

**Dissection level within aortic wall layers is associated with
propagation of type B aortic dissection: A Swine Model Study**

Short Title: *Intimal tear impacts on the progression of TBAD*

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22 **Word Count (Body): 3337**

23 There are no conflicts of interest. This manuscript is a single journal submission and
24 has not been submitted to another journal simultaneously.

25 Baolei Guo, Zhihui Dong and Selene Pirola contributed equally to this work and share
26 co-first authorship.

27

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29 **What does this study/review add to the existing literature and how will it**
30 **influence future clinical practice**

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32 This *in vivo* study shows that the deeper intimal tear, especially when the primary tear
33 occurred on the adventitial side of the media, results in a greater dissection
34 propagation in a swine model of type B aortic dissection. This might have important
35 consequences for clinicians to understand the complex pathology and hemodynamics
36 of aortic dissection.

ABSTRACT

Objective: Hemodynamic and geometric factors play pivotal roles in the propagation of acute type B aortic dissection (TBAD). The aim of this study was to evaluate the association between dissection level within aortic all layers and the propagation of acute TBAD in porcine aorta.

Methods: Twelve pigs of the acute TBAD model were created. In Model A, the aortic wall tear was superficial and close to the intima (thin intimal flap), whereas in Model B, it was deep and close to the adventitia (thick intimal flap). The dissection propagation was evaluated using angiography or computed tomography scans, and the hemodynamic measurements were acquired using Doppler wires. Most pigs were followed up at 1, 3, 6, 12, 18 and up to 24 months, 4 animals were sacrificed at 3 and 6 months, respectively (2 from each group).

Results: Both models were successfully created. No statistical difference was observed for the median antegrade propagation length intraoperatively between the two models ($P=0.092$). At 24 months, the longitudinal propagation length was significantly longer in Model B than in Model A ($P=0.016$). No statistical difference was noted in the retrograde propagation length in the models ($P=0.691$). Over time, aortic wall dissection progressed most notably over the first three months in Model A, whereas it continued over the first 12 months in Model B. The flow velocity was significantly higher in the true lumen than in false lumen at the level of the primary tear ($P=0.001$) and in the middle of the dissection ($P=0.004$). The histopathological

58 images at 3 and 6 months, respectively, demonstrated the fibers were stretched
59 linearly at the outside wall of false lumen in both models, while the depth of intimal
60 tears developed to be superficial and similar at the distal dissection.

61 **Conclusions:** In this swine model of TBAD, a deeper intimal tear resulted in a greater
62 dissection propagation.

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64 **Key Words:** Type B aortic dissection, Intimal tear, Propagation, Swine model

INTRODUCTION

Recent developments in endograft design and endovascular procedures for TBAD treatment have led to timely appraisals and improved understanding of the hemodynamics of dissection.¹ The pressure of the pulsatile blood within the aortic wall after dissection causes extension of the dissection. The dissection flap may be localized, or it may spiral along the entire length of the aorta. Arterial pressure and shear forces may lead to further tears in the intimal flap, producing secondary tears or reentry tears that create blood flow communications between the true lumen (TL) and false lumen (FL). However, the propagation of a dissection is an acute phenomenon that is rarely observed clinically. At present, the biomechanical factors responsible for the initiation and propagation of TBAD are not fully understood.^{2,3}

Model studies focusing on aortic morphology and dissection propagation may provide insights into the role of flap movement and primary and secondary entry tears in better understanding the pathology of TBAD. Recent work has concentrated on examining the hemodynamic forces in TBAD, primarily using computational fluid dynamic models,⁴⁻⁶ finite-element analysis,^{7,8} or fluid-structure interaction simulations of TBAD.^{9,10} However, most of these simulations have been based on simplifying assumptions and non-patient-specific boundary conditions, which can give rise to substantial bias and many limitations.

Regardless of the complexity of blood flow, vascular geometry and hemodynamics play pivotal roles in the initiation, acute propagation, and chronic

development of TBADs.¹¹ Therefore, *in vivo* histologic and hemodynamic studies of TBAD are the preferred method for defining the underlying pathophysiologic mechanisms. At present, few *in vivo* studies have provided direct observations of the pre- and post-propagation conditions of dissection. In this study, we prepared *in vivo* TBAD models to evaluate the association between dissection level within aortic wall layers and the propagation of acute TBAD in porcine aorta.

Methods

The study was approved by the Institutional Animal Care and Use Committee of Fudan University. All surgical experiments and euthanasia were performed according to the principles of laboratory animal care advocated by the animal experiment committee of Zhongshan Hospital Fudan University. The animals were provided by the Laboratory Animal Center of Gateway (Shanghai, China).

Animal Care

Twelve Shanghai Landrace pigs (age, 7-10 months; 7 males), weighing an average of 71.2 kg (range 67.4-72.5 kg), were used in the present study. Each animal was sedated with an intramuscular injection of ketamine hydrochloride (15 mg/kg) and atropine sulfate (0.04 mg/kg). General anesthesia was induced with isoflurane (5%) administered with a face mask and a target controlled infusion (TCI) of remifentanyl at 4 ng/ml. To facilitate endotracheal intubation, rocuronium was given at 0.5 mg/kg. After intubation, anesthesia was maintained with isoflurane (1.5–3%) and oxygen (0.8–1.5 L per minute) under mechanical ventilation. The TCI of remifentanyl was

107 reduced to match the level of surgical stimulation.

108 **Creation of TBAD Model**

109 After induction of general anesthesia and prophylactic amoxicillin/clavulanate
110 (antibiotics) administration, the swine was placed in supine position. Invasive blood
111 pressure monitoring was established in the left femoral artery. Heparin (50 IU/kg) was
112 administered intravenously, with additional doses as required to achieve an activated
113 clotting time (ACT) of >300 seconds. One stab incision was made in the right groin
114 and an introducer sheath (7F) was inserted via the right femoral artery. A 0.035-inch
115 guidewire (Terumo, Tokyo, Japan) and a 4F pigtail catheter were advanced into the
116 thoracic and abdominal aorta to allow a full angiographic evaluation of the aorta and
117 its branches.

118 All procedures were performed by two experienced operators. We approached
119 the descending aorta via a left thoracotomy at the fifth to seventh intercostal space.
120 The descending aorta was mobilized for 20–25 cm, from the arterial ductus ligament
121 to the distal of the descending aorta. Two pairs of intercostal arteries in the operative
122 area were ligated. Once the hemodynamic status was stable, the descending aorta was
123 totally cross-clamped at both ends of the distally mobilized area. The descending
124 aorta was then incised transversely along one third to half ($1/3$ to $1/2$) of its
125 circumference to create the entry tear. The dissecting aortic layers was made in the
126 plane of media in the 12-o'clock position, first with a Freer elevator and then with a
127 Debaquey forcep that created an entry pocket extending to $1/4$ of the aortic

circumference. In Model A (n=6), the primary tear was created on the intimal side of the media in the descending aorta (Figure 1, A1). In Model B (n=6), the primary tear was created on the adventitial side of the media (Figure 1, B1). The media was then mobilized approximately 1–2 cm distally to make the entry pocket. The adventitia and part of the media were then sutured with 6-0 Prolene continuous U-shaped sutures, which resulted in the pathological basis of the aortic dissection. The anastomosis was reinforced with 7-0 Prolene interrupted sutures.

The distal clamp was removed to check for bleeding at the anastomosis. The proximal clamp was then loosened step by step and completely removed when the hemodynamics was stable. The creation of the dissection was then evaluated using angiography and the thoracotomy was closed in layers. A chest tube was inserted through a short cut in the skin beside the wound. The sheath in the femoral artery was removed and hemostasis was achieved by manual compression. The animals were extubated and returned to their cages.

Propagation Observations and Image Examinations

All animals underwent post-procedural aortography. Technical success was defined as the successful creation of a dissection (with a length of FL >20 mm), as identified by the final angiography. A propagation was defined as an increase in the size of a FL. The animals were maintained on a normal diet until follow-up evaluation. Acetylsalicylic acid was administrated at a dosage of 100 mg daily. Follow-up

observations were performed by computed tomography angiography (CTA) at 1, 3, 6, 12, 18, and 24 months, in all animals that were not sacrificed.

Hemodynamic Evaluation by Doppler Wire

Hemodynamic evaluation of the TBAD models were performed at 1 month post procedure using Doppler wires. The intravascular Doppler device used in our study was the ComboMap system (Volcano Corporation) (Supplementary materials).

Histology Analysis.

Some animals were sacrificed at 3 months (n = 2, one from each group) and 6 months (n = 2, one of each group). For histologic evaluation, the aorta of each pig was carefully removed with its adipose tissues and fixed in 10% phosphate-buffered formaldehyde. Five mm cross-sections of the vascular tissues were obtained and embedded in paraffin. Subsequently, serial sections of 3–5 μ m thickness were cut at the level of proximal (2 cm below the proximal entry tear) and distal dissection (2 cm above the distal entry tear) respectively, which were stained with resorcinol fuchsin stains to depict the elastic fibers. These sections were examined by light microscopy by an experienced pathologist.

Statistical Analysis

Data were assessed for normality and expressed as number (%) for category and median (range) for continuous variables. Continuous variables were compared using the Mann-Whitney U test for the data of non-normal distribution. Categorical variables were compared using the Chi-square test or Fisher exact test. The velocity

between TL and FL and the increase of aortic diameter over time between the two models were compared using the non-parametric Wilcoxon signed-rank test for paired data. The study data were analyzed using SPSS version 20.0 (SPSS Inc., Chicago, III). A P value of < 0.05 was considered to indicate statistical significance.

Results

TBAD model. Table 1 shows the average diameters of the aorta and branches in the 12 studied animals. The TBAD was successfully created and confirmed by angiography and/or CTA in all animals (Figure 2). Intraoperative angiography revealed luminal flow with clear delineation of the septal flap. The median time for establishing the TBAD models was 45.1 min (range 30.6–53.6 min), and the duration of total aortic occlusion was 18.3 min (range 15.7–28.9 min). These variables did not differ statistically between the two models. The initial aortic diameter at the primary tear of the created dissection ranged from 13.9 to 24.1 mm. The intraoperative longitudinal propagation length was 39.0 mm (range 30.6–48.4 mm) in Model A and 57.0 mm (range 47.4–65.4 mm) in Model B ($P=0.092$, Figure 3, A). The intraoperative maximum diameter of the dissection aorta was much larger in Model B than that in Model A ($P = 0.022$, Figure 3, B). At the first post-procedural day, two animals died, one of anesthesia-related complications (in Model A) and a second of aortic rupture (in Model B). One animal suffered an incision infection. No other complications occurred in the nine remaining animals.

Hemodynamics and dissection propagation

Over 30 days of follow-up, hemodynamic measurements were successfully performed using the Doppler wire in seven out of ten animals. Three animals were excluded for hemodynamic analysis in the study, because the short FL and movement of dissection flap seriously influenced the quality of FL's measurements. A stable high-quality signal of the Doppler wire was hard to obtain in a small FL during cardiac cycle. The heart rate was maintained in a stable range (median 86 per min; range 78-95 per min) under general anesthesia. The average peak velocity was significantly higher in the TL than in the FL at the level of the primary tear ($P = 0.001$) and the middle of dissection ($P = 0.004$) (Figure 4). Dissection propagations of all animals were observed according to the CTA findings at 30-day follow-up. There was a significant difference in the median propagation length between the two groups (73.4 mm, range 51.9-95.0 mm, in Model A vs 161.2 mm, range 109.2-213.1 mm, in Model B; $P = 0.016$). During the follow-up, eight animals showed reentry tears located at the ostium of the aortic branch vessels (8 of 10, 80%), including 4 tears at the intercostal artery, 2 at the celiac trunk, and 2 at the superior mesenteric artery (Figure 5). The antegrade propagation length at 24 months was significantly longer in Model B (180.4 mm, range 127.5-251.6 mm) than in Model A (81.8 mm, range 52.8-113.2 mm; $P = 0.016$). The retrograde propagation length did not differ between the two models ($P = 0.691$). The total propagation length was observed longer in Model B than in Model A during the follow-up ($P = 0.032$, Figure 3). Notably, the acute dissection propagation occurred any time but most common at the first 3 months in Model A and at the first

12 months in Model B. The maximum diameter of dissection in Model A at 24-month follow-up was observed larger than that at 1-month follow-up ($P=0.046$), while it seemed to arise apparently in Model B after 12 months of the onset. However, no statistical difference of the maximum diameter was observed in Model B ($n=3$) during the second year's follow up (27.8 mm at 12 months vs 33.8 mm at 24 months, $P=0.11$, Figure 6). During the follow-up, no thrombosis in the FLs was found in both models according to the CTA.

Histologic findings.

Microscopy examinations showed that the created dissection was located correctly in the different planes of the medial layer of the aorta. Histologic findings of the two models were generally concordant with the macroscopic examinations. Microscopy examination revealed that the dissecting plane was located deep within the inner media in Model A, whereas this plane was much closer to the adventitia in Model B (Figure 7, A). The different locations of intimal tears were observed obviously at the proximal dissection in the two models, however, the intimal tears developed to be superficial and similar at the distal dissection (Figure 7, B and C). In both models, the shape and orientation of elastin and collagen fibers were different on both sides of the FL. The elastin and collagen were of a wavy arrangement inside the FL, whereas the fibers were in alignment on the outside of the FL. The fibers were much more stretched on the adventitia and outside the media than on the intima side.

Discussion

Acute TBAD is the result of a tear in the intimal arterial layer, which allows blood to propagate within the medial layer. Generally, the created intimal flap divides the aorta into two channels, resulting in the hemodynamic redistribution.^{12,13} However, it is unclear whether the layers of dissecting flap impacts on the propagation of TBAD according to the current guidelines.^{13,14} The swine TBAD models in the presented study demonstrated that a deeper intimal tear resulted in a greater aortic dissection propagation. This finding may shed new light on the role of dissecting flap in the evolvement of aortic propagation and dilatation.

Numerous unsatisfactory attempts have been made to simulate human aortic dissection in canine¹⁵⁻¹⁷, while only few studies were conducted with swine.^{18,19} Previous study²⁰ demonstrated that there seemed to be few structural differences between human and porcine thoracic aortic tissue. Especially in the ascending aorta, the stiffness of young porcine aortic tissue (0.5-12 months) showed good correspondence with human tissue aged <60 years. The *ex-vivo* models in porcine aorta reported by Qing et al.²¹ also proved to be useful and reproducible to study the complex hemodynamics of TBAD. The presented swine TBAD models are reproducible and resemble human models, but swine models do have some shortcomings, including anesthesia tolerance and postoperative management.

In the models presented here, our findings suggested that the depth of the initial dissected flap significantly influences subsequent dissection propagation, especially for the animal with deep intimal tear. A similar finding has been reported by Mitsui et

al.,²² who suggested that the development of a dissection depends upon whether the intimal tear reaches the first one-third of the external media. This previous in vitro study using canine aortas demonstrated that a dissection progressed more often (85.7% of the time) when the intimal tear was located in the first one-third of the external media than when it was in any other layer. Additionally, van Baardwijk et al.²³ reported an association between a deeper intimal tear and a slower dissection rate, and they suggested that the depth of the intimal tear likely determined whether a dissection extended into a branch or ripped around the base of the branch. There may be some reasons for this completely contrary finding of van Baardwijk et al.²³ First, their *ex-vivo* experiments of aortic dissection in canine thoracic aorta was carried out in 1978, using a simple pulsatile pressure system with no flow, which might lead to a rough result. Second, the dissection rate was only observed during the limited period of experiment instead of the process of propagation over time in vivo environment, giving a misplaced impression of the dissection propagation.

Studies on the pathogenesis of dissection are viewed as clinically important in risk stratification because any further progression of the dissection may cause rupture by tearing to the adventitial side or may cause reentry by tearing to the intimal side.^{1,24} However, the question of how the dissecting layer influences the dissection propagation remains unanswered.

Interestingly, dissections can propagate either toward the internal elastic membrane or toward the external elastic membrane during peeling in the axial

direction.²⁵ The histologic findings in the present study indicated that the fibers on the adventitia and outside the media were much more stretched than those inside the media in both models, which suggested that the outside collagen fibers of the FL would reach their straightened lengths and that the adventitia would change to a stiff “jacket-like” tube that would prevent arterial overstretching and rupture. Van Baardwijk et al.²⁶ observed that some layers of elastin in sheep aorto-intercostal junctions extended continuously from the aorta into the intercostal media, whereas other aortic elastin was joined to the internal elastic lamina. Therefore, if the dissecting layer stays toward the external media, the dissection would extend into the branch media and potentially cause malperfusion of the branches. If the dissecting layer remains more toward the intimal side, then the dissection could extend around the branch site or reenter the aortic lumen around the base of the branch. In our study, the reentry tears were found superficial and most frequently (80%) at the ostia of the aortic branch vessels in both models, which may be related to the biomechanics of dissection propagation. The superficial reentry tears in both models also suggested that the dissecting layers would reenter the aortic lumen. Faure et al. visually confirmed the finding that the abdominal aortic side branches, as the preferred location for re-entry tears, are anatomic barriers against distal and aneurysmal expansion of a dissection.²⁷

Factors that influence the TBAD hemodynamic distribution (pre-TEVAR) and redistribution (post-TEVAR) were identified to be the key indicators of late adverse events.²⁸ For example, the intimal flap separates the TL and FL and its movement

balances the blood pressures in the channels during cardiac cycles and during the transition from the acute to the chronic stage. Peterss et al. demonstrated an association of elastin fragmentation and subsequent increased fibrosis with imaging findings of thickened dissection flaps that showed loss of mobility.²⁹ The presented models were created by the same experienced vascular surgeons and established the protocol after a period of exploration and training. Thin or thick intimal flap was created with same pockets and circumferential cuts. Intraoperatively, a notably longer dissection propagation length was observed in animals with thick intimal flaps (Model B), suggesting that different intimal shear stress and aortic wall strength caused by different aortic wall layers may play a major role in the acute propagation of dissection. Our findings also demonstrated that the acute dissection propagation occurred any time but most common at the first 3 months in Model A and at the first 12 months in Model B. Notably, the diameter of dissection aorta seemed to grow faster when the dissection propagated slowly. In acute and subacute stages, an increase in inflow and low or no outflow would increase the FL pressure, which would cause the TL to collapse or will trigger acute propagation.³⁰ In the chronic stage, the increased diameter or thrombosis in FL may be other factors to keep this balance. No thrombosis in the FLs formed in our results may be related to the antiplatelet therapeutics and the continuous inflow and outflow through the tears.

In the present study, the hemodynamic measurements using Doppler wires were deemed feasible and valuable for understanding the flow velocity distribution in both

the TL and FL. The findings suggested that although inflow increased in the FL, the average peak velocity was significantly lower than that in the TL. At the early stage of dissection, a high resistance existed in the FL, as no reentry tear developed. Consequently, the flow velocity remained much lower in the FL than in the TL, despite the increased volume and inflow in the FL. Notably, one prominent limitation for Doppler wire measurements is the lack of details available in a cycle. Peelukhana et al.³¹ suggested that, during the systolic phase, the flap curved towards the FL and caused a complete obstruction of the TL. Flow distribution in TBAD is influenced by the primary tear, the flap, the flow resistance, and the morphology of the TL and FL (Figure 8).

The present study had some limitations. It utilized only a limited number of animals in each TBAD model, even though both were confirmed as repeatable models and achieved promising results. Our models were also created using healthy swine, which had no intrinsic aortic disease; however, dissections in humans mostly occurs in cases of hypertension, atherosclerosis, or degenerative changes in the media, so dissection propagation in the swine models may differ from dissections in human patients. This was also the first attempt to use Doppler FloWires for aortic dissection measurements, so we can draw only on our own experiences (supplementary materials).

Conclusion

In this swine model of TBAD, the depth of the intimal tear has a significant direct relationship with aortic dissection propagation, especially for the model with deep tear. The *in vivo* TBAD model may provide valuable insight into the research of hemodynamics and propagation in human aortic dissection.

Acknowledgments

We would like to thank professor Nigel Wood (Chemical Engineering Imperial College London) for his supports of aortic hemodynamics. We also thank Wood David for his excellent technical assistance in Doppler measurements.

Sources of Funding

This research is financially supported by the National Natural Science Foundation of China (81470573, 81770474, 81371648, 81770508), and is also sponsored by Shanghai Sailing Program (No.18YF1404000), and Shanghai Committee of Science and Technology, China (No.16410722900).

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Table 1. Diameters of the aorta and peripheral arteries in the 12 swine

Variable	Median (range, mm)
Ascending aorta	25.4 (23.0-26.8)
Aortic arch	21.2 (18.6-26.6)
Innominate artery	11.0 (9.3-13.6)
LSA	10.4 (8.5-11.9)
Proximal TA	23.5 (17.9-26.9)
Middle TA	19.6 (14.6-22.8)
Distal TA	16.2 (12.6-18.6)
Celiac trunk	6.2 (5.3-7.8)
SMA	8.8 (7.2-9.4)
Renal artery	6.7 (5.6-8.3)
Proximal AA	13.3 (12.3-18.4)
Middle AA	12.2 (11.0-16.3)
Distal AA	12.0 (10.4-15.9)
Iliac artery	7.8 (7.4-9.6)
Femoral artery	6.2 (5.9-6.9)

AA, abdominal aorta; LSA, left subclavian artery; SD, standard deviation; SMA, superior mesenteric artery; TA, thoracic aorta.

Figure Legends

Figure 1. A schematic diagram of the two type B aortic dissection models in swine (A1–A3 for Model A, and B1–B3 for Model B). In both models, an intimal tear, which included the intima and parts of media, was made at the proximal descending thoracic aorta using a transverse incision. The proximal free edge of the aortic wall and the outer layer of the distal aortic wall were sutured with 6-0 Prolene while the

animals were under general anesthesia (A2 and B2). Macroscopic examination revealed that the created dissections at 3 months after the procedure showed different characteristics of the propagations and flaps (A3 and B3).

Figure 2. Dissection propagations developed during 6 months of follow-up in the two models (A1–A3 for model A, and B1–B3 for model B). Aortography immediately after creation of the dissections showed no dissection propagation in Model A (A1), whereas a significant longitudinal propagation occurred in Model B (B1, red arrow). In both models, the extension of the dissection in the thoracoabdominal aorta showed a similarity at 1 month after the first procedure (A2 and B2) to the imaging findings obtained with computed tomography angiography at 6 months (A3 and B3).

Figure 3. Intraoperatively (A-B), animals in Model B had greater aortic propagation length and maximum diameter of dissection than those in Model A. During the follow-up (C-E), the antegrade and total propagation length were both significantly longer in Model B than in Model A ($P = 0.016$ and $P = 0.032$, respectively). However, the retrograde propagation length did not differ between the two models ($P = 0.691$).

Figure 4. Box and whisker and line plots of the average peak velocity (APV) measured by Doppler wires in the true and false lumens. The box plots provide a graphical description of the differences between the true and false lumens, whereas the individual line plots show paired observations for each swine in the type B aortic dissection models and demonstrate the variations between swine. The median APV is greater in the true than in the false lumen at the levels of the primary tear and the

middle of the dissection. The APV shows an apparent increase from the primary tear to the middle of dissection based on overall observations of the true lumen. However, the APV in the false lumen does not differ significantly between the two segments.

Figure 5. In Model A, the CT imaging of one animal during follow-up showed a re-entry tear located just at the ostium of an intercostal artery (A). In Model B, a flap tear occurred back to the aortic lumen around the base of the SMA (B). CT, computed tomography; CA, celiac artery; SMA, superior mesenteric artery.

Figure 6. The trends of average propagation length (A) and maximum diameter of dissection (B) between the two models over time.

Figure 7. Microscopy examination of elastin staining (resorcinol alkaline fuchsin stain, magnification $\times 10$, A) showing the destruction of elastic lamellar architecture in the media layer of aortic wall. In both models, the elastic fibers were much more stretched on the adventitial side of false lumen than those on the intimal side. In the proximal dissection (hematoxylin and eosin staining, B), the intimal tear of Model B was identified to be deeper than that in Model A. However, the intimal tears in two groups developed to be superficial and similar in the distal dissection (C).

Figure 8. Diagram of the hemodynamic distribution and dynamic flap motion in aortic dissection. Flow distribution in an acute dissection propagation demonstrated that the movement of the flap, inflow, outflow, primary tearing, and re-entry tearing contributed to maintaining the stability of the dissection hemodynamics. Intravascular ultrasound imaging revealed that the intimal flap was thin at the acute phase,

498 indicating large-scale motion over the course of the cardiac cycle. However, the flap
499 thickened and straightened over time, resulting in reduced motion. TL, true lumen; FL,
500 false lumen

Figure 1
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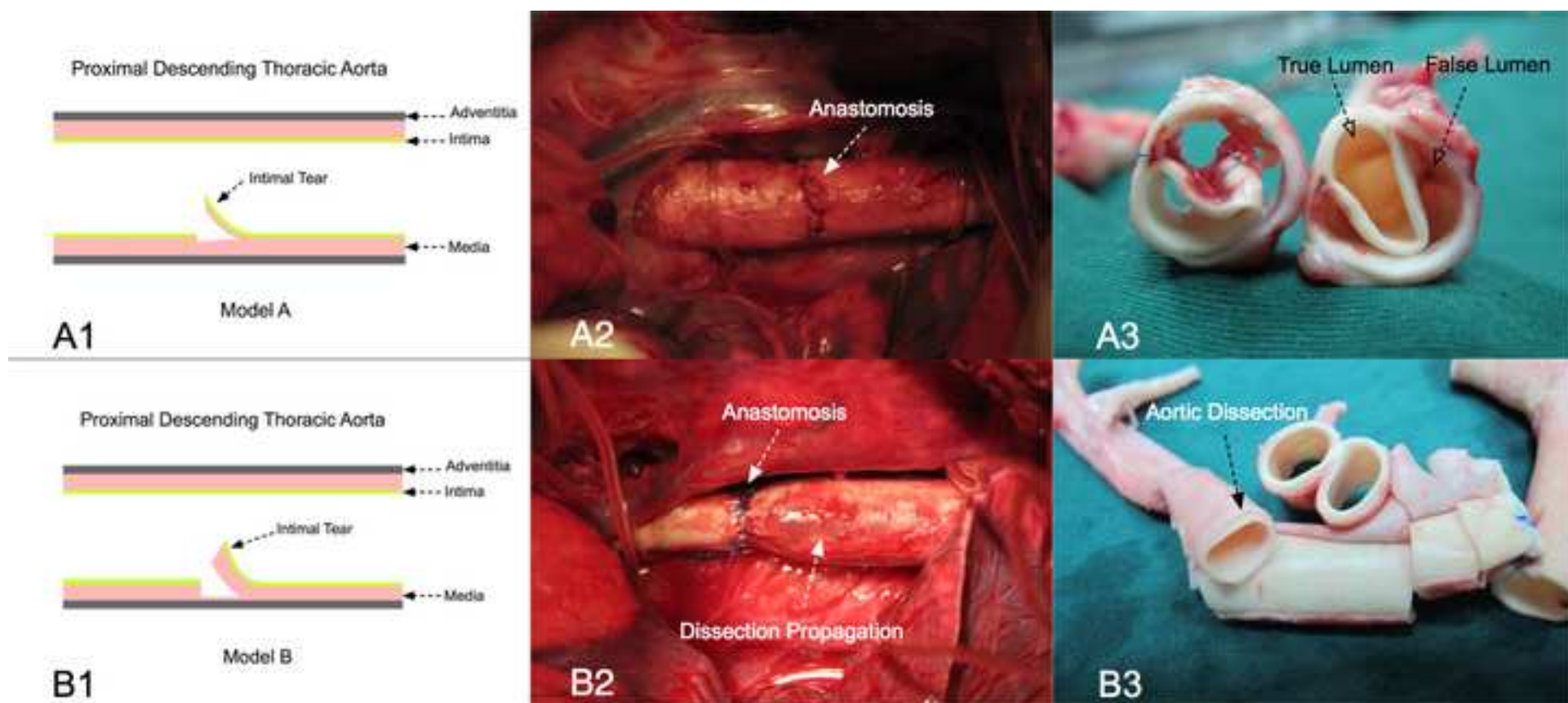


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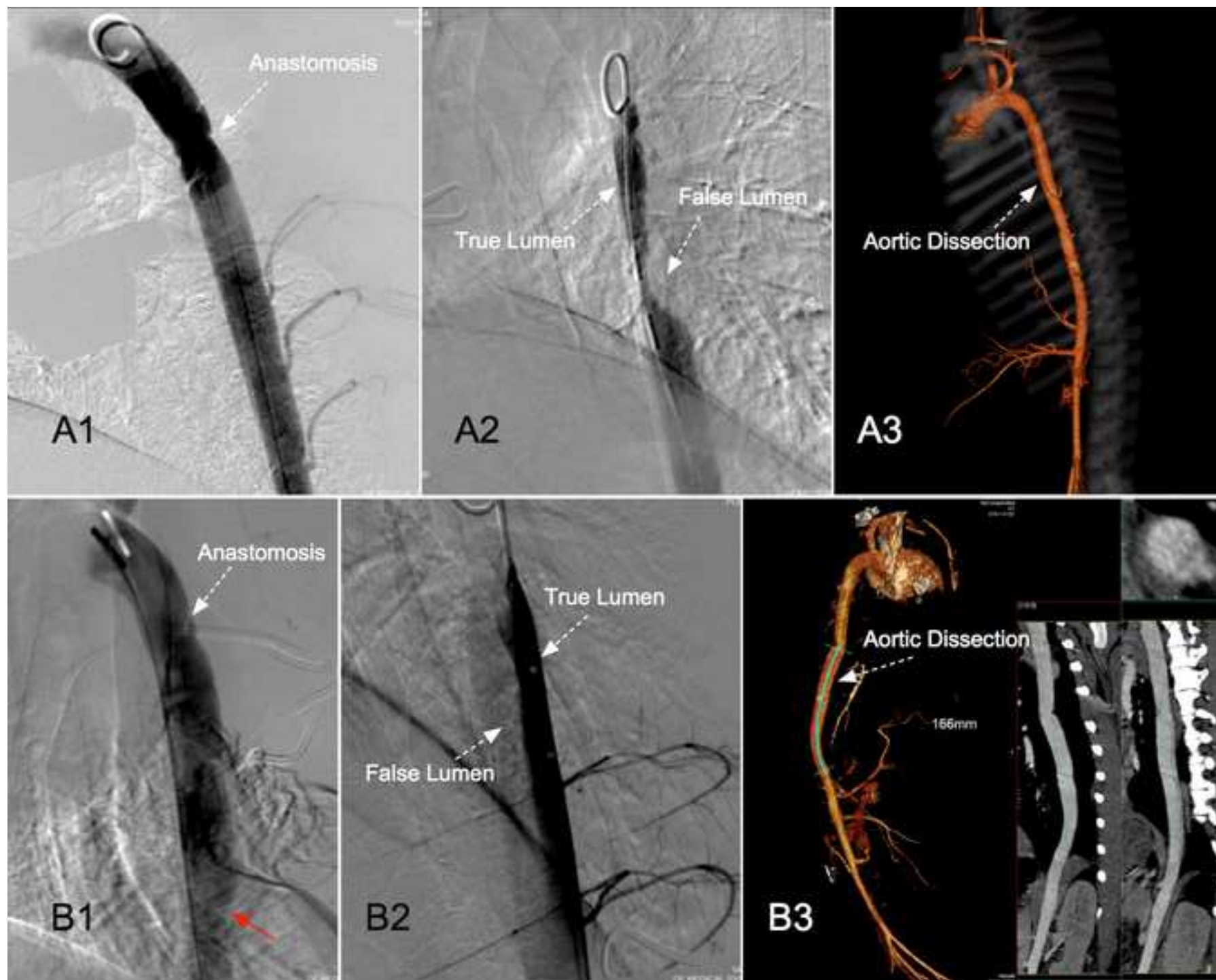
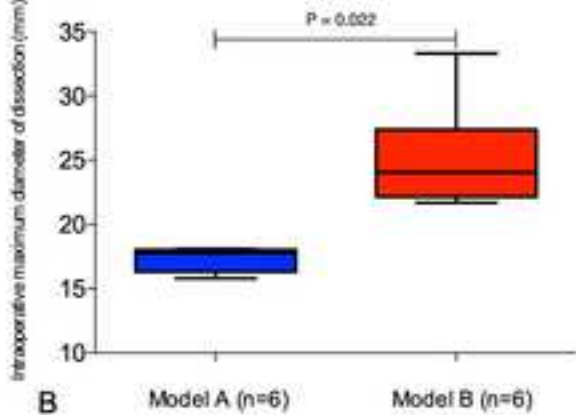
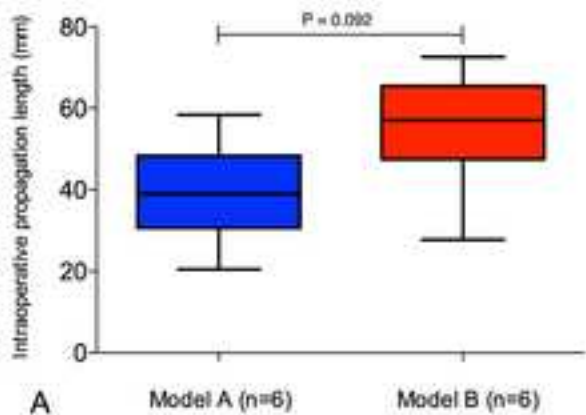


Figure 3
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Intraoperative propagation



Follow-up propagation

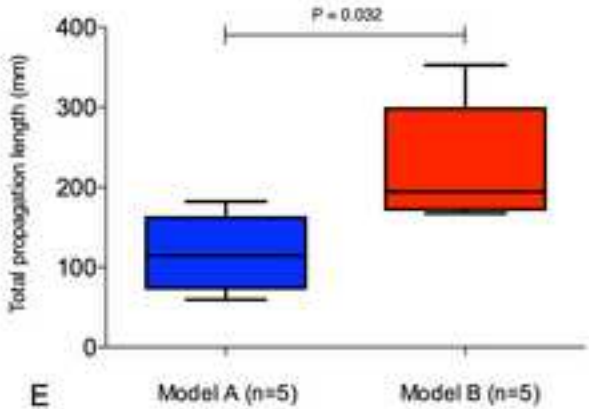
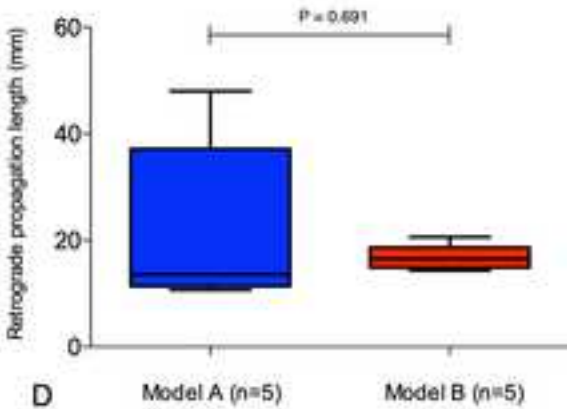
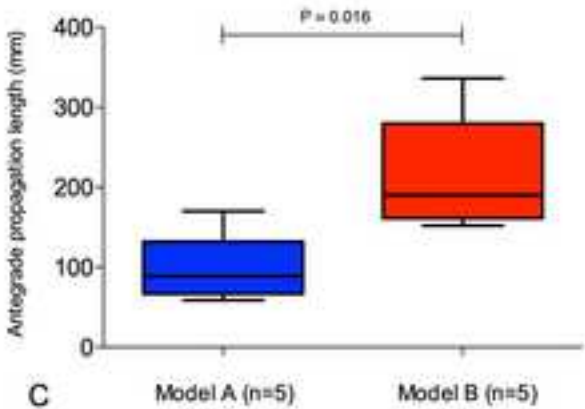
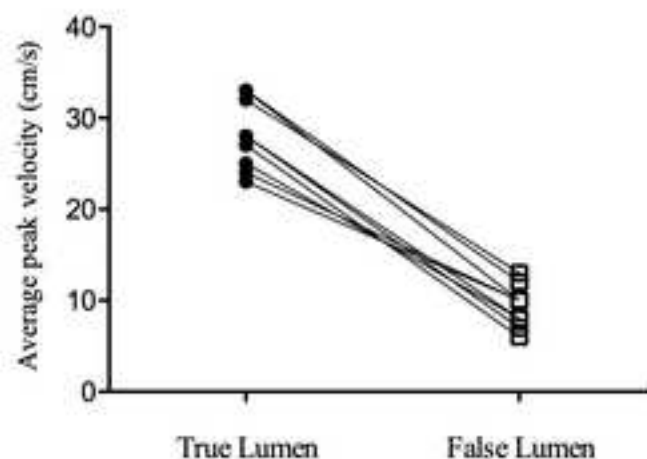
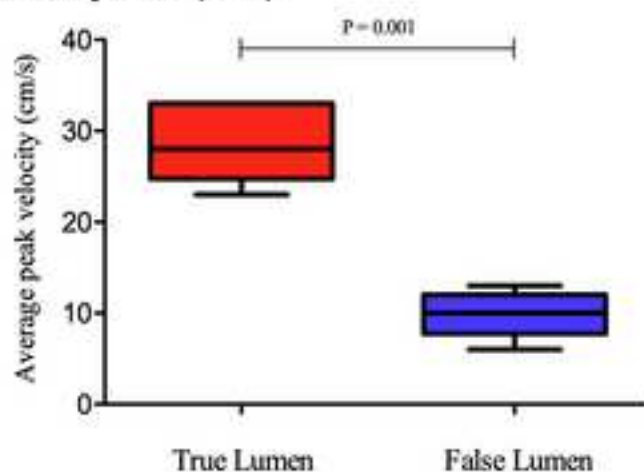
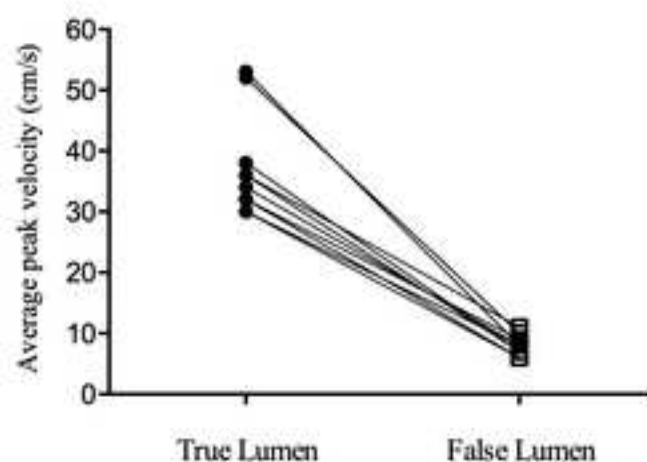
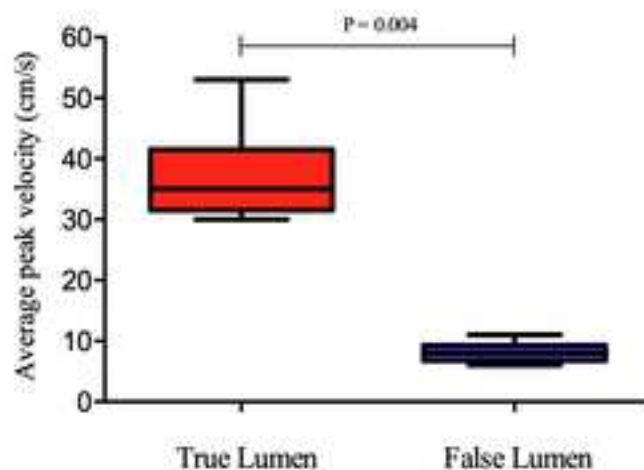


Figure 4
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Primary tear (n=7)



Middle of dissection (n=7)



Overall (n=7)

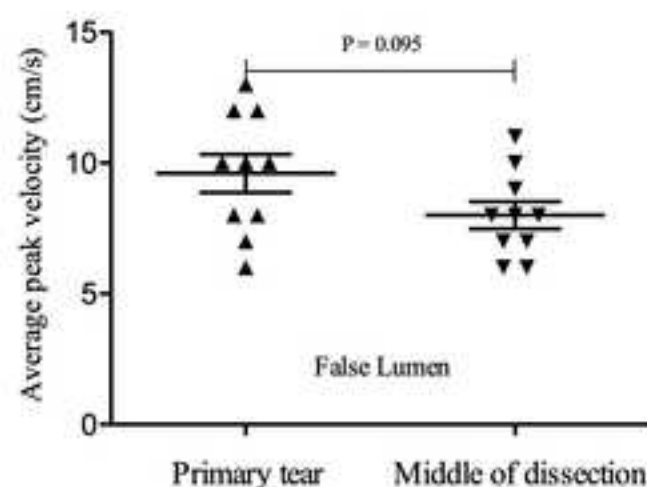
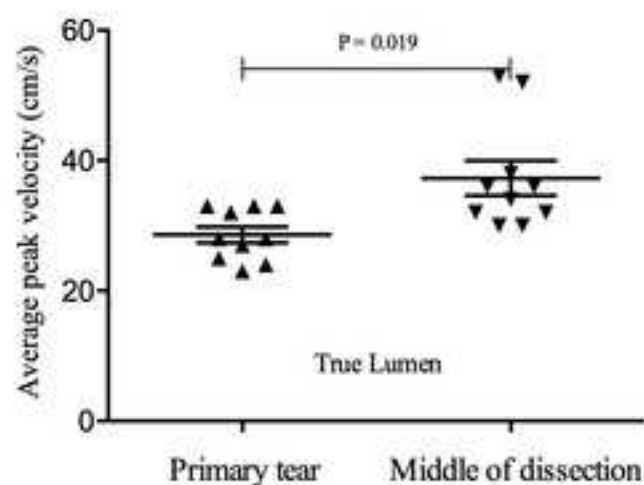


Figure 5
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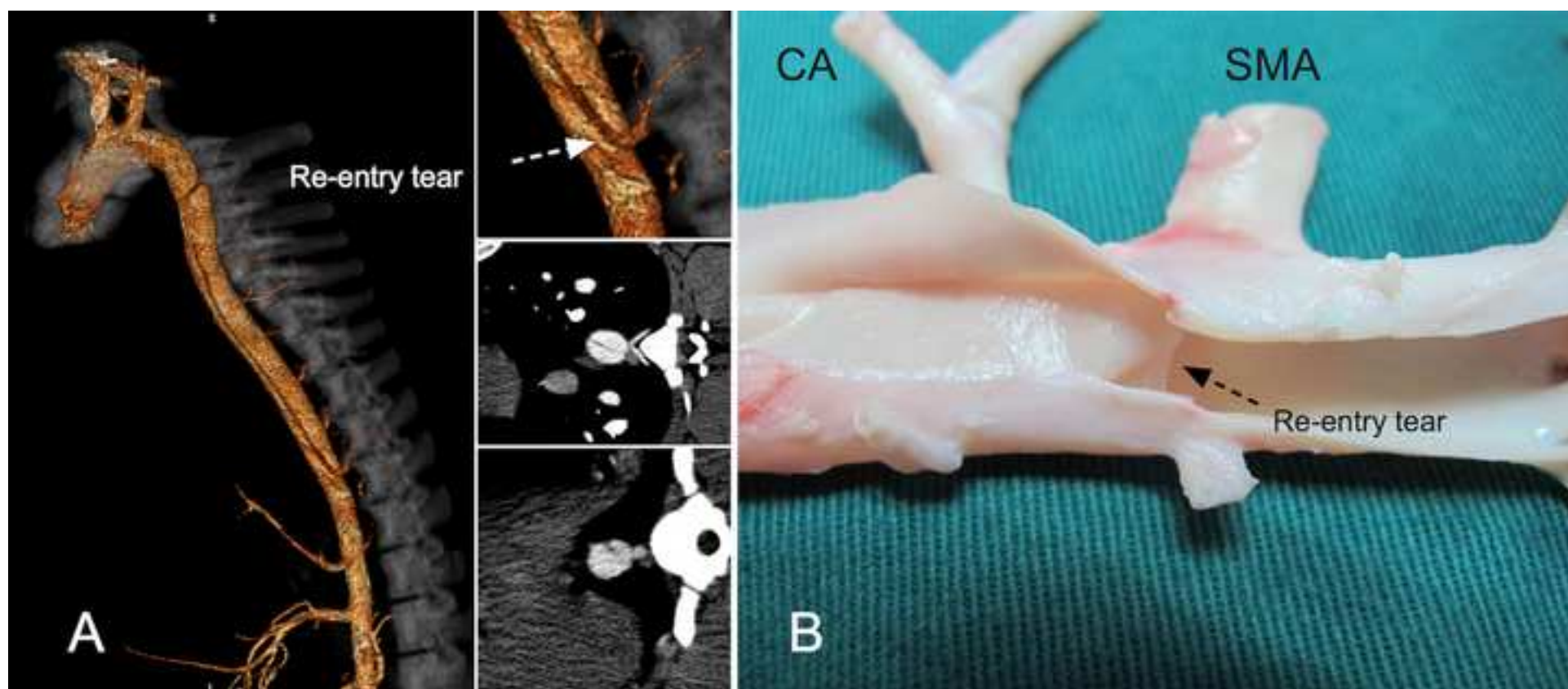


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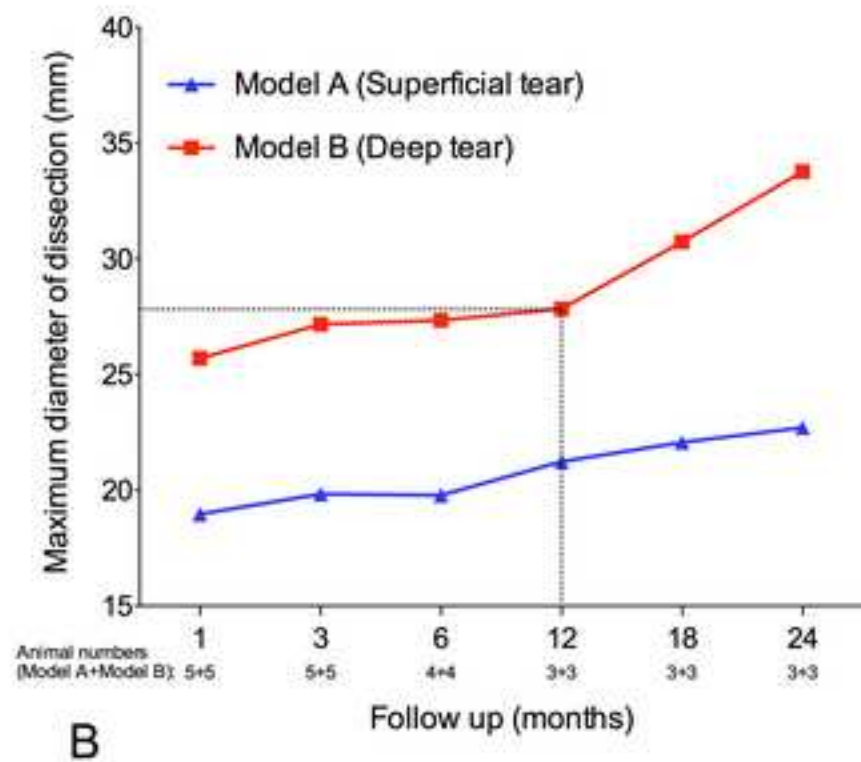
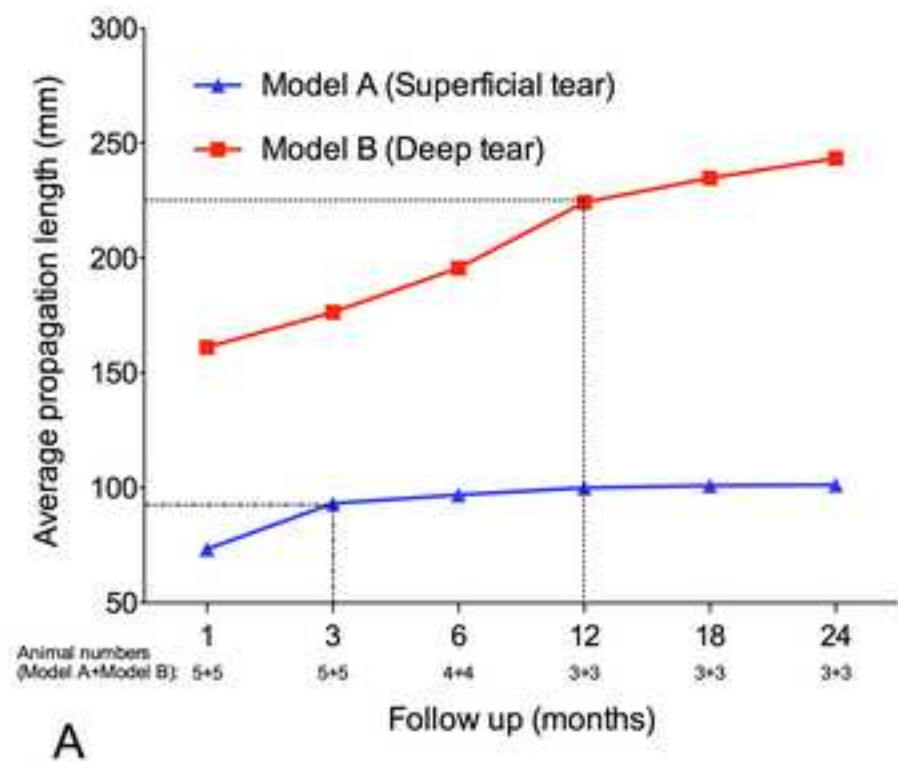
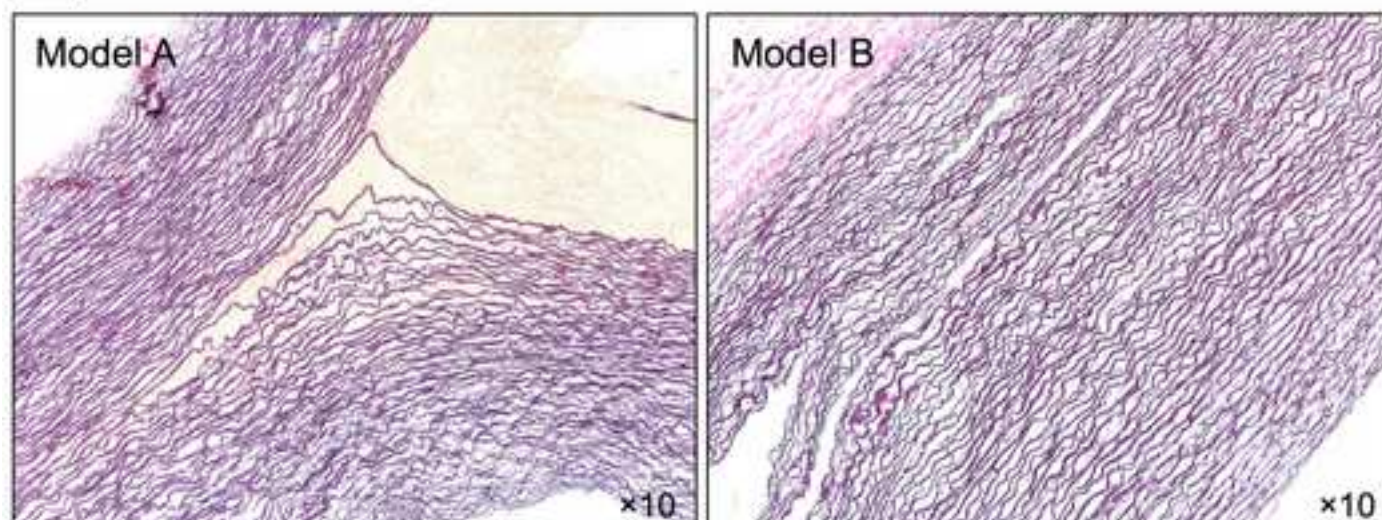
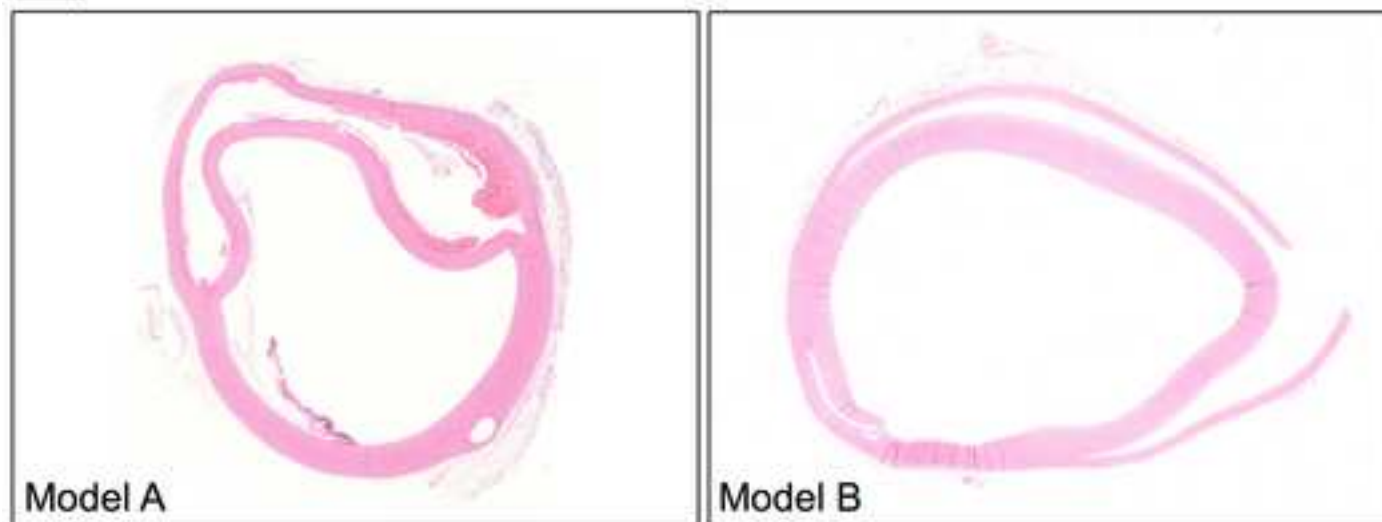


Figure 7
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A Elastin staining



B Proximal dissection



C Distal dissection

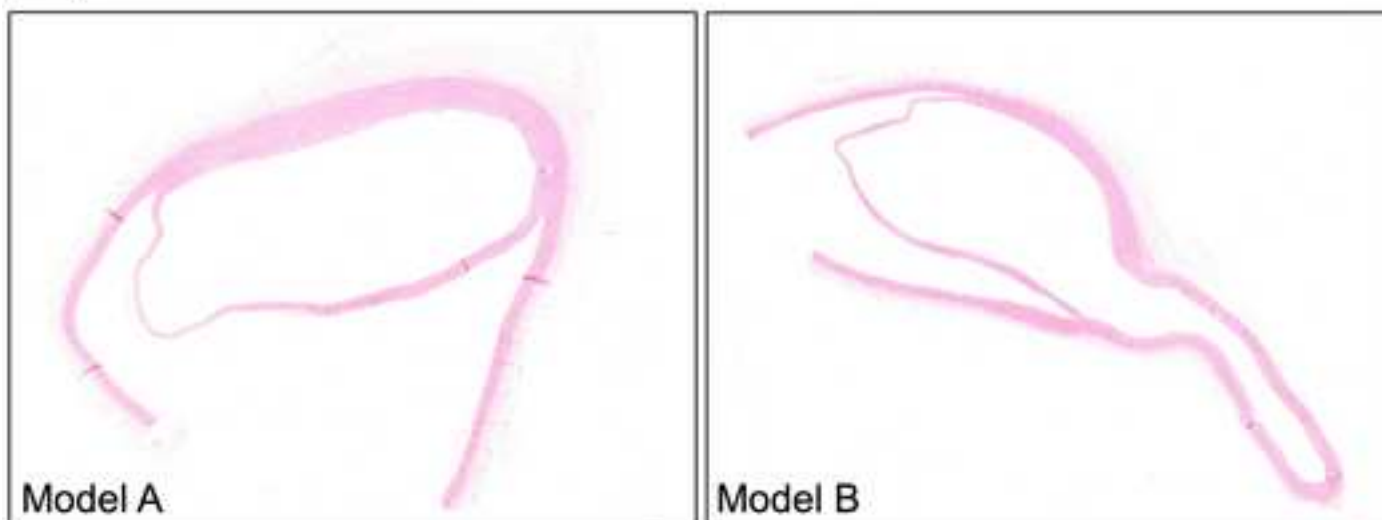


Figure 8
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