Annals of Medicine and Surgery 4 (2015) 30–35

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Induction of continuous expanding infrarenal aortic aneurysms in a large porcine animal model

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HIGHLIGHTS

- A large porcine animal model of AAA disease that mimics human aneurysm pathology.
- The first large AAA animal model to demonstrate a continuous AAA expansion over time.
- A potential model for further research into the natural history and prognosis of AAA's.
- Due to preserved lumbars a potential model for further EVAR/Endoleak research.

ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form
13 October 2014
Accepted 15 October 2014

Keywords:
Abdominal aortic aneurysm
Balloon dilatation
Elastase
Porcine model
Endoleaks

ABSTRACT

Background: A large animal model with a continuous expanding infrarenal aortic aneurysm gives access to a more realistic AAA model with anatomy and physiology similar to humans, and thus allows for new experimental research in the natural history and treatment options of the disease.
Methods: 10 pigs (group A) underwent infrarenal aortic dissection, balloon dilatation, infusion of elastase into the lumen and placement of a stenosing cuff around the aorta. 10 control pigs (group B) underwent a sham procedure. The subsequent 28 days the AP-diameters of the aneurysms were measured using ultrasound, hereafter the pigs were euthanized for inspection and AAA wall sampling for histological analysis.
Results: In group A, all pigs developed continuous expanding AAA's with a mean increase in AP-diameter to 16.26 ± 0.93 mm equivalent to a 57% increase. In group B the AP-diameters increased to 11.33 ± 0.13 mm equivalent to 9.3% which was significantly less than in group A ($p < 0.001$). In group A, a significant negative association between the preoperative weight and the resulting AP-diameters was found. Histology shoved more or less complete resolution of the elastic tissue in the tunica media in group A. The most frequent complication was a neurological deficit in the lower limbs.
Conclusion: In pigs it's possible to induce continuous expanding AAA's based upon proteolytic degradation and pathological flow, resembling the real life dynamics of human aneurysms. Because the lumbars are preserved, it's also a potential model for further studies of novel endovascular devices and their complications.

1. Introduction

Abdominal aortic aneurysms (AAA) in human adults defined present when the infrarenal aortic diameter exceeds 3.0 cm, are most often asymptomatic but highly lethal with an overall mortality around 80–90% when rupture occurs [1]. The disease is a major health problem, as it affects 5–9% of the male population over the age of 65 years [2].

Today surgical or endovascular repair are the only treatments. Consequently, many animal models have been developed to study the natural history and treatment options of AAA's in vivo.

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http://dx.doi.org/10.1016/j.amsu.2014.10.001

When Ponseti IV et al., in 1952 studied the disease Epidemic lathyrism by putting white rats on a diet containing 50% of sweet peas (*Lathyrus odoratus*), whose seeds contain β-amino-propionitrile that prevents the cross-linking of collagen, he accidentally in 6 of 8 rats induced thoracic aortic medial necrosis with aneurysm formation and dissection, and thus came across the first animal model with aneurysm disease [3]. Since then a broad spectrum of techniques has been used in attempts to develop arterial/aortic aneurysm disease in various animal models. These models can generally be divided into three main categories [4], genetically predisposed animals like the blotchy mouse [5], early used physical models characterized by physical destruction of the vessel integrity for example by surgical resection of the aortic media and adventitia [6], or by mechanically inducing a crushing injury to the aortic wall [7] and finally chemically induced models with extra- and/or intraluminal application of calcium chloride ($CaCl_2$) [8] and/or elastase [9] or by continuous subcutaneous infusion of angiotensin-II in Apo −/− mice [10]. Since it is known that increased elastolytic activity in the media plays a key role in the initial pathophysiology in human aneurysms [11], the use of elastase based models seems most proper when studying the natural history of the disease. However, small animal models don't allow experiments to sophisticate endovascular treatment or develop novel surgical treatment possibilities. Attempts in larger animals have been performed, but so far none that mimics the natural history including initial elastin fragmentation and proteolytic degradation, have been able to demonstrate a continuous progressive AAA expansion over time [12–14], which is a key characteristic of the disease, since it's a dynamic condition with changes in properties over time. Consequently, the aim of this study was to develop a reliable, large AAA animal model with a satisfactory and consistent AAA formation, that shows no sign of halting in the progressive expansion over time, mimicking the real life dynamics of human aneurysm disease, which makes it a potential model for further research into the natural history, prognosis and treatment options of the disease.

2. Materials and methods

20 female Danish Landrace pigs were divided into either intervention group A (n = 10, mean weight 34 kg (range 31–38 kg)) or control group B (n = 10, mean weight 34 kg (range 30–38 kg)).

2.1. Anesthesia and surgical procedure

Anesthesia was induced by intramuscular injection (mg/kg BW) of 1.25 mg tiletaminchdrochlorid, 1.25 mg zolazepamhydrochlorid, 0.25 mg butorphanoltartrat, 1.25 mg ketaminhydroclorid and 1.25 mg xylazin. After tracheal intubation, the pigs were placed in the supine position and ventilated with oxygen 4 L/min and atm. air (1:1, v/v) and anesthesia was extended by continuous intravenous infusion of 10 mg propofol and 25 μg fentanyl per kg BW/h.

A transabdominal ultrasound scan of the infrarenal aorta in the systolic state was performed in both the transverse and longitudinal plane to measure the preoperative external anterior-posterior diameter (AP0). After 1500 mg of intravenous cefuroxime a midline longitudinal laparotomy was made and a retrocolic prerenal transperitoneal approach to the infrarenal aorta was performed. The aorta was dissected from the lowest renal artery to the trifurcation (Fig. 1A). After intravenous administration of 5000 IU of unfractionated heparin sulfate, the lumbars and the inferior mesenteric artery and the aorta itself were temporarily clamped. The sham group B had the clamps removed after 30 min. In group A a 2.5 mm arteriotomy in the aorta was made at the level of the inferior mesenteric artery through which a 10 mm × 4 cm high-pressure balloon catheter (Johnson & Johnson – Cordis PowerFlex P3) was placed and inflated for 5 min (Fig. 1B). Hereafter a curved beaded knop needle was introduced through which 10 ml of porcine pancreatic elastase (Sigma–Aldrich Denmark A/S, E1250-100MG, Type-I ≥4.0 units/mg protein) was gradually manually infused into the aortic lumen over 30 min. Then a 12 mm × 4 cm high-pressure balloon catheter (Johnson & Johnson – Cordis PowerFlex P3) was introduced and inflated for 5 min where after

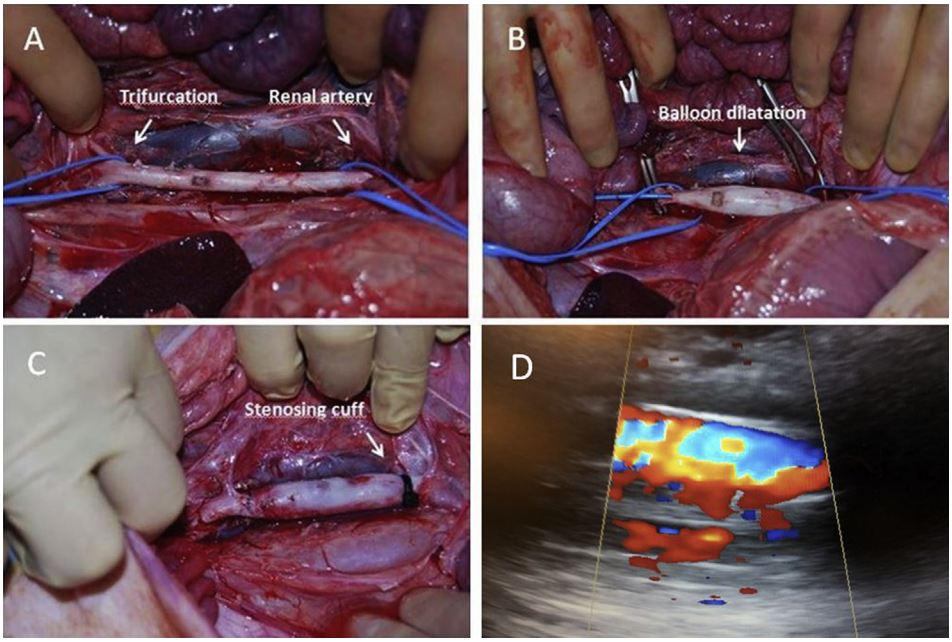

Fig. 1. Induction of infrarenal AAA. A Surgical isolation of the infrarenal aorta. B Proximal and distal clamping and temporary clamping of the side branches. Endovascular balloon dilatation to 10 mm with 10 atm. for 5 min. Infusion of 10 ml of porcine elastase for 30 min. Endovascular balloon dilatation to 12 mm with 6 atm. for 5 min. C Placement of an infrarenal stenosing plastic cuff to stimulate turbulent flow. (Notice the early intraoperative AAA formation after the procedure). D Postoperative Doppler sonography showing turbulent flow in the infrarenal dilated segment.