Preclinical evaluation of a new left atrial appendage occluder (Lifetech LAmbre™ Device) in a canine model

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ARTICLE INFO

ABSTRACT

Objectives: The study evaluated the feasibility and safety of a novel left atrial appendage (LAA) occluder (LAmbre™, Lifetech Scientific Corp., China) in canines.
Background: Transcatheter LAA occlusion is comparable to warfarin in preventing atrial fibrillation-related strokes.
Methods: Twenty-two healthy dogs (28 ± 3 kg) received LAmbre implants. The device is delivered by an 8–10 French sheath and has full recapture and repositioning capabilities. All dogs received 1-week antibiotics and 4-week aspirin (80 mg daily) after implants and they were sacrificed in groups at Days 1–3 ($n = 5$), 1- ($n = 7$), 3- ($n = 4$) and 6-months ($n = 6$) for pathological examinations. Transthoracic echocardiography (TTE) was performed immediately after implant, at Day 3 and before sacrifice.
Results: The LAmbre was successfully implanted, retrieved, repositioned and re-implanted in all dogs. The mean implant size was 24 ± 3 mm and the device chosen was $36 \pm 7\%$ larger than the measured landing zone diameter. Improper device selection (only 21% oversizing) resulted in dislodgement and death of 1 dog on Day 3. Post-implant angiography and TTE showed well-positioned device without pericardial effusion or impingement on surrounding structures. Late complications included device-related thrombus at 1 month ($n = 1$) and clinically insignificant pericardial effusion at Day 3 ($n = 1$). Complete healing on the atrial facing surface with optimal LAA obliteration was confirmed by gross and microscopic examinations in dogs that have been followed up ≥ 3 months ($n = 10$). No infarct was detected in major organs.
Conclusions: Our preliminary data suggested the LAmbre™ device is feasible with high success rate in canines. Further studies are needed to evaluate its safety and efficacy.

1. Introduction

Warfarin is the standard medical therapy to prevent stroke associated with atrial fibrillation (AF) but it is difficult to be used safely and conveniently [1]. More than 90% of atrial thrombi associated with AF were found in left atrial appendage (LAA) and transcatheter LAA occlusion has been developed as an alternative strategy to warfarin for stroke prophylaxis in AF patients [2–5]. LAA occlusion is an attractive solution to AF-related stroke because this local therapy potentially addresses both the concerns of inconvenience (no issue with drug interaction, blood monitoring and compliance) and safety (bleeding) issues associated with long term oral anticoagulant usage [6].

WATCHMAN device (Boston Scientific Inc., US) and Amplatzer Cardiac Plug (St Jude Medical Inc., US) are 2 commercially available devices with reported efficacy in humans [4,5,7–9]. However, both devices have limitations including the need for relatively large delivery sheaths (9–14 Fr) and limited recapture and repositioning capabilities [10]. LAmbre™ (Lifetech Scientific Corp., Shenzhen, China) is a novel; self-expanding LAA occluder constructed from a nitinol mesh and polyester membranes and consists of an umbrella and a cover connected by a short central waist. The device is delivered by an 8–10 French sheath and has full recapture and repositioning capabilities. In this report, we aimed at evaluating the feasibility and safety of percutaneous implantation of the LAmbre LAA occluder in a healthy canine model.

2. Methods

2.1. LAmbre LAA closure system

The name "LAmbre" is a derivative from "an umbrella in the left atrial appendage". The LAA closure system consists of an implant and its delivery system. The implant is a

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nitinol-based, self-expanding device comprising a hook-embedded umbrella and a cover connected with a short central waist (Fig. 1). The waist acts as an articulating, compliant connection between the cover and the umbrella, allowing the cover to self-orient to the cardiac wall. The cover is 4 to 6 mm larger in diameter than the umbrella, covering the LAA orifice and provides apposition against the chamber wall under gentle tension. The proximal cover is filled with sewn in polyethylene terephthalate (PET) fabric. The distal umbrella comprises 8 claws with individual stabilizing hooks attaching to them to facilitate anchoring to LAA wall. The umbrella was specially engineered to allow for complete collapse and repositioning (Video 1). An additional PET membrane has been introduced to the umbrella in the newer version of the implant to ensure LAA sealing in case the cover fails to achieve optimal occlusion (Fig. 1). Several sizes of the implants (16–36 mm) have been developed to accommodate the variation of LAA anatomy and they were delivered by sheaths ranged 8–10 Fr in size.

The delivery system consists of a sheath, dilator, delivery cable, loader and vise. The delivery sheath allows for contrast injection both in LAA and proximal to the occluding surface to assess sealing and device positioning at the interface of LAA orifice and left atrial wall.

2.2. Animal preparation

The canine model was chosen for the animal model in this study because of the similarity to the human appendix with an angle similar to the human appendage and typically has a constricted LAA orifice. This model has also been tested in other dedicated LAA occluders with success, allowing the direct transfer of the technology to human trials [11–13].

22 healthy farm dogs 8–18 months of age and 20–35 kg in body weight, identifiable by ear tags were included in the study. The study was conducted in an independent, commercialized animal facility (Gateway Medical Innovation Center, Shanghai, China) under proven laboratory practices for GLP studies. Dogs were fed commercially available normocholesterolemic canine food once daily.

Anesthesia prior to implant was induced using a mixture of ketamine/xylazine/atropine (i.m), followed by cannulation of the ear vein, and maintenance by pentobarbital (i.v.) and tracheal intubation. During implant the dogs were maintained under the general anesthesia with 0–5% isoflurane adjusted to effect. Post-operative care included close observation of the animal until fully conscious, followed by regular monitoring for 24 h. Animals were then monitored daily for the duration of the study. Any animals found to be in distress were assessed by a veterinarian, and necessary action is taken, that included treatment or euthanasia. For periodic assessment of the animals, a mixture of ketamine/xylazine or ketamine/diazepam (i.m.) was administered to sedate the animals. At the end of the study, animals were euthanized under isoflurane anesthesia with an intravenous overdose of potassium chloride and the entire carcass was submitted for pathological examinations by designated persons.

2.3. Implantation procedure

The dog was anesthetized and the procedure was performed via femoral vein approach under fluoroscopic and angiographic guidance. Transseptal puncture was performed using conventional Brockenbrough technique by an 8 Fr transseptal sheath (SL1, St Jude Medical, US) and needle, and the LAA was reached over a guidewire. A heparin bolus of 1800–3000 (80–100 units/kg) is administered after successful transseptal puncture. The diameters of the orifice and length of LAA are measured from LAA angiogram in right anterior oblique (RAO) cranial projection. The size of the implant would be 4–8 mm larger than the measured LAA orifice, based on the clinical judgment of the implanting physician using other anatomical and procedural considerations. A generous over-sizing strategy (the chosen device diameter was 25–45% larger than measured landing zone diameter) was adopted in this study as bench testing showed that the device would not deform with even up to 50% compression.

The delivery sheath containing the implant was placed to the proximal part of LAA. The umbrella of the implant was partially deployed by slowly pushing out the device from the delivery sheath. The whole system is then gently push "en-bloc" forward to the desired landing zone to allow better flowering of the umbrella and grasping of LAA walls by the retention hooks. The sheath was then withdrawn to expose the disc, allowing it to expand in the left atrium and covering the LAA ostium by gently pushing the delivery cable forward. Once the implant was placed in LAA, left atrial angiogram was performed to check device positioning, LAA sealing and impingement on surrounding cardiac structures. Gentle tug test by applying tension to the delivery cable is performed to ensure device stability. The implant is intentionally recaptured, completely retrieved and re-deployed for at least 2 times in all dogs to ensure the safety of these maneuvers (Fig. 2, Videos 2 & 3). Acute procedural success is defined as proper and stable implant in LAA without peri-device leakage or impingement on surrounding cardiac structure. The implant would be released from delivery cable once acute procedural success is achieved.
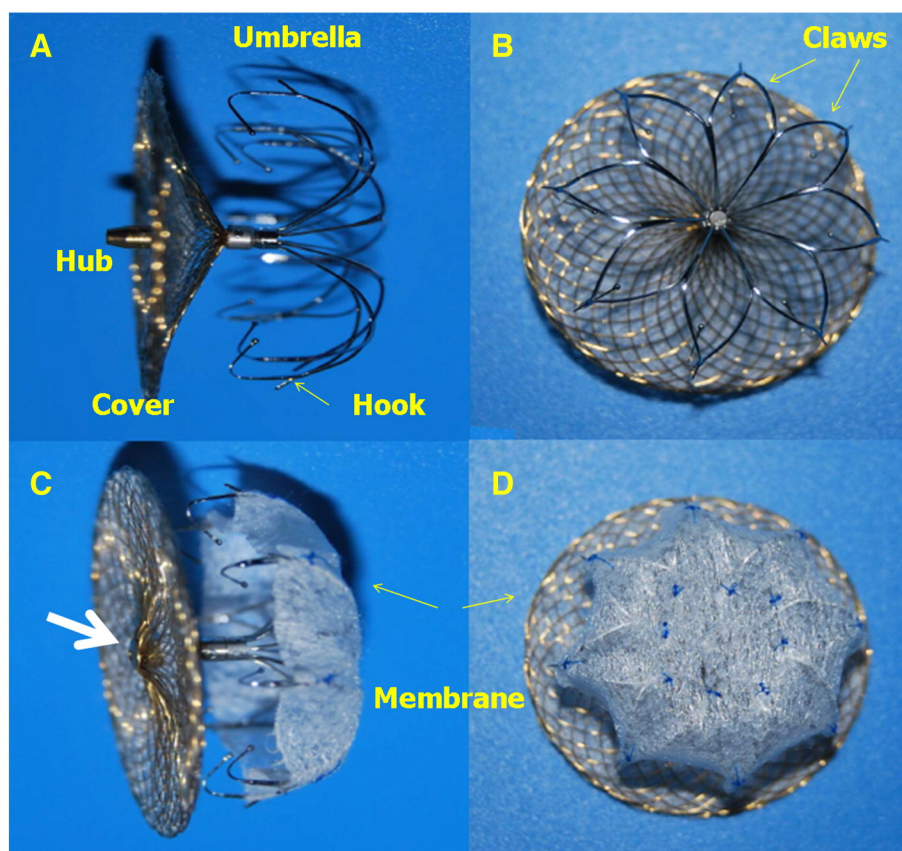
Fig. 1. The LAmbre™ is a nitinol-based, self-expanding device consisting of a fabric-enriched cover and an umbrella connected with a short central waist, and 1 attachment hub (A). The umbrella comprises 8 claws with individual stabilizing hooks attaching to them (B). The hub is recessed to the surface of the cover (white arrow) and an additional membrane was introduced to the umbrella in the newer version of LAmbre™ (C and D).
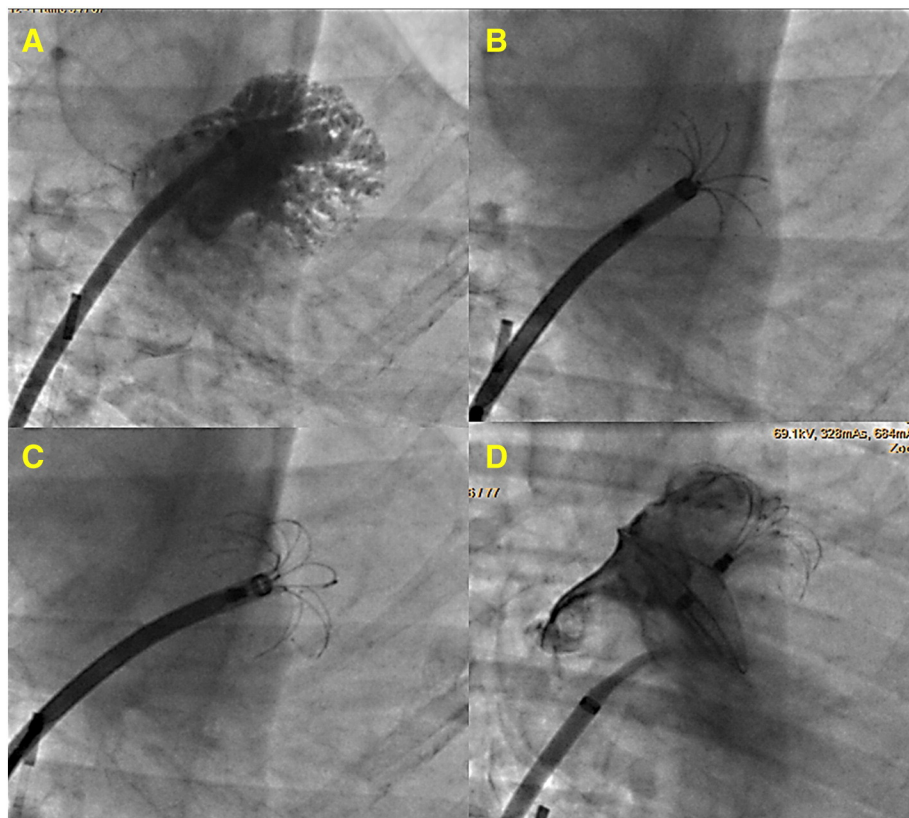
Fig. 2. The delivery sheath was positioned in the proximal portion of the left atrial appendage (LAA) (A) and the umbrella was partially deployed (B) by slowing pushing the device out of the sheath. The whole system is then advanced to the desired landing zone of LAA to allow flowering of the umbrella and engagement of the stabilizing hooks into the LAA walls (C). The cover is then deployed to seal the LAA ostium by withdrawing the delivery sheath and left atrial angiogram is performed after device release to check for LAA sealing (D).

Transthoracic echocardiography (Acuson Cypress Plus Portable Ultrasound Machine, US) was performed immediately after implant to monitor the presence of pericardial effusion or interference of other cardiac structures. Ampicillin 500 mg was given orally within 24 h of the procedure and then 250 mg twice daily for 7 days after each catheterization procedure. Enteric-coated aspirin 325 mg was given 1 day before the implantation and then 80 mg once daily for 4 weeks with the animal's food for 4 weeks post-operatively.

2.4. Follow-up

Transthoracic echocardiography was performed immediately after implant, at Day 3 and before sacrifice. The dogs were euthanized in groups at 4 time points after LAA occlusion: 1–3 days, 1-, 3- and 6-months. They were heparinized and death was induced by lethal intravenous doses of a commercial solution. The gross- and histo-pathologic analyses were carried out via standard methods.

The implant was photographed in situ at necropsy, and the heart was prepared for histological examination of tissue response and endothelialization. For those animals sacrificed at 1-, 3- and 6-months, in addition to hearts, their brains, kidneys, lungs and spleen were examined grossly and histologically for signs of ischemia/necrosis caused by embolism.

2.5. Specific outcome measures

The feasibility end-point was defined as the achievement of acute procedural success (proper and stable implant in LAA without peri-implant leakage or impingement on surrounding cardiac structures).

The safety end-points were defined as the occurrence of clinical events related to heparin/aspirin (bleeding events) or procedure (catheter-related thrombus formation, air embolism, pericardial effusion, implant embolization, procedural-related transient ischemic attack, stroke or death).

The imaging end-points are listed as followings:

- Echocardiographic (pericardial effusion, interference of mitral valve function or pulmonary venous flow)
- Angiographic (sealing of LAA orifice, device migration)

The pathological end-points included:

- Gross specimen
  ○ Evidence of infarct in other organs (kidney, spleen, brain and lung)
  ○ LAA (device positioning, appearance of atrial prosthetic device surface, thrombus formation on device, penetration of umbrella claws or retention hooks)

  ○ Suboptimal sealing of LAA orifice was defined as the presence of a peri-device leak with the largest measured dimension ≥3 mm during autopsy examination of the dogs sacrificed at 1-, 3- or 6-months
- Histological specimen
  ○ Evidence of infarct in other organs (kidney, spleen, brain and lung)
  ○ LAA (inflammation, endothelialization, sealing of LAA, tissue response surrounding and within the implant, embedding of retention hooks into LAA wall)

2.6. Statistics

The occurrence of events was expressed as absolute numbers and percentage whereas the continuous variables are summarized by mean ± standard deviations.

3. Results

3.1. Acute procedural outcome

Table 1 listed the clinical characteristics of the canines. No animals were excluded from the current study. The first 18 dogs received older devices while the remaining 4 dogs had the newer devices. The LAmbre was successfully implanted, retrieved, repositioned and re-implanted in all dogs. By observation, the device being deployed in the distal portion of the LAA was associated with a higher chance of peri-device leak when assessed by angiography because part of the LA cover was drawn inside LAA and therefore it could not adequately cover the LAA opening. The final positions of all the deployed devices were adjusted proximally in this study in order to achieve optimal LAA sealing.

The mean implant size was 24 ± 3 mm and the device chosen was 6 ± 1 mm (36 ± 7%) larger than the measured landing zone diameter. Post-implant contrast angiography confirmed proper and stable implant in LAA without device migration, significant peri-implant leakage or impingement on surrounding cardiac structures in all dogs.

Table 1
Case information.

Case no	Weight, kg	Follow-up period	LAA landing zone, mm	Implants, mm	Oversizing, %	Complications
1	26.5	6 mo	16.6	22	32.5	
2	27	3 mo	20	26	30.0	Device-related thrombus, uneventful
3	30.5	1 day	17.1	24	40.4	
4	34.5	6 mo	17.8	24	34.8	
5	34	6 mo	17.5	24	37.1	
6	27	6 mo	18.3	26	42.0	Hook penetration, uneventful
7	25.5	1 mo	18.7	26	39.0	
8	22.5	6 mo	12.5	18	44.0	
9	26.5	1 mo	18	24	33.3	
10	24.5	1 mo	20.5	26	26.8	Small effusion at Day 3, uneventful
11	30.5	6 mo	19.1	26	36.1	
12	30.5	3 mo	17.1	22	28.6	
13	30	3 days	18.2 (15.2)[a]	22	20.8	Device embolization, sudden death
14	30	3 mo	12.4	18	45.1	
15	25	1 mo	15.1	22	45.7	
16	24	1 mo	15.1	22	45.7	
17	29	1 day	17.0	24	41.1	
18	32.5	1 day	21.1	28	32.7	
19	28.5	3 mo	17.2	24	39.5	
20	27	1 day	21.4	28	30.8	
21	30	1 mo	21	28	33.3	
22	25	1 mo	20.3	28	37.9	

no = number; kg = kilograms; mm = millimeters; LAA = left atrial appendage; mo = month(s).

[a] LAA landing zone diameter used for selection of device size.

TTE immediately after the implants showed neither mitral valve dysfunction nor pulmonary venous obstruction.

However, improper device selection (only 21% oversizing) resulted in subacute implant dislodgement to left ventricular outflow tract and early death of 1 dog on Day 3. A small amount of pericardial effusion <1 cm was observed by TTE at Day 3 in another dog without hemodynamic significance and the dog was later sacrificed per protocol at 1 month. Otherwise, there was no severe bleeding event, other procedural-related complications or late deaths.

3.2. Follow-up results

Routine neurological examination was not performed during follow-ups, but there was no apparent neurological deficits or behavioral problems detected by clinical observation. Scheduled echocardiographic examinations revealed no delayed pericardial effusion, mitral valve dysfunction or pulmonary venous obstruction.

Gross pathological examinations showed that all umbrellas except the one embolized to the left ventricular outflow tract were appropriately placed within LAA, beyond the appendage/atrial ostium. The former LAA ostia were all occluded by the cover of the implants. Small leaks (all ≤3 mm) were present at the inferior edges of the covers in 4 out of 7 dogs sacrificed at 1 month. In addition, 2 out of 4 dogs sacrificed at 3 months were found to have 1 mm leaks. No leak was found in 6 dogs sacrificed at 6 months. A glistening white pannus layer covering the left atrial surface of the device with optimal obliteration of the former LAA opening (LAA sealing without significant peri-device leak) was observed in dogs that been followed up ≥3 months (n = 10) (Fig. 3). An immobile thrombus measured 8 × 10 mm was found on device surface in 1 dog at 3 months. Besides, another dog was found to have penetration of 1 retention hook through LAA wall with epicardial fibrous healing and without pericardial effusion at 6 months. Both findings did not result in adverse clinical events.

The local atrial tissues tolerated the device well and no inflammatory or foreign body response was noted histologically at 1 month. At 3- or 6 months, the atrial aspect of the device was covered by layers of endothelial cells which indicated healing (Fig. 4). This organized neointima spread across the device–left atrial interfaces to seal the LAA openings completely in 8 out of 10 dogs. The LAA cavity distal to the cover was filled up with organized thrombus. The claws of the umbrella were well opposed to the native appendage walls and were

covered again by neointima, with no evidence of tissue necrosis. Retention hooks were seen embedded into the appendage walls. Both gross and light microscopic examinations of the major organs showed no evidence of infarct, indicating the absence of thrombo-embolic events.

4. Discussion

This is the first study to report the feasibility and safety of implanting a new Lifetech LAmbre LAA occluder in a healthy canine model. The LAmbre was successfully implanted, retrieved, repositioned and re-implanted in 22 dogs via an 8–10 French sheath and pathological examination revealed optimal sealing of LAA orifice at 3-month follow-up. Device embolization was the only severe complication which could be prevented by selection of a bigger-sized device. Three other clinically insignificant complications included small pericardial effusion, device-related thrombus, and penetration of a retention hook.

Atrial fibrillation causes >50,000 strokes and $12 billion in medical expenditure each year in United States. Warfarin used to be the Holy Grail in preventing AF-related stroke but it is difficult to be used conveniently and safely [1]. Newer oral anticoagulants may be comparable to warfarin in terms of clinical efficacy but the benefit does not come without the price of increased bleedings [13–15]. PROTECT-AF trial suggests that LAA occlusion was non-inferior to warfarin therapy for stroke prevention in NVAF patients [7]. 2012 European Society of Cardiology (ESC) atrial fibrillation guidelines therefore recommended that transcatheter LAA occlusion may be considered in NVAF patients with a high stroke risk and contraindications for long-term oral anti-coagulation [16]. The number of the LAA closure procedures is expected to rise in foreseeable future. However, currently available devices still have a number of problems to be addressed [10]. WATCHMAN device is relatively long and therefore not suitable for patients with shallow LAA. Recapturing the device beyond the level of retention barbs is not recommended with this device because of the risk of damaging the barbs and this limits its repositioning flexibility. On the other hand, there is a tendency for the lobe of the Amplatzer Cardiac Plug to jump forward to proximal LAA after deployment and thereby demanding extra skills from the implanting physicians [12]. Lastly, both devices needed to be delivered via relatively large-sized sheaths (14 Fr and 9–13 Fr for WATCHMAN and Amplatzer Cardiac Plug, respectively) which are inherently associated with more vascular complications
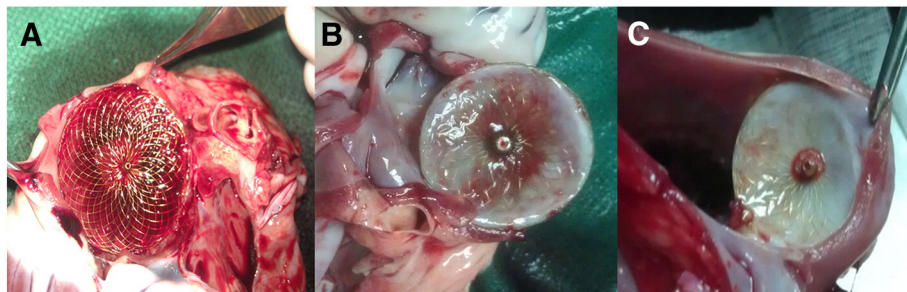
Fig. 3. Gross anatomical views of the LAA ostia at Day 1 (A), 1 month (B) and 3 months (C) after occlusion by the devices.

and air-embolic events. LAmbre is a short device to be placed within 2 cm from LAA ostium, consists of a specially designed hook-embedded umbrella to allow multiple device recapture/repositioning, remains stable during deployment and is delivered by a relatively small sheath (8–10 Fr). In this study, we achieved 100% acute procedural success and there was no problem encountered during recapture and repositioning. The device chosen was 6 ± 1 mm larger than the measured landing zone diameter and no change of device size was needed for all implants.

A major difference between LAmbre and the other 2 devices is the deployment sequence. During deployment of LAmbre device, the delivery catheter is positioned at the very proximal portion of LAA and the whole system is then gently push "en-bloc" forward to the desired landing zone to allow better flowering of the umbrella and grasping of LAA walls by the retention hooks. LAA perforation and pericardial effusion are less likely to occur by avoiding both deep seating of the delivery catheter and device manipulation at distal portion of the LAA. In our series, device embolization caused early death of 1 dog on Day 3. This was due to wrong measurement of landing zone diameter (15.2 mm) and hence a smaller device (22 mm) was chosen. The actual landing zone diameter was 18.2 mm when the measurement was repeated later by another person blinded to the event. We believe that this device would not have big stability concern as there are 3 mechanisms playing together to anchor the device inside the LAA: 1) engagement of the retention hooks into LAA walls, 2) stenting effect against the LAA wall generated by an over-sized umbrella, and 3) trapping of individual claws of the umbrella by the pectinate muscles located at mid to distal portion of LAA. In another dog, small pericardial effusion was noted on TTE at Day 3, which did not progress and was hemodynamically insignificant. It was unclear whether this

was caused by transseptal puncture or device deployment. This dog was sacrificed as planned at 1 month and there was no evidence of pericarditis or penetration of retention hooks or claws through LAA walls. One dog was found to have an 8×10 mm immobile, thrombus on the hub of the device surface at 6 months. Fortunately no infarct was detected in her major organs. Delayed, device-related thrombus formation has also been reported in humans with 2 commercially available devices and the exact determinants remained unclear [5,7]. Given the observation that most of the thrombus formed around the protruding hub used for connection to the delivery cable, the hub was made recessed in the revised LAmbre device.

It must be stressed that at this early stage of device development all noticed safety issues should be emphasized and this single canine study was not enough to conclude that this device is perfectly safe. Stabilizing hook penetration and pericardial effusion were both observed in this study. In future one of the major safety issues with this device will be device penetration through LAA wall. The umbrella of this device has a PET membrane to ensure LAA sealing in case the cover fails to achieve optimal occlusion and this design may reduce the risk of significant pericardial effusion should small LAA perforation occur. The possibility of adopting a less generous over-sizing strategy should also be explored in future studies.

4.1. Study limitations

This is a small animal series with limited follow-up duration up to 6 months. Only 1 dog had device-related thrombus despite only receiving 4-week aspirin therapy. Of course, the examinations could not be continuous and therefore it is not possible to completely exclude transient, small, mobile device-related thrombi. Pathological examinations
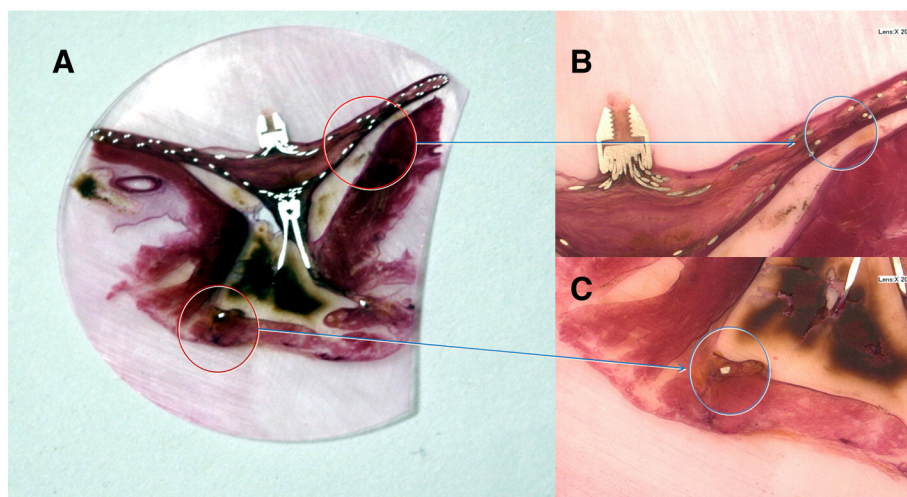
Fig. 4. Sagittal section through the center of the appendage and device shows tight apposition of the device to LAA wall and sealing of the device–appendage wall interface (A). Close-up microscopic views showed neointimal coverage over the device surface (B) and engagement of a stabilizing hook into the appendage wall (C), respectively.

showed no evidence of infarct in major organs anyway. Lastly, the dogs' LAAs differ from humans by having less angulated lobes and the adaptability of LAmbre device to humans having angulated appendage therefore remains largely unknown.

5. Conclusions

Our preliminary data suggested that the LAmbre™ device is feasible with high success rate in canines. Potential advantages of this device include small delivery system and the ability to be fully retrievable and repositionable during implantation. Human trials are underway to further evaluate its safety and efficacy.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2013.06.083.

Conflict of interest

Dr Yat-Yin Lam is a consultant of St Jude Medical, Boston Scientific and Lifetech Scientific Corp. Dr Shephal Doshi is a consultant of Boston Scientific Corp. Dr Jai-Wun Park is a consultant of St Jude Medical. Mr. Anning Li and Deyuan Zhang are employees of Lifetech Scientific Corp.

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