

CNS Aneurysms & Vascular Malformations: Radiologic Perspective

Take-home messages:

- 1) While depiction and follow-up of CNS vascular disorders following morphological criteria remains the first step of an MR analysis, emerging techniques such as 4D Flow MRI can also provide important functional criteria.
- 2) 4D flow MR imaging can accurately delineate the hemodynamic conditions within intracranial aneurysms, leading to improved characterization and better risk stratification.
- 3) The role of inflammation in cerebral aneurysm pathogenesis can be assessed in vivo, providing important clinical information that may impact aneurysm management. Macrophage (ferumoxytol)-specific inflammatory imaging is a current experimentally efficacious methodology.
- 4) Fast high resolution 4D Flow imaging techniques are now applicable in clinical routine, with an average scan time of 6 minutes per encoding speed. Quantitative flow parameters including velocity, pressure and wall shear stress, add a new dimension to non-invasive angiography.

MR imaging developments provide new tools for characterization of brain vascular disorders, such as CNS aneurysms, arteriovenous malformations and brain dural arteriovenous fistulas. The aim of MRI is first 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. Whereas diagnostic angiography remains the reference for the evaluation and pre treatment planning of CNS vascular disorders, its invasiveness, risks related to catheter placement and use of contrast agents have made MRI the examination of choice in patients with chronic headaches, seizure disorders of unknown etiology, and pulsatile tinnitus.

While depiction and follow up of morphological criteria of CNS vascular disorders remains the first step of an MR analysis, emerging imaging techniques open new potentials in the development of functional criteria that might characterize factors of evolution and 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 thanks to 4D Flow imaging (shear parietal) [4-6]. This course 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 MRI, inflammation imaging, and get familiar with their application in clinical routine.

We will discuss their applications in CNS vascular disorders: aneurysms, arteriovenous malformation, dural arteriovenous fistulas, and illustrate their potential in the development of individual rupture risk criteria in brain vascular disorders.

Emerging techniques :

1) 4D Flow MRI

Shortly after the introduction of clinical MR imaging in the 1980s, Moran[7] demonstrated that velocity and flow could be measured noninvasively 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 MR 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 acquisition. Recent advances in accelerated acquisition and undersampled reconstruction open the possibility of extending angio MR to functional information[9]. Acquisition times have been reduced by using strategies such as compressed sensing[10] and radial k-space trajectories[9]. Shorter TEs 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 increases 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 utilizing 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 be post processed into two types of information: qualitative (flow visualization) and quantitative measurements.

Qualitative information provides, for each voxel, the flow direction. 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 traveled per second. The Virtual MR cartography obtained[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 direct values of velocity and, derived from the velocity parameters, pressure map and wall shear stress (WSS)[12]. Pressure maps are interesting to compute, in order to have access to the pressure variations within neurovascular diseases. 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 drag 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].

2) Parietal inflammation and bio-imaging markers

Histopathologic evidence from human studies of aneurysm tissue and findings from animal models of cerebral aneurysms support the concept that inflammation plays a major role intracranial aneurysm formation and progression. Aneurysm formation is thought to occur after hemodynamic insult, which elicits a series of proinflammatory 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]. However, because we cannot have access to the parietal wall of human aneurysms in vivo, indirect ways must be developed to follow this inflammatory process. One approach is based on image

analysis using inflammation biomarkers: Ferumoxytol[16] (AMAG Pharmaceuticals, Inc., Lexington, Massachusetts), an 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, FDA approved. USPIOs are known to be phagocytosed by macrophages, and linked to their iron core, their presence induces a signal loss on T2* images. This loss of signal can be imaged, as a marker of macrophages inflammation.

Application to CNS vascular disorders: towards functional criteria of rupture risk

1) Aneurysms

The prevalence of intracranial aneurysms is high in the adult population, estimated between 3 and 5 % [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, 19]. The annual risk of rupture of an aneurysm is of 1%. Therefore, a systematic preventive treatment of an unruptured intracranial aneurysm can not be considered. Furthermore, no recent study could demonstrate the superiority of preventive treatment on simple follow-up. The decision to treat an unruptured intracranial aneurysm is currently on a case by case basis, including both the risks of the natural evolution and the risks of treatment. The main factors that influence treatment decisions are the patient's age, size and location of the aneurysm. However, aneurysms, with identical morphology and same patient profile, can be stable or unstable, remain unchanged for years or rupture, highlighting the need for new specific markers of rupture risk.

Inflammation imaging:

Macrophages infiltration correlates with the risk of cerebral aneurysm rupture in humans and macrophage depletion halts aneurysm formation in mice [20]. Ferumoxytol-Enhanced MR targeted imaging of inflammatory cells [16] is an interesting strategy that may provide information on the natural history of aneurysms. Ferumoxytol acts also as an intravascular contrast agent and an inflammatory marker when imaging is delayed as it is cleared by macrophages (usually within 24–72 hours). Hasan et al [21] showed that the optimal technique for imaging macrophages in aneurysm wall is infusion of 5 mg/kg of ferumoxytol and imaging at 72 hours after injection. This group also demonstrated that the findings of ferumoxytol-enhanced MRI may well predict the risk of aneurysm rupture: uptake of ferumoxytol in aneurysm walls within the first 24 hours strongly suggests aneurysm instability and probability of rupture within 6 months, and may warrant urgent intervention [16].

This technique may allow physicians to differentiate unstable aneurysms that require intervention from stable aneurysms where observation is appropriate. Specifically, this technique could prove particularly useful in identifying rupture-prone aneurysms in patients that often pose a therapeutic dilemma, namely patients with small aneurysms (<5–7 mm).

This technique may also help monitoring of new therapeutic options, e.g. anti-inflammatory pharmacological therapies [22].

4D Flow MRI:

Hemodynamic parameters of velocity fields potentially represent key determinants of rupture risk : the location of the flow impaction on the aneurysm pouch, the size of the impingement zone, the terminal flow pattern type and the wall shear stress (WSS) seem to be of particular interest [23]. 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 [24]. 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[23].

2) Arteriovenous malformations and dural arteriovenous fistulas

Arteriovenous malformation (AVM) is an abnormal connection between arteries and veins, bypassing the capillary system. Although many AVMs are asymptomatic, they can cause epilepsy, neurological deficits via a steal phenomenon, and are at risk of bleeding. The Spetzler-Martin classification is well-known and gives a scoring of the potential risk of a surgical treatment. However, it is important to determine individual bleeding risk factors for AVMs.

The power of 4D flow MR imaging is that it 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[25].

4D flow MR imaging can be used to improve the characterization of brain AVMs by incorporating physiologic information into the imaging assessment[26]. 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 within each major arterial feeder, arteries near the AVM, and contra lateral arteries permitting a global assessment of flow across the entire cerebrovascular network[27].

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 color code. 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 AVM compartmentalization. Its application on dural arteriovenous fistula has already shown its ability to classify this disorder, following the Cognard or Borden classification, in which the type of venous drainage is proportional to a rupture risk[13]. No study have yet analyzed the role of inflammation in such disorders, though it should be of interest.

Conclusion:

4D Flow imaging and inflammation imaging allow clinical investigators to have access to individual functional criteria of evolution and rupture risk of CNS vascular disorders. However, although this information is very relevant, it is yet to be determined whether it can significantly contribute to the selection of patients for open surgical resection, endovascular treatment, radiosurgery, and combined therapy and provide information regarding individual risk stratification.

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