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Transcatheter Closure of Patent Foramen Ovale Without an Implant Initial Clinical Experience

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Background—Currently available catheter techniques for closure of a patent foramen ovale (PFO) rely on the placement of an implantable closure device. The objective of the Paradigm I study was to evaluate the safety and feasibility of transcatheter closure of PFO using radiofrequency energy without an implanted device in patients with cryptogenic stroke or transient ischemic attack.

Methods and Results—Thirty patients were enrolled (15 females; mean age 48 years). Mean PFO size was 8.5 ± 2.7 mm. Technical success (ie, successful application of radiofrequency energy) was achieved in 27 patients. The remaining 3 patients received an implantable closure device. All 30 patients were free from serious procedure-related adverse events. No recurrent strokes, deaths, or perforations occurred as a result of the procedure. The mean follow-up was 6 months, and 13 (43%) of the 30 patients experienced PFO closure after the first procedure. Nine of the patients whose PFOs remained patent after the first procedure elected to receive a second procedure using radiofrequency. The PFO was closed for 6 of those patients after the second procedure, which resulted in a secondary closure rate of 63%.

Conclusions—This study demonstrates that transcatheter closure of an intracardiac defect without a permanent implant is technically feasible. Achievement of improved primary closure rates through technique and device modifications will warrant randomized clinical comparison to permanently implanted devices. (*Circulation*. 2007;116:1701-1706.)

Key Words: heart defects, congenital ■ stroke ■ embolism ■ catheterization ■ catheter ablation

The patent foramen ovale (PFO) is a right-to-left interatrial communication between the nonadherent septum primum and septum secundum normally present in the fetal circulation. After birth, the foramen ovale typically closes spontaneously. In some individuals, however, the septum primum and septum secundum remain unattached, which results in a persistent unidirectional, right-to-left interatrial communication referred to as a PFO.¹

Clinical Perspective p 1706

PFO is quite common, with prevalence estimates from 10% to 27% of patients as determined by ultrasound and autopsy studies, respectively.²⁻⁹ PFO occurs with equal frequency in men and women and tends to decrease in prevalence with increasing age.^{2,5} Associations between PFO and atrial septal aneurysm, Chiari network, and mitral valve prolapse have been demonstrated; however, no clear clinical predictors exist of the presence of PFO in otherwise asymptomatic patients.^{1-3,5} The link between PFO and several diagnoses, including cryptogenic stroke, transient ischemic attack (TIA), decom-

pression illness, and migraine headaches, has been well detailed in many scientific articles.^{1,3,6-8,10-20} In addition, studies have shown that PFO is significantly more prevalent in patients with these conditions.^{3,8,11,16,21-24} The association between PFO and these pathological processes has led to the development of percutaneous closure techniques.^{1,11-13}

These percutaneous techniques rely on the placement of a permanent implant device for PFO closure. There have been a number of large studies evaluating the implant devices, and the results with these devices for PFO closure have been promising. These percutaneous closure techniques have been associated with favorable safety and efficacy in terms of secondary stroke prophylaxis.¹¹⁻¹³ Despite the benefits of these devices, disadvantages exist with a foreign structure that remains in the heart. Potential complications associated with PFO implant devices include thrombus formation, device erosion, device embolization, and atrial fibrillation.²⁵⁻²⁷

The technology described here involves the application of radiofrequency (RF) energy in the right atrium to weld together the tissues of the PFO, septum primum, and septum

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secundum, thereby closing the PFO without leaving an implantable device in the heart and while applying the treatment exclusively within the right atrium.

To evaluate the technical feasibility of the concept, pre-clinical animal studies were performed with the PFx closure system (Cierra, Inc; Redwood City, Calif) in 29 pigs (weight 48.5 ± 9.3 kg). A native PFO was present in 7 of the 29 pigs, and the septum was crossed at the superior rim of the fossa ovalis in the remaining 22. The pathology was evaluated in 19 of the pigs at time periods of 7 days ($n=10$), 6 weeks ($n=4$), and 3 months ($n=5$).²⁸

RF energy (4 to 36 kJ) was successfully applied in all cases, and 6 of the 7 native PFOs were closed. First-degree atrioventricular block occurred in 2 of the first 17 animals, but a modification in electrode shape and procedural technique eliminated this in the remaining 17 pigs, and no other complications occurred.

At 7-day histology, an ellipsoid lesion over the fossa ovalis was present in the right atrium with some loss of endothelium and thrombus formation. A smaller lesion was evident on the left atrial side with minimal endothelial loss and thrombus. The device iteration with the modified electrode improved outcomes and resulted in similar lesions with no left atrial surface thrombus at 7 days. At 6 weeks, all animals had healing fibrosis and inflammation with complete endothelialization of both right and left atrial surfaces without thrombus. At 3 months, lesion inflammation was resolved, and complete healing had occurred. These preclinical animal studies confirmed that the PFx closure system is feasible and safe in pigs.²⁸

Here, we describe the results from the first-in-human, single-center experience with the PFx closure system in 30 patients with PFO.

Methods

Patients

The Paradigm I clinical study was conducted to demonstrate the safety and feasibility of the PFx closure system for the treatment of PFO in patients indicated for closure. The study was conducted as a prospective, nonrandomized, single-center trial in patients between the ages of 18 and 65 years of age with a documented PFO as determined by positive bubble study. Patients enrolled had a history of cryptogenic stroke or TIA due to a presumed paradoxical embolism through the PFO. Exclusion criteria were active infection at the time the transcatheter procedure was scheduled, pregnancy, thrombus at or near the PFO on transesophageal echocardiography, presence of atrial septal defect, and a history of stroke or TIA within the past 14 days. At the initiation of the study, no exclusion criteria were present relative to PFO diameter; however, this was later amended to a maximum diameter of 10 mm to accommodate device size availability.

The PFx-15 device was used in accordance with the investigational protocol approved by the institution's ethics committee and the competent health authorities, and all patients gave informed consent. Procedural ECG recordings were reviewed by the study core laboratory, eResearch Technology, in Philadelphia, Pa.

Device Description and Techniques

The PFx-15 closure system is a percutaneous system that employs monopolar RF energy to effect closure of a PFO by welding the tissues of the septum primum and septum secundum together. The majority of the procedure is performed from the right atrial side of the septum, with the intention of reducing the potential complica-

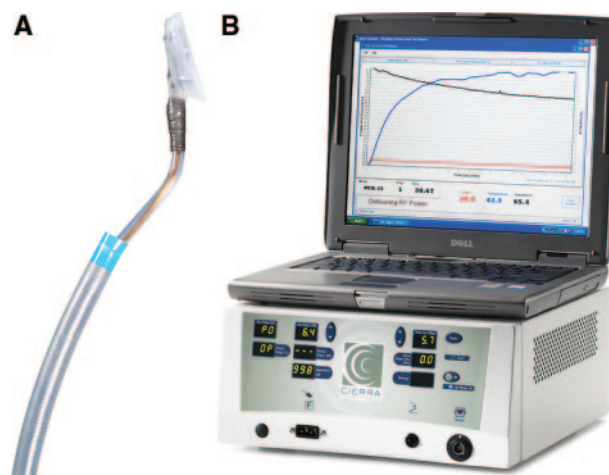


Figure 1. PFx closure system.

tions associated with left atrial catheterization. Welding and PFO closure are achieved via application of energy delivered at levels below those used in many cardiac ablation procedures.

The PFx closure system consists of a catheter with a metal electrode at the distal end of the device and an elastomeric distal housing covering the electrode (Figure 1A). The Paradigm I study evaluated the PFx-15 catheter, which has an electrode width of 15 mm. The electrode is contained within the open mouth of the distal housing. An outer sleeve covers and collapses the distal housing. Electrical leads extend through the catheter shaft to the proximal end, where they exit the device and connect to an RF generator via standard medical-grade electrical connectors. The RF generator uses impedance monitoring and automatic shutoff capabilities similar to those found in currently available cardiac ablation systems (Figure 1B). Monopolar energy is used to effect the weld, with a standard dermal ground pad used as the return electrode.

During the procedures, both transesophageal echocardiography and fluoroscopic imaging were utilized. Via a percutaneous approach, a multipurpose catheter was placed into the femoral vein and advanced through the inferior vena cava into the right atrium and then across the PFO tunnel. Once the catheter was positioned, a guidewire was inserted into the catheter across the tunnel, and the catheter was removed. A sizing balloon catheter was then placed across the PFO, and the balloon was inflated with contrast. The balloon was inflated until a waist in the balloon was clearly identified, and then a measurement of the PFO diameter was made and documented. The balloon was then deflated and removed, and additional bubble studies were performed at rest and with Valsalva maneuver. The vascular access sheath was replaced with a 16F sheath, and the PFx-15 catheter was prepared for insertion.

The PFx-15 catheter was introduced over the guidewire and through the 16F sheath with fluoroscopic guidance and advanced to the right atrium with the distal housing collapsed within the sleeve. When the catheter tip was within the right atrium, the sleeve was pulled back to deploy the distal housing. The catheter was then advanced over the guidewire to seat the distal housing against the atrial wall such that the electrode was covering the PFO. Positioning of the device was confirmed with echocardiographic guidance and contrast injection under fluoroscopy. Transesophageal echocardiography was used to assess superior-inferior positioning via the bicaval view ($\approx 90^\circ$ view), and the short-axis view (0° view) was used to evaluate anterior-posterior positioning. Final confirmation of proper positioning of the PFx-15 catheter over the PFO was evaluated with a contrast injection through the PFx-15 catheter flush port.

Once proper positioning was achieved, suction was applied, and the adequacy of the vacuum seal was assessed throughout the procedure. Assessment of the seal was performed with fluoroscopy. This assessment included visualization of the flattening of the distal housing during suction while the color and volume of blood flow through the suction tubing were monitored. Once a good seal was

confirmed, the guidewire was removed. After final seal confirmation, the generator was engaged to deliver RF energy to the PFx-15 catheter via the interconnect cable into the cardiac tissue. RF energy was applied to the PFO in accordance with a prescribed power algorithm that resulted in heating of the cardiac tissue. The tissue temperature increase was previously found to denature collagen and other proteins that, once cooled after completion of the energy application, cause a tissue bond between the septum secundum and septum primum. Once the application of energy was complete, the catheter was removed, and a bubble study was performed to evaluate the acute closure result. The conclusiveness of the bubble study was dependent on the adequacy of the Valsalva performed by the patients. PFO closure was considered achieved if fewer than 5 bubbles were observed in the left atrium. After PFO closure, the vascular access sheath was removed and hemostasis achieved with standard techniques.

Postprocedure Regimen

All patients were instructed to take aspirin 100 mg minimum and clopidogrel 75 mg daily for a minimum of 3 months after the procedure. At the investigator's discretion, medication was continued as appropriate for the presenting indication for any patient whose PFO was not closed at last follow-up. Patients were routinely discharged from the hospital the day after the closure procedure.

Follow-Up Examination

The purposes of the follow-up protocol were to assess the persistence of a right-to-left shunt after attempted closure with the PFx closure system and to record any device-related adverse events. The primary end point for the present study was evidence of PFO closure as measured by echocardiographic evaluation at 30 days after the procedure. Secondary end points included (1) PFO closure as measured by transesophageal echocardiography at subsequent follow-up visits through 6 months after the procedure; (2) all causes of mortality within 30 days of procedure or until hospital discharge (whichever was greater), categorized as fatal stroke, cardiovascular death, and noncardiovascular death; (3) procedure-related adverse event rates for all patients through 30 days of follow-up or hospital discharge, whichever was greater; and (4) serious adverse event rates for all patients. Major complications were defined as death, periprocedural stroke and TIA, or bleeding that required transfusion or surgery. Minor complications included minor bleeding or prolonged hospital stay related to the procedure. Any patients returning for follow-up beyond the 6-month visit as part of the standard of care were also evaluated for PFO closure status and adverse event incidence, although this follow-up was not required by the protocol.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patients

From April 2005 through October 2005, patients diagnosed with cryptogenic stroke, TIA, or paradoxical embolism and PFO were enrolled in the Paradigm I study. A total of 30 patients were enrolled, with a mean age of 48 years (range 18 to 65 years). Female patients constituted 50% of the study population. Twenty of the patients were treated for the indication of stroke, with the remaining 10 treated for TIA. Five (17%) of the patients had an atrial septal aneurysm as defined by a deflection of greater than 10 mm. The average PFO size was 8.5 ± 2.7 mm in diameter, with a range of 3 to 15 mm.

Procedural Experience

Among the 30 enrolled patients, successful positioning of the PFx-15 catheter over the PFO site was achieved in 27 patients

(90%). Of the remaining 3 patients, 2 had a PFO diameter >14 mm, which was significantly larger than the maximum limitation eventually determined to be appropriate for the 15-mm electrode. The protocol was eventually modified to reflect a maximum PFO diameter of 10 mm for treatment with the PFx-15 catheter. RF energy could not be applied in the third case because of a PFO fenestration, which prevented adequate positioning of the PFx catheter and which was identified by performance of a positive bubble study with simultaneous occlusion of the PFO tunnel with a sizing balloon. In all 3 cases, treatment with an implantable device was successful.

Total procedure time from venous puncture to device removal was 52 minutes (range 27 to 90 minutes). The mean PFx catheter time was calculated from the time of PFx-15 catheter insertion to removal and averaged 26 minutes (range 11 to 55 minutes). The mean time of RF application was 6.6 ± 2.1 minutes (range 3 to 10 minutes). Blood loss resulting from the vacuum suction applied during catheter positioning and RF energy application averaged 170 mL (range 0 to 525 mL). Only 1 patient experienced blood loss greater than the maximum recommendation of 500 mL, and this patient was adequately treated with oral rehydration. None of the patients required blood transfusions after the procedure. In addition, none of the patients reported any pain during the application of RF energy, which could be attributed to the local sedation used during the procedure.

The mean follow-up period was 5.8 months (range 1 to 10 months). All 30 patients (100%) were free from serious procedure-related adverse events. No device- or PFO-related deaths, strokes, cardiac/intracardiac perforations, or instances of thrombus occurred. One groin access site arteriovenous fistula required a prolonged hospital stay. Other events were related to vascular access hematoma (2), 1 report of transient ST-segment elevation, 2 cases of transient atrial bigeminy, and 1 case of gastrointestinal bleeding attributed to the postprocedure aspirin and clopidogrel, which were discontinued. In addition, 1 TIA was reported at the 3-month follow-up visit in a patient whose PFO was not completely closed by the procedure. All events resolved without clinical sequelae.

Closure Experience

The primary success rate of PFO closure after the first procedure with the PFx-15 was 43% (13 of 30) as determined by echocardiographic evaluation at the last follow-up (Figure 2). Two patients did not return for their 6-month follow-up, but their PFOs were determined to be patent on the basis of their 3-month follow-up. Mean PFO diameter in patients whose PFOs remained patent after the first procedure was 8.8 mm compared with a mean diameter of 7.3 mm in the patients whose PFOs were closed successfully. Of the 14 patients with residual shunts, 5 were enrolled before the protocol modification and had a PFO diameter ≥ 10 mm. No other anatomic or procedural differences were noted between the 2 groups.

Nine of 14 patients whose PFOs were not closed after the first procedure gave their consent for retreatment. On the basis of balloon sizing during the second procedure, the average PFO size had decreased from 8.9 ± 2.2 to

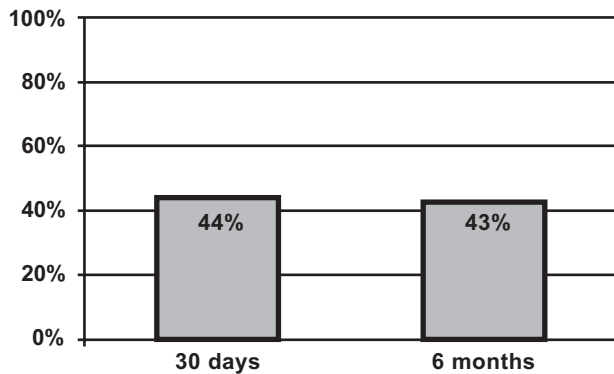


Figure 2. Primary closure rate with Pfx closure system.

5.4±1.8 mm (38%) after the first RF application. All patients experienced a decrease in PFO diameter from the first procedure, with a range of 15% to 68%. Two of the 9 patients were treated with an implantable device during the second procedure as a result of incomplete immediate closure based on the results of the procedural bubble study. Treatment with an implantable device after RF energy application was well tolerated. Six of the remaining 7 patients demonstrated complete closure on 30-day follow-up.

Including the primary and secondary treatments, RF energy was applied in 36 procedures (Figure 3); the secondary closure rate as defined by closure including a repeat procedure was 63% (19 of 30). During the present study, the permanence of closure was also demonstrated, because PFO closure at 30 days was maintained through subsequent follow-up periods. There have been no instances of a PFO determined to be closed that reopened at a later follow-up.

Discussion

The objective of this first-in-human study was to evaluate the safety and feasibility of transcatheter closure of PFO in 30 patients with cryptogenic stroke or TIA using RF energy. Primary PFO closure occurred in 43% of the patients after the first procedure, and a second procedure was performed in 9 patients. Including secondary procedures, PFO closure occurred in 63% of the patients enrolled in the study. The reported adverse events were minor and without clinical sequelae.

Rates of important periprocedural complications in studies evaluating PFO closure with implanted devices range from 2% to ≈10%.²⁵ The most common events are associated with vascular access (0% to 5%),^{14,25} air embolism (0% to 4%),^{14,25} ST elevation (0% to 2%),^{25,26} and arrhythmia (0% to 2%).²⁵ In the Paradigm I study, 3 events associated with vascular access (7.7%, 3/39), and 1 associated with ST-segment elevation (2.6%, 1/39) occurred. Other periprocedural complications from implanted devices are associated

with device embolism (0% to 3%), which is not a risk with the Pfx procedure because no implant is left in place. No other periprocedural complications were noted with the Pfx-15 catheter.

Implanted device-related complications during follow-up include atrial fibrillation (0% to 8%),^{25,27} thrombus formation (0% to 3%),^{25,26} TIA (0% to 2%),²⁵ and device fracture (0% to 9%).²⁵ The present study includes no reports of atrial fibrillation or thrombus formation during the follow-up period. Complications associated with device fracture during follow-up were not observed because no implant remains in the septal wall. One TIA (2.6%) was reported at the 3-month follow-up in a patient whose PFO was not completely closed by the procedure. In 2 patients (5.1%, 2/39), core laboratory evaluations of ECGs noted transient atrial bigeminy, with no clinical symptoms or sequelae.

The initial clinical experience with the Pfx -15 demonstrated the feasibility of a nonimplant closure device, because no events were reported during follow-up associated with atrial fibrillation or thrombus. One TIA was reported during follow-up in a patient with a residual shunt after the first procedure; therefore, it cannot be determined whether or not this was device related. The most significant procedural complications were not related to the device itself or the application of RF energy but to the need for a 16F sheath. In general, the reported events were comparable to those identified in larger studies evaluating implant devices.

Over the course of the study, device and technique modifications were implemented in an effort to improve on the early closure rates. Technology modifications were intended to improve device positioning and included changes to the geometric shape of the electrode and the angle of the guidewire exit lumen. Furthermore, the maximum PFO diameter was limited to 10 mm based on the width of the 15-mm electrode. Six patients were enrolled after these modifications were implemented, and 5 (83%) of those patients were determined to have a closed PFO on the basis of the 6-month echocardiographic evaluation. These modifications, although implemented toward the end of the study, appear to have had a positive impact on procedure and closure results and will be further evaluated in future studies.

Larger studies have been completed to evaluate the safety and efficacy of PFO closure using currently available implant devices. In these studies, PFO closure rates with implant devices have ranged from 66% to 99%, with most studies demonstrating a follow-up closure rate exceeding 90%.^{25–27} The Paradigm I study demonstrated PFO closure is technically feasible without an implant device; however, the primary and secondary closure rates were below those demonstrated by implant devices.

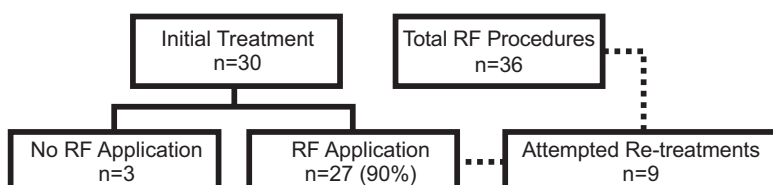


Figure 3. RF treatment group.

In a small subset of patients with a PFO diameter <10 mm enrolled after device modifications, the primary closure rate improved and was more comparable to that seen with implant devices. Clinical trials are currently under way to further evaluate these changes and determine whether the closure rate can be sustained in a larger number of patients. Larger devices are also currently under development and evaluation to treat a broader range of PFO diameters. Although a larger distal housing and electrode should be able to cover a broader range of diameters of the fossa ovalis, the device will require a greater degree of compliance to accommodate more variability in anatomy and irregularities of the septum and adjacent structures.

This initial experience demonstrated PFO closure without an implant is technically feasible. Improvement in both the primary closure rate and the availability of devices to treat a broader range of PFO diameters is necessary to evaluate safety and efficacy compared with currently available implant devices.

Our center has performed >1100 PFO closure procedures using a variety of implant devices, including the CardioSEAL/STARFlex (NMT Medical, Boston, Mass), the Amplatzer PFO Occluder (AGA Medical, Golden Valley, Minn), and the Helix Septal occluder (WL Gore & Associates, Flagstaff, Ariz). According to our experience with the aforementioned devices, they can be implanted successfully in almost every patient during the first attempt, regardless of anatomic variations. In our experience, device embolization, pericardial effusion, and thrombus formation on the device surface area are rare complications and occur in fewer than 2% of cases. Closure rate at the latest follow-up of at least 6 months' duration is >90%. Twenty-one patients experienced a recurrent embolic event (TIA, stroke, or peripheral embolism) during a follow-up period. Although the closure rate with the Pfx system is below the rates noted above, the concept of closing the PFO without leaving any foreign material behind is appealing to physicians and patients because it may mitigate the risks associated with an implant.

Long-term experience with percutaneous transcatheter PFO closure to prevent stroke and migraines is under way. Randomized studies are required to evaluate whether transcatheter closure is advantageous to medical therapy or surgery. The Pfx closure system is the first nonimplant device to demonstrate PFO closure in a clinical trial, and other technologies are being developed using RF energy and fully bioabsorbable material as nonimplant alternatives. Although PFO closure without a permanent implant is theoretically desirable, randomized trials of this treatment compared with permanent implants will be required to determine whether this new approach is as safe and efficacious.

Conclusions

The Paradigm I study demonstrated that PFO closure using RF energy without an implant device is feasible and safe, because closure was achieved in a subset of patients with a safety profile comparable to that for implant devices. If primary closure rates are improved by technique and device modifications, a randomized trial to compare this strategy with permanently implanted devices will be warranted.

Source of Funding

The Paradigm I trial was sponsored by Cierra, Inc.

Disclosures

Professor Sievert is a consultant for Cierra and has an investment in the company. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

The treatment of symptomatic patients with a patent foramen ovale who have failed medical therapy is either surgical closure or percutaneous closure with permanently implanted closure devices. Although effective, short- and long-term complications occur. This report details the first-in-human experience performing patent foramen ovale closure without an implantable device, with radiofrequency energy used to seal the patent foramen ovale. The technique was successful in 63% of the first 30 patients. In addition, the article discusses the potential improvements in closure rates and range of patent foramen ovale diameters that may one day be treated with nonimplantable device technology. This study demonstrates a novel therapy and potential clinical application, provides the basis for future improvements in the technique, and supports the need for future clinical trials.