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Preclinical assessment of a modified Occlutech left atrial appendage closure device in a canine model

Jung-Sun Kim [a,c,1], Seul-Gee Lee [b,1], Sung-Kyung Bong [b], Se-Il Park [c], Sung-Yu Hong [c], Sanghoon Shin [d], Chi Young Shim [a], Geu-Ru Hong [a], Donghoon Choi [a,c], Yangsoo Jang [a,c,**], Jai-Wun Park [e,f,*]

[a] Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[b] Graduate Program in Science for Aging, Yonsei University, Seoul, Republic of Korea
[c] Cardiovascular Product Evaluation Center
[d] Division of Cardiology, Department of Internal Medicine, NHIS Ilsan Hospital, Goyang, Republic of Korea
[e] Department of Cardiology, Angiology, and Pneumology, Coburg Hospital, 96450 Coburg, Germany
[f] Department of Cardiology, Charite Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany

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ABSTRACT

Background: LAA occlusion has a similar stroke prevention efficacy compared to anticoagulation treatment for non-valvular atrial fibrillation.
Objective: The objective of this study was to assess the feasibility and safety of a modified Occlutech® left atrial appendage (LAA) closure device in a canine model.
Methods: The device was implanted in 10 dogs (33 ± 1 kg) using fluoroscopy and transesophageal echocardiography (TEE) guidance. The modified Occlutech® LAA occlusion device was compared with the current version, the Watchman device, and the Amplazter cardiac plug (ACP). LAA occlusion and anchoring to the LAA were evaluated. All dogs were assessed using angiography, TEE, and a gross anatomy examination.
Results: The 10 LAA occlusion devices were to be implanted into 10 dogs (5 modified Occlutech devices, 3 current version of Occlutech devices, 1 Watchman, and 1 ACP). LAA implantation was not performed in one dog due to transeptal puncture failure. The three current version of Occlutech devices were embolized immediately after implantation, so three modified devices of the same size were implanted securely without embolization. The mean implant size was 20.1 ± 2.0 mm. The devices chosen were a mean of 23.3 ± 10.6% larger than the measured landing zone diameters. Post-implant angiography and TEE revealed well-positioned devices without pericardial effusion or impingement on surrounding structures.
Conclusions: The results of this acute animal study suggested that a modified Occlutech® LAA occlusion device was feasible and had greater anchoring performance in canines. Additional large clinical studies are needed to evaluate safety and efficacy.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in a clinical setting and is associated with cardioembolic stroke [1]. Anticoagulation has been a standard treatment modality used to effectively prevent a cardioembolic stroke during atrial fibrillation with a high stroke risk [2]. However, anticoagulation can increase the risk of bleeding events and is limited in its application to patients with a high bleeding risk, even as novel anticoagulants are introduced [3]. A previous review of 23 studies revealed that >90% of thrombi are detected in or originate from the left atrial appendage (LAA) in non-valvular AF [4]. In this context, LAA ligation or occlusion has been proposed as an alternative strategy to anticoagulation for stroke prevention in non-valvular AF [5]. The Watchman device (Boston Scientific, Natick, MA) and the Amplatzer cardiac plug or Amulet device (ACP, St. Jude Medical, St. Paul, MN) are widely used in clinical practice. This use is supported by evidence for efficacy and safety. However, the sharp barbs that anchor the devices to the LAA may damage the soft tissue and increase the difficulty of device retrieval [6]. Unlike previous designs, rounded loops are present at the distal rim side of the Occlutech device, and are used to anchor it to the LAA [7].

Studies in human subjects have revealed that implantation of the presently used Occlutech LAA occlusion device configuration is limited

* Correspondence to: J.-W. Park, Department of Cardiology, Angiology, and Pneumology, Coburg Hospital, 96450 Coburg, Germany.
** Correspondence to: Y. Jang, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Republic of Korea.
E-mail addresses: jangys1212@yuhs.ac (Y. Jang), jai-wun.park@charite.de (J.-W. Park).
[1] These authors contributed equally to this study.

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to certain LAA anatomies. There are also safety issues related to anchoring the device to the LAA. Recently, the device design has been modified to shorten the length during implantation and improve anchorage to the LAA. The objectives of this study were to further evaluate the safety and efficacy of the Occlutech LAA occlusion device in a canine model and to compare the performance of the previous device design with the performance of the new design and that of approved LAA occlusion devices (Watchman and ACP).

2. Methods

The new design of the Occlutech LAA occlusion device requires evaluation using an in-vivo model before implantation into humans. The protocol was reviewed and approved by the Animal Ethics Committee and the Institutional Animal Care and Use Committee (IACUC) at the Cardiovascular Product Evaluation Center of the Yonsei University College of Medicine (Seoul, Korea, CPEC-IACUC-151,007). All animals received humane care in compliance with the Animal Welfare Act and the "Principles of Laboratory Animal Care" formulated by the Institute of Laboratory Animal Resources (National Research Council, NIH Publication No. 85–23, revised 1996).

The primary objective was to evaluate the performance (deployment and successful implantation) of the modified design of the Occlutech LAA occlusion device immediately after implantation. The performance (deployment and successful implantation) of the modified design was also compared with the current version of the Occlutech LAA occlusion device, the Watchman, and the ACP device. The assessment included evaluation of device protrusion into the left atrium (assessed using imaging), device penetration of the LAA (assessed using gross examination of explanted hearts), and sealing of the LAA. Closure was defined as a leak that was <3 mm (assessed using imaging).

2.1. Experimental animal model

A canine model (mongrel dog) was chosen because of the anatomic similarities in cardiac shape and size to the human heart. The circulatory system in these dogs is large enough to allow for heart catheterization using a 12F catheter. This model has also been used successfully for testing of other dedicated LAA occlusion devices and allows for the direct transfer of the technology to human trials [8,9]. A total of 11 male dogs (8 months of age, body weight 30 to 35 kg), were used in the study. The study was performed at an independent animal facility (Cardiovascular Product Evaluation Center, Yonsei University College of Medicine, Osong, Korea) accredited by the Korea Ministry of Food and Drug Safety. This facility was approved for evaluation of the modified Occlutech LAA design.

The animals were sedated using intramuscular injections of 0.01 mg/kg of medetomidine hydrochloride (Domitor®), 0.2 mg/kg of xylazine, and 0.04 mg/kg of atropine. Once sedated, they were anesthetized using isoflurane and oxygen, which were delivered via facemask. The animals were then intubated and anesthesia was maintained using isoflurane and oxygen. After each animal was transferred to the procedure table, isoflurane was delivered through a volume-regulated respirator. End-tidal CO_2 was maintained within individual physiological ranges. Medication for appropriate anesthetic management was also available, and was used if indicated. At the end of the study, each animal was anesthetized using isoflurane and was euthanized using an intravenous overdose of potassium.

2.2. Left atrial appendage device description

The Occlutech LAA occlusion device (Occlutech®, Jena, Germany) was described previously [7]. Briefly, this device has a self-expanding, flexible, nitinol mesh structure with a cylindrical shape. Unlike the previous version, the distal end of the device has an inverted floor instead of a flat floor; this structural change results in reduced elongation during deployment and enhanced anchoring stability (Fig. 1).

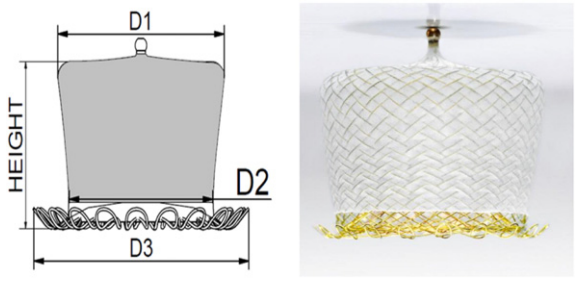

Fig. 1. Design of device. The left atrial appendage (LAA) closure device (Occlutech® LAA occlusion device) is a flexible nitinol-based, self-expanding device consisting of an outer surface covered with a non-woven, bio-stable poly (carbonate) urethane layer. The device's proximal section has a larger diameter to seal the orifice and a distal loop rim that helps to maintain the implanted device in position.

2.3. Interventional procedure

After induction of anesthesia, a groin incision was used to expose the femoral vein. After sheath placement, 3000 IU (100 units/kg) of unfractionated heparin was given through the sheath after successful septal puncture. Additional heparin was administered if a thrombus was detected in the catheter or sheath during the implantation.

The left atrium was accessed via standard transeptal puncture using a Brockenbrough needle (BRK™ Transseptal Needle, St. Jude, St. Paul, MN) and an 8 Fr transeptal sheath (SL1, St Jude Medical, St. Paul, MN). The procedure was performed using fluoroscopic and transesophageal echocardiography (TEE) guidance.

The devices were delivered to the LAA using appropriately-sized catheters and pushers (delivery system) and a standard implantation procedure. The LAA was measured using TEE and contrast angiography. The LAA was imaged in multiple planes (0°, 45°, 90°, and 135°) to define the maximum LAA width and length. D1 was measured from the circumflex artery to slightly below the "ridge" between the left superior pulmonary vein and the LAA (Fig. 2, white arrow). D2 (the landing zone) was measured along a plane parallel to D1 (Fig. 2). The device was approximately 10% oversized compared to the measured maximum size of D2.

The LAA occlusion device was mounted on the delivery system and advanced through the sheath into the left atrium. Correct placement of the device and occlusion was confirmed using a gentle tug test, TEE, and contrast fluoroscopy (Fig. 3). The device was (re)positioned until occlusion was seen (contrast fluoroscopy). If satisfactory closure could not be achieved, the device was recaptured and replaced with a device that was the same model but of a different size. The sealing rate was graded using a 0 to 3 color Doppler scale (0 if no leak, 1 if a trivial leak (<3 mm), 2 if a small leak (3–5 mm), and 3 if a significant leak (>5 mm), was present). If the device was embolized after detachment, a modified Occlutech device of the same size was implanted in the animal.

A computed tomography assessment of LAA morphology and size was performed on one case with a modified Occlutech device before the procedure, and for the position of the device after the procedure (Fig. 4).

2.4. Gross specimen evaluation

Each heart was carefully explanted. Care was taken to ensure that the device did not penetrate the LAA wall during the explantation procedure. The LAA exterior was examined macroscopically for device perforation. After this examination, the left atrium was cut open without damage to the LAA, and the placement of the occluder was exposed (Fig. 5). A tug test was performed, and the force needed to remove the device from the LAA was recorded using a manual manometer. To document the results, photographs were taken of the entire explanted heart, and of opened hearts in which the LAA and the occluder were visible.

2.5. Statistical analysis

Statistical analysis was performed using SPSS (version 20.0.0, IBM, Armonk, NY, USA). The results were expressed as mean ± standard deviation, or percentage (%) values. Comparisons were made using Chi-square statistics or Fischer's exact test for the categorical data and Student's *t*-test for the continuous variables. If a distribution was skewed, a non-parametric test was used. A p-value <0.05 was considered to indicate a statistically significant result.

3. Results

The characteristics of the implanted devices are presented in Table 1. Of the 11 dogs that were included in this study, 5 dogs received a modified Occlutech LAA occlusion device, 3 received a current version of an Occlutech device, 1 received a Watchman, and 1 received an ACP device. One animal did not receive a device because septal puncture failure and cardiac rupture occurred during the procedure. The modified version of the Occlutech device was successfully implanted, retrieved, repositioned, and re-implanted into five animals. Among these 5 dogs, 3 received devices that were embolized immediately after the implantation. Three additional modified devices of the same size were then implanted securely without embolization. The mean implant size was 20.1 ± 2.0 mm and the device chosen was 23.3 ± 10.6% larger than the measured landing zone diameter. Post-implant contrast angiography confirmed proper and stable implantation into the LAA. Device migration, significant peri-implant leakage, or impingement on surrounding cardiac structures did not occur in any of the dogs. TEE performed immediately after implantation revealed no mitral valve dysfunction or pulmonary venous obstruction. The TEE results indicated that successful occlusion of the appendages in all of the implanted devices had been accomplished (sealing rate 0: 3 modified Occlutech, sealing rate 1: 5 modified Occlutech and 1 ACP, and sealing rate 2: 1 Watchman). Each modified Occlutech device had an acceptable closure