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ORIGINAL ARTICLE

An experimental model of Stanford type B aortic dissection with intravenous epinephrine injection

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Abstract The aim of this study was to create an experimental model of aortic dissection (AD) with a long-term patent false lumen to develop new treatments for Stanford type B aortic dissection. Sixteen adult beagle dogs (weight 14—18 kg) were used. After exposure and partially clamping, the descending aorta was cut through the adventitia to one-third of the depth of the tunica media. The aortic wall was divided into two layers by raspatory. Then half the circumference of the inner layer was cut transversely. All of the proximal layers and the distal outer layers were anastomosed together. Epinephrine was immediately used to expand the false lumen, and the effect was terminated using nitroglycerin when necessary. All dogs underwent both digital subtraction angiography (DSA) and computed tomography angiography (CTA) immediately after and 1 week and 1 month after surgery. The dogs were followed up at 1 day, 3 months, 1 year, and 2 years. The surgery was successful in 12 dogs. Dissection formation was observed immediately after epinephrine administration and confirmed by DSA and CTA. Our results showed typical characteristics of AD, such as a tear, septum, and true and false lumens. This is an easy and feasible way of developing a Stanford type B AD model by intravenous injection of epinephrine. In this canine model of AD, the false lumen has excellent long-term patency and the dissection plane is histologically similar to that in human AD. This model may contribute to the development of new treatments for Stanford type B AD.

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Introduction

Aortic dissection (AD) is a potentially life-threatening condition in which there is bleeding into and along the wall of the aorta, the major artery carrying blood out of the heart; the survival rate of affected patients is low, irrespective of surgical or medical treatment [1—3]. AD is a frequently occurring pathology with a natural history, including a significant number of severe complications, including stroke, aortic valve insufficiency, cardiac tamponade, and aortic rupture.

AD is classified as type A or B. Type B AD initiates from the descending part of the aorta. Successful treatment of Stanford type B AD by intravascular stent grafts was first reported by Dake et al. in 1998 [4]. This endovascular technique is a mini-invasive, rapid, and effective treatment for AD. At present, it is the first treatment option for complicated type B AD and is used by vascular surgeons worldwide [5—7]. Various novel apparatuses for endovascular therapy have been developed and introduced [8—10]. Therefore, an ideal animal model for type B AD is required to investigate the effects of experimental treatments and pathological changes in this condition over time.

Current methods for development of an AD animal model are complex, time-consuming, and difficult to follow, or are not similar to the characteristics of typical human AD [11—16]. In this paper, we describe an easy method of developing a canine Stanford type B AD model by intravenous injection of epinephrine.

Materials and methods

Animals

Sixteen beagle dogs (weight 14.0—18.0 kg) provided by the Laboratory Animal Center of Zhongshan Hospital were used. The study was approved by the Institutional Animal Care and Use Committee.

Surgical methods

Each dog was fixed in the right lateral position on an operating table. The skin of the left chest and thigh was shaved, and antibiotics were administered through an intravenous access point that was established through the tongue. The right femoral artery was intubated for direct blood pressure monitoring. General anesthesia was administered using intravenous 2.5% sodium pentothal (1 mg/kg); mechanical ventilation was then applied via tracheal intubation. During surgery, anesthesia was maintained with 1 ± 1.5% isoflurane under mechanical ventilation.

An incision was made at the third and fourth intercostal space to access the thoracic cavity. Then the descending thoracic aorta and the left innominate artery (LIA) were carefully exposed by severing the surrounding soft tissues. Two or three pairs of intercostal arteries were ligated to prevent bleeding during anastomosis. To facilitate aortic suspension and prevent possible excessive intraoperative hemorrhaging, two plastic blocking bands were placed, one around the portion of the descending aorta immediately distal to the LIA origin and the other ~4 cm distal to the first one. After systemic heparin infusion (100 IU/kg), the descending aorta was partially clamped using the blocking bands and the proximal part of the aorta was suspended to facilitate surgery. The portion of the descending aorta immediately distal to the LIA origin was carefully cut transversely through the adventitia up to approximately one-third of the depth of the tunica media, along one-third of the aortic circumference. Subsequently, a raspatory was used to divide the aortic wall into an inner and an outer layer and thus formed a small dissection. The outer layer consisted of the adventitia and the tunica media up to approximately one-third of its original width. The descending aorta was secured completely using two clamps, one placed proximal and the other distal to the incision. Then the inner layer was cut open transversely along half of its circumference, and part of the distal inner layer was trimmed off. All layers proximal to the incision and the outer layer distal were anastomosed together using a 6/0 prolene suture to ensure that blood flowed into the false lumen.

Subsequently, 0.05 mg/kg epinephrine was injected via the peripheral vein to increase the blood pressure and pressure gradient. As the blood pressure increased, the dissection immediately enlarged and propagated distally. To avoid vascular rupture, this expansive effect was eliminated by administrating nitroglycerin when the dissection extended beyond the level of the diaphragm. The blood pressure was monitored by electrocardiography before and after epinephrine and after nitroglycerin injection. The thoracic wall was closed and the dissection formation was completed (Fig. 1). Each experimental animal underwent digital subtraction angiography (DSA) immediately after the operation. All surviving animals underwent magnetic resonance angiography (MRA) or computed tomography angiography (CTA) 1 week or 1 month later. Blood vessels were stained with hematoxylin and eosin, elastica van Gieson, and azan stain.

Results

Sixteen dogs underwent surgery. Of these, four died during the operation due to aortic rupture ($n = 2$), sudden unexplained cardiac arrest ($n = 1$), or anesthetic drug overdose ($n = 1$). Mean blood pressure before and after epinephrine injection and after nitroglycerin injection were 149.5 ± 7.3/86.7 ± 9.1 mmHg, 189.3 ± 22.5/124.5 ± 19.5 mmHg, and 123.1 ± 11.7/84.5 ± 8.9 mmHg, respectively. Among the 12 dogs that survived, one developed paraplegia on the second postoperative day, one had ischemia of the hind limbs and died of ulceration and infection 2 weeks later, and one had bowel ischemia and died 1 week later.

The other nine dogs were reared for a certain period. DSA (Fig. 2), performed immediately after the procedure, and CTA (Fig. 3), performed 1 week or 1 month later, showed that the false lumen was patent. The morphology of the dissection was typical. After euthanasia, the true and false lumens of the aorta were clearly observed (Fig. 4). Microscopic examination showed that the dissection created during surgery was located in the medial layer of the aorta. It was similar to the AD that usually occurs in

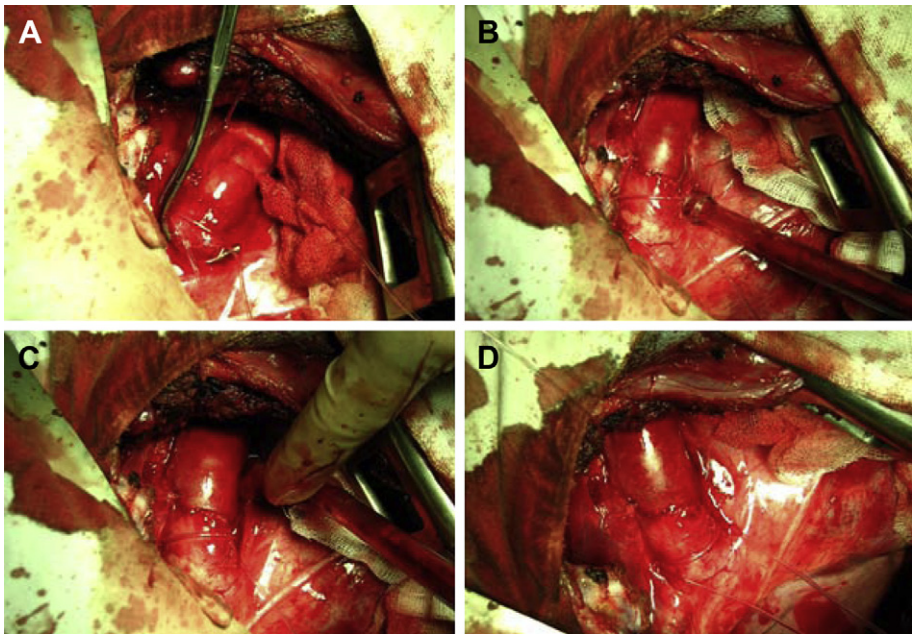

Figure 1. The procedure for developing an aortic dissection model. (A) A small dissection is first made using a raspatory. (B—D) The false lumen expands in the transverse and longitudinal directions after intravenous injection of epinephrine.

humans. A layer of endothelial cells was present on the false lumen (Fig. 5).

Discussion

An ideal animal model is required for investigation of endovascular therapy for type B AD. An ideal AD model should be easy to operate, have a high success rate, and have typical characteristics of AD, such as a false lumen and tears in the aortic wall.

Blanton et al. were the first to describe a surgical method for simulating AD [11]. A short entry pocket was created by mechanical dilation and the inner layer of the descending aorta was then sutured to the opposite aortic wall. Thus, the true lumen was compressed by a stitch at the level of the tear. Most subsequent experimental models of AD have been modifications of this method [12—14]. Angouras et al. reported a different method for AD development in pigs that involved destroying the adventitia of the descending aorta to promote differential blood supply to the inner and outer layers of the media. However, this method requires longer postoperative duration for development of a false lumen and the length of the false lumen is relatively short [15].

Some authors reported the development of an AD model via elastase perfusion in the tunica media, but this model lacks stability and the rate of successful AD development is

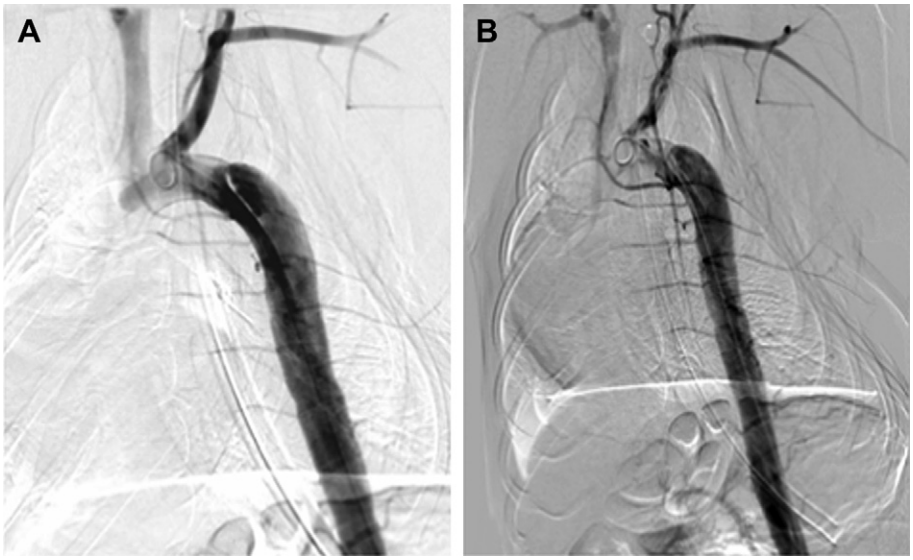

Figure 2. Digital subtraction angiographic image of the aorta: (A) anteroposterior view and (B) 30° left anterior view. The spectrum between the false and true lumens is evident.

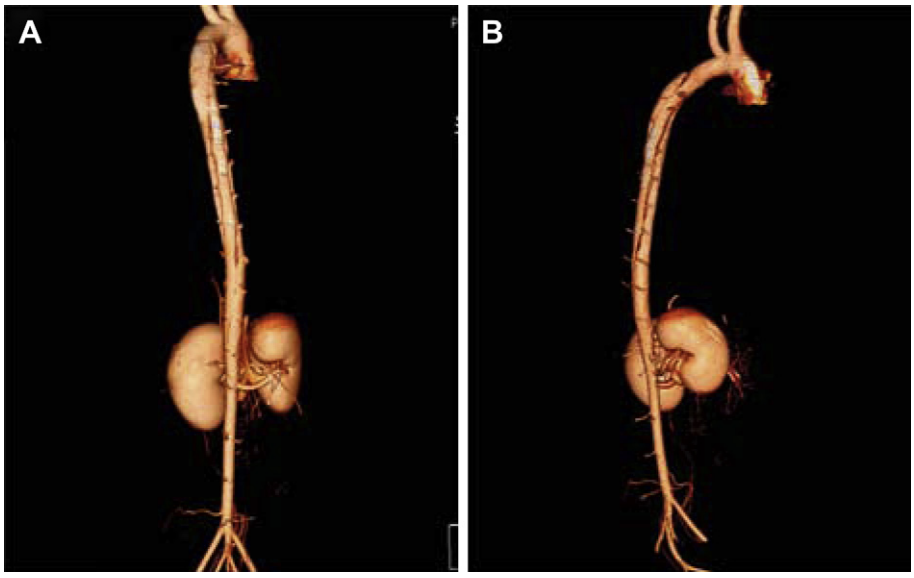

Figure 3. Computed tomography 3D reconstruction images of the aorta: (A) right—left view and (B) 30°. The false lumen is apparent and the true lumen is compressed by the false one.

relatively low [16]. Razavi et al. were the first to report an endovascular method for developing an AD model [17]. A proximal tear was made using a Colapinto needle under fluoroscopic guidance. The dissections were extended to a predefined position in the aorta. The proximal and distal tears were dilated with a balloon expansion. The shortcomings of this method are that the procedure is very complex and time-consuming, and the rate of successful AD development is low. We first tried to create a pocket or separation in the aortic wall using a homemade apparatus. This separation was then dilated by balloon expansion or saline injection. Although the AD in this model highly resembles AD in humans, the rate of successful AD development was low, and the false lumen was sometimes relatively narrow and short [18].

Figure 4. General appearance of the model aorta specimen in cross-section. The false lumen is apparent and the true lumen is compressed by the false one.

Cui et al. reported a two-end intimal flap suturing method for establishing an AD model [19]. This method ensures patency of the proximal tear. However, a homemade apparatus is used to dilate the interspaces of the tunica media and therefore the false lumen is relatively short and small, and the vessel is susceptible to rupture under mechanical force [19].

Epinephrine injection causes increases in mean blood pressure and pulse pressure in canines. The blood flow at high pressure expands the small dissection made with a raspatory. Initially, we developed dissections using mechanical force with a homemade apparatus and without epinephrine administration. In this approach the aortic wall (including the inner and exterior layers) is extremely susceptible to rupture. Hence, the rate of successful AD development was very low and most of the animals died because of massive hemorrhage during the procedure. In our new technique, only a very short segment of the tunica media has to be split. Hence, the difficulty in performing the procedure is much lower and the success rate is much higher. A false lumen was apparent after the operation, and the true lumen partially collapsed because of compression by the false lumen.

Our model mimics and helps to explain the actual mechanism of AD development in humans. In addition, after injection of epinephrine, blood pressure increased, the dissection rapidly spread distally, and the false lumen enlarged. These phenomena corroborate the classic etiological theory of dissection and hypertension. Application of an anti-hypertension drug prevented propagation of the false lumen, which partially shrank. This observation points to the significance of anti-hypertension therapy in the treatment of AD. Therefore, our approach is a relatively stable and achievable method for developing an AD model with a noticeable false lumen and a compressed true lumen.

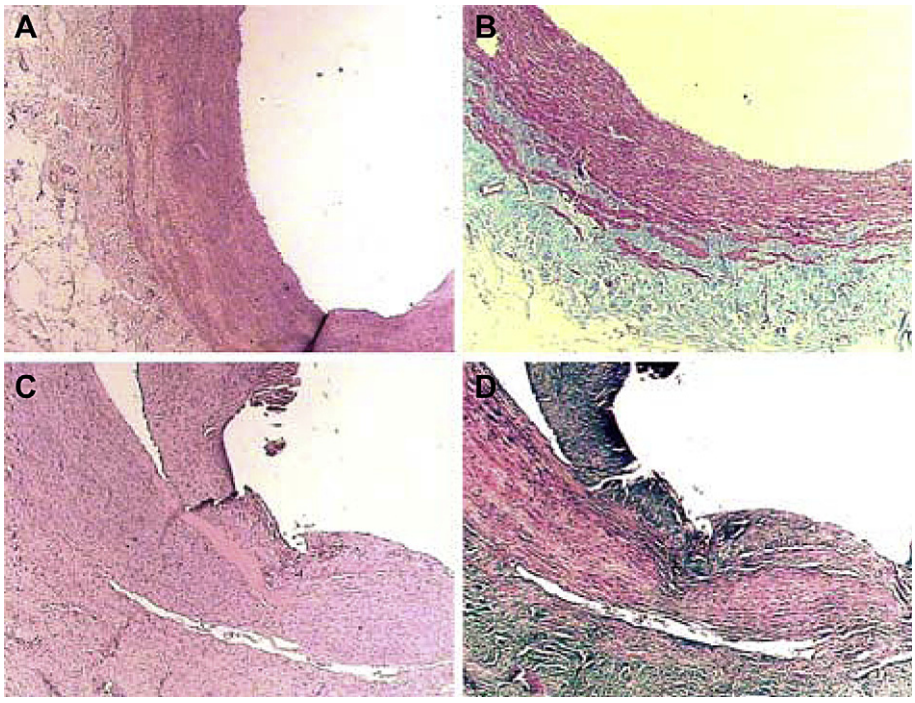

Figure 5. Microscopic examination of aorta specimens. (A) Micrograph of a normal canine aorta (hematoxylin and eosin [HE] stain; magnification 40×). The three layers of the aorta are integrated. (B) Micrograph of a normal canine aorta. Elastic fibers and collagen are clearly evident. (C) Micrograph of aorta in which a dissection was formed (HE stain; magnification 40×). The dissection is located in the medial layer of the aorta and is thus identical to typical aortic dissection in humans. (D) Micrograph of the dissected aorta (Masson stain; magnification 40×). The dissection is located in the medial layer of the aorta.

Complications, including ischemia of the visceral arteries, paraplegia, rupture of the dissection, and ischemia of the lower limbs, occurred after AD formation. These complications of our model are similar to those occurring in humans with AD. The inflammation reaction in the region surrounding the aorta was also similar to that in humans with AD. Thus, the model is suitable for studying physical parameters and pathophysiological features after AD. In addition, the model, with entry and multiple re-entries, can maintain long-term patency of the lumen and can be used (with imaging methods, such as CTA) to investigate the natural history of AD. Our model may also be used to study the effects of hemodynamic changes in the dissected aorta and of treatments such as mini-invasive stent graft placement. Moreover, the model is stable and achievable and resembles the spontaneous AD observed in clinical practice.

In summary, the canine model of Stanford type B AD, established using intravenous epinephrine injection, is similar to human Stanford type B AD. The model can be applied in experimental studies on Stanford type B AD.

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