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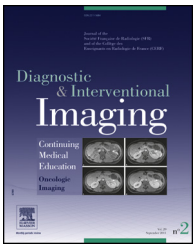

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Advanced technologies applied to physiopathological analysis of central nervous system aneurysms and vascular malformations

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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 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 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 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 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 phagocyted 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.

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