Elastase-Induced Aneurysm in Swine: Proof of Feasibility in a First Case

A Technical Note

S.L. GOERICKE*, N. PAROHL*, J. ALBERT*, M. DUDDA†, M. FORSTING*

*Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital; Essen, Germany

†Department of Surgery, University Hospital Bergmannsheil, Ruhr University; Bochum, Germany

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Summary

This is the first description of a modified endovascular elastase-induced aneurysm model in swine. The advantage of this model is the combination of an aneurysm of true vessel continuation with arterial wall and the possibility of using large femoral access devices. Imaging revealed a successful aneurysm creation at the origin of the right CCA. High personal and financial expense and partial thrombus formation might limit the routine use and this model might be reserved for exclusive issues.

Introduction

Endovascular therapy has a great impact on the recent treatment of cerebral aneurysms. Due to new endovascular devices more and more vascular diseases are treatable. However these devices need to be tested in animal models preclinically and physicians have to be trained practically.

Numerous animal models of aneurysm creation in different species have been described¹⁻⁴. The elastase-induced aneurysm model in rabbits has proved to be rapid, reliable and reproducible. It is suitable for testing new devices and train neurointerventionalists in endovascular therapies. One drawback of this in our department intensively used model is the limitation of access: a maximum of 5F sheath can be placed due to the small diameter of the femoral artery.

Therefore we wanted to convert the elastase-induced aneurysm model in swine. Previous experimental aneurysm in swine are surgically induced with the disadvantage of different vessel tissue due to venous graft, scar forming and different hemodynamic features compared to human aneurysms and elastase-induced aneurysms in rabbits⁵. By using the endovascular elastase-induced method in swine we expect the advantage of an aneurysm of true vessel continuation with an arterial wall and the option of using large femoral access devices in one model.

Technique

The study was approved by the local animal protection committee. Aneurysm creation was performed in a female mini pig (45 kg) using the precepts of the previously in detail described rabbit elastase-induced aneurysm model⁶⁻⁸. Anaesthesia was achieved by intramuscular injection of 30 mg/kg ketamine (Ceva, Germany), 0.03 mg/kg atropine (Braun, Germany) and 2 mg/kg azaperon (Janssen, Germany), 5 mg bolus midazolam (Roche, Germany) was given twice and anaesthesia was maintained by intravenous propofol 1% (3 mg/kg/h). The animal was intubated and automatically ventilated with an oxylog® respirator (Draeger, Germany), circulation parameters were monitored continuously. The animal received three bolus injections of 0.05 mg fentanyl for analgesia.

Employing a sterile technique, a neck ventral midline incision (~10 cm) was performed. The

Figure 1 MIP reconstruction of CE MRA shows the aneurysms at the origin of the right CCA with significant thrombus formation in the aneurysm dome.

right CCA was exposed in its mid portion and ligated distally. A 2 mm arteriotomy was made, and a 7F vascular sheath was advanced retrograde in the CCA. A 6F Fogarty balloon was pushed through the sheath under fluoroscopic guidance and was inflated in the CCA origin. A mixture of 1.5 ml porcine elastase (84IU/ml, Worthington Biochemical Corporation, USA) 0.75 ml sodium chloride 0.9% and 0.75 ml iodinated contrast agent (Ultravist® 300, Schering, Germany) was injected through the sheath into the dead space of the CCA and incubated for 20 minutes. Balloon and sheath were removed. The right CCA was ligated below the sheath entry and incision was sutured. Anaesthesia was ended and the animal rested under observation with sufficient analgesia for the first three days.

Figure 2 Intraarterial DSA shows the contrasted lumen of the aneurysm with thrombus formation in the aneurysm dome (arrow).

Eight weeks after aneurysm creation imaging was obtained using MRI and DSA in one session. Anaesthesia was achieved as described above. MRI was performed on a 1.5 T MRI scanner (Siemens Espree, Erlangen, Germany) using the standard surface coil. CE MRA (Magnevist®, Schering, Germany, through an angiocath in the ear vein) and T2-weighted images were acquired. For intraarterial DSA a femoral incision was made. The left CFA was exposed and ligated distally. A 2 mm arteriotomy was made, and a 4F vascular sheath was advanced retrograde in the CFA. A 4F catheter was advanced through the sheath under fluoroscopic guidance and final control DSA (Ultravist® 300, Schering, Germany) was performed. External markers were used to determine the contrasted aneurysm dimensions.

Still under general anaesthesia the animal was sacrificed by intravenous injection of pentobarbital (WDT, Germany), and the vessel dissection extracted.

Imaging revealed a successful aneurysm creation at the origin of the right CCA using the elastase-induced model. Eight weeks after induction the contrasted lumen of the aneurysm was high x dome x neck width 1.2 x 0.8 x 0.6 cm in MRA and 1.4 x 0.6 x 0.5 cm in DSA. In the dissected, collapsed lumen the aneurysm surface diameter was high x dome x neck width 3.4 x 0.7 x 0.5 cm. MRI and DSA showed thrombus formation in the aneurysm dome with reduced signal in the MRA and thrombus formation in the DSA explaining the difference in aneurysm diameter in vivo imaging versus dissection.

Discussion

The elastase-induced aneurysm creation is a common method in rodents^{1,7,8}. Marinov et Al infused porcine elastase into an isolated segment of the aorta in mini pigs. Although elastic fibers were destroyed no aneurysmal dilatation was observed⁹. Porcine elastase has been shown to destroy elastic network even in swine¹⁰. We suppose an additional effect of the hemodynamics in the carotid bifurcation to produce our aneurysm. Spontaneous thrombosis of surgically induced aneurysms in dog and swine is a major problem in these models^{2,11}. Equal to our own data no thrombosis was observed in the elastase-induced model in rabbits in a study with 20 aneurysms over a 24 months period¹².

We observed thrombosis in the upper part of the aneurysm dome in swine, the lower half of the aneurysm was patent, but the complete true lumen was adulterated. Kallmes et al. showed spontaneous thrombosis just in the early post-operative period, but surgical sidewall aneurysm stayed patent if open after two weeks¹¹. In rodents we observed stable findings in aneurysm size and geometry in follow-up up to three months¹³. Therefore we postponed our imaging control for eight weeks. After this one case experience we cannot exclude potential later or increasing thrombosis, therefore further studies with more animals and longer follow-up are needed. One could discuss additional heparinization to prevent spontaneous thrombosis, but might distort aneurysm occlusion after endovascular embolization.

Rodents are qualified for the experimental setting because of their cost-benefit-consideration regarding personal, financial and anaesthesiology effort. Although mini pigs are easier to handle than domestic pigs the experimental expense is clearly higher compared to rabbits.

We performed this first case to proof technical feasibility of endovascular elastase-induced aneurysm creation in swine first of all independent of aneurysm size and histologic findings of the created aneurysm. Larger animal series are planned to determine the reliability of this elastase-induced aneurysm model regarding aneurysm size and stability. Additional histopathologic evaluation is needed to proof digestion of the elastic lamina by porcine elastase and assess intraluminal thrombus formation inside the aneurysm.

In this elastase-induced aneurysm model in swine one would have the option of larger vascular access for special issues regarding testing of new endovascular devices. Even though 5F guiding catheter are sufficient in most cases due to development of new flow diverting devices larger accesses could be desirable. We used only

Figure 3 Anatomical dissection shows the aneurysm surface (arrows).

4F sheath for control DSA because this access was sufficient for diagnostic catheterization, but application of femoral sheaths up to 8F are known as unproblematic in swine.

The endovascular elastase-induced aneurysm model in the carotid origin in swine has never been reported in the recent literature. In this first reported implementation in swine we created a large aneurysm suitable for endovascular treatment with the advantage of an aneurysm with an arterial wall and the option of using large femoral access devices in one model.

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Sophia L. Goericke, M.D.
 Institute of Diagnostic
 and Interventional Radiology
 and Neuroradiology,
 University Hospital Essen
 Hufelandstraße 55
 45122 Essen, Germany
 E-mail:sophia.goericke@uni-essen.de