4D Flow MRI in Neuroradiology: Techniques and Applications

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Abstract: Assessment of the intracranial flow is important for the understanding and management of cerebral vascular diseases. From brain aneurysms and arteriovenous malformations lesions to intracranial and cervical stenosis, the appraisal of the blood flow can be crucial and influence positively on patients' management. The determination of the intracranial hemodynamics and the collateral pattern seems to play to a major role in the management of these lesions. 4D flow magnetic resonance imaging is a noninvasive phase contrast derived method that has been developed and applied in neurovascular diseases. It has a great potential if followed by further technical improvements and comprehensive and systematic clinical studies.

Key Words: 4D flow MRI, arteriovenous malformations, cerebral aneurysms, intracranial stenosis, phase contrast MRI

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Due to the poor accessibility and small size of the cerebrovascular anatomy, the hemodynamic assessment of the intracranial circulation is a challenging topic that involves different imaging methods.

Transcranial Doppler (TCD) is the most frequently used method for measuring cerebral flow and velocities.[1] Thanks to its low cost and transportability, this technology is widespread for the monitoring of various neurovascular diseases such as stenosis, vasospasm, strokes and for the determination of the vascular reserve.[2] However, the precision of the measurement depends on a variety of factors. For instance, the low ultrasound penetration through the skull requires the use of specific bone windows in order to optimize the signal to noise ratio. Furthermore, the probe orientation being a crucial factor for the quantitative flow velocities assessment, the measurement precision and repeatability depends strongly on the experience of the operator and the equipment.[1] This technique is currently restricted to 1D and 2D velocity measurements,[3] and is therefore not adapted to complex 3D velocity fields as those encountered in intracranial aneurysms (IAs).

Alternatively, the analysis of contrast agent (CA) motion from video densitometry allowed for per-operative flow measurements. For this purpose, various postprocessing methods[4] were tested such as bolus tracking using time intensity curves (TICs), distance intensity curves (DICs), model-based flow quantification, or optical flow (OF). Recently, the evaluation of flow by digital subtracted angiography (DSA) gained special interest to study the efficacy of IAs and acute stroke treatments.[5–10] However, these measurements require an invasive procedure that may be related to technical risks. Furthermore, the quantitative interpretation of CA motion on 2D x-ray images is still debated. Indeed, the intensity of these images is related to the cumulative x-ray absorption of CA in the beam direction and therefore averages velocity information along this direction.

Magnetic resonance imaging (MRI) has been first used to measure the functional aspects of brain. With the development of MR angiography (MRA), the imaging of cerebral vasculature also became possible without negative effects related to x-ray imaging, that is, radiation and injection of CA. More recently, four-dimensional (4D) time-resolved MRA has emerged as a promising angiographic technique with additional temporal resolution. Two different techniques are currently explored. The first with CA (eg, TWIST, 4d TRACK, TRICKS) not only provides morphologic but also dynamic information of flow with the possibility to obtain pure arterial and venous phase images.[11–13] The second so-called phase contrast MRI (PC-MRI) does not need the use of CA and also provides flow velocity information along the cardiac cycle without the use of CA. Nowadays, 4D PC-MRI is the only safe and efficient method for quantitative in vivo 3D flow assessment.[14] Due to its constant increase of spatial and time resolution made possible by the numerous improvements of acquisition sequences (gradient echo, SENSE, compressed sensing) and hardware (magnetic fields, gradients, coils), 4D PC-MRI is the most promising technique for intracranial flow assessment. In this review, we discuss the current status of 4D PC-MRI technique and its applications in neuroradiology and research perspectives.

TECHNIQUES

The velocity measurement based on phase contrast MRI relies on the dephasing of moving spins submitted to a defined gradient. More precisely, the phase component of an MR signal produced after the application of a magnetic gradient is the sum of 2 effects. First, a phase shift also affecting stationary molecules is proportional to the local gradient intensity. The second impacts only flowing molecules that experience different gradient intensity when moving in the direction of the imposed gradient. By applying a bipolar gradient (meaning that its shape is half positive and half negative), the first effect is nullified and the remaining phase affecting only moving molecules is directly proportional to the gradient amplitude, its duration (which are known), and to molecules velocity. However, as field inhomogeneity always induces locally an undesired phase shift, an additional reference measurement (with/without a reverse gradient for example) is necessary to remove this effect. The principles of this technique have been described many years ago but only recently applied in clinical settings, as it is a long acquisition that now benefits from the development of acceleration techniques.[15] In practice, the velocity-encoding gradients are added to a gradient echo sequence; the magnitude of the MR signal therefore gives a structural image wherein the anatomy can also be visualized. Furthermore, the velocity information can be used in an efficient manner to create images in which vascular anatomy and flow velocities are depicted.[16]

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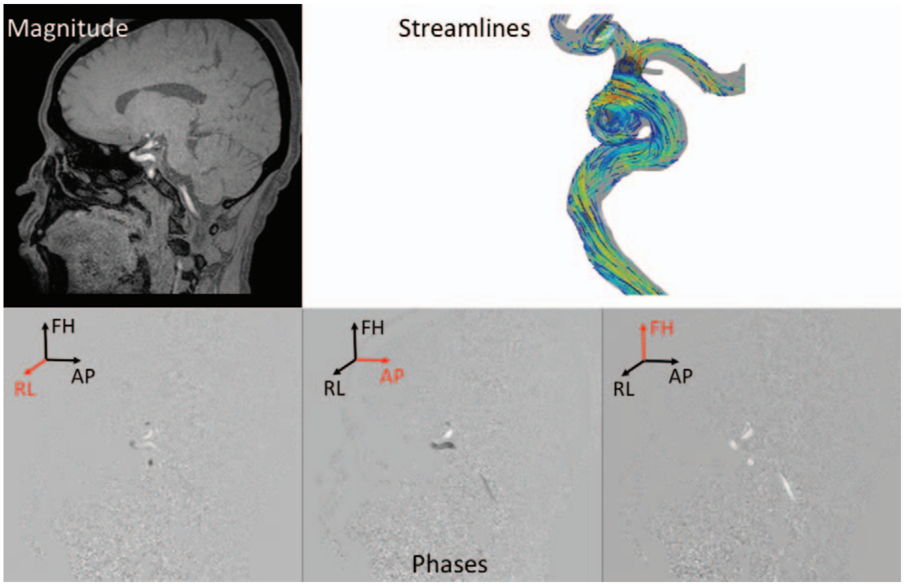

FIGURE 1. Illustration of a 3D velocity encoding acquisition using PC-MRI in a patient harboring a sidewall IA. The magnitude (corresponding to the 3 velocity encoding directions, i.e., right-left [RL], feet-head [FH], and anterior-posterior [AP]) of the acquired images are shown along with the corresponding streamlines computed from the measured velocities.

PC-MRI was first developed for 2D imaging, and with a single flow direction velocity encoding that could be either through plane or in-plane. As the flow is varying through the cardiac cycle, the acquisition must be synchronized with the patient ECG, thus providing full-time resolved (CINE) datasets. Later on, new sequence development and acceleration techniques allowed measuring flow in a 3D volume with the 3 spatial directions of the velocity field in a reasonable acquisition time. This 4D (3 spatial and temporal direction) phase contrast imaging proved to be very useful in locations in which the flow is complex and would require multiple 2D acquisitions to be characterized efficiently. The acquired dataset showing the full 3D velocity field can then be introduced in dedicated postprocessing tools to visualize the 3D flow features with the help of, for example, streamlines or vector representation (Fig. 1).

An important parameter for this sequence is the velocity encoding (VENC). It is an operator selectable parameter generally measured in cm/second that defines the highest potentially measured velocity. As the velocity is encoded through the phase images, the VENC corresponds to a 180° phase shift, which is the maximal unambiguous phase shift. When higher velocities are measured, these result in aliasing in the phase image. Furthermore, the imposed VENC determines the degree of sensitivity to slow or fast flows by adapting the amplitude and duration of the bipolar gradients. Therefore, the choice of the VENC must be taken with special care balancing aliasing artefacts and sensitivity to low velocities. In practice, each vessel or regions have its own velocity range for which the optimized VENC has been determined.[14] Pathological conditions that could alter the velocities such as stenosis or aneurysms should be compensated on the VENC determination as well (Fig. 2).

APPLICATIONS IN NEURORADIOLOGY

The hemodynamic evaluation of intracranial vasculature can be of extreme importance for the evaluation, understanding, and management of vascular diseases affecting these vessels. The brain corresponds to 2% of the body weight and demands approximately 20% of the blood that flows from the heart. This intense energy requirement uses 4 arteries to conduct the blood into the intracranial space: 2 carotid arteries and 2 vertebral arteries. These arteries navigate through the skull base in a tortuous route and progressively bifurcate into smaller arteries to irrigate all intracranial structures in the deepest locations. Consequently, this arterial system absorbs an intense stress due to the high volume and velocity flow. Evaluating this system may help the understanding, for example, aneurysm initiation or rupture.[17–20] The majority of the aneurysms are located in bifurcations,[21] zones of a complex hemodynamics, and until now the pathomechanism is unclear. Vasospasm, stenosis, and arteriovenous malformations are other vascular issues that may benefit from a hemodynamic assessment of the intracranial circulation.

Intracranial Aneurysms

IAs are a life-threatening clinical condition that can produce severe intracranial bleeding, a subarachnoid hemorrhage,[21] with an estimated prevalence of between 2% and 5% of the population.[21] Most of the aneurysms are discovered after rupture. However, due to the improvement of diagnostic imaging access worldwide, there is an increasing number of incidentally discovered aneurysm patients who will require an evaluation for potential treatment or follow-up. In this context, the balance between treatment risk and rupture risk, to be considered in the orientation of the clinical decision, became a challenging biomedical research domain. In particular, lots of efforts have been made to refine the rupture risk prediction, for example, by including hemodynamic factors involved in the rupture process.

Due to the lack of precise in vivo measurement tools, significant investigations have been first conducted by modeling the blood flow behavior using computational fluid dynamics (CFD).[22,23] CFD is a powerful tool not only widely used in industry but also applied in few medical applications as in coronary disease to determine fractional flow reserve using cardiac computed tomography (CT).[24] However, CFD calculations require many assumptions to resolve Navier-Stokes equations, which govern fluids movements in a discretized domain. For instance, physiological conditions (velocity, pressure)

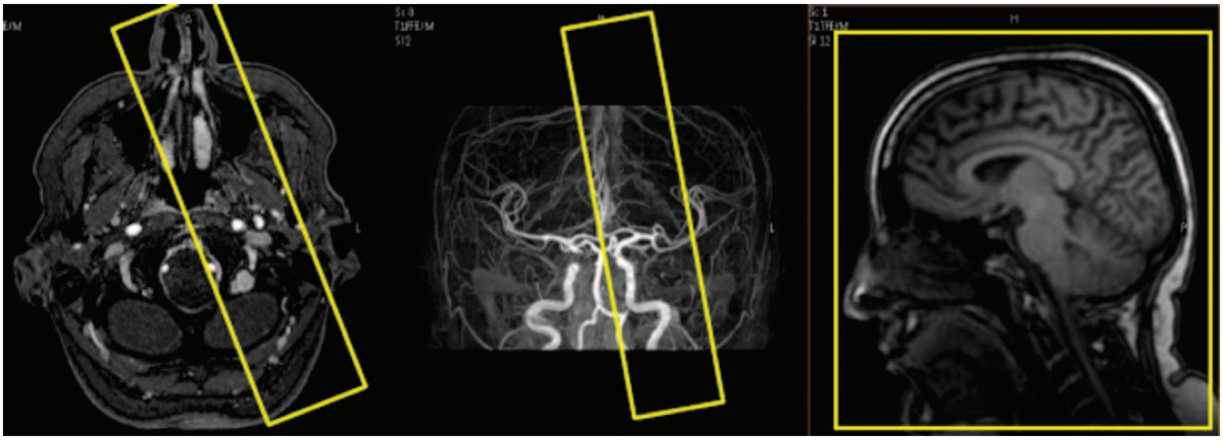

FIGURE 2. Practical aspects of a 4D TOF imaging acquisition of a brain vessel. After placing the patient on the equipment, an ECG or PPU is connected to trigger the sequences. A time of flight sequence of the intracranial vessels is performed to determine the volume of the acquisition. Careful attention should be made with the angles and directions of the region of interest (ROI). See an example of the definition of the volume for a left internal carotid artery examination.

must be imposed at the extremity of the 3D calculation domain (ie, boundary conditions [BCs]). So far, flow models were not able to link unambiguously hemodynamics and aneurysms' rupture, essentially due to the small sample size of the studies, the different modeling methodologies, and assumed flow conditions.

The recent advances in 4D PC-MRI have allowed the in vivo measurement of 3D velocity fields with a decent spatial and time resolution for cerebral circulation investigations. In particular, 4D PC-MRI was used to compare qualitative and quantitative flow behaviors with other measurements or simulations, for example, CFD or in vitro methods for validation purposes. Furthermore, 4D PC-MRI can provide BCs for modeling real patient flow conditions. Von Ooij et al[25] compared 3D PC-MRI of 8 aneurysm patients with CFD using patient-specific BCs from both the 2D and the 3D PC-MRI sequences.[26] They found, in general, a good agreement regarding the flow patterns visualization at systole. At diastole, 4D PC-MRI failed to correlate with CFD results, probably due to the low velocity-to-noise ratio. Quantitatively, there were significant relative differences between the velocities magnitudes on the CFD results depending on 2D or 3D BCs modeling, which might be due to different spatial resolution. These measurements were extended to the calculation of wall shear stress (WSS) and showed a good correlation on the direction of the WSS on IAs models even if WSS computed from 4D PC-MRI was generally lower and did not show quantitative correlation.[25] Another group performed a similar experience and found a good correlation between MRI-based CFD and 4D PC-MRI[27] for streamlines and 3D velocity fields but lower correlation of computed WSS. The improvement of WSS assessment would requires lower noise and higher resolution which are present limitations of 4D PC-MRI. Indeed, WSS is computed from spatial derivatives of the measured velocity field which are very sensitive to the data resolution and signal-to-noise ratio.

Although 4D PC-MRI has a high potential for CFD validation and patient flow modeling, its temporal resolution remains low compared with the temporal fluctuations of real physiological conditions. Furthermore, the data being acquired over multiple cardiac cycles and compiled at the end of the sequence give an averaged velocity field. For these reasons, transient and high frequency features might be omitted by this technique.

Recently, 4D PC-MRI was involved in the hemodynamic evaluation of patients treated with low-porosity flow diverter stents (FDS). These stents are used for the treatment of large and complex IAs. The induced modification of intra-aneurysmal flow is known to promote aneurysmal thrombosis and eventually the IA healing. Even if this treatment carries a high success rate,[28,29] there is no possibility to predict the 15 to 20% of occlusion failings. For this purpose, per-operative flow assessment methods have been developed on the basis of DSA imaging using different CA tracking methods such as OF imaging[5–7] or time density curves.[9,10] Although DSA flow reduction indicator shows a significant correlation with thrombosis formation, this method cannot provide the flow reduction quantitatively. Alternatively, 4D PC-MRI investigations of these flow changes were conducted by our team.[30] Even if MRI is not intuitively the modality of choice for assessment of stent effect due to metal artifacts, we found interesting patterns and perspectives by conducting this pilot study (Figs. 3 and 4). We could quantitatively compute the intra-aneurysmal flow reduction after FDS implantation and identify a velocity threshold correlated with complete aneurysm thrombosis at 6 months.[30] We reported stent artifacts in all of the cases, more prominent on the extremities, probably related to stent markers and close to the intra and extraluminal surfaces. Furthermore, the low signal to noise ratio prevented the visualization of the streamlines in cases presenting aneurysmal velocities below ~8 cm/s,[30] that is, 10% of the VENC. These limitations emphasize the importance of the VENC, which should be set to a lower value to capture the stented IA velocities precisely. For future studies and experiments, the possibility to perform dual VENC acquisitions should be considered.[30] Despite of its evident limitations, this study demonstrated how nicely 4D PC MRI flow could improve outcome prediction after FDS treatment.

Brain Arteriovenous Lesions

Brain arteriovenous malformations (AVMs) are a group of complex vascular lesions that are characterized by the rapid flow connection from the arterial to the venous system. Over time, the capillary structures become a complex network of fragile vessels called nidus. Furthermore, the venous system is constantly overloaded and/or dilated. One of the potential treatments for these pathological conditions is the endovascular embolization with polymers that will disconnect the arterial to venous system reducing the flow or ideally occluding the whole nidal vascular network. Recent studies demonstrated how 4D MRI flow could help understanding the

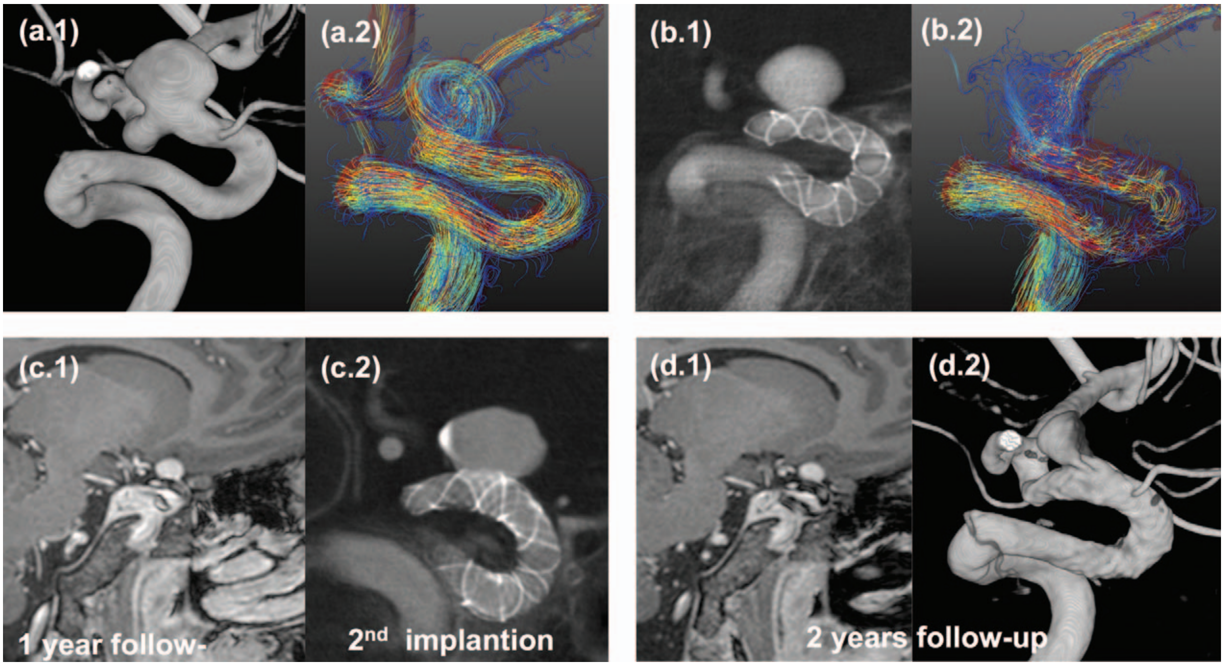

FIGURE 3. A 42-year-old male with a left carotid ophthalmic aneurysm visible on 3D angiogram (a.1). The streamlines representation of 4D-PCMR velocity fields before implantation (a.2) shows a clockwise vortex with an aneurysm inflow jet entering at the level of the distal part of the neck. In (b.1), enhanced cone beam CT (CBCT) showing the final position of a 4–30 silk stent. In (b.2), the streamlines representation of 4D-PCMR velocity fields after implantation shows a remaining inflow jet with a reduced magnitude, associated with an altered intrastent signal. The calculated PVRR was 42.7 % of flow reduction based on pre and poststent 4D-PCMRI sequences. At 1-year follow-up MRI on contrast-enhanced T1 sequences (c.1), the aneurysm was fully circulating. Consequently, a second layer of flow diverter (PED) was added as visible in the postprocedure-enhanced CBCT (c.2). At 2 years follow-up, the aneurysm was still patent as showed by MRI contrast-enhanced T1 sequences (d.1) and catheter angiogram (d.2). Note that MRI images were right-left flipped to be oriented as 4D PCMR and catheter angiogram images.

complex morphologic and hemodynamic changes inside these AVMs and also the impact of staged embolization on the velocities on the arterial and venous side.[31,32] Within limits of its resolution, it may show better arterial feeding patterns and venous drainage pathways in complex AVMs.[31,32] Other MRA-derived techniques such as 4D-hMRA or HYPRflow can probably grossly evaluate the anatomy, but their temporal resolution is inferior to PC-4D MRI.[33] Potentially, in the future, it may also be able to identify the intranidal fistulas, determine hemodynamic parameters after embolizations, and potentially identify benign or malignant patterns. There are some applications on dural arteriovenous fistula (AVF) cases.[34] A cavernous AVF that was treated with trapping and by-pass had the hemodynamic assessment and by-pass patency evaluated with 4D flow MRI.[34] In another report, a complex AVF had a pre and post-treatment evaluation with flow measures on the arterial and venous structures to assess treatment result. Their main limitation on measuring the whole vascular structure was vascular tortuosity.[35] Future studies evaluating unruptured AVFs on follow-up may help predicting their evolution or pattern changes.

Cerebrospinal Fluids

It is very challenging to evaluate the circulation of the cerebrospinal fluid (CSF) inside the cranial cavity and in the spinal canal. The related clinical applications of 4D PC-MRI are as follows:

1. To study hydrocephalus from different origins (idiopathic stenosis of the aqueduct of Sylvius, tumors, postinfection, surgery, etc.) in pediatric and adult population can be difficult to assess particularly in cases in which there is an obstruction,
2. Syndrome of the Trephined.[36]
3. To illustrate whether the cyst is communicating or not in the spinal canal in case of cysts after trauma and to facilitate surgical planning.

Recently, Stadlbauer et al[37] showed how the measurement of CSF can help to treat some types of hydrocephalus related to dementia in adults. In a feasibility study, they evaluated 21 patients with ‘‘hydrocephalus’’ appearance of the ventricles and they could differentiate the etiological subtypes on the basis of the flow visualized on MRI. They found hypomotility in patients with aqueduct stenosis, normal flow in ex vacuo atrophy, and they could control the flow on a 3rd ventriculostomy in a case. Figure 5 nicely demonstrated a similar case. We believe that these preliminary data should be correlated with clinical signs and longitudinal follow-up.

Intracranial Stenoses

Intracranial stenoses are related to recurrent strokes and merciless long-term cognitive outcomes if not managed correctly. Understanding the impact of the stenosis on the brain perfusion and on the hemodynamics of the circle of Willis is crucial for the clinical management and therapeutic decision-making process. 4D flow MRI has challenges on evaluating these cases because of the size of the vessels, wide velocities ranges, and length of straight segments to allow measurements. Hope et al[38] used 4D flow MRI in addition to MRA to evaluate 2 patients with intracranial stenosis and they could

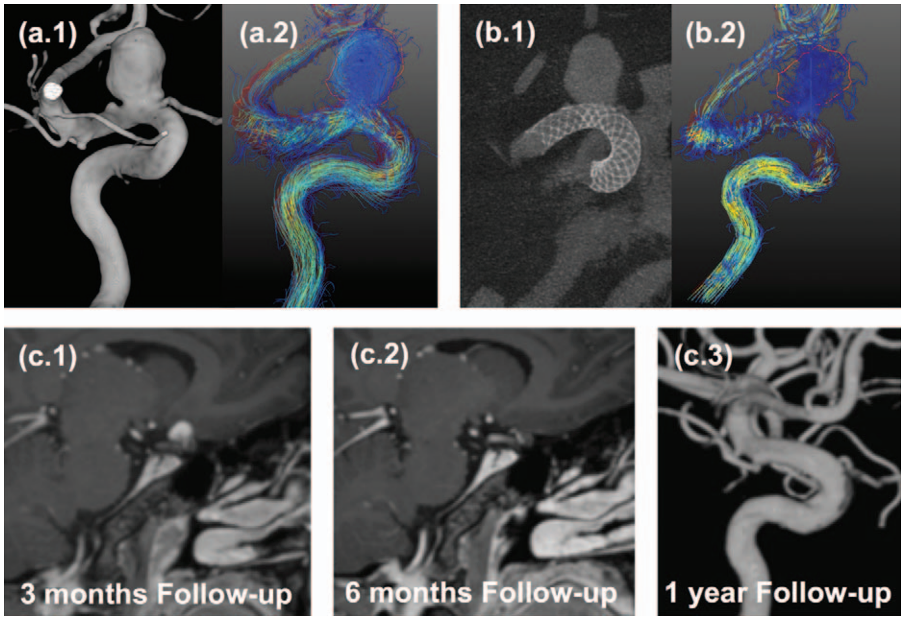

FIGURE 4. A 44-year-old female with a right carotid-ophthalmic aneurysm visible in 3D angiogram (a.1). The streamlines representation of 4D-PCMR velocity fields before implantation (a.2) shows a clockwise vortex with an aneurysm inflow jet of low velocity magnitude. A PED 4.25–16 was implanted and its final position is shown on an enhanced CBCT image (b.1). After implantation, the streamlines representation of 4D-PCMR (b.2) shows an absence of reliable and understandable velocity fields with an altered signal inside the stent. In this case, the flow reduction was important with a PVRR of 71.1%. Follow-up MRI with enhanced T1 sequences at 3 (c.1) and 6 months (c.2) show an absence of aneurysm patency at 6 months (MRI images were right-left flipped to be oriented as 4D PCMR and catheter angiogram images). Catheter angiogram (c.3) at 1 year confirms the complete exclusion of the aneurysm.

better calculate the stenotic degree by adding ‘‘Doppler-like’’ information to compensate the limitations of the anatomic imaging. Harloff et al[39] showed that 4D flow underestimated the velocities compared with Doppler measurement of about 20 to 25% but mentioned a good reproducibility of this method. One of the most important 4D techniques described in the evaluation of the intracranial flow is a combination 3D time of flight (TOF) imaging, 2D PC-MRI, and a postprocessing using marching cube algorithm called NOVA software.[40] Optimal perpendicular scan plan is calculated by a line-fitting algorithm; a retrospectively gated 2D phase contrast scan is performed with a double-oblique prescription that was perpendicular to the vessel flow direction.[41] VENC is adjusted

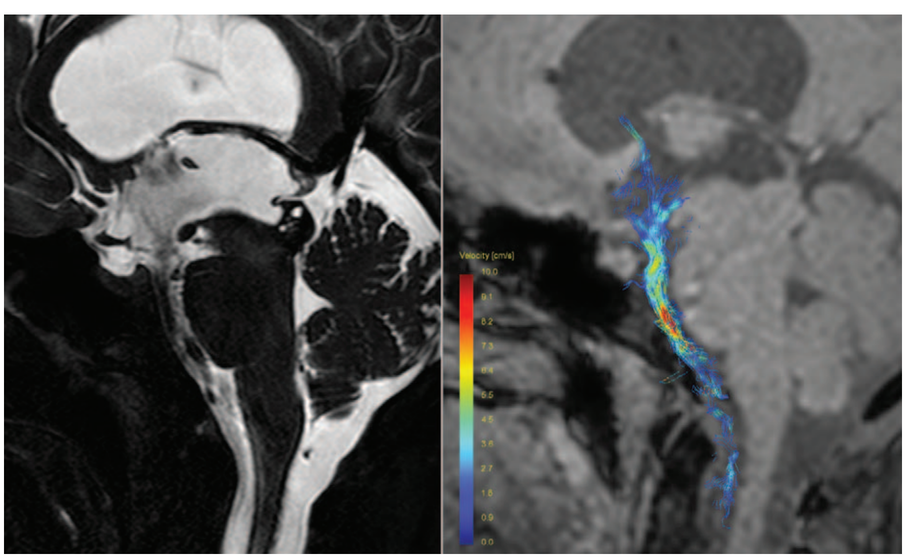

FIGURE 5. PC-MRI measurements of cerebrospinal fluid motion. A 46-year-old female known for noncommunicating hydrocephalus. Streamlines of 4DMRI flow sequence illustrate CSF flow through the floor of third ventricle, proving the patency of the ventriculostomy in a noninvasive way.

following the cube algorithm, and QMRA acquisition is acquired and transferred to a workstation for vessel flow/size quantification using a cardiac gating 20 data points per cardiac cycle.[41] They were able to calculate velocities in vessels of the Willis circle. Intracranial stenosis significantly changes the intracranial hemodynamic balance of the Willis circle and the pial collateral network. A collateral network can/must be formed to permit optimal cerebral perfusion. When it fails to supply the flow to the correspondent territory of a stenotic vessel, acute or chronic cerebral changes may develop. Evaluation of the collateral flow is crucial for the decision-making process and treatment strategy in case of recurrent stroke symptoms. A prospective study examined the use of 4D flow and hemodynamic information in the management of symptomatic atherosclerotic vertebrobasilar occlusive disease.[42] In this study, the group of patients with low distal flow were at risk to develop recurrent stroke in the following year in spite of best medical treatment.[42] Identification of high-risk patients may be relevant when considering further recanalization strategies.

CONCLUSIONS

Intracranial circulation assessment is important for the evaluation of cerebral vascular diseases. 4D MRI flow is a noninvasive method that can be applied to acquire blood velocities on vessels and vascular structures such as aneurysms or venous dilations from arteriovenous malformations. It has also been used to predict outcome after treatment of giant aneurysm with flow-diverting stentings or to measure the flow distal or proximal to an intracranial stenosis. Future clinical studies evaluating these techniques as well as further technical improvements such as multi-VENC acquisitions or improving the temporal resolution may consolidate their clinical applications.

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