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Percutaneous left atrial appendage closure with a novel self-modelizing device: A pre-clinical feasibility study

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ABSTRACT

The aim of the study is to evaluate the feasibility and safety of a new left atrial appendage (LAA) occluder.
Twelve pigs were included. In 2 pigs the implantation process failed due to pericardial tamponade in 1 pig and device embolization in the other pig. The placement of the devices was controlled via TEE and fluoroscopy. After 6 weeks of implantation the hearts were explanted.
The devices were found to be easy to deploy and showed a very good adaptation to the LAA tissue. Eight out of 10 pigs had full closure of the LAA directly after implantation.
After six weeks, due to the self-modelizing properties of the device, all pigs had a full closure of the LAA. The macroscopic evaluation of the explanted hearts showed that all devices were securely integrated in LAA tissues. There was one case of mild pericarditis but no macroscopic signs of inflammation on the device surrounding endocardium. The explantation revealed that device loops had penetrated the LAA tissue in three pigs. However, no signs of bleeding, pericardial effusion, or other damage to the LAA wall could be detected and the pigs were in good condition with normal weight gain and no clinical symptoms.
The Occlutech® LAA occluder achieved complete closure of the LAA in all pigs, and remained in the LAA, with benign healing and no evidence of new thrombus or damage to surrounding structures. Moreover, the uncompromised survival of all implanted pigs demonstrates the feasibility and safety of the device.

1. Introduction

Atrial fibrillation (AF) is the most common tachyarrhythmia in clinical practice [1] and can result in thromboembolic events leading to serious illness or even death. Eight to 21% of patients scheduled for a cardioversion attempt present with left atrial thrombi [2,3]. Over 90% of these thrombi are located in the left atrial appendage (LAA) [4]. Emboli originating from the LAA often cause stroke, associated with a mortality of 38% in 12 months and a 12 month recurrence rate of 17% [5]. The risk of embolization of left atrial thrombi depends on the atrial size, sludge formation, and blood flow velocity in the left atrial appendage, patients' age, risk factor profile, and other factors [6]. The main risk of an embolic event in atrial fibrillation, however, is the lack of adequate anticoagulation [7]. Oral anticoagulation (OAC) is very effective and relevantly reduces the stroke risk by 62% [5].

Patients at high risk of embolic stroke, but with contraindications for OAC are in a need of an alternative approach that is not associated with a long-term risk of hemorrhage or other adverse events. This is particularly necessary for those patients who have survived intracranial hemorrhage but remain at high risk for cardiogenic embolism. A reasonable alternative may be the exclusion of the LAA cavity from circulation, using either surgical or percutaneous catheter-based procedures. Currently, the excision of the LAA at the time of mitral valve surgery is recommended for reduction of future stroke risk [8]. The efficacy of LAA exclusion in patients undergoing elective coronary artery bypass graft surgery was shown in the LAA Occlusion Study (LAAOS) [9].

The frequency of thrombus formation in the LAA of patients with AF and its suspected role as a source of embolism led to the hypothesis that resection or obliteration of the LAA might reduce the risk of stroke. Johnson et al. [10] performed atrial appendectomies in 437 patients during cardiac surgery. They found no strokes that were attributed to AF, and no patients were found to have atrial clots on TEE during follow-up [10]. Nevertheless, surgical LAA closure has not been accepted due to its invasive nature. But, based on the surgical experience, the development of a less invasive percutaneous approach to close the LAA by

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implantation of a mechanical device was a logical consequence. Since 2001 clinical studies using different systems (PLAATO®, Amplatzer®, Watchman®) were performed [11–14]. However, these devices have limitations in terms of limited recapture and repositioning capabilities as well as significant leaks after implantation, which increase by time [15].

In the present study the feasibility and safety of the Occlutech® LAA occluder were analyzed in a big animal model study.

2. Methods

In accordance with the "Position of the American Heart Association on Research Animal Use," adopted by the AHA on November 11, 1984 and after approval of the study protocol by the Department of Animal Science University of Kaposvár, Hungary at the Test Facility, twelve young pigs were included in the study. The Test Facility is accredited by the Hungarian Government (9/2001.(III.30.) EüM-FVM) and is registered to conduct research in laboratory animals. All the conditions of testing conform to the national and international Animal Welfare Act.

The primary objective of this study was to evaluate the safety of a novel LAA occluder device. Secondarily, to prove the completeness of LAA closure (efficacy).

The primary safety endpoint was the absence of device related adverse events.

The device is considered safe if:

1 There is no device related disruption of heart function.
2 Device associated thrombus formation is absent after 6 week implantation (evaluated macroscopically and histologically).
3 The device does not embolize or protrude in to the left atrium.
4 The device does not puncture the left atrial appendage (LAA).
5 The device shows good tissue integration and absence of extensive device related inflammation or irritation (evaluated macroscopically and histologically).

2.1. Animal preparation

12 young pigs (species: *Sus scrofa*, strain: DanBred Hybrid) with a body weight of 40–45 kg were included. A porcine heart model was chosen because of its anatomical similarities to the human heart.

The goal was to have 10 animals implanted with the device and followed up over 6 weeks.

Animal preparation was in accordance with "Position of the American Heart Association on Research Animal Use," adopted by the AHA on November 11, 1984. The animals were given ketamine hydrochloride (10 mg/kg) and 0.2 mg/kg xylazine and 0.04 mg atropine i.m. Once sedated, the animals became anesthetized with isoflurane and oxygen, delivered through a facemask. The animals were then intubated and maintained in anesthesia with isoflurane. After the animal was transferred to the procedure table, isoflurane was delivered through a volume-regulated respirator. The ECO2 was maintained within physiological ranges.

2.1.1. Medication

To prevent or reduce the occurrence of thrombotic events, animals were treated on Day-1 with aspirin 250 mg, per os (PO) and clopidogrel (300 mg, PO). During the implantation procedure, 5000 IU unfractionated heparin was given through the sheath. The animals were then treated daily with acetylsalicylic acid (500 mg, PO) and clopidogrel (75 mg, PO) until explantation.

To prevent infection, animals were given Benzathine-Procaine Penicillin G (40,000 U/kg, IM) and the anti-inflammatory agent Algopyrin (4.3 ml IM) prior to device deployment on Day 0.

2.2. Occluder device

The LAA occluder (Occlutech®, Jena, Germany) consists of a self-expanding, flexible nitinol mesh. It has a tapered cylindrical shape that adapts to the shape of the LAA (Fig. 1). The proximal part has a larger diameter to seal the orifice. The loops at the distal rim aid to keep the implanted device in position. The outer surface of the occluder is covered with a non-woven, bio-stable Poly (carbonate) urethane layer. Since all implantations using the soft device passed the tug test, only soft devices were implanted.

2.3. Implantation technique

The size of the LAA closure device was chosen according to the LAA landing zone with a device size D2 (diameter of distal part) about 3–5 mm oversized. In a few cases, a deliberate over or under sizing was performed. The implantation was started with the softer occluder design and if the tug test failed, it was planned to use the stiffer design. Since all of the soft devices passed the tug test, no device with a stiffer design was implanted.

Through transseptal puncture, a long (280–300 cm) 0.035 guiding wire was placed into the left atrium. Using the angiographic position (RAO 30°/Caudal 20°), the LAA was displayed and measured applying radiographic contrast medium and the delivery catheter was placed into the LAA. The measurement with transesophageal echocardiography (TEE) was used when significant differences between fluoroscopic and echo measurements occurred.

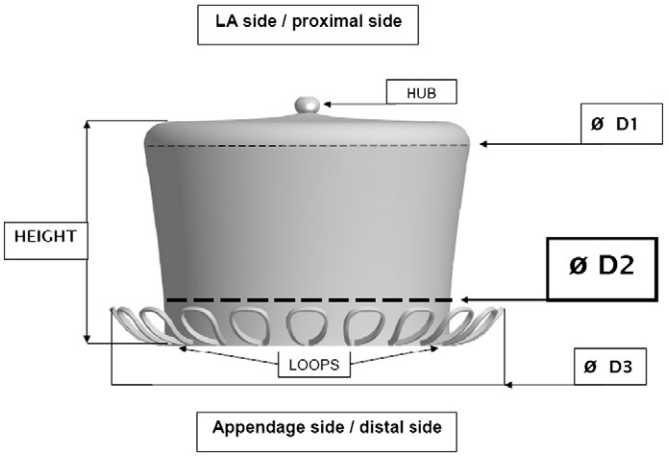

Fig. 1. Schematic drawing of the device.

The LAA occluder was mounted on the delivery system and advanced through the delivery sheath to the LAA. First a partial deployment was done by pushing half of the occluder into the orifice, so that the distal rim loops could unfold and point backwards. At the final step the occluder was held in position and the delivery catheter was unsheathed. Then a visual inspection of the unfolded device was performed to secure that the loops were folded in the correct position. The device was retracted and repositioned in case positioning and LAA occlusion were not correct. The correct placement of the device and occlusion was confirmed by tug test, TEE and contrast fluoroscopy. The leakage aperture was graded from 0 to 3 where 0 is no leak, 1 is a trivial leak (<3 mm), 2 is a small leak (3–5 mm) and 3 is a significant leak (>5 mm).

Once successfully positioned, the LAA device was released. After experiencing a device loss and embolization during release, the procedure was changed so that the tip of the sheath had contact with the proximal end of the device to hold it in place while slowly opening the jaws and pulling back the pusher (Fig. 2).

The sheath and pusher were retrieved, the vein was ligated and the skin closed in 2 layers. The animals were then allowed to recover from anesthesia.

2.4. Follow-up

To guide the intervention procedure and to evaluate the placement of the device, fluoroscopy was performed at baseline and post-treatment on Day 0. Images were also recorded pre- and post-mortem after 6 weeks. For the 6 week imaging of the device, no contrast media were used. In addition, TEE was used on Day 0 to guide the implantation procedure, to measure the LAA anatomy and to evaluate acute LAA sealing rate. TEE was also used to evaluate the sealing rate after 6 weeks.

3. Results

Details of the implanted devices are shown in Table 1. Two procedure-related complications caused by heart perforations occurred during transseptal puncture due to difficulties in visualizing the atrial septa. One pig died due to tamponade and the other pig had a small pericardial effusion, but recovered fully and had no further complications. These complications depended on difficulties in TEE visualizing the atrial septa due to the anatomy of the pig heart and could not be attributed to the device. In one pig a device embolization to the abdominal aorta occurred during occluder release. This pig had to be euthanized. This explains that 12 pigs were included to enable a complete analysis of 10 pigs.

3.1. Gross examination and histological assessment

A macroscopical external evaluation of the explanted heart was performed to evaluate the presence of cardiac perforation, inflammation (diffuse or localized pericarditis) and device perforation of the LAA.

The heart was then cut open and a macroscopical evaluation of the dissected fresh heart was performed before tissue fixation in respect to thrombus formation, tissue irritation, device placement, device position, device adaptation to the LAA, sealing rate, PU-cover integrity, and device ingrowth.