity field. As a result, 4D Flow MRI can provide full volumetric coverage of the vessel of interest and thus give more comprehensive spatial and temporal (4D = 3D + time) coverage. In this article, we describe the latest technical progress and data analysis protocols of the 4D Flow MRI for the Siemens platform, and we present different examples for clinical cardiothoracic and intracranial applications.

Technical advances

4D Flow data acquisition

Initial limitations for including 4D Flow MRI into clinical daily routine standard MRI protocols were related to long scan times of up to 20 min-

utes. Methodological improvements based on k-t parallel imaging or Compressed Sensing have been successfully employed to achieve significant imaging acceleration and reduced times [9, 10]. Combination with advanced respiration control [11, 12] for cardiothoracic and abdominal applications today allows the acquisition of 4D Flow MRI data within clinically acceptable scan times on the order of 5-10 minutes.

Continued developments based on alternative data sampling strategies such as radial or spiral data readout have high potential to further reduce scan times. For example, a recent study showed that the combination of highly efficient spiral sampling with dynamic compressed sensing can achieve major acceleration, which allowed for the acquisition of abdominal 4D Flow MRI data during a single breath-hold [10]. Ongoing methodological improvements focus on the acquisition of dual-ventricle acquisitions [13-15] which are expected to be of great benefit for the simultaneous assessment of low and fast flow velocities, e.g. in the brain or in congenital heart disease (CHD), where a high dynamic range is critical

¹ The product is still under development and not commercially available yet. Its future availability cannot be ensured.

	venc	respiration gating, R _{eff}	acceleration factor R	spatial resolution	temporal resolution	total scan time
aorta/PA	150-400 cm/s	60-80%	5	(2.2-2.8 mm) ³	35-45 ms	5-8 min
whole heart	150-400 cm/s	60-80%	5	(2.8-3.2 mm) ³	35-45 ms	8-12 min
head	80-120 cm/s	N/A	5	(1.0-1.2 mm) ³	35-45 ms	8-10 min
abdomen	60-120 cm/s	60-80%	5	(2.5-3.0 mm) ³	35-45 ms	10-15 min

Table 1: 4D Flow MR imaging scenarios for different application areas based on adult subjects with heart rates on the order of 60-70 bpm. For cardiothoracic and abdominal applications, respiratory navigator gating is typically used to minimize breathing artifacts. The combination with advanced data acquisition strategies (respiratory driven phase encoding) allows for high scan efficiencies (R_{eff}) on the order of 60-80%. The selection of the lower end of the velocity sensitivity (venc) is based on the expected maximal normal blood flow velocities in each vascular territory which will have to be adapted to higher velocities in patients with cardiovascular disease such as aortic valve stenosis. PA = pulmonary artery.

to cover the wide arterial and venous flow velocity spectrum.

A summary of imaging protocols for different application areas is provided in Table 1 and illustrates currently achievable spatio-temporal resolution and scan times based on recently described k-t accelerated 4D Flow MRI methods with high acceleration factors of $R = 4 - 6$ [16-18].

4D Flow data analysis workflow

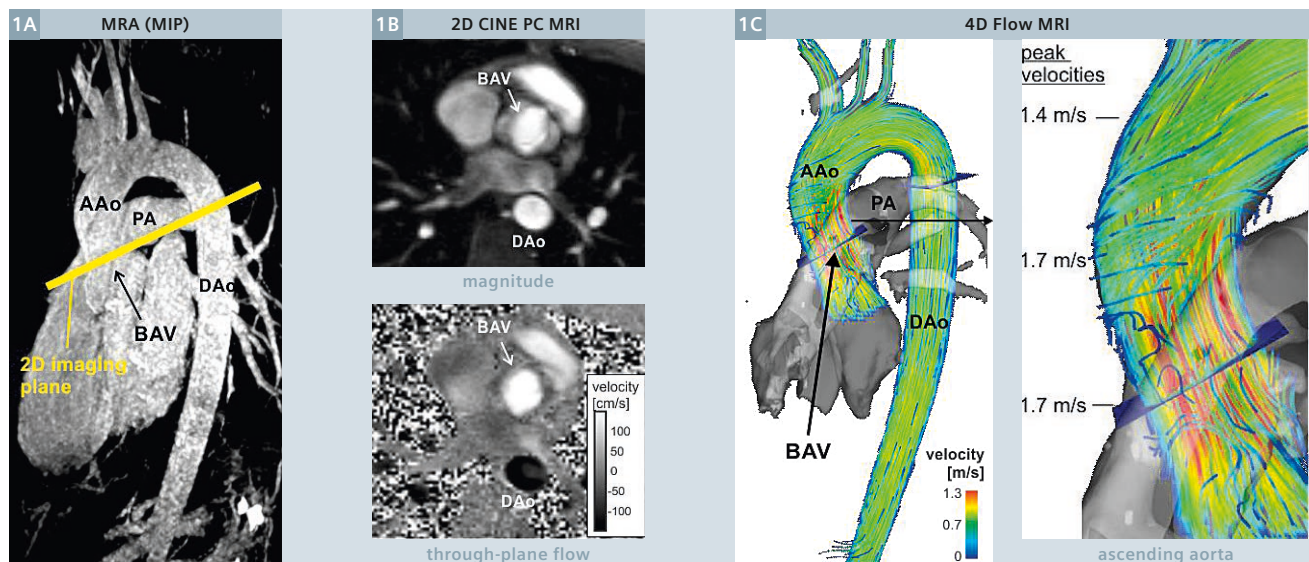
For the visualization of cardiovascular flow patterns, commonly used techniques are 3D streamlines and time-resolved 3D pathlines to depict changes in hemodynamics associated with disease. Figure 1 illustrates the use of 3D streamlines to depict systolic 3D flow patterns in the thoracic aorta of a patient with a bicuspid aortic valve. Time-resolved 3D pathlines utilize the full 4D (3D and time) information and can be used to visualize the spatio-temporal dynamics of pulsatile 3D blood flow patterns.

An example of aortic 4D Flow MRI and comparison of the resulting imaging findings with standard MRI techniques is shown in Figure 1. A benefit compared to traditional 2D PC-MR imaging

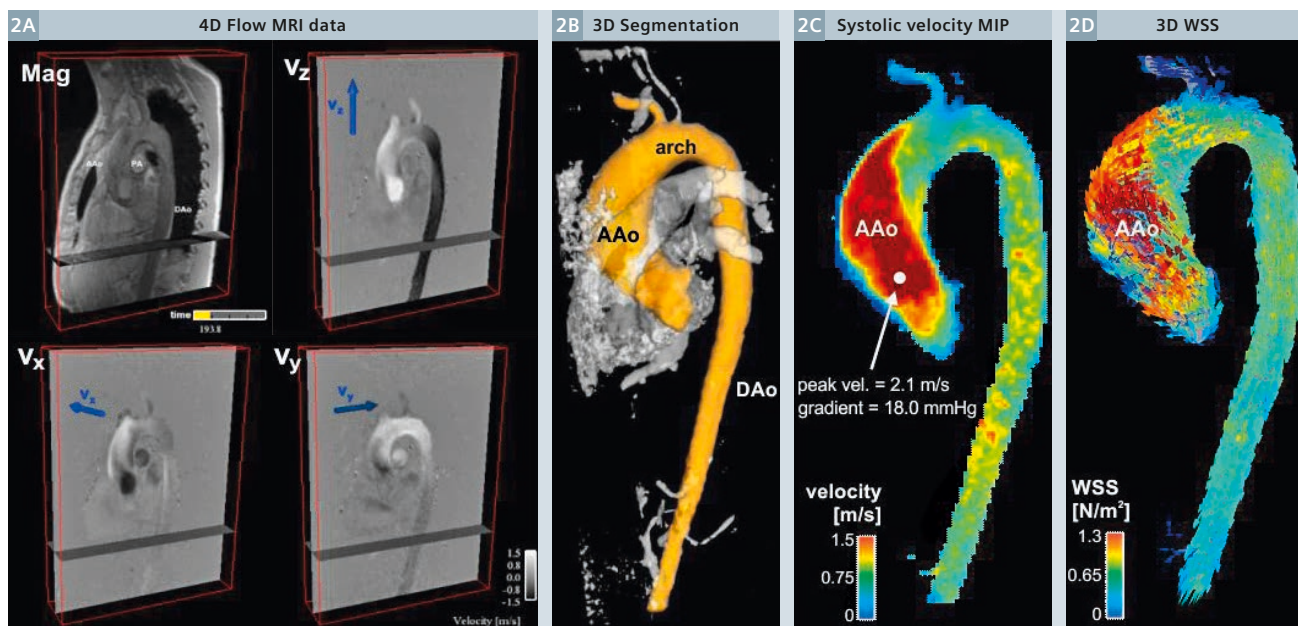
is related to the possibility for retrospective and flexible quantification and visualization of cardiovascular blood flow without being limited to 2D planes as in standard 2D CINE PC MRI. 4D Flow MRI offers a single and easy to prescribe data acquisition (3D volume covering cardiovascular region of interest) instead of multiple 2D planes for flow analysis with standard 2D CINE PC MRI that may be difficult to position in cases with complex vascular architecture (e.g. congenital heart disease, liver vasculature). As a result, 4D Flow MRI may help to avoid missing regions of interest for flow quantification where 2D CINE PC MRI may not have been acquired or planes were misplaced. Recent studies have confirmed that volumetric analysis based on 4D Flow MRI allows for improved assessment of aortic and pulmonary peak velocities which may be underestimated by 2D CINE PC MRI [19, 20].

The anatomic and velocity information of the 4D Flow data can additionally be used to calculate a 3D phase contrast angiogram (3D PC-MRA) which can be combined with 3D blood flow visualization to

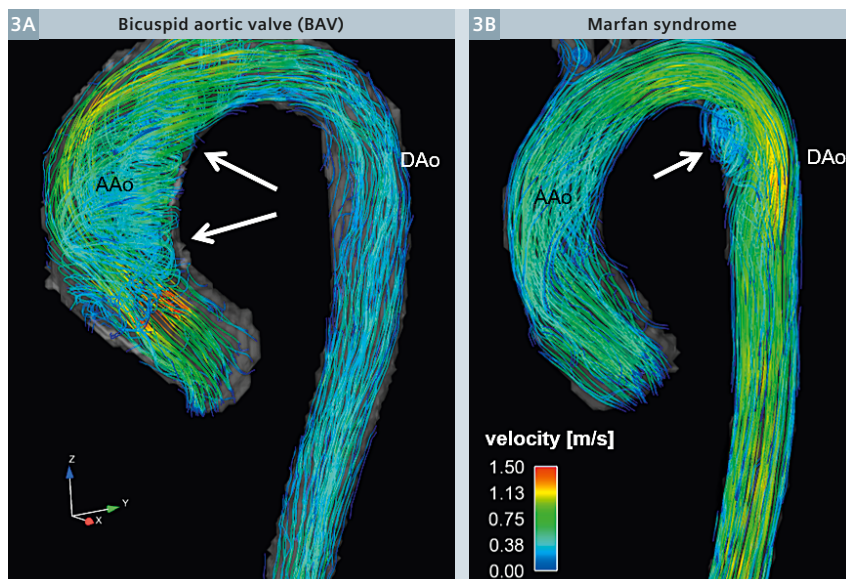
guide anatomic orientation (see Figs. 1-3). In addition, the 3D PC-MRA data serve as a basis for the 3D segmentation of vessels to improve 3D visualization or to provide the ability to mask the underlying velocity data to calculate systolic 3D velocity maximum intensity projections (MIP). As shown in Figure 2C, systolic velocity MIPs are an easy to use tool to give an overview over the 3D velocity distribution as well as automated quantification of peak velocities v_{peak} and thus estimate pressure gradients Δp using the simplified Bernoulli equation ($\Delta p = 4v_{\text{peak}}^2$). The increased complexity of 4D Flow data (3D + time + 3-directional velocities) offers the opportunity to derive new physiologic and pathophysiologic hemodynamic parameters, such as wall shear stress (WSS), pulse wave velocity, 3D pressure difference maps, or turbulent kinetic energy. These advanced hemodynamic measures can provide quantitative information on the impact of vascular pathologies on cardio- or cerebrovascular blood flow patterns beyond currently available techniques. For example, methods have been developed to compute volumetric



1 MR angiography (MRA, depicted as a maximum intensity projection, MIP) and 2D CINE PC-MRI in a patient with bicuspid aortic valve (BAV) disease. The patient underwent standard MR angiography (1A) as well as 2D CINE PC-MRI (1B) for the assessment of valve morphology and flow quantification at the level of the aortic valve in the ascending aorta (AAo). 1B shows the maximum aortic valve opening and blood flow during peak systole. The yellow line in 1A shows the imaging plane for 2D CINE PC-MRI acquisitions in 1B. (1C) 3D streamline visualization of systolic blood flow in the thoracic aorta as assessed by 4D Flow MRI. Note that 4D Flow MRI provides full volumetric coverage of the thoracic aorta and flexible retrospective quantification of peak systolic velocities at multiple locations in the thoracic aorta which revealed a peak velocity of 1.7 m/s distal to the BAV. DAo = descending aorta, PA = pulmonary artery



- 2** Data analysis workflow for the assessment of aortic velocity distribution and 3D WSS in a patient with bicuspid aortic valve (BAV) and ascending aortic (AAo) dilatation. **(2A)** 4D Flow MRI data with full volumetric coverage of the thoracic aorta including anatomical and 3-directional flow data. **(2B)** 3D segmentation based on 3D PC-MRA data (gray shaded iso-surface) is used to isolate the aortic lumen. **(2C)** The 3D segmentation is used to mask the measured time-resolved 3D velocity data and calculate a systolic velocity maximum intensity projection (MIP). The velocity MIP data can be used to automatically extract the peak systolic velocity and pressure gradient (estimated via the simplified Bernoulli equation) without the need for manual analysis plane placement. Results indicate mild BAV stenosis causing mildly elevated pressure gradient. **(2D)** Advanced hemodynamic analysis can be employed to map peak systolic wall shear stress (WSS) vectors onto the aortic surface which indicate substantially elevated WSS (red color) along the outer curvature of the ascending aorta. DAo = descending aorta.



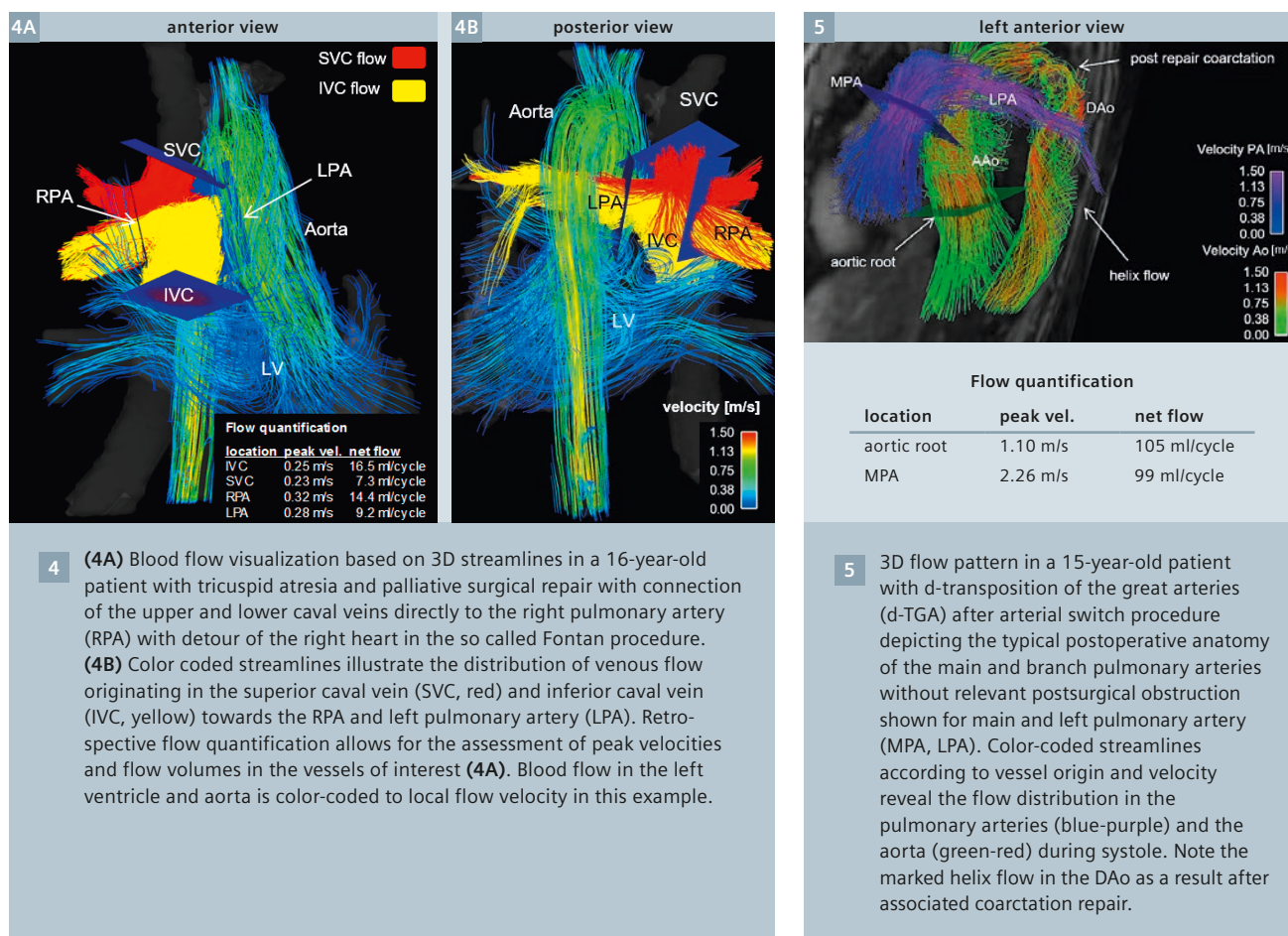
- 3** Systolic 3D streamline visualization in two patients with different aortic disease. **(3A)** 56-year-old patient with bicuspid aortic valve (BAV) demonstrates pronounced helix flow in the dilated ascending aorta (AAo) while blood flow in the descending aorta (DAo) is normal. **(3B)** In contrast, this 22-year-old patient with Marfan syndrome who has no marked aortic ectasia shows physiological flow in the AAo but an abnormal localized vortex flow pattern in the proximal DAo.

3D WSS, a known pathophysiological parameter implicated in vascular remodeling, along the segmented surface of the entire aorta (Fig. 2D) [21, 22]. The application of this technique in patients with aortic disease demonstrated that a 3D WSS mapping technique allows for compact visualization and regional quantification of hemodynamic parameters assessed across multiple subjects [23].

For a detailed overview of 4D Flow MRI developments and its use for 3D flow visualization and quantification throughout the human circulatory systems the reader is referred to a number of recently published review articles [1-7] and 4D Flow MRI consensus statement [24].

Clinical applications

In recent years, 4D Flow MRI has been increasingly applied in various vessel territories and diseases ranging from aortic pathologies to complex CHD,



abdominal indications and intracranial applications.

Thoracic aorta

A number of studies indicate the important role of 4D Flow MRI for the comprehensive analysis of the impact of focal aortic abnormalities (aortic valve abnormality, coarctation, aortic dilatation) or genetic disorders (e.g. Marfan syndrome) on changes in 3D blood flow affecting the entire aorta [25-28]. Changes in flow patterns due to aortic valve stenosis or congenitally abnormal valves such as bicuspid aortic valve (BAV) affect predominantly the ascending aorta but can also expand into the aortic arch and descending aorta. In addition, the application of 4D Flow MRI in patients with aortic coarctation provides an overview of the hemodynamic changes which are not limited to the coarctation site and might be overlooked or misjudged by 2D CINE PC MRI. In addition, flow derived parameters such as WSS have

shown high potential to derive better understanding of the underlying pathophysiology for aortic disease progression. Figure 3 depicts flow alterations in two representative patients with focal (BAV) and global (Marfan) aortic disease.

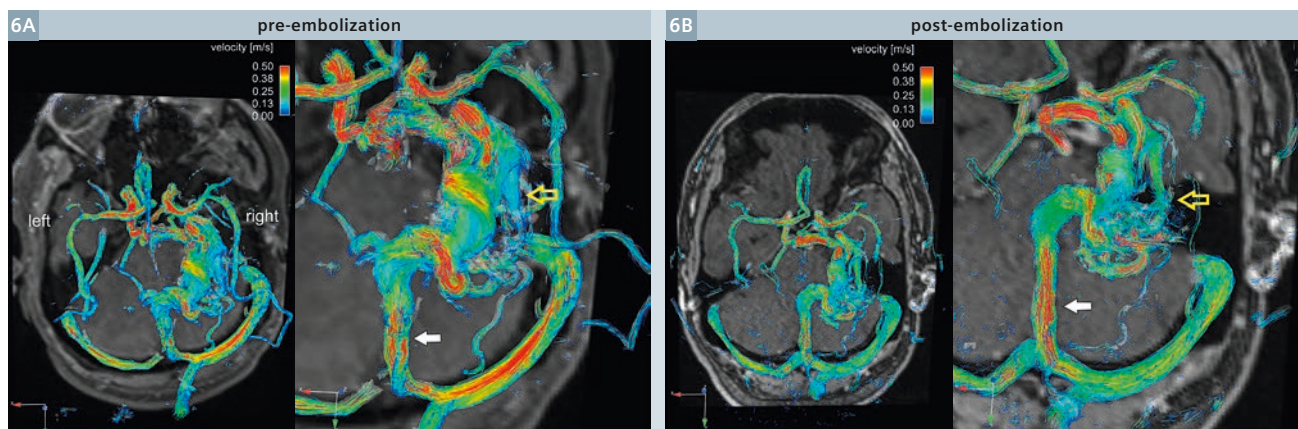
Complex congenital heart disease

Whole heart 4D Flow MRI techniques allow for a non-invasive comprehensive assessment of cardiovascular hemodynamics in the heart and its surrounding great vessels. While scan times are still long due to full volumetric coverage of the entire heart (8-12 minutes depending on heart rate and respiration control efficiency), it facilitates the systematic assessment of blood flow in multiple vessels and enables the retrospective analysis of any region of interest within the imaging volume. The examination of the pulmonary arteries and the right heart commonly has priority in CHD, and postsurgical assessment of the pulmonary blood flow is crucial

to rule out potential re-stenoses or postsurgical sequelae which need re-intervention such as in patients with tetralogy of Fallot, transposition of the great arteries, or in subjects with functional single ventricle (see Figs. 4 and 5). Correct plane placement and flow assessment by 2D CINE PC MRI is particularly challenging in these cases. Previous studies have shown that the 4D Flow technique can reliably identify altered 3D flow characteristics related to the post-interventional status in patients with CHD. In addition, 4D Flow MRI based flow quantification has been shown to be equivalent or even improved when compared to 2D techniques, while needing less imaging time than time needed for positioning and acquisition of multiple planes [29-33].

Cerebrovascular disease

In clinical practice, transcranial Doppler ultrasound is routinely used for cerebrovascular flow measure-



6 Intracranial 4D Flow MRI for the assessment of arterial and venous cerebrovascular hemodynamics. 3D blood flow visualization using time-integrated 3D pathlines in a 29-year old male patient with a large unruptured AVM centered in the right mesial temporal lobe with compact nidus prior to treatment (**6A**) and following invasive staged embolization therapy (**6B**: DSA guided endovascular superselective occlusion of AVM feeding arteries with nidal penetration). Complex arterial feeding and convoluted hemodynamics as well as differences in pre- and post-embolization vascularization and hemodynamics are clearly visible. Staged embolization resulted in compaction of the AVM with reduced blood flow velocities (yellow arrows) and reduced flow velocities for venous drainage (white arrow).

ments. However, the technique is operator-dependent and significantly limited by the available acoustic windows of the head, mainly in adults. 2D PC-MRI can provide flow measurements in large intracranial arteries and veins. However, small and tortuous vessels, complex vascular anatomy and the need for the manual placement of 2D imaging planes in multiple vessel segments represent challenges [34]. In contrast, 4D Flow MRI offers 3D blood flow visualization and retrospective flow quantification with full coverage of cerebral arteries and veins. Emerging applications include the hemodynamic evaluation of intra-cranial aneurysms, arteriovenous malformations (AVM), and intracranial atherosclerotic disease (ICAD), as well as venous flow. Figure 6 demonstrates the potential of 4D Flow MRI for the evaluation of global and regional AVM flow characteristics and treatment-induced changes in cerebrovascular flow distribution [35, 36]. In patients with cerebral AVMs, the pathological vascularization (direct shunting of blood from arterial to the venous sides without an intervening capillary bed) leads to abnormal hemodynamics. Flow information is potentially valuable for a better understanding of the impact of a focal AVM on the flow redistribu-

tion in the brain and/or in treatment planning by attempting to identify the feeding arteries with highest flow, enabling efficient and targeted embolization treatment.

Conclusion

A large number of studies have provided evidence that 4D Flow MRI can help to better understand altered hemodynamics in patients with cardiovascular diseases and may lead to improved patient management and monitoring of therapeutic responses. The novel hemodynamic insights obtained are also likely to provide new risk stratification metrics in patients that have prognostic significance and can also impact individualized treatment decisions to optimize patient outcome. Future research efforts will improve the clinical applicability of 4D Flow MRI and provide results in larger cohort studies.

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Contact

Michael Markl, Ph.D.
Department of Radiology
Northwestern University
737 N. Michigan Avenue Suite 1600
Chicago, Illinois 60611,
USA
Phone: +1 312-695-1799
Fax: +1 312-926-5991
mmarkl@northwestern.edu



James Carr



Michael Rose



Cindy Rigsby



Julia Geiger



Michael Markl