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## Patent Foramen Ovale Closure by Radiofrequency Thermal Coaptation

### First Experience in the Porcine Model and Healing Mechanisms Over Time

Hidehiko Hara, MD; Thomas K. Jones, MD; Elena R. Ladich, MD; Renu Virmani, MD; David C. Auth, PhD; Joseph E. Eichinger, BS; Robert J. Sommer, MD; Robert A. Van Tassel, MD; Robert S. Schwartz, MD

**Background**—Percutaneous transcatheter patent foramen ovale (PFO) closure is now standard practice and may limit embolic complications for at least 10 years. Implantable PFO closure devices may be complicated by thrombosis, infection, device fracture, or embolization. A novel strategy uses radiofrequency-based thermal energy to seal PFO membranes, with no implanted device. We successfully used this method and examined histopathologic events in swine to characterize safety and efficacy.

**Methods and Results**—Thirteen domestic swine were examined over time after thermal PFO closure. Three animals were euthanized within 1 hour of treatment, 5 after 7 days, and 5 at 28 days. Gross and histopathologic findings were examined. Radiofrequency energy was delivered successfully in all cases, and PFOs were closed in 12 of 13 cases. One case was not suitable for histological examination because of laceration at euthanasia, and the other PFO was clinically closed, with no shunt at 7 days, but was histologically open. All of the other PFOs were confirmed closed histologically. Acute histological results showed edema, hemorrhage, and myocyte necrosis. Minimal thrombus formation occurred on the left atrial endocardial surface. At day 7, transmural thermal effects occurred through the atrial wall that extended to the epicardial surface. At day 28, thermal effects showed excellent scar formation. Collagen, matrix, and neovascularization were present in all cases. No animal experienced adverse events.

**Conclusions**—Thermal PFO closure is feasible, safe, and effective in swine. Thermal healing is nearly complete by 4 weeks and consists of collagen formation and tunnel closure. This technique may allow substantial reduction in PFO closure risk over current device-based therapy. (*Circulation*. 2007;116:648-653.)

**Key Words:** atrium ■ catheterization ■ pathology

Patent foramen ovale (PFO) has been successfully treated percutaneously for more than a decade, and such treatment is becoming more common as indications for PFO closure grow. Device-based therapies are associated with complications related to the procedure and the implanted devices, including thrombosis, device fracture, and embolization.<sup>1</sup> Other potential complications include infection (endocarditis), the potential for supraventricular arrhythmias due to inflammation, and the fact that the device may impede left atrial access for electrophysiological procedures such as ablation of atrial fibrillation. These procedures also have the potential to cause serious events such as perforation and cardiac tamponade or aortic laceration. PFO closure without a permanently implanted prosthesis may provide a solution to

#### Clinical Perspective p 653

some of these concerns. A novel PFO closure strategy uses radiofrequency (RF)-based thermal energy to seal the PFO without an implanted device. Because histology of the atrial septum and foramen ovale during healing is poorly characterized, the objectives of the present study were to document atrial septal tissue healing over time after RF-based heating by use of histopathology and to determine the mechanisms of sealing.

#### Methods

##### Animals

Thirteen domestic crossbred swine (LyChron, LLC, Mountain View, Calif) with proven PFO were used for the present study. All animals

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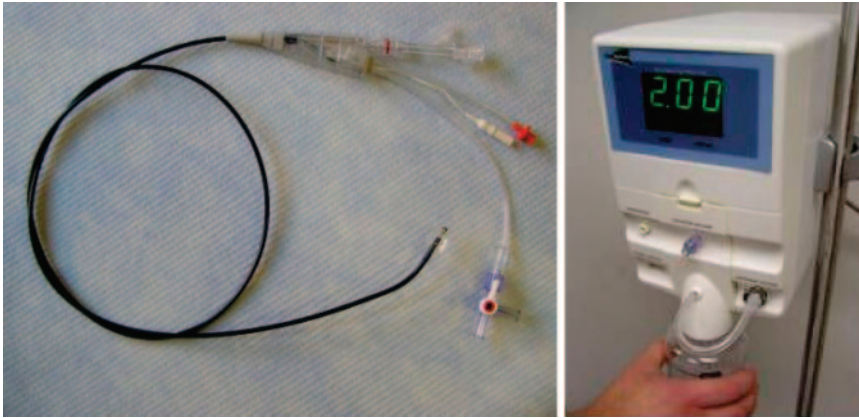
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**Figure 1.** Disposable catheter and console with disposable cartridge. The overall length of the catheter is  $\approx 120$  cm, with a 110-cm shaft length.

were screened by transesophageal echocardiography and treated according to the US Department of Agriculture Animal Welfare Act as specified in the "Guide for the Care and Use of Laboratory Animals." The porcine model was chosen because of its anatomic similarities to human heart. We previously reported on the porcine model for right and left PFO opening areas in both humans and swine. Tunnel lengths are significantly longer in swine. PFO prevalence in swine is  $\approx 21\%$ , very similar to humans.<sup>2</sup> This model has been used successfully in other preclinical PFO closure studies,<sup>3</sup> as well as historically for RF studies in other cardiac devices.<sup>4</sup>

At least 1 day before the procedure, each animal was given oral aspirin (650 mg) and clopidogrel (300 mg) to inhibit thrombotic events that might have theoretically occurred from thermal injury to the left atrial side of the septum. Animals were aseptically prepared and anesthetized. ECG, heart rate, respiration rate, mean arterial pressure, and airway gases were monitored before, during, and immediately after the procedure. An intravenous line was placed for fluid administration. Baseline activated clotting time and blood pressure measurements were taken. A heparin bolus (100 to 200 IU/kg) was administered intravenously to establish an activated clotting time  $>200.200$  s) in second paragraph under Methods, "Animals." Additional heparin was administered as needed during the procedure to maintain the desired activated clotting time range.

### Device Description

The RF energy-based catheter is a single-use percutaneous system with an external power console (Figure 1). This console contains an RF generator and an internal vacuum source designed to provide a single dose of monopolar RF energy to the catheter tip. The vacuum provides tissue coaptation at the distal tip of the catheter. Energy is in the range of 1200 to 1500 J, depending on the impedance of the target tissue. Vacuum and RF energy are delivered individually. The catheter-electrode tip has a compliant balloon positioned just proximal to the electrode surface, which allows alignment with the fossa ovalis and which contains a guidewire port for insertion and alignment with the PFO tunnel.

### Experimental Procedures

The catheter was inserted into the femoral vein and advanced to the right atrium with a 14F sheath. It was inserted into the right atrium and positioned at the entrance of the PFO tunnel. Application of the vacuum drew the thin septum primum to the septum secundum, which allowed a monopolar RF field to heat the connective tissue, sealing the septum primum and septum secundum together. The procedure was done with the aid of intracardiac echocardiography and fluoroscopy.

Treatments comprised administration of a prescribed RF power level ( $\approx 12$  W) for a specified period of time (maximum of 120 seconds). An ECG was recorded during treatment. Treatment was "complete" if a full 2 minutes of thermal energy application occurred, in which case the RF energy was automatically turned off,

or if the electrical impedance of the tissues rose to a predetermined level that indicated tissue desiccation.

Once treatment was complete, the balloon was deflated and the catheter withdrawn. After treatment, an ECG was recorded, and the right and left atria were scanned with intracardiac echocardiography to evaluate thrombus formation. A Valsalva bubble study was completed before and immediately after the procedure to evaluate right-to-left shunting grade and to assess the acute PFO seal. The Valsalva strain was given by use of ventilator controls with a manometer at  $>40$  mm Hg of pressure for at least 10 seconds. Treatment success was defined as a negative bubble study with Valsalva in addition to closure by histological examination at euthanasia. PFO size was measured by intracardiac echocardiography during the procedure, and patency was similarly assessed by intracardiac echocardiography with bubble injection.

### Postprocedural Management

The femoral incision was closed by ligation of the femoral vein and a single layer of suture, and the animal recovered and survived according to a schedule (Table). The animals were observed daily for signs of illness or abnormal behavior. Buprenorphine hydrochloride was prescribed for pain management at the discretion of the veterinary staff. The antibiotic enrofloxacin (5 mg/kg IM) was administered once per day for 7 days after the procedure. Clopidogrel (75 mg PO) was administered once per day for the first 28 days of survival, and aspirin (81 mg PO) was administered once per day until the scheduled termination date. This dual-antiplatelet therapy was performed to limit or prevent thrombus formation, especially on the left side of the atrial wall. Immediately before euthanasia, ECG, heart rate, respiration rate, mean arterial pressure, and airway gases were monitored, and a bubble study was performed again.

### Histopathologic Analysis

After euthanasia, all major body cavities and their viscera were opened and inspected during necropsy. The heart, representative sections of other major organs (ie, lungs, liver, spleen, kidneys, and brain), and major blood vessels (ie, aorta and pulmonary arteries) were harvested and examined for evidence of gross pathology. After examination, the heart was fixed with 10% buffered formalin and sent to the CV Path Institute (Gaithersburg, Md) for histological examination. Before histopathologic sampling, the "sealing" was tested by the pathologist using both gross visual inspection and water

### Porcine Schedule for Euthanasia

Days After Treatment	Pigs Treated
0	3
7	5
28	5

pipette testing, which avoided the need for probing, because we did not want to disrupt the thermal results in and around the sealing site. If no water passed across the treated foramen ovale, it was considered sealed.

For histopathologic sampling, 4 to 6 tissue sections (4 to 5 mm thick) were obtained from the treated PFO area. Tissue sections were taken perpendicular to the interatrial septum and sectioned sequentially from the anterior aspect of the foramen ovale (near the flap opening on the left atrial surface) toward the posterior border of the fossa. The first section (anterior) included the posterior aspect of the aorta (anterior to the treatment site); the mid sections included the treated area of the septum primum and septum secundum identified grossly. Histological sections included the atrial septum superior to the treatment site and a portion of the ventricular septum with attached mitral or tricuspid valve for orientation. A grossly unremarkable section posterior to the treatment site was also submitted.

All tissue sections were cut at 4 to 6  $\mu$ m with a rotary microtome, mounted on a slide, and stained with hematoxylin and eosin and Movat pentachrome. Sections were examined by light microscopy for thrombus, hemorrhage, foreign material, inflammation, necrosis, calcification, and healing (as evidenced by granulation tissue and fibrosis).

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

## Results

Thirteen pigs were evaluated. Intracardiac echocardiography and contrast injection were used to confirm PFO sizes in a range from 2 to 5 mm (average 4 mm), and tunnel length ranged from 10 to 20 mm (average 14 mm). An atrial septal aneurysm was observed in 1 case but was completely sealed. Valsalva bubble study was positive in 8 of 13 cases before treatment. Two cases showed positive bubble studies immediately after treatment, and only 1 was positive at final study. Seven (87.5%) of the 8 cases rated 0 in the bubble study before euthanasia and were clinically closed.

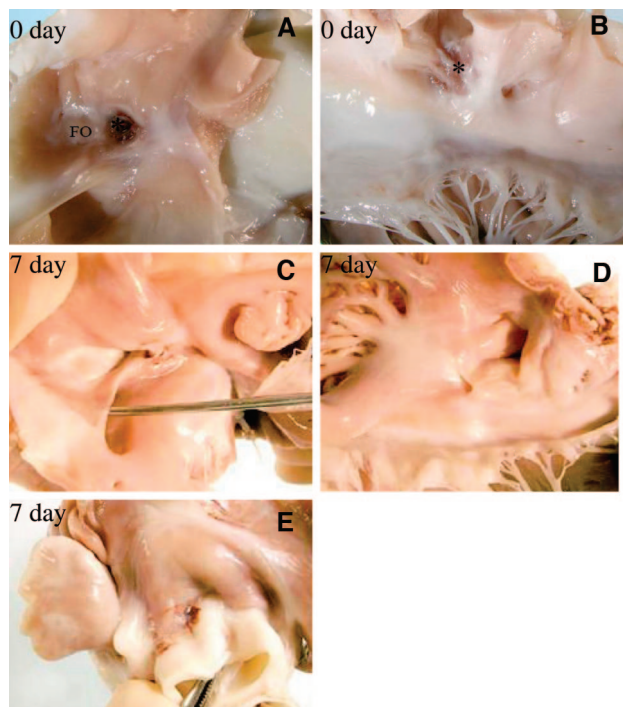
At pathological examination, 11 (91.7%) of 12 PFOs were sealed. One case was not suitable for histopathologic evaluation because of a laceration through the treatment site at euthanasia.

## Device Performance

ECGs recorded at pretreatment, peritreatment, and posttreatment time points demonstrated no arrhythmias, except benign sporadic premature atrial contractions after treatment. RF energy was halted automatically and successfully in all cases, and all RF energy treatments were delivered for the prescribed time. The device was easily and safely removed with no adverse events. No problems were encountered inserting the catheter into the femoral vein or during advancement to the right atrium. Vacuum lock to coapt the septum primum and secundum was achieved in all cases with successful coaptation of the 2 tissues, and the majority of cases (10/13) required only 1 attempt. Blood loss was measured in 10 of 13 cases and was small, <5 mL in the majority of cases; the greatest blood loss measured 155 mL.

## Gross Pathology

The heart, representative sections of other major organs (including lungs, liver, spleen, kidneys, and brain), and major blood vessels (including aorta and pulmonary arteries) showed no evidence of myocardial infarction or thromboem-



**Figure 2.** Gross pathology of the treated area at day 0 and day 7. A, Right atrium: friable hemorrhagic lesion at treatment site (\*) at day 0. B, Left atrium: hemorrhagic lesion beneath flap (\*) at day 0. C, Right atrium: treated area of foramen ovale (FO) shows 1-cm irregular tan-brown hemorrhagic lesion at day 7. D, Left atrium: no apparent lesion and widely PFO at day 7. E, External surface of posterior aorta: 0.5×0.3-cm tan-brown lesion behind noncoronary cusp at day 7.

bolic events. Gross examination of all hearts showed no structural abnormalities of chambers or valves and no gross ventricular myocardial necrosis in any case. Gross observation showed a tan scar in some cases. Twelve of the 13 PFOs were sealed on gross examination; 1 animal demonstrated patency on gross examination.

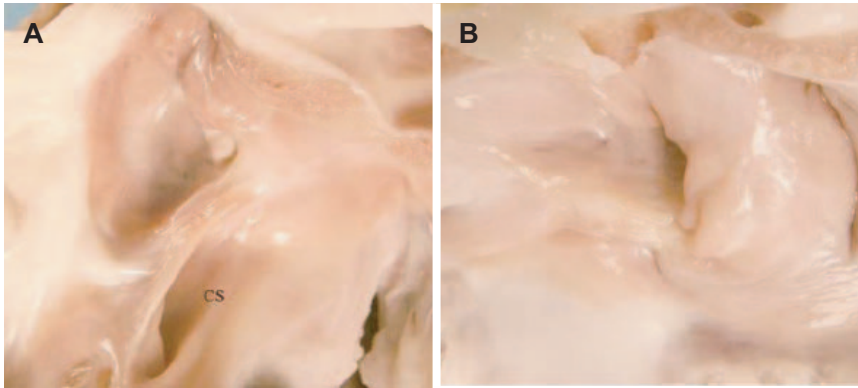
At day 0, no gross lesions attributable to thermal energy treatment were identified. Small hemorrhagic lesions were observed at the treatment site on the right atrial surface, with focal hemorrhage present opposite the treatment site on the left atrial surface as well (Figure 2). The epicardium on the left side was unremarkable. Grossly, all PFOs were sealed on gross examination by visual inspection and water pipette testing. At day 7, resolving hemorrhage as evidenced by hemosiderin was seen, with minor superficial hemorrhage at the aortic root observed in a minority of cases (Figure 2). At day 28, a tan-white scar was observed at the treatment sites. The left atrial surface opposite the treatment site showed no lesions, and the epicardium was unremarkable (Figure 3).

## Histology of Acute Cases

### Histology at Day 0

Histology in 3 acute (day 0) animals showed an acutely inflamed surface with platelet thrombus formation lining the right atrial septum. Underlying coagulative myocyte necrosis, edema, and hemorrhage were evident (Figure 4). Platelet thrombus was also seen within the tunnel, which also showed





**Figure 3.** Gross pathology at day 28. A, Right atrium: treated area of foramen ovale shows 0.4-cm tan-white scar. B, Left atrium: left atrium shows no gross lesion; fossa appears grossly sealed. CS indicates coronary sinus.

interstitial transmural edema and hypereosinophilic myofibers with early myocyte damage on the atrial surface. This sometimes extended to the superior epicardial surface, to the aorta superficially, and to the ventricular septum near the right-sided conduction fibers. No histopathologic evidence of AV nodal involvement or damage to the individual conduction fibers was observed.

In 1 animal, the left atrial surface opposite the treatment site showed adherent platelets with small thrombus adherent to the roof of the atrium extending from the tunnel. The posterior margin showed focal hypereosinophilic myocytes in the atrial septum and primum.

#### *Histology at Day 7*

Day 7 examination showed clearly delineated ovoid areas of transmural or nearly transmural coagulation necrosis, edema, and hemorrhage associated with chronic inflammation. This included numerous macrophages and lymphocytes demarcated by early granulation tissue, intermixed with clusters of calcified and necrotic individual myocytes associated with a giant cell reaction. Chronic inflammatory cells consisted predominantly of macrophages, lymphocytes, plasma cells, and scattered eosinophils as an infiltrate (Figure 5). This area showed extension to the left atrial and superior epicardial surfaces, and 1 case revealed invasion to both left and right

atria. Fibrin thrombus was observed in 4 of 5 animals, was generally focal, and was limited to the right atrial surface and tunnel. Resolving hemorrhage ( hemosiderin) was also seen.

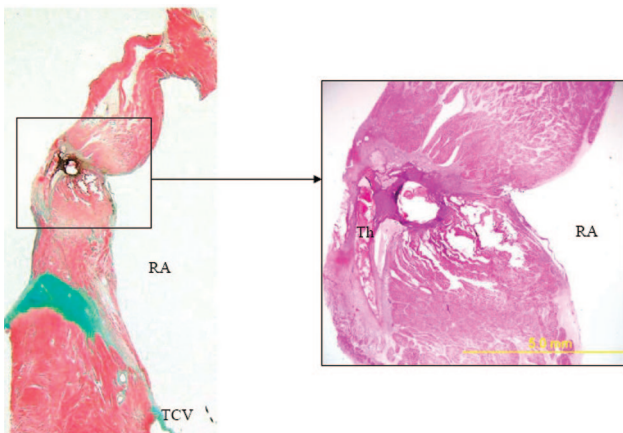
#### *Histology at Day 28*

The predominant finding at 28 days was healing in all animals by collagen-rich granulation tissue near the right atrial endocardial surface, which consisted of giant cells, macrophages, and lymphocytes (Figure 6.). Focal myocyte necrosis and hemorrhage and chronic inflammation were persistent to varying degrees. Complete endothelialization of the right atrial surface was seen. The posterior margins of the aorta were unremarkable. These histological sections revealed no foreign material.

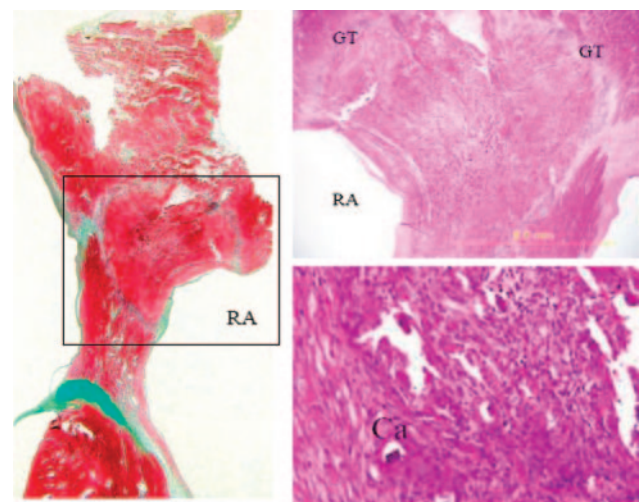
### Discussion

#### **PFO as a Clinical Problem**

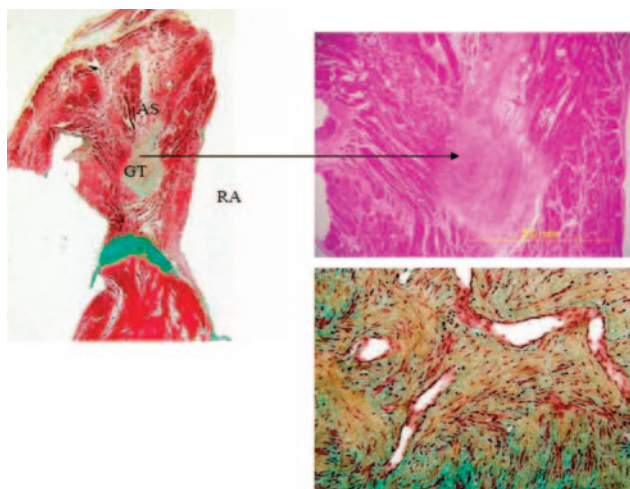
Clinical consequences of PFO include paradoxical embolism<sup>5</sup> manifesting as cryptogenic stroke,<sup>6,7</sup> platypnea-orthodeoxia syndrome,<sup>8</sup> adverse outcomes in patients with pulmonary



**Figure 4.** Histology at day 0. Boxed area of atrial septum shows transmural injury. Higher magnification at right shows coagulative myocyte necrosis and marked tissue edema. Platelet thrombus (Th) is noted within the tunnel beneath the flap on the left atrial side. TCV indicates tricuspid valve; RA, right atrium.



**Figure 5.** Histology at day 7. A, Whole-mount Movat-stained section shows rim of granulation tissue occupying more than three-fourths of the atrial septum. B, Hematoxylin and eosin-stained section corresponds to boxed area at left (left and right reversed). Note rim of granulation tissue (GT). RA indicates right atrium. C, Higher magnification at right shows calcified myocytes (Ca) and chronic inflammation including giant cells adjacent to granulation tissue.



**Figure 6.** Histology at day 28. A, Whole-mount view above showing granulation tissue (GT) shrunk in the atrial septum (AS). RA indicates right atrium. B, Hematoxylin and eosin-stained section corresponds to GT at left. C, Higher magnification of GT demonstrates capillaries with proteoglycan and collagen deposition.

embolism,<sup>9,10</sup> decompression sickness syndrome,<sup>11,12</sup> and possibly migraine headache.<sup>13,14</sup> Several devices are either under investigation or under development for percutaneous PFO closure; however, device-based therapies may fail due to residual shunting, device migration, strut fracture, and excessive thrombus formation even in the chronic phase after repair.<sup>1,15–19</sup> Such intracardiac devices also are prone to endocarditis, may be the cause of supraventricular arrhythmia due to inflammation, and may impede future catheter access to the left atrium. Many percutaneous closure therapies are based on implanted devices, whereas others use only energy to create a seal, which causes tissue injury, and they rely on normal healing to close the PFO tunnel.<sup>20</sup> The present report is the first to describe the histopathology of atrial septal healing after an energy-based strategy that involves no implanted devices.

### Mechanism of Healing Via Collagen and Elastin

The present preclinical study showed that thermal injury triggers inflammatory responses that in turn cause platelet/fibrin thrombus and subsequent scar formation. Dual-antiplatelet therapy was used in the present study, similar to other PFO closure technologies, in an attempt to limit potential thrombus volume. Most PFO closure devices show thrombus on the left atrial side to some degree, a finding that facilitates healing. Only 1 case showed microscopic platelet thrombus in the acute time frame, showing minimal thrombus formation on the left atrial wall in the present study.

Denaturation of native collagen induced added granulation tissue and eventually atrial septal fibrosis, with both septal membranes attached together by the thermal energy. Subsequent healing resulted in a single closed atrial septal membrane. The platelet/fibrin thrombus at the treatment site initially served as scaffolding between the primum and underlying septum, bonding them together. Over the ensuing 28 days, the thermally damaged atrial septum tissue pro-

gressed through normal healing stages without myocardial infarction, thromboembolic events, or other serious adverse events in any animal. These results with no adverse events are encouraging and will result in larger preclinical studies to confirm safety.

The RF energy-based approach takes advantage of atrial tissue characteristics. The septum primum is thin ( $\approx 0.5$  to 1.0 mm), and both it and the septum secundum are principally connective tissue that consists of cardiac muscle and fibrous/collagenous and elastic tissue. The elastic components of the septum primum permit distension without rupture. The septum primum consists of a layer of cardiac muscle lined on the inferior side with a layer of collagen and elastin. The thicker septum secundum has a similar structure, with the cardiac muscle layer being much thicker.<sup>21</sup> Tissue distensibility allows a vacuum to coapt tissues before sealing. The vacuum stretches the connective tissue of the septum primum and septum secundum around the catheter, bringing them tightly together in front of the catheter. Thermal RF energy seals the PFO entrance. Thermal treatment likely caused collagenous tissue shrinkage, as structural proteins were denatured by the heat. It is this shrinkage that may assist with an immediate reduction in shunting.

After the immediate sealing effects from thermal treatments, heat-damaged tissue undergoes normal wound healing and tissue remodeling that provides permanent PFO closure and a normal-appearing right atrium. Thus, this RF strategy achieved successful PFO sealing in the porcine model both clinically and histopathologically. Eight of 13 cases had a positive pretreatment bubble study rating of 1 or greater, and all 8 had a reduced bubble study immediately after treatment.

The concept of this closure technique is to leave no device behind in the heart. The traditional atrial septal double-disk occluder devices have potential for embolization, thrombus, and erosion due to cardiac movement, which may cause cardiac tamponade even long after device implantation. Recently, biodegradable materials have been used for PFO occlusion,<sup>3</sup> and these might be useful in addressing these long-term concerns; however, possibilities still exist for device migration and embolization, as well as late device fracture. Device-free PFO therapy is theoretically more attractive than traditional device implantation because of safety issues. Such new technologies for PFO closure may herald a new treatment era.

### Limitations of the Study

The present study focused on gross and histopathologic, anatomic results of a device-free technology. It was conducted with a limited number of hearts and provided only short-term follow-up data. These limitations are recognized and can be addressed by other long-term animal studies and then human studies with this nonimplantable device.

### Clinical Implications

Current PFO closure devices typically have components that remain within the heart forever and that may cause unfavorable adverse events. This RF-based strategy may represent a non-device-based alternative for PFO treatment. Although

adverse events in device implantation are fortunately rare, RF or other device-free strategies are theoretically attractive.

## Conclusions

The present study demonstrates histopathologic events of atrial septum healing after energy therapy. PFOs can be safely and effectively sealed in pigs by use of this strategy. The treated tissue progresses through the well-defined healing stages without apparent adverse events by 28 days after treatment.

## Acknowledgment

The authors thank Deborah Sheffield, who provided tremendous support for this manuscript.

## Disclosure

Dr Jones is a principal investigator of the present study, and he and Dr Sommer have served as consultants to CoAptus Medical Corporation, which is an early-stage medical device company developing a nonimplantable, therapeutic catheter device for PFO closure. J. Eichinger is cofounder, director, and president of CoAptus Medical Corporation. Drs Auth, Schwartz, and Van Tassel are consultants and shareholders of CoAptus Medical Corporation. The remaining authors report no conflicts.

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## CLINICAL PERSPECTIVE

Patent foramen ovale (PFO) is experiencing much clinical interest as a congenital cardiac lesion that persists into adulthood. It is a risk factor for several serious clinical syndromes, and recent evidence further implicates PFO as a possible cause of migraine headache, through mechanisms not yet understood. Current closure devices are designed to be delivered and close the lesion; however, device failure modes include residual shunt, migration, and fracture, even late after implantation. Radiofrequency energy is a method for PFO closure that uses no implantable device. This lack of a permanent prosthesis has both theoretical and practical appeal. Multiple studies have examined PFO closure in human subjects; however, careful investigation into histopathology of the PFO membranes has not been reported in detail. The porcine PFO model appears satisfactory to examine PFO closure technologies. The present animal study documented the efficacy of radiofrequency-based PFO closure from both histopathologic and clinical events. It represents successful application of a membrane-sealing technology that does not entail a residual device. Histopathologic examination of this technology in pigs not only shows clinical efficacy but also documents the cellular events of healing over time, findings likely applicable to other devices and PFO closure technologies.