Effects of heparin on the hemodynamic characteristics of intracranial aneurysms

A 58-year-old woman presented with a history of sudden onset of severe headache and loss of consciousness. She had a past medical history of deep vein thrombosis and was taking long-term warfarin for that. Her Glasgow Coma Scale score at the time of admission was 13. An urgent CT scan of the head revealed the presence of subarachnoid hemorrhage. The patient was recruited to the @neurIST project (www.aneurist.org) after obtaining the proper consent.

Four-vessel cerebral angiography demonstrated the presence of two intracranial aneurysms (Fig. 1). The first aneurysm (Aneu-1) was a tiny 'bleb'-type aneurysm located on the ophthalmic segment of the right internal carotid artery. It was considered a pre-aneurysm lesion. The second aneurysm (Aneu-2), which ruptured, was located at the origin of the right posterior communicating artery (PCommA) and was coiled with GDC® (Guglielmi Detachable Coils). Throughout her hospital stay, the patient received low-molecular weight (LMW) heparin (enoxaparin, Clexane®). However, as the tiny 'bleb' aneurysm was unsuitable for coiling, it was followed by magnetic resonance angiography (MRA).

Three-dimensional computer models of the intracranial aneurysms were created from 3D angiograms (Fig. 1). Boundary conditions were applied proximally at a distance of at least 10 vessel diameters and distally at 2–3 vessel diameters. Hemodynamic factors were computed with the help of @neuFuse software, using physiological values ($\mu_{untreated} = 0.0045 \text{ Pa s}$) of blood viscosity (BV). The analyses were then repeated, using the values of BVs specific to heparin ($\mu_{heparin} = 0.0025 \text{ Pa s}$), as reported in the literature. The latter simulates the effect of heparin at an average therapeutic concentration of 0.0075 mg/mL. The 3D unsteady Navier–Stokes equations were solved with the use of finite control volume ANSYS®-CFX™ software. Qualitative (Fig. 2) and quantitative (Table 1) comparisons were made between the hemodynamic parameters computed in both settings.

Findings showed that heparin administration decreased the maximum values of time-averaged wall shear stress (t-av-WSS) in both aneurysms, with a dramatic increase in the area affected by infraphysiological wall shear stress (< 0.4 Pa) in both lesions. The values for the oscillatory shear index (OSI) and pressure were decreased in the pre-aneurysm lesion, whereas an increase was observed in the ruptured lesion (Table 1).

Ruptured aneurysms remain a major cause of morbidity and mortality [1], and recent evidence indicates that hemodynamics are an important underlying factor in their etiopathogenesis [2]. As confirmed by others [3], the hemodynamics of the intracranial vasculature is dependent upon the rheological properties of blood, including BV. It is then logical to speculate that the factors affecting BV can also influence the hemodynamic environment of intracranial aneurysms, thereby affecting their initiation, growth and rupture.

In the present study, we investigated the effects of heparin on the hemodynamic characteristics of aneurysms. High wall shear stress (WSS) values have been associated with heparin initiation by increasing the production of MMP-13, while low values are thought to be responsible for aneurysm growth and rupture [4] by increasing inducible nitric-oxide (iNOS) synthesis, resulting in vessel wall damage. Heparin (and its derivative enoxaparin) is a widely used injectable anticoagulant for preventing venous thrombosis and pulmonary embolism. It inhibits the factors involved in blood-clotting (factor Xa), causing instantaneous inactivation of thrombin, thereby reducing BV [5] and, in turn, altering the hemodynamics of the blood circulation. Hitosugi and co-workers demonstrated a decrease in BV by
55.6% with the use of heparin at a therapeutic concentration of 0.75 IU/L.

However, heparin may also induce significant derangements of the hemodynamics of intracranial aneurysms and may even facilitate the rupture of existing aneurysms, albeit while perhaps inhibiting the formation of new aneurysms. In addition, similar effects might be achieved with other pharmacological agents, thus warranting further investigations. However, so far, it is difficult to draw any definitive conclusions based on only two aneurysms in one patient.

### Conflict of interest statement

None.

### References


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Diffusion tensor imaging in human global cerebral anoxia: Correlation with histology in a case with autopsy

We report the case of a 58-year-old man (Fig. 1) in a profound coma after a 30-min-long cardiac arrest who benefited of a brain MRI 6 weeks after the accident (1.5-T MRI scanner, Siemens Avanto MR, Erlangen, Germany) with DTI acquisition (30 directions, $b = 1000 s/mm^2$, $TR = 6800 ms$, $TE = 99 ms$, $FOV = 230 mm^2 \times 230 mm^2$, matrix $128 \times 128$, 3.5 mm slice thickness). FA, parallel diffusion ($D_{//}$) and perpendicular diffusion ($D_{⊥}$) maps were computed and compared voxelwise to a probabilistic voxel-based atlas of fractional anisotropy as well as parallel and perpendicular diffusion based on 19 healthy subjects. Z-score maps were computed. The patient died from sepsis. An autopsy was performed. Brain sections were stained with Luxol fast blue cresyl violet to analyse myelin and immunostained for neurofilaments to detect white matter axons. DTI images analysis demonstrated extensively reduction of white matter FA, whereas $D_{//}$ and $D_{⊥}$ were elevated. $D_{//}$ and $D_{⊥}$ modifications reflect axonal and myelin lesions, respectively, whereas FA reflects white matter global disorganisation. Histological analysis