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Very large and giant microsurgical bifurcation aneurysms in rabbits: Proof of feasibility and comparability using computational fluid dynamics and biomechanical testing

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HIGHLIGHTS

- We describe a microsurgical model of very large and giant aneurysms in rabbits.
- This study proves feasibility and reproducibility of this novel model.
- Hemodynamic characteristics of experimental aneurysms are comparable to human conditions.
- The presented model is suitable for evaluating novel treatment options preclinically.

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ABSTRACT

Background: Giant aneurysms are challenging lesions with unacceptable high rates of aneurysm recanalization and rerupture following embolization. Reliable in vivo models are urgently needed to test the performance of new more efficient endovascular devices.
Materials and methods: Aneurysms were created in 11 New Zealand white rabbits (4.5–5.5 kg): A long venous pouch (length 25–30 mm) mimicking the aneurysm sac was derived from the external jugular vein and sutured into a microsurgically created bifurcation between both common carotid arteries. After 4 weeks the rabbits underwent 3 T Magnetic resonance angiography (3T-MRA). Exemplary computational fluid dynamics (CFD) simulations were performed to compare the flow conditions of giant rabbit and human aneurysms. We used species-related boundary conditions, in particular, we measured blood viscosity values. Biaxial mechanical tests were performed for the mechanical characterization and comparison.
Comparison with exisiting method(s): None.
Results: No peri- or postoperative mortality was observed. 3T-MRA showed aneurysm patency in 10 out of 11 aneurysms (90.9%). Aneurysm lengths ranged from 21.5–25.6 mm and aneurysm necks from 7.3–9.8 mm. CFD showed complex flow profiles with multiple vortices in both, rabbit and human aneurysms. Lower blood viscosity values of the rabbit (3.92 mPa s vs. human 5.34 mPa s) resulted in considerable lower wall shear stress rates (rabbit 0.38 Pa vs. human 1.66 Pa). Mechanical tests showed lower stiffness of rabbit aneurysms compared to unruptured human aneurysms.
Conclusions: The proposed model showed favorable aneurysm patency rates, low morbidity and good

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hemodynamic comparability with complex flow patterns. Biomechanical testing suggests that experimental aneurysms might be even more fragile compared to human aneurysms.

1. Introduction

Endovascular embolization of intracranial aneurysms has become an equivalent alternative to aneurysm clipping for ruptured aneurysms, especially looking at short-term results (Molyneux et al., 2002). However disappointing long-term results with unacceptably high rates of aneurysm recanalization (Sherif et al., 2012) and late aneurysm rerupture were shown in large clinical trials (Mitchell et al., 2008). Especially for very large and giant aneurysms recent studies showed unsatisfying rates of incomplete aneurysm occlusion and high rates of recanalization reaching up to 69% of all aneurysms (Sluzewski et al., 2003). Therefore new embolization concepts such as flow-diverters (Brinjikji et al., 2013; D'Urso et al., 2011) or WEB, an intrasaccular flow disrupter, have been proposed (Pierot et al., 2012). But despite promising initial experimental findings first human short-term meta-analyses on flow-diverting stents showed again rates of total aneurysm occlusion reaching no more than 76% and major complication rates like ischemic stroke in 6% and aneurysm rehemorrhage in 4% (Brinjikji et al., 2013; D'Urso et al., 2011). One major reason for the disappointing differences between preclinical and clinical findings may be the lack of appropriate preclinical models. True bifurcational aneurysm models for giant aneurysms were not available for many years. Thus, most studies were performed on sidewall models or the elastase model with no true aneurysm bifurcation and/or normal sized aneurysm lengths of no more than 12 mm and neck widths of about 3 mm (Kallmes et al., 2009; Sadasivan et al., 2009; Ding et al., 2011). Facing this problem several authors have recently introduced very large and giant bifurcation aneurysm models in canines for the testing of endovascular devices (Ysuda et al., 2012; Darsaut et al., 2014). The canine model is a well-established and widely used preclinical model with very good reproducibility and high aneurysm patency rates, whereas comparability of the coagulation system is less optimal (Bouzeghrane et al., 2010).

Comparing rabbit, canine and rat models, the rabbit model showed advantageous comparability to the human coagulation system and best cost-effectiveness (Dai et al., 2005; Shin et al., 2005; Abruzzo et al., 1998). Thus, the aims of the present study were:

1) to assess the feasibility and reproducibility of giant bifurcation aneurysms using the established improved microsurgical venous pouch arterial bifurcation model in the rabbit (Sherif et al., 2011a,b; Marbacher et al., 2011, 2012).
2) To compare the flow properties and biomechanical aneurysm wall properties with human conditions using computational fluid dynamics (CFD) simulations and biaxial biomechanical testing.

2. Materials and methods

The aneurysms were created in 11 large New Zealand White Rabbits (Charles River, D-97633 Sulzfeld, Germany) with a body weight of 4.5–5.5 kg. All surgical procedures were performed at the Department of Biomedical Research of the Medical University of Vienna, Austria. The study was approved by the responsible ethical committee. The study was funded by a grant of the Scientific Fund of the Major of Vienna.

2.1. Microsurgical aneurysm creation

All procedures were performed under general intravenous (iv.) anesthesia. The detailed description of anesthesiological and microsurgical procedures and postoperative care are described elsewhere (Sherif et al., 2011a). Shortly, a solution of 130 mg/kg xylazine and 8 mg/kg ketamine in 100 ml 0.9% saline was iv. administered via a perfusor with a rate of 1 ml/s. In this study all animals were intubated and arterial blood pressure and heart rates were continuously monitored. All animals received a preoperative single-shot antibiosis with 50 mg of penicillin i.v. Postoperative pain management comprised application of a transdermal fentanyl matrix patch releasing 12.5 μg/h for 72 h in the previously shaved neck region.

All operative procedures were performed under sterile conditions. A midline incision was made from the manubrium sterni up to the jaw. First, a 25–30 mm long segment of the right external jugular vein without venous branches was prepared, and ligated proximally and distally with 4-0 silk, see Fig. 1(A). When venous branches arose from the selected segment these branches could be easily ligated using 10-0 sutures. Then the venous segment was resected and kept in heparinized saline (a mixture of 1000 IU heparin in 20 ml 0.9% saline and 1 ml papaverin HCl 4%).

In this study we created the aneurysms at the right CCA. Therefore right CCA was prepared over a distance of about 5 cm, starting from the aortic arch to the carotid bifurcation. The left CCA was then also isolated and mobilized up to the carotid bifurcation and proximally down to the bracchiocephalic branching. At that point the animals received 1000 IU heparin intravenously. Then the left CCA was temporarily clipped distally just below the carotid bifurcation, and then proximally ligated above the brachiocephalic branching and cut just above this ligature. The segment of the right CCA planned for the anastomosis was temporarily clipped distally and proximally. Between the clips a controlled elliptical arteriotomy (10 mm) was performed to accommodate the circumferences of the left CCA and the venous pouch. The posterior circumference of the left CCA-stump was now sutured into the arteriotomy in the right CCA, using running sutures. (Ethilon® 10-0, Ethicon Inc., New Jersey, USA). Then a longitudinal cut (5 mm) was made in the stump of the left CCA to accommodate half the circumference of the venous pouch. The back side of the venous pouch wall was now first anastomosed with the arteriotomy in the right CCA, using again running sutures, and then anastomosed at the backside with the cut in the right CCA with running sutures. The same procedures were performed in the same order at the anterior side of the anastomosis, see Fig. 1(B and C). The suture lines around the anastomosis and the aneurysm neck were now covered with small pieces of adipose tissue for additional hemostasis. During operation 4% papaverin HCl solution and antibotic solution (neomycin sulfate 5 mg/ml) was frequently applied topically on the anastomoses to prevent vasospasm and local infections.

2.2. Anticoagulation management

Immediately after finishing operation, all animals received 10 mg/kg acetylsalicylic acid i.v. All animals received daily 100 IU/kg low molecular heparin subcutaneously for 2 weeks.