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Advanced technologies applied to physiopathological analysis of central nervous system aneurysms and vascular malformations


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Abstract While depiction and definition of morphological and architectural characteristics of CNS vascular disorders remains the first step of an MR analysis, emerging imaging techniques offer new functional information that might help to characterize rupture risk of CNS vascular disorders. Two main orientations are suggested by recent studies: inflammation of the vessel wall and analysis of physical constraints of blood flow using 4D flow imaging (shear parietal). This paper will focus on radiological application of 4D flow imaging and inflammation imaging, in the characterization of potential prognostic markers of CNS vascular disorders. We will review the basic technical considerations of 4D flow MRA, inflammation imaging and discuss their applications in CNS vascular disorders: aneurysms, arteriovenous malformation, dural arteriovenous fistulas. We will illustrate their potential in the development of individual rupture risk criteria in brain vascular disorders.

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MR imaging developments provide new tools for characterization of brain vascular malformations, such as intracranial aneurysms, arteriovenous malformations (AVM) and dural arteriovenous fistulas (DAVF). The first aim of brain MRI is to be able to depict a vascular disorder. This has been a real challenge over the years 1990s and 2000, where the application in clinical routine of time-resolved contrast enhanced MR angiography [1] and non-contrast-enhanced MR angiography (e.g. 3D time-of-flight) sequences [2] added the possibilities of MR imaging to depict AVMs and aneurysms. Although catheter angiography remains the reference for the evaluation and pretreatment planning, irradiation, catheterism risks and use of contrast agents have made MRI the examination of choice in patients with suspicion of intracranial vascular malformation.

While depiction and definition of morphological and architectural characteristics of CNS vascular disorders remains the first step of an MR analysis, emerging imaging techniques offer new functional information that might help to characterize rupture risk of CNS vascular disorders. Two main orientations are suggested by recent studies: inflammation of the vessel wall [3] and analysis of physical constraints of blood flow using 4D flow imaging (shear parietal) [4–6].

This paper will focus on radiological application of 4D flow imaging and inflammation imaging, in the characterization of potential prognostic markers of CNS vascular disorders. We will review the basic technical considerations of 4D flow MRA, inflammation imaging and discuss their applications in CNS vascular disorders: aneurysms, arteriovenous malformation, dural arteriovenous fistulas. We will illustrate their potential in the development of individual rupture risk criteria in brain vascular disorders.

**Emerging techniques**

**4D Flow MRI**

Shortly after the introduction of clinical MR imaging in the 1980s, Moran [7] demonstrated that velocity and flow could be measured non-invasively by using flow-encoding gradients integrated into conventional MR imaging techniques. This innovation was quickly implemented, resulting in 2D and 3D phase-contrast MRA [8]. However, initial excitement in 4D flow MRI imaging was dampened by low resolution, loss of signal due to complex flow, difficulty in selecting the velocity encoding, and the long scanning times for 4D acquisitions. Recent advances in accelerated acquisition and undersampled reconstruction open the possibility of extending MRA to functional information [9]. Acquisition times have been reduced by using strategies such as compressed sensing [10] and radial k-space trajectories [9]. Shorter TEz have reduced signal loss, and new encoding strategies have improved the dynamic range of velocities that are detected [11]. 3T scanners and 32-channel coils provide substantial increase in signal and signal detection, enabling higher spatial resolution examinations [12]. Fast high-resolution 4D flow imaging techniques are now applicable in clinical setting, with an average scan time of 6 minutes per encoding speed. Quantitative flow measurements including velocity, pressure and wall shear stress, adds a new dimension to non-invasive angiography.

Phase-contrast sequences are the basis of 4D flow MRI techniques using the change in the phase shift of the flowing protons to create an image. Spins that are moving along the direction of a magnetic field gradient receive a phase shift proportional to their velocity [9]. Phase-contrast acquisition comprises sequences with and without encoding of the flows that produce the images in magnitude (“anatomical” aspect of flows) and in phase (“quantitative” aspect: flow direction and velocity). A suitable encoding speed must be chosen beforehand to avoid an aliasing source of errors in high-speed measurement [11]. Data obtained can provide qualitative (flow visualization) and quantitative measurements. Qualitative information provides the flow direction in each voxel. The flow network can be further defined by generating velocity-derived flow-path lines providing an overview of the dominant flow channels. The vascular anatomy can be eloquently displayed by using the velocity data within each voxel to derive streamlines weighted by the distance travelled per second. The resulting virtual MR cartography [13] requires segmentation of vessel boundaries followed by manual positioning of the plane emitter by using vessel cross-sections and blood-flow-tracking within these vessels by generating velocity-based selective streamlines. A selective cartography of the vascular malformation can be displayed by choosing the starting point of the flow-tracking.

Quantitative measurements include velocity and, derived from the velocity parameters, pressure and wall shear stress (WSS) maps [12]. Pressure maps may provide access to the pressure variations within a vascular malformation. Wall Shear Stress is defined as the derivative of velocity with respect to the distance from the wall, multiplied by the viscosity. It represents the constraint that parallel flowing fluid imposes on the wall. High spatial resolution is necessary to accurately acquire WSS at the boundary zone of the vessel [14].

**Parietal inflammation and bio-imaging markers**

Histopathologic evidence from human studies of aneurysm tissue and experimental models of cerebral aneurysms support the concept that inflammation plays a major role in intracranial aneurysm formation, progression and rupture. Aneurysm formation is thought to be the consequence of pro-inflammatory changes in endothelial cells. This is followed by the infiltration, activation, and proliferation of inflammatory cells. These processes act in concert to weaken the arterial wall progressively, resulting in dilatation, aneurysm formation and, ultimately, rupture [15].

Several approaches have been proposed to image in vivo the aneurysms walls in humans. One approach is based on image analysis using inflammation biomarkers. Ferumoxytol [16] (AMAG Pharmaceuticals, Inc., Lexington, Massachusetts), a FDA approved iron oxide nanoparticle coated by a carbohydrate shell, is a member of the class of nanoparticles known as ultrasmall superparamagnetic particles of iron oxide (USPIO)s. USPIOs are phagocytosed by macrophages, and linked to their iron core, they induce a signal loss on T2* images. This can be imaged as a marker of macrophages inflammation.
Application to CNS vascular disorders: towards functional criteria of rupture risk

Aneurysms

The prevalence of intracranial aneurysms is as high as 3 to 5% in the adult population [17]. Their treatment, whether surgical or endovascular, is at risk, with a cumulative rate of morbidity and mortality between 3 and 10% depending on the technique used [18–20]. The estimated annual risk of bleeding of an untreated aneurysm is less than 1% [21]. Therefore, a systematic preventive treatment cannot be considered. Furthermore, no recent study has demonstrated the superiority of a preventive surgical or endovascular treatment over a simple follow-up. Consequently, the decision to treat an unruptured intracranial aneurysm is currently taken on a case-by-case basis, weighing risks of the natural evolution and those of the treatment. The main factors that influence treatment decisions are the patient’s age, size and location of the aneurysm. However, aneurysms, with identical morphology in patients that share the same profile, can be stable or unstable, remain unchanged for years or rupture, highlighting the need for additional markers of rupture risk.

Inflammation imaging

Macrophage infiltration correlates with the risk of cerebral aneurysm rupture in humans and macrophage depletion halts aneurysm formation in mice [22]. Ferumoxytol-enhanced MR aneurysm wall imaging of inflammatory cells [16] may provide information on the natural history of aneurysms. Ferumoxytol acts as an inflammatory marker as it is usually cleared by macrophages within 24–72 hours after intravenous injection. Hasan et al. [23] demonstrated that the findings of ferumoxytol-enhanced MRI may predict the risk of aneurysm rupture: uptake of ferumoxytol in aneurysm walls within the first 24 hours strongly suggests aneurysm instability and higher probability of rupture within 6 months, and may warrant urgent intervention [16]. This technique may allow physicians to differentiate unstable aneurysms from stable aneurysms, for which observation may be more appropriate. Specifically, this technique could be useful in identifying prone to rupture aneurysms in the “no one knows what to do with them” population of patients with small lesion (<5–7 mm). This technique may also help monitoring of new therapeutic options, e.g. anti-inflammatory pharmacological therapies [24].

4D flow MRI

Hemodynamic parameters of velocity fields (Fig. 1) potentially represent key determinants of rupture risk: the location of the flow impaction on the aneurism wall, the size of the impingement zone, the terminal flow pattern type and the wall shear stress (WSS) seem to be of particular interest [25]. WSS represents the tangential force produced by blood moving across the endothelial surface. This stress acts on endothelial cell function and gene expression in addition to having an impact on the shape and structure of cells [26]. It may play an important role in aneurysm initiation, growth and rupture. Low wall shear stress and high oscillatory shear index trigger an inflammatory-cell-mediated pathway, which could be associated with the growth and rupture of large, atherosclerotic aneurysm phenotypes, while high wall shear stress combined with a positive wall shear stress gradient trigger a mural-cell-mediated pathway, which could be associated with the growth and rupture of small or secondary bleb aneurysm phenotypes [25].

Arteriovenous malformations and dural arteriovenous fistulas

Arteriovenous malformation (AVM) is an abnormal connection between arteries and nearby veins, by passing the capillary system. Although many AVMs are asymptomatic, they can be revealed by either epilepsy, neurological deficits, or hemorrhagic stroke. A recent randomized control trial [27] in unruptured brain AVM showed that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke. However, this trial did not establish whether the disparities would persist over 33 months of follow-up. Consequently, it remains important to determine individual bleeding risk factors for AVMs. 4D flow MR imaging allows simultaneous measurement of flow in the entire cerebrovascular system throughout the cardiac cycle, encompassing both arteries and veins. It provides magnitude images that display the vascular anatomy and 3D velocity flow fields that can be used to derive flow-path, flow-tracking cartography [13] and to estimate important parameters such as wall shear stress and pressure gradients [28].

4D flow MR imaging can be used to improve the characterization of brain AVM by incorporating physiological information into the imaging assessment [29]. It is now possible to extend the characterization to not only include important anatomic features such as size, location, and vascular components of arterial supply and drainage patterns, but also the flow conditions (Fig. 2) within each major arterial feeder, arteries near the AVM, and contralateral arteries permitting a global assessment of flow across the entire cerebrovascular network [30]. The global flow network can be further defined by generating velocity-derived flow-tracking cartography, providing an overview of the dominant flow channels, with a chosen colour code (Fig. 3). The application of a virtual MR flow-tracking cartography allows a precise assessment of AVMs, distinguishing the different arterial feeders, the venous drainage type, and may help in the comprehension of functional AVM architecture. In dural arteriovenous fistula, virtual MR flow-tracking cartography demonstrated similar classification of lesions than that obtained using a DSA defined bleeding risk classification, e.g. the Cognard classification. Type of venous drainage, which is associated with the risk of rupture in a DAVF, was correctly defined using this technique [13].

Conclusion

4D flow and inflammation MR wall imaging may provide individual functional criteria of evolution and rupture risk of CNS vascular disorders. However, although this information is potentially relevant, whether it contributes to treatment decision and provide information regarding individual risk stratification, remains to be determined.
Figure 1. Application of 4D flow MRI on a supra-centimetric aneurysm. Anterior (A, B) and sagittal (C) views of a dynamic digital subtraction angiography with a 1-second temporal resolution. Streamlines pattern (D, E, F) of flow within an aneurysm, showing the inflow jet and the recirculatory pattern. Velocity vectors (G), allowing to visualize the flow orientation, and pressure maps (H, I) derived from velocities.
Advanced technologies in neurovascular disorders

Figure 2. Before (A) and after (B) partial embolization of an AVM. The white arrow shows the decrease in size of the nidus after embolization. Velocity measurements in the arterial feeders shows a significant decrease after embolization (C).

Figure 3. MR flow-tracking cartography applied to an arteriovenous malformation. (A) Sagittal view of digital subtraction angiography. (B) Arterial feeders of the AVM derived from initial tracking of the internal carotid artery. (C) Arterial feeders of the AVM derived from initial tracking of the vertebro-basilar axis. (D) Global cartography of the AVM showing arterial feeders in red and orange, the nidus in blue and the deep venous drainage in green.

Clinical case

A 46-year-old man consults for left pulsatile tinnitus. A standard MR exam is done, and added to it, a 4D flow MRI. The Fig. 4 shows the application of an MR flow-tracking cartography on its vascular disease, compared to digital subtraction angiography (DSA).

Questions

1. The MR vascular cartography allows to identify an AVM with a deep venous drainage.
2. The MR vascular cartography identifies a dural arteriovenous fistula and allows classifying it following the Cognard classification as a type III.
3. The MR vascular cartography identifies a dural arteriovenous fistula but does not help to classify it with an MR Cognard classification.
4. No vascular disorder is visualized.

Answer

Indeed a pathological shunt is individualized between feeding arteries and retrograde cortical venous drainage, defining a dural arteriovenous fistula. There is no direct opacification between the shunt and venous sinuses. This allows classifying it following the Cognard classification, as a type III. The correct answer is 2.
TAKE-HOME MESSAGES

- While depiction and follow-up of CNS vascular disorders following morphological criteria is the first step of an MR analysis, emerging MR techniques such as 4D flow can provide important functional criteria.
- 4D flow MR imaging can delineate the hemodynamic conditions within intracranial aneurysms, leading to improved characterization and hence, potentially risk stratification.
- Fast high-resolution 4D flow imaging techniques are now applicable in clinical routine, with an average scanning time of 6 minutes per encoding speed. Quantitative flow parameters including velocity, pressure and wall shear stress, add a new dimension to MR angiography.
- The role of inflammation in cerebral aneurysm pathogenesis can be assessed in vivo, providing information that may impact aneurysm management.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


