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4D MRI flow examinations in cerebral and extracerebral vessels. Ready for clinical routine?

Susanne Schnell[1], **Can Wu**[1,2], and **Sameer A. Ansari**[1,3,4]

[1]Dept. of Radiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

[2]Dept. of Biomedical Engineering, Northwestern University, Evanston, Illinois

[3]Dept. of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

[4]Dept. of Neurological Surgery, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

Abstract

Purpose of review—To evaluate the feasibility of 4D flow MRI for the clinical assessment of cerebral and extracerebral vascular hemodynamics in patients with neurovascular disease.

Recent findings—4D flow MRI has been applied in multiple studies to qualitatively and quantitatively study intracranial aneurysm blood flow for potential risk stratification and to assess treatment efficacy of various neurovascular lesions, including intra-aneurysmal and parent artery blood flow after flow diverter stent placement and staged embolizations of arteriovenous malformations and vein of Galen aneurysmal malformations. Recently, the technique has been utilized to characterize age-related changes of normal cerebral hemodynamics in healthy subjects over a broad age range.

Summary—4D flow MRI is a useful tool for the non-invasive, volumetric and quantitative hemodynamic assessment of neurovascular disease without the need for gadolinium contrast agents. Further improvements are warranted to overcome technical limitations before broader clinical implementation. Current developments, such as advanced acceleration techniques (parallel imaging and compressed sensing) for faster data acquisition, dual or multiple velocity encoding strategies for more accurate arterial and venous flow quantification, ultra-high field strengths to achieve higher spatial resolution, and streamlined post-processing workflow for more efficient and standardized flow analysis, are promising advancements in 4D flow MRI.

Keywords

4D flow MRI; intra- and extracranial; hemodynamics; cerebrovascular disease

Corresponding Author: Susanne Schnell, 737 N. Michigan Avenue, Chicago, IL 60605, USA, Telephone: +1-312-695-3099, Susanne.schnell@northwestern.edu.

Conflicts of interest

There are no conflicts of interest to report.

Introduction

The study of hemodynamic alterations in patients with cerebrovascular disease is integral to understanding a component of the pathology, potentially improving diagnostic capabilities and therapeutic planning. Intracranial atherosclerosis and aneurysms develop at locations with complex vascular geometry such as bifurcations and siphons (1, 2), where individual blood flow patterns may influence the pathogenesis of neurovascular disease (3). Abnormal blood flow patterns, such as turbulent blood flow, may contribute to disease progression (4, 5). Conversely, laminar blood flow in straight and large vessels appears in parallel layers promoting normal endothelial cell function (6). However, in areas with complex geometry (e.g. bifurcations or post-stenotic regions), the blood flow patterns can be neither laminar nor turbulent. Such flow disturbances can induce shear force alterations, endothelial dysfunction, and thus promote disease via vascular remodeling (7).

Digital subtraction angiography (DSA) and computed tomography angiography (CTA) are considered gold standards to evaluate the cervical and intracranial vasculature with high resolution and even qualitative flow dynamic information, but are either invasive or require iodinated contrast and radiation exposure. Magnetic resonance angiography (MRA) is an alternative safe imaging modality, but can require gadolinium contrast with limited hemodynamic information requiring advanced 2D phase contrast techniques. Carotid and transcranial Doppler ultrasound can be employed, but is limited by small field of view, operator dependency, and sensitivity to a poor acoustic window. Alternatively, 4D flow MRI combines ECG-synchronized 3D phase-contrast MRI with advanced post-processing strategies has been successfully applied to quantitatively evaluate in vivo 3D blood flow with full volumetric coverage of the vessels of interest (8, 9).

In this review, we will explore the recent applications of 4D flow MRI to assess cerebral and extracerebral vascular hemodynamics and discuss its current limitations in clinical implementation.

Review

4D flow MRI is primarily used for research purposes and has been extensively validated in the aorta (10–12) and carotid arteries (13–15). Several groups reported comparable 3D blood flow patterns in IA phantoms using 4D flow MRI compared to particle image velocimetry measurements and computational fluid dynamics (CFD) (16–18). Multiple studies (19–29) have applied 4D flow MRI for the in vivo evaluation of normal intracranial vasculature, cerebral arteriovenous malformations, vein of Galen aneurysmal malformations, intra-aneurysmal flow and flow modification post- flow diverter stent placement. Some IA studies also evaluated wall shear stress (WSS) (23, 30, 31).

Despite the extensive use of 4D flow MRI in research studies, it is rarely applied clinically due to existing technical limitations and cumbersome post-processing pipeline (see Figure 1) of high dimensional MRI data. To make 4D flow MRI clinically relevant, further efforts are required from the MRI community and vendors to address the technical limitations, standardize the analysis workflow and increase availability for clinical users.

We will review the recent applications of 4D flow MRI and then discuss the challenges that must be overcome for it to become a valuable diagnostic modality in the evaluation of intra- and extracranial neurovascular disease.

Normative Data of Healthy Control Cohorts

Using 4D flow MRI in a healthy cohort, Bammer et al.(32) investigated the influence of different field strengths (1.5 and 3T), temporal resolution as well as GRAPPA acceleration factors (R=1, R=2 and R=3) on intracranial blood flow and demonstrated that 4D flow MRI is feasible for the measurement and visualization of blood flow in the major intracranial vessels with a required temporal resolution of <65ms. Others reported similar findings (19, 33) studying the venous system (29, 34, 35), ultra-high field strengths (36, 37), comparative studies with 2D PC-MRI (38) and Doppler ultrasound (24), or carotid hemodynamics (13) using reduced TE and spiral 4D flow MRI (39).

Normal or baseline cerebral flow values are important to understand the pathophysiology and/or progression of cerebrovascular diseases (29, 32). Cerebral arteriovenous malformations (AVMs) and intracranial atherosclerotic stenoses predictably result in abnormal hemodynamics, often affecting the systemic intracranial circulation (40, 41). Cerebral blood flow dynamics are also significantly disturbed in other cerebrovascular diseases, such as Moyamoya disease (42), dural venous sinus thrombosis (43, 44), and vein of Galen aneurysmal malformations (45, 46). Therefore, it is of interest to establish a reference of normal cerebral hemodynamics, accounting for differences in patient age and sex.

Using intracranial 4D flow MRI, Wu et al. (29) reported reference values of age-related normal cerebral hemodynamic parameters in a cohort of 52 healthy subjects with ages ranging from 7 months to 61 years. Figure 2 illustrates the differences of cerebral 3D blood flow patterns and regional flow characteristics in a pediatric (age 6 years) and an adult (age 55 years) volunteer, respectively. The authors showed that total cerebral blood flow (TCBF), cardiac/cerebral indexes, brain volume, and global cerebral perfusion were highly associated with age, underlying the importance of age-matched control data for the characterization of intracranial hemodynamics.

Evaluation of Intracranial Aneurysms

IAs are potentially life-threatening lesions and can rupture leading to subarachnoid hemorrhage (47, 48). Current standard diagnostic methods for risk stratification and treatment planning are based on natural history and empirical parameters (e.g. patient age, aneurysm anatomy, size, morphology, and location), ruptured or unruptured status, or systemic risk factors for rupture (hypertension, smoking/alcohol/drug abuse or family history) (49, 50). Previous studies have postulated that these measures provide an incomplete assessment disregarding hemodynamic factors (4, 7, 30). The identification of new predictive biomarkers of aneurysm rupture or progression is of interest for risk stratification, improved patient selection and treatment planning. Irregular flow patterns (vortical and helical flow) have been shown to be associated with vascular alterations and may potentially

constitute new risk factors (7). Other studies showed the diagnostic value of WSS along the IA wall to assess risk of rupture (23). Recently, feasibility studies (19–26) have applied 4D flow MRI for the in vivo evaluation of intra-aneurysmal flow and WSS (23, 31), demonstrating that intra-aneurysmal 3D velocity distribution and WSS correlate with aneurysm size, shape and type (30) (Figure 3).

An interesting 4D flow MRI study by Pereira et al (51) studied IAs post-treatment with flow diverter stent (FDS). Unlike traditional endovascular coil embolization techniques, a FDS reduces intra-aneurysmal flow and promotes progressive and stable thrombosis. 4D flow MRI was used to evaluate post-FDS flow modifications in 10 patients and identified post-treatment blood flow reduction of 35–71%. Despite metal artifacts and slow velocities, qualitative and quantitative hemodynamic evaluation of FDS patients was possible. Another study investigated the feasibility of 4D flow MRI to assess hemodynamics in patients with extracranial-intracranial bypasses (52) and concluded that it can also provide unique qualitatively and quantitatively information for assessing flow dynamics.

In order for 4D flow MRI to become clinically relevant for IA risk stratification, significant development of automated techniques is required for the detection and quantification of regions with irregular flow as well as prospective studies to predict outcome measures such as aneurysm rupture or growth/progression. Furthermore, 4D flow MRI derived hemodynamics could be combined with other advanced methodologies including high resolution vessel wall MRI or aneurysm wall permeability using dynamic contrast enhanced MRI to assess IA rupture risk (53).

Evaluation of Cerebral Vascular Malformations

Due to their complex vascular architecture, cerebral vascular malformations are promising candidates for 4D flow MRI evaluation to characterize lesion hemodynamics. Cerebral AVM exhibit high-flow shunts from the artery to the venous system through an intermediate vascular nidus. Pathological arterialization of the nidus and draining veins predisposes patients to complications of headaches, seizures, ischemia, or intracranial hemorrhage secondary to arterial steal and venous hypertension mechanisms. For high-flow cerebral AVMs, endovascular embolization is often employed prior to surgical resection, allowing for safe and complete AVM resection. It is typically performed in staged treatments to minimize complications, such as intraoperative hemorrhage and normal/reperfusion pressure breakthrough.

Quantitative 4D flow MRI data of the AVM feeding arteries and draining veins may provide valuable information for embolization treatment planning by identifying and targeting feeding arteries with the highest flow. In addition, absolute measures of the AVM hemodynamics may better delineate therapeutic efficacy, treatment outcome, and/or risk of complications. Chang et al. (54) observed AVM hemodynamic markers derived from radial 4D flow MRI that were associated with clinical presentations, i.e. increased WSS in AVM feeding arteries was more prevalent with severe patient symptoms. Another study (55) demonstrated the utility of 4D flow MRI combined with contrast-enhanced 4D MRA (HYPRFlow) to obtain high-resolution angiography and quantitative flow assessment of the

entire AVM vasculature. Additional studies explored the comprehensive evaluation of cerebral 3D blood flow patterns, regional flow characteristics and post-embolization induced hemodynamic changes in patients with cerebral AVMs (27, 56, 57), providing an individualized assessment of AVM hemodynamics and longitudinal evaluation of treatment-induced flow redistribution. With 4D flow MRI, the vascular connectivity and arterial flow contribution of different arterial feeders can be depicted using selective vascular cartography (Figure 4). Other investigators correlated 4D flow MRI metrics (macrovascular flow) with perinidal tissue perfusion (microvascular flow using MR-PWI), and Spetzler-Martin grade anatomic classifications. In a small group of six pediatric patients with vein of Galen aneurysmal malformation (VGAM), 4D flow MRI was shown to be a promising technique for longitudinal characterization of cerebral arterial inflow, arteriovenous shunt flow, and cerebral flow redistribution following staged embolizations (28).

In future applications, 4D flow MRI evaluation of intracranial AVMs and vein of Galen malformations may assist in treatment planning and monitoring hemodynamic changes during embolizations, to assess efficacy and risk for reperfusion complications, but further study is required.

Atherosclerosis (Intra-/Extra-Cranial Atherosclerotic Disease)

Intra-/Extra-cranial atherosclerotic disease represents a major cause of ischemic stroke. Atherosclerotic plaque along the vessel wall results in either thromboemboli or progressive intraluminal stenosis, restricting blood flow to the distal intracranial vasculature. Quantitative hemodynamic markers (e.g. peak velocity, volume flow rates) have been postulated to be valuable in stratifying the risk of atherosclerotic plaque rupture and/or perfusion dependent recurrent stroke. Doppler ultrasound (58–61) and 2D phase-contrast MRA (62–64) are two established techniques that have been applied to quantitatively evaluate atherosclerosis-induced regional hemodynamic alterations, recently with clinical trial evidence that low flow status predisposes to ischemic stroke in vertebral-basilar atherosclerotic disease (65). Other hemodynamic parameters that may provide insight into atherosclerotic disease progression in carotid stenosis include WSS and blood flow velocity in the common carotid artery and carotid bifurcation (66). However, the impact of focal atherosclerotic lesions on flow redistribution across the intracranial vasculature remains incompletely understood, with complex flow patterns due to direct Circle of Willis and indirect pial collaterals.

Very few studies reported on 3D blood flow characteristics and their diagnostic value in intra-/extra-cranial atherosclerotic disease using 4D flow MRI. In a preliminary study, Hope et al. (21) suggested time-of-flight MRA to be inferior to 4D flow MRI in the hemodynamic assessment of patients with intracranial atherosclerotic disease. In a separate study, 4D flow MRI characterized asymmetric flow indices in patients with intracranial atherosclerotic disease compared to age-appropriate controls (67), influencing both distal and ipsilateral collateral arterial hemodynamics. Quantitative hemodynamic data using 4D flow MRI may provide additional insight into the pathophysiology and risk stratification of intra-/extra-cranial atherosclerotic disease based on tissue susceptibility to low flow states or poor augmentation of collateral flow.

Intra-/Extra-Cranial Venous Flow

The importance of venous flow on intra-/extracranial vascular disease is underestimated since previous studies primarily focused on arterial flow characteristics. It has been reported that abnormal venous hemodynamics contribute to the pathophysiology of several cerebral disorders, such as chronic cerebrospinal venous insufficiency, idiopathic intracranial hypertension due to venous stenosis, pulsatile venous tinnitus, and dural venous sinus thrombosis (68–73). However, venous hemodynamics are more sensitive to physiological variations (e.g. heart rate, respiration pattern) and patient positioning (e.g. head and limb), presenting a challenge for accurate and reliable venous flow measurements (74, 75).

4D flow MRI has been applied to measure 3D blood flow characteristics of pathological cerebral veins. Hope et al. (35) reported that venous flow through the superior sagittal sinus was increased 5.1 times in a patient with a large cerebral AVM compared to healthy subjects. Other 4D flow MRI studies confirmed reliable assessment with high reproducibility to perform hemodynamic measurements in patients with intracranial venous pathologies (34, 76).

Challenges to overcome and potential solutions

Our review highlights the developing clinical applications of 4D flow MRI, as it matures to become a reliable diagnostic tool for intra- and extracranial hemodynamic assessment. However, several limitations (e.g. relatively long acquisition time, limited spatiotemporal resolution and velocity range, time-consuming post-processing) remain and need to be addressed prior to clinical utilization. Ongoing technical developments are promising and may overcome these limitations, enabling broader acceptance and implementation.

1. Accelerating Data Acquisition

Long acquisition times are a major drawback of 4D flow MRI due to its four-dimensional data acquisition. Scan times range from 5–20 minutes depending on the spatiotemporal resolution, heart rate, imaging coverage and undersampling strategies. Acquisition time can be significantly shortened by using acceleration methods such as parallel imaging or recently compressed sensing (77–79). Conventional parallel imaging such as SENSE (sensitivity encoding) (80) or GRAPPA (GeneRalized Autocalibrating Partially Parallel Acquisitions) (81) allow an acceleration of data acquisition of up to R=3 (82); with the necessity to acquire some additional data in the k-space center (autocalibration lines for GRAPPA or training data for SENSE) the nominal acceleration R_{net} is slower compared to R. The temporal domain has been used in TSENSE and TGRAPPA to omit these additional lines in central k-space yielding to $R_{net} = R$ (83, 84). More advanced spatio-temporal parallel imaging acceleration methods such as *k-t* SENSE (85) and *k-t* GRAPPA (86) or compartment-based *k-t* principal component analysis (*k-t* PCA) (87) have potential to further accelerate 4D flow MRI. Previous reports have demonstrated that such techniques can reduce total 4D flow scan time substantially by using an acceleration factor up to R=5 (88–92). Dyvorne et al. showed combination of spiral sampling and compressed sensing allowed an abdominal 4D flow MRI scan within a single breath hold (93). However, it is well known that *k-t* acceleration can

induce temporal and spatial blurring and thus may impact 3D flow visualization and quantitative accuracy of the velocity data.

2. Improving Spatial Resolution and Coverage

A major limitation of 4D flow MRI apparent in all intra- and extracranial applications is the lack of spatial resolution to capture the hemodynamics of small vessels as well as small IAs. Spatial resolution significantly affects the accuracy of flow quantification, particularly in cerebral vessels with small diameters such as AVM feeding arteries. Insufficient spatial resolution may result in overestimation of blood flow due to partial volume effects. At least 16 voxels are required over the vessel lumen for <10% flow quantification errors (94), which means the spatial resolution must be 0.5–1.2mm (*x, y, z* dimension) for accurate flow measurement in cerebral vessels with typical 2–5mm diameters. Higher spatial resolution can be achieved by sacrificing total scan time, imaging coverage, and signal-to-noise ratio. Ultra-high field has been successfully employed in several studies (36, 37, 95), where higher spatial resolution can be achieved without signal-to-noise ratio degradation.

A large spatial coverage is critical to characterize the entire arterial and venous system, such as in complex AVM feeding and draining pathways. Radial and spiral sampling strategies have advantages over standard Cartesian sampling schemes in obtaining larger spatial coverage via undersampling methods. In fact, total scan time for a 4D flow MRI study covering the entire intracranial vasculature was reported between 4–8 minutes using a highly optimized radial 4D flow sequence (3D PC-VIPR) (76, 96, 97).

3. Extending Dynamic Velocity Range

All 4D flow MRI studies evaluating intra- and extracranial hemodynamics were limited due to an inability to capture the wide range of velocities within IAs (high flow jet, low unstable flow, vortex and helix flow types), or AVM arterial inflow and venous drainage. Current MRI protocols measure flow using one defined velocity sensitivity (venc) and thus lack the dynamic range to reliably assess the full velocity spectrum. To address these limitations, low- and high-venc 4D flow MRI can be performed serially (dual-venc) resulting in high-venc data that can then be used for complete anti-aliasing of low-venc data. Dual-venc could thus provide improved quantification of the entire velocity spectrum. Previous studies have investigated various dual-venc approaches based on multiple serial 4D flow MRI acquisitions: set of two or more vencs and post-processing methods (98–100), five-point balanced flow encoding to reduce noise and aliasing in phase images (101), varied velocity encoding for acquiring data points during systole or diastole (102). Another approach by Binter et al. (103) uses multipoint phase-contrast imaging in combination with Bayesian analysis to map both mean and fluctuating velocities over a large dynamic range.

Conclusion

In conclusion, 4D flow MRI has been demonstrated to be a unique imaging modality for the assessment of cerebral and extracerebral hemodynamics. Although limited to research feasibility studies in various neurovascular pathologies, promising technological advancements in 4D flow MRI techniques and patient validation studies will continue to

improve the technique's accuracy for in vivo hemodynamic analysis and clinical implementation. Additional qualitative and/or quantitative hemodynamic information from 4D flow MRI studies may eventually assist in risk stratification schemes of IAs, AVMs, or cervical/intracranial atherosclerotic disease. Furthermore, the technique may be valuable for post-treatment monitoring after endovascular or surgical intervention of IAs, intracranial stenosis, venous pathologies, or planning safe and effective staged embolization treatment of AVMs. We remain optimistic in overcoming the technical challenges to allow clinical utilization of 4D flow MRI techniques, complementing the diagnosis and treatment planning of intra- and extracranial neurovascular disease.

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Key points

1. Importance of hemodynamic parameters in cerebral and extra-cerebral vascular diseases
2. 4D flow MRI as a potential diagnostic imaging modality for the risk stratification of neurovascular disease progression.
3. 4D flow MRI for potential treatment planning and/or post-treatment monitoring of neurovascular diseases to assess interventional therapies.
4. Important technical developments to speed up acquisition times, improve spatial and temporal resolution, and dynamic velocity range will allow for broader clinical implementation of 4D flow MRI.

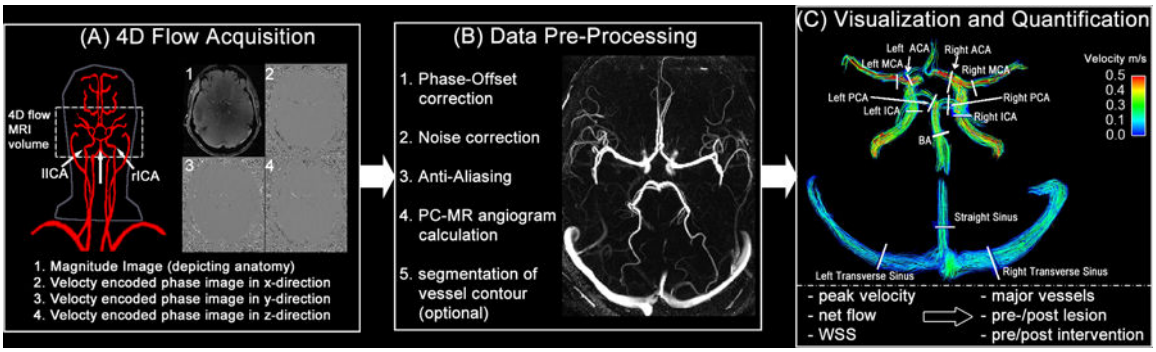

Figure 1.

Intracranial 4D flow workflow example including (A) data acquisition of the time-resolved 3D volume, (B) the data pre-processing such as phase offset correction, anti-aliasing and the phase-contrast MR angiogram calculation in order to segment the vessel wall or to mask the measured velocities within the vessel constraints. Panel (C) illustrates the visualization of blood flow using color-coded streamlines at peak systole and the locations of potential quantification of hemodynamic parameters such as peak velocity, net flow and WSS.

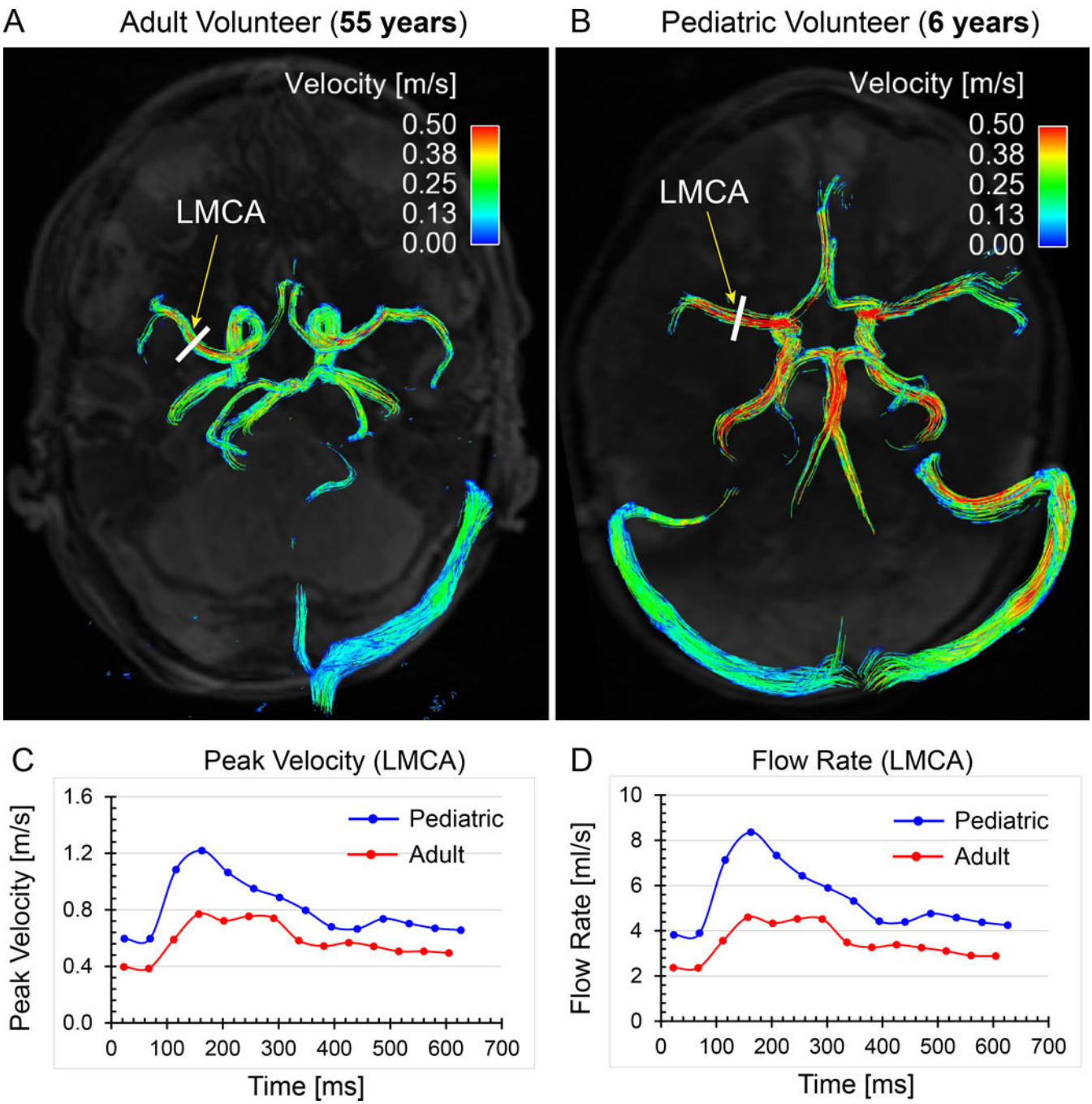

Figure 2.

Comparisons of normal cerebral blood flow between a healthy adult volunteer (55 years) and a pediatric volunteer (6 years). Time-integrated 3D pathlines show overall higher cerebral blood flow velocities in the pediatric volunteer (B) compared to the adult volunteer (A). Regional flow measurements at the left middle cerebral artery (LMCA) quantitatively illustrate the differences of LMCA peak velocity (C) and flow rate (D) between the adult and pediatric volunteers.

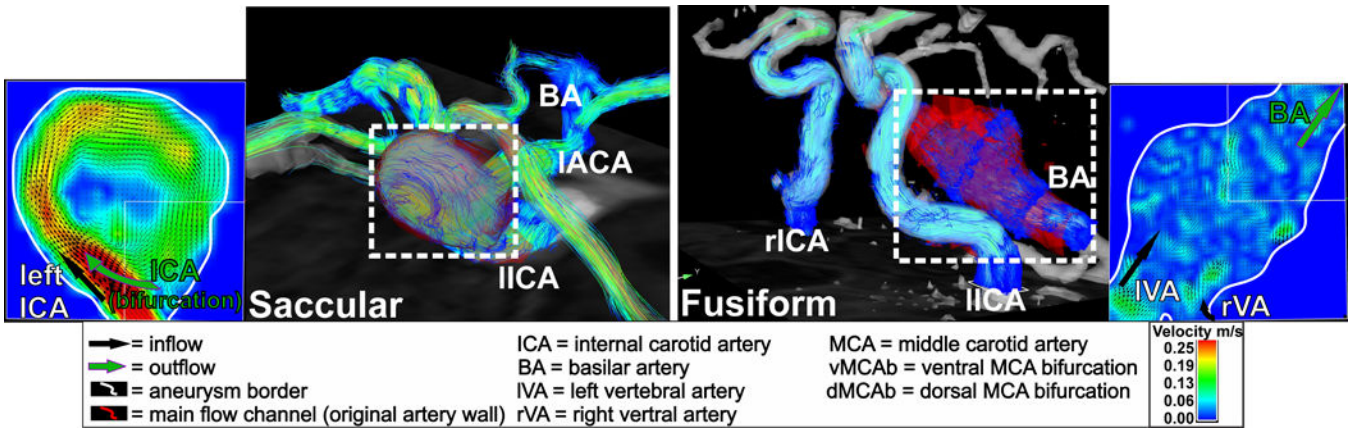

Figure 3.

4D flow MRI of a saccular left C4 segment ICA aneurysm (left) and a fusiform basilar artery aneurysm (right). It could be shown that small saccular aneurysms have significant largest peak velocities and WSS compared to large and giant saccular aneurysms and fusiform aneurysms. Fusiform aneurysms expressed significant lowest peak velocity and WSS along the vessel wall (30).

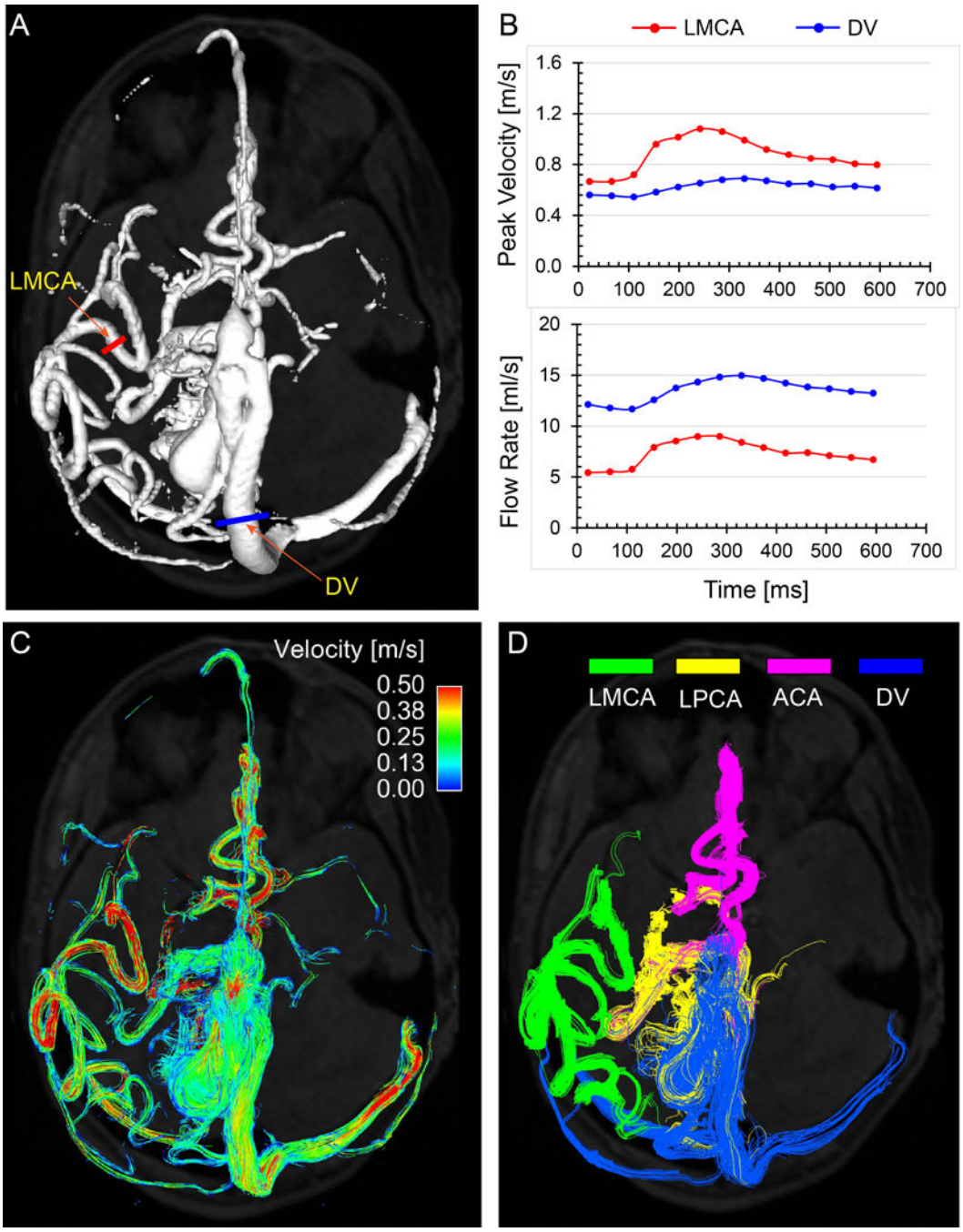

Figure 4.

Illustration of 4D flow MRI for hemodynamic assessment in a patient with cerebral AVM (age 40 years, female, Spetzler-Martin grade = 4). A: 3D phase-contrast MR angiogram (PC-MRA) used for the orientation of 2D analysis planes. B: regional flow characteristics (peak velocity and flow rate) at user-defined vessel locations (examples for the feeding LMCA and the largest draining vein). C: Cumulative flow pathways of the entire cerebral vasculature over one cardiac cycle are depicted using time-integrated 3D pathlines which are color-coded according to local vascular velocity magnitude. D: selective vascular

cartography illustrating connectivity and flow contribution of the major feeding arteries and draining vein. LMCA: left middle cerebral artery (green), LPCA: left posterior cerebral artery (yellow), ACA: anterior cerebral artery (pink), DV: draining vein (blue).