Percutaneous Left Atrial Appendage Occlusion (PLAATO) for Preventing Cardioembolism

First Experience in Canine Model

Toshiko Nakai, MD; Michael D. Lesh, MD; Edward P. Gerstenfeld, MD; Renu Virmani, MD; Russell Jones; Randall J. Lee, MD, PhD

Background—Atrial fibrillation is associated with a high risk for cardioembolic stroke. The left atrial appendage (LAA) is the source of the vast majority of these thromboemboli. A novel implanted device for percutaneous LAA transcatheter occlusion (PLAATO) has been designed to seal the LAA. The purpose of this study was to test the feasibility and safety of transcatheter LAA occlusion in dogs.

Methods and Results—A PLAATO implant was delivered to the LAA through a 12F transseptal catheter in 25 dogs. The PLAATO device was repositioned until occlusion was seen, or it was recaptured and replaced with a different size. LAA sealing was confirmed by intracardiac echocardiography and contrast fluoroscopy. Follow-up was performed 2 days to 6 months after implantation. After imaging assessment, dogs were euthanized and LAA was examined for device healing, migration, perforation, and any thrombosis, both grossly and histologically. The LAA was occluded in all cases. No mobile thrombi associated with the implantation were seen. Healing on the atrial-facing surface was 90% at 1 month and was complete by 3 months, which was confirmed by gross and histological examination. Light microscopic examination of brain, kidney, and spleen showed no evidence of emboli or infarct.

Conclusions—Transcatheter LAA occlusion is simple and feasible. At the follow-up study, the device remained in the LAA, with benign healing and no evidence of new thrombus or damage to surrounding structures. This new strategy may provide an alternative treatment for patients with nonvalvular atrial fibrillation who are less than optimal candidates for warfarin. (Circulation. 2002;105:2217-2222.)

Key Words: atrial fibrillation • prevention • stroke • thrombosis

Atrial fibrillation (AF) is responsible for 20% of all strokes.1–3 Several large randomized clinical trials repeatedly have demonstrated the efficacy of anticoagulation with warfarin to reduce the annual rate of stroke in patients with AF.4,5 Warfarin is underused in clinical practice, however, because of the difficulty with administering the drug and the risk of bleeding.6,7

It has long been recognized that the majority of clots in patients with AF form in the left atrial appendage (LAA).8–10 That observation has led to the hypothesis that removal of the LAA could prevent stroke. Blackshear and Odell11 reviewed 23 studies in which the LAA was examined; they found that 222 (17%) of 1288 nonrheumatic AF patients had a left atrial (LA) thrombus, and 201 (91%) of these 222 were isolated to the LAA (P<0.0001). They concluded that LAA obliteration is a strategy of potential value for stroke prophylaxis in nonrheumatic AF.

The idea of removing the LAA to prevent stroke in patients with AF dates back to the earliest procedures for rheumatic mitral stenosis in the 1930s.8,9 It has now become routine in many centers to ligate the LAA at the time of mitral valve surgery. Indeed, the American College of Cardiology/American Heart Association guidelines for mitral valve surgery recommend the amputation of LAA at the time of operation to reduce the stroke risk.12 It is also a routine part of the Maze operation.13 There are even advocates for removing the LAA in all patients having heart surgery, regardless of the indication and including coronary bypass.14

If the appendage could be obliterated by a simple, minimally invasive technique, it would provide an alternative strategy for preventing stroke in patients with nonrheumatic AF. Recently, a novel implantable device for percutaneous LAA transcatheter occlusion (PLAATO) was developed. The purpose of this study was to test the feasibility, safety, and healing characteristics of transcatheter LAA occlusion in dogs.

Methods

Animal Preparation

In accordance with the guidelines of the American Society of Physiology and with approval of the Committee on Animal Re-
Device for PLAATO

The LAA occlusion system consists of an implant and a delivery catheter. The implant is composed of a nitinol metal cage with multiple struts that are outwardly bent (Figure 1). The frame is produced by laser-cutting a single tube of nitinol, which is then formed and heat-set to create the self-expanding cage. The occlusive membrane of expanded polytetrafluoroethylene (ePTFE), which is laminated directly to the frame, is supported so that the perimeter has intimate contact with the inner wall of the appendage. The purpose of the ePTFE is both to occlude the orifice of the LAA and to promote healing of the device in place, in particular to encourage benign healing on the surface facing the LA chamber.

The delivery catheter allows for contrast injection both distal to the device—ie, in the LAA—and proximal to the occluding surface to assess sealing and device positioning at the interface with the LAA ostium. The delivery system allows for collapse and repositioning or complete removal to replace the implant with a different size. Removal is possible until the final release of the device. Several sizes of the device have been developed to accommodate the variations in LAA anatomy.

PLAATO Implantation

Transseptal catheterization was performed using conventional techniques. A heparin bolus (2000 to 3000 U) was administered. A contrast fluoroscopic “appendogram” was performed in 2 views to assess the size and shape of the LAA (Figure 2a). The initial choice of device diameter was based on the LAA orifice diameter, with a goal of 20% to 40% oversizing. The delivery catheter containing the implant was placed into the LAA and withdrawn to reveal the implant, which was allowed to expand. Once the device was placed in the LAA, contrast fluoroscopy and ICE imaging were performed to assess device positioning. The device was repositioned or a different size introduced until complete sealing was obtained. The criteria for device release were based on observing adequate sealing by contrast fluoroscopy and ICE, as well as device stability when a tug, displacing the device by 1 to 2 cm, was applied (Figure 2b). In addition, the last 8 animals, evidence of 10% to 20% residual compression of the implant was required.

A final contrast fluoroscopy was obtained via injection into the LA (Figure 2c), and sealing was evaluated using the following 5-point criteria for device release were based on observing adequate sealing by contrast fluoroscopy and ICE, except for the 2-day follow-up group, in which LA cannulation was not performed to avoid disruption of the healing surface. In all cases, ICE evaluation was performed to confirm sealing and the absence of migration or clot and to assess mitral valve function and pulmonary venous flow.

After restudy, dogs were euthanized, and the heart was harvested. Both before and after dissection of the pericardium and removal of the heart, the condition of the pericardium and surrounding tissues was carefully examined. After formalin fixation, the LA was dissected, and the surface of the implant was grossly examined, followed by histological evaluation. In the animals euthanized at 1 month, the kidneys, brain, and spleen were examined grossly and histologically for signs of ischemia/necrosis caused by embolic activity.

Results

PLAATO Device Implantation

A total of 25 dogs underwent PLAATO, which was successful in all (Table). Procedure time (transseptal access until device release) was 73±19 minutes. Procedure time decreased with operator experience. The mean orifice diameter and length of the LAA were 16.6±2.6 and 21.0±3.1 mm, respectively. The final implanted device diameter ranged from 17 to 29 mm (median, 23 mm), which was 22% to 54% (mean, 37%) larger than the measured LAA diameter. Residual compression of the device was 0% to 27% (mean, 14%). Device recapture was required for achieving a more favorable location in 13 cases, and device recapture, removal, and replacement with a different-sized device were required in 7 cases.

Proximal contrast injection was useful to confirm that the atrial-facing surface was within 5 mm of the ostium. In addition, on the basis of the pattern of dimpling between the device surface and the LAA/LA interface, one could assess whether all 3 rows of anchors were engaged in the tissue.
Optimally, all 3 rows would be engaged, although if 2 rows were engaged and the other release criteria were met (device stable, good seal), the result was considered acceptable. The distal contrast injection was used additionally for a stability test, during which the catheter attached to the implant is tugged 1 to 2 cm. No movement of the implant relative to the tissue indicated good engagement between the anchoring hooks and the LAA wall. The average sealing score for the device in its final position after release was 4.5 by contrast fluoroscopy.

Left coronary angiography was performed in the first 6 animals to evaluate the patency of the left circumflex artery, which runs adjacent to the inferior aspect of the LAA. No changes were seen in the circumflex artery associated with PLAATO implantation either acutely or chronically at 1 month.

The relationship of the implant to the LAA and LA wall was visualized clearly by ICE in all cases (Figure 3, a and b). Figure 3c is an example of color Doppler showing a leak around the implant indicating an undersized implant, which subsequently was replaced with a larger size.

In 1 dog, a small pericardial effusion was noted on ICE at the implant procedure, which did not progress and was hemodynamically insignificant. It was unclear whether this was caused by the transseptal puncture or implant deployment. This animal was euthanized 2 days after implantation, and a small amount of fresh blood was noted in the pericardial space at explantation. No perforation site was found.

There were no major complications. With the use of either ICE or contrast fluoroscopy, we found no evidence of device migration or dislodgement, no disruption of mitral valve function or pulmonary vein inflow, and no thrombus associated with implantation.

Long-Term Follow-Up Study
Follow-up imaging was performed at 2 days (6 dogs), 2 weeks (4 dogs), 1 month (6 dogs), and 3 months (3 dogs) after the PLAATO procedure. Six dogs have not yet been euthanized to allow for 6-month to 1-year follow-up, and the results during the implant procedure are reported here. These 6 dogs are all alive and doing well, and all have had radiographic imaging to confirm the device is still present in the LAA. ICE imaging, including color Doppler, and contrast fluoroscopy confirmed that the LAA was occluded with no dislodgement. The average sealing score based on contrast fluoroscopy was 4.7 at long-term follow-up.

In 2 animals euthanized at 2 days, a small (<1 cm) rent was noted in the parietal pericardium in an area adjacent to a tissue anchor, which could be seen barely penetrating through the myocardial wall. In these 2 animals, there was no pericardial effusion or blood, and the small rents appeared to be healing. Otherwise, there was no evidence of perforation or erosion at the time of euthanasia. Likewise, there was no evidence of device migration or dislodgement, no disruption of mitral valve function or pulmonary vein inflow, and no atrial thrombus associated with the device.

Gross Examination and Histological Assessment
Gross examination of the LAA showed that the device was stable in the LAA in all cases. Figure 4 shows representative gross anatomic views of the LAA ostium at 1 month and 3 months after implantation. Macroscopic evidence of tissue attachment around the edges of the implant can be seen, and the device is completely incorporated into the LAA wall. Histological examination confirmed healing (Figure 5). The surface of implant occlusion membrane is completely covered with organized neointima. Neointimal growth is continuous with the atrial walls, and the interfaces are sealed. A tight layer of endothelium over the lateral wall of the appendage is continuous with the implant surface. Toward the center of the implant, the endothelium...
appears more loosely arranged. Implants show greater peripheral healing with granulation tissue and neovascularization of the thrombus within the implants than those of the 1-month group. All struts are well apposed to the native appendage walls and are covered with neointima, with no evidence of tissue necrosis or ischemia. High-power view of appendage/device interface shows well-organized fibromuscular coverage of the device surface.

Implants from 5 animals were examined with scanning electron microscopy to evaluate the presence of thrombus formation and organization and endothelial coverage on the surfaces of the implants. At 3 months, the atrial-facing surface of the occlusion membrane is completely covered with a smooth intact neointimal layer (Figure 6a). The neointima is continuous with the atrial wall, effectively sealing the appendage orifice. The outer surface near the atrial wall is covered with a well-formed endothelial layer of cobblestone shaped cells with prominent nuclei and tight junctions (Figure 6b).

Light microscopic examination of brain, kidney, and spleen showed no evidence of emboli or infarct. No abnormality was seen in the left circumflex arteries.

**Discussion**

**Main Findings**

This is the first report of a novel device to be implanted in the LAA, the clinical purpose of which is to prevent cardioembolism. The PLAATO was performed successfully in a series of dogs. The seal created by the device during the acute implantation procedure either was complete or allowed only a trace of injected radiocontrast agent to pass the device.

**Case Information**

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Sealing rate scores: 1 indicates severe leak; 2, moderate leak; 3, mild leak; 4, trace leak; and 5, no leak.

Six dogs are alive and were assessed only during the acute stage.

![Gross anatomic views of the LAA orifice with device present at 1 month and 3 months. The surface of implant fit snugly into the LAA ostium.](http://circ.ahajournals.org/)

Figure 4.
There was no evidence of device migration, dislodgement, or erosion. Additionally, there was no disruption of mitral valve function or pulmonary vein inflow, and no atrial thrombus associated with the device at any of the follow-up periods from 2 days to 3 months. No device fractures or delamination of the ePTFE occlusive membrane from the nitinol frame were noted.

Comparison With Prior Investigation
Since the earliest days of mitral valve surgery in the 1930s and 1940s, cardiac surgeons, recognizing that the majority of atrial clots reside in the LAA, advocated removal or obliteration of the LAA to prevent stroke in patients with AF.8,9 Unfortunately, many early surgical patients had rheumatic mitral disease and often giant immobile left atria. LAA ligation was not always effective, because in such patients clots can arise from the body of the LA itself.

In the modern era, when the vast majority of patients with AF have a nonrheumatic cause, surgical LAA obliteration, either during open cardiac surgery13 or during a thoracoscopic procedure, 15,16 has found new advocates.

The more frequent use of transesophageal echocardiography in patients with AF has confirmed that the majority of LA clots, when present, arise from the LAA. For example, in the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) pilot study, 13% of patients were observed to have evidence of an LA clot, and the LAA was the location in 86% of patients.17

The LAA participates during atrial contraction and during atrial filling. Al-Saady et al18 suggested that although LAA ligation may help to reduce strokes in AF patients, these strategies might bring undesirable results such as reduced atrial compliance or loss of physiological properties. In the present study, we demonstrated that there was no significant change in transmittal flow or pulmonary venous flow before and after device implantation. This suggests the PLAATO does not interfere with LA function in these normal dogs in sinus rhythm. Of course, during AF, the LAA plays a much less important role during atrial mechanical systole than during sinus rhythm, meaning that occlusion of the LAA in our target patient population is even less likely to have an effect on atrial function.

The PLAATO Device and Procedure
The PLAATO device and procedure had to meet a number of design criteria: after implantation, the LAA must be sealed and separated from the LAA. The device could not be allowed to dislodge and embolize, migrate from its implanted position, erode into the pericardial space or other surrounding structures (such as the circumflex coronary artery), interfere with atrial function or blood flow through the mitral valve or from the pulmonary vein, or itself be the source of emboli. The procedure had to be relatively easy to perform. And given the variability in size and shape of the LAA, even with good criteria for initial device size selection, there had to be a way to collapse and completely remove and replace a given device with another size.

The implant, laser-cut from a single tube of nitinol and then shape set, incorporates a number of features that allow the device to meet the design requirements. The self-expanding nitinol cage allows implant diameters up to 36 mm to be delivered through a 12F transseptal sheath. The thin layer of ePTFE laminated to the nitinol cage provides both a mechanical barrier to communication between the LA and LAA, as well as a smooth intact neointimal layer that completely covers the implant occlusion membrane surface and proximal hub. The neointima is continuous with the atrial wall, effectively sealing the appendage orifice (a). The atrial wall is covered with a well-formed endothelial layer of cobblestone shaped cells with prominent nuclei and tight junctions (b).
a substrate for rapid healing. Tiny tissue anchors, projecting from the edges of the device and angling toward the proximal (atrial) end of the device, serve both to prevent migration or dislodgement and to promote tissue ingrowth onto the ePTFE.

**Limitations of the Present Study**

The follow-up period in the present study was limited to 3 months. A longer-term follow-up study may be necessary to assess long-term device performance. Note that 6 animals are still alive and clinically well an average of 5 months after implantation, and they show no evidence of device migration, embolization, or fracture. Nearly complete endothelialization of the atrial-facing surface was already seen by 1 month of follow-up and was complete by 3 months. Furthermore, the space behind (ie, distal to) the device showed complete encapsulation by 3 months. No device fractures were observed, but longer follow-up may be needed to completely exclude that possibility.

No clots were observed on the device, but examination could not, of course, be continuous. Therefore, it is impossible to completely exclude transient device-related mobile thrombi. However, there was no evidence of infarction in the distal organs from gross and histological examination (brain, spleen, kidney, and heart) at 1 month, suggesting that transient cardioembolization was very unlikely.

In a few cases, there were trace leaks around the occlusion surface noted during forceful contrast injection in the LA. These were almost all resolved at follow-up and may represent an artifact of testing, because forcing contrast agent at high pressure at the surface of the device could allow some agent to slip past the unhealed surface, even though no blood would actually be flowing. This phenomenon may have been exaggerated by rather large pectinate muscles near the ostium of the LAA, a situation quite different from the pectinate effacement seen in human LAAs in patients with AF. It is interesting that after open surgical closure of the LAA, up to one third of patients have residual communication between LA and LAA noted at follow-up transesophageal echocardiography. Nonetheless, residual leaking around the device could give rise to a new source of thromboemboli, which needs to be evaluated during a clinical trial.

We used dogs for this study. Canine LAA size approximates that of humans. Furthermore, the fact that the dog atria were vigorously beating during sinus rhythm implies a more rigorous test of stability than that which will be the case in humans during AF. However, healing in these healthy dogs may have been faster and more complete than that in diseased human atrial during AF.

**Clinical Implications**

Of the >2 million Americans with AF, at least 1.2 million have risk factors that would meet the American College of Chest Physicians (ACCP) guidelines for recommendation of warfarin therapy. Although long-term warfarin reduces the risk of thromboembolism, it is, in practice, one of the more difficult medications to administer. Despite clear consensus guidelines from the ACCP, warfarin is underused or misused on a large scale, either because of known contraindications for its use or because of the difficulty of administering the drug and the perceived risk of bleeding. As shown in the present study, transcatheter LAA obliteration is feasible and relatively simple to perform using this novel technology. If this minimally invasive procedure were shown to be safe and effective for preventing stroke, the PLAATO may be a strategy for the large number of patients with AF who cannot or will not take warfarin and may ultimately become an alternative for those who can.

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**References**

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