Visualized Balloon Catheter Ablation of Atrial Fibrillation

Experimental Feasibility and First-in-Human Multicenter Clinical Outcome

Vivek Y. Reddy, MD; Petr Neuzil, MD, PhD; Sakis Themistoclakis, MD; Stephan B. Danik, MD; Aldo Bonso, MD; Antonio Rossillo, MD; Antonio Raviele, MD; Robert Schweikert, MD; Sabine Ernst, MD; Karl-Heinz Kuck, MD; Andrea Natale, MD

Background—Electric isolation of the pulmonary veins (PVs) can successfully treat patients with paroxysmal atrial fibrillation. However, it remains technically challenging to identify the left atrial–PV junction and sequentially position the ablation catheter in a point-by-point contiguous fashion to isolate the PVs. In this study, a novel endoscopic ablation system was used to directly visualize and ablate tissue at the left atrial–PV junction with laser energy.

Methods and Results—This study consisted of 2 phases: a short-term (n=9) and long-term (n=11) canine experimental validation phase and a multicenter clinical feasibility phase (n=30 paroxysmal atrial fibrillation patients). After transseptal puncture, the balloon-based endoscopic ablation system was advanced to each PV ostium, and arcs of laser energy (90° to 360°) were projected onto the target left atrial–PV junction. Electric PV isolation was defined with a circular multielectrode catheter. In the short-term preclinical experimental phase, 15 of 17 targeted PVs (88%) were successfully isolated. Pathological examination revealed well-demarcated circumferential lesions with minimal endothelial disruption. In the long-term experiments, 9 of 10 targeted veins (90%) remained persistently isolated (at 4 to 8 weeks). In the clinical phase, 105 of 116 PVs (91%) were successfully isolated. After a single procedure, the 12-month drug-free rate of freedom from atrial fibrillation was 60% (18 of 30 patients). There were no significant PV stenoses, but adverse events included 1 episode of cardiac tamponade, 1 stroke without residual defect, and 1 asymptomatic phrenic nerve palsy.

Conclusion—This study establishes the feasibility of a novel paradigm for AF ablation: direct visualization to guide catheter ablation of the left atrial–PV junction. (Circulation. 2009;120:12-20.)

Key Words: ablation ■ atrial fibrillation ■ catheter ablation ■ lasers ■ pulmonary veins

Since the seminal observation that pulmonary veins (PVs) play a critical role in the pathogenesis of paroxysmal atrial fibrillation (AF), electric PV isolation has become the generally accepted procedural end point during catheter ablation.1,2 Although conceptually straightforward, its clinical application has been hindered by important technical hurdles related to the complexity and patient-to-patient variability of PV anatomy, as well as the difficulty in manipulating the ablation catheter to the peri-PV locations. This is compounded by the lack of a distinct separation between the left atrium (LA) and PVs; each of the ovoid veins is often observed to widen gradually and asymmetrically as they coalesce to join the body of the LA.3,4 Accordingly, there is a tendency for the ablation catheter to slip inadvertently into the targeted vein, thereby adversely affecting both the safety and efficacy of the procedure. Specifically, ablation within the vein increases both the potential for causing PV stenosis and the possibility of leaving proximal AF triggers unaffected by the distal level of isolation.

Clinical Perspective on p 20

Electric PV isolation during catheter ablation is further encumbered by the inability of the electrophysiologist to directly visualize the LA–PV junction and thereby place ablation lesions with a high level of anatomic accuracy. This has been alleviated partially by the advancement of auxiliary imaging, including electroanatomic mapping systems, intracardiac echocardiography, and the integration of 3-dimensional...
image renderings of the LA-PV anatomy derived from computed tomography (CT), magnetic resonance imaging (MRI), or rotational angiography. Nevertheless, AF ablation remains a technically challenging procedure inaccessible to inexperienced operators. This has spurred significant scientific and technological efforts to develop novel approaches to facilitate electric PV isolation. One such class of ablation devices is balloon ablation catheters, which have facilitated the surmounting of many of the aforementioned technical hurdles.5-11 However, the variability in PV architecture still poses significant challenges in developing a “one-size-fits-all” device.

These considerations have led to the development of a balloon ablation catheter equipped with an endoscope that allows direct visualization of the LA-PV junction.12 An optical fiber within the balloon can then deliver an arc of ablative laser energy to the tissue visualized on the face of the balloon. As during surgery, this approach has the potential to enable the operator to visualize the target tissue and adapt the lesion strategy to the highly variable PV anatomy. The utility, safety, and efficacy of this endoscopic ablation system (EAS) for PV isolation were examined in this 2-phase study. Phase I included a series of short-term and long-term canine experiments; phase II, a multicenter registry of patients undergoing catheter ablation for drug-resistant paroxysmal AF.

Methods

Phase I, the preclinical canine phase (n=20; 9 short term, 11 long term), was approved by the Massachusetts General Hospital Subcommittee of Research Animal Care according to the American Association for Laboratory Animal Care standards for proper research animal care. Phase II, the clinical phase (n=30), was approved by the human ethics committees at all 3 participating sites: Homolka Hospital in Prague, Umberto Hospital in Venice, and St Georg Hospital in Hamburg.

Endoscopic Ablation System

The EAS (CardioFocus Inc, Marlborough, Mass) is available in 3 sizes: 20, 25, and 30 mm at maximal diameter. It consists of 2 major components: the delivery sheath and the ablation catheter (Figure 1). The former is a deflectable 12F internal diameter sheath with 180° deflection capability; the latter has 2 important elements: the endoscope and the arc generator.

The reusable 500-μm diameter endoscope has a 110° field of view and is positioned at the proximal end of the balloon to visualize the face of the balloon. This enables real-time direct visualization of the intravascular cardiac anatomy when the balloon is inflated. Where the balloon is in contact with blood, the operator sees red; at regions in contact with tissue, the operator sees the tissue blanched white (Figure 2). Of note, the field of view is partially distorted in the region behind the central shaft that traverses the balloon.

The arc generator consists of an optical fiber located within the central shaft, which projects an arc of light onto the tissue in contact with the balloon face. This arc can be advanced/retracted and rotated with ease for positioning along the balloon face, as far proximal as the point of maximal balloon diameter. The arc incorporates visual cues for enhanced endoscopic visualization. By projecting an aiming beam of red or green light either separately or simultaneously, the location where the laser energy (980 nm) will be delivered is illuminated. Red light is reflected by both tissue and blood; green light is reflected only by tissue. When combined red and green light is projected onto the tissue, a yellow arc is seen; when projected onto blood, only red is seen (Figure 2). This color difference in the aiming beam allows balloon contact with tissue and blood to be highlighted. The arc generator was available in 90°, 150°, or 360° arcs/circles for phase I; for phase II, only the 90° or 150° arcs were used.

Figure 1. Visually guided ablation catheter. Shown are the ablation catheter with the projected green arc of the aiming beam (A) and a schematic showing the location of the endoscope at the proximal end of the balloon (B).

Figure 2. Using the endoscopic image. When the balloon is positioned apposed to the PV ostium, the area of balloon contact with the atrial and PV ostial tissue blanches to a whitish color; the remaining areas without tissue contact are visualized red. Once the balloon is positioned, the arc of the aiming beam can easily be manipulated—rotated and advanced/retracted—to the desired location for ablation. Of importance, the arc is positioned so that energy is not delivered into the “static” blood distal to the face of the balloon because this can result in thrombus formation. On the other hand, with the laser dose used, overlap of the arc with the proximal “free-flowing” blood is safe because it does not result in thrombus formation. Note that because of the central shaft (which extends to the tip of the catheter), a wedge of the endoscopic image is partially obscured (dotted lines); though distorted, the tissue behind this region is still visualized adequately enough to guide ablation. The small arrows indicate the faint line seen at the point of maximal diameter of the balloon.
Once the arc is appropriately positioned to target the tissue of interest, a continuous 980-nm arc of laser energy is delivered via the same optical fiber, ie, to the same location identified by the green/red arc. Multiple such arcs of energy are applied to “stitch” individual lesions together to achieve a continuous circumferential lesion set. An internal cooling mechanism circulates sterile fluid within the balloon to avoid overheating of the tissue being ablated. In addition, the green/red arc can be monitored continuously during laser energy delivery to ensure the sustained accuracy of positioning.

Preclinical Phase

Ablation Procedure

After an overnight fast, 9 female mongrel dogs weighing between 20 and 30 kg were anesthetized with ketamine (10 mg/kg) and diazepam (0.1 mg/kg), intubated, and maintained under general anesthesia with isoflurane (0.5% to 1.5%). After transseptal puncture with a Brockenbrough needle, the deflatable 12F sheath was placed into the LA. The procedure was performed under continuous intravenous heparinization.

The EAS was delivered through the deflatable sheath and positioned at the ostium of each targeted PV; the ostia of the inferior PVs were not typically targeted because PV potentials were not usually appreciated within these veins at baseline. Various denominations of laser frequency, duration, and dose were tested to determine the optimal parameters. Energy at a wavelength of 980 nm was delivered between 6.3 and 7.6 W/cm² for a total duration of 45 to 120 seconds per lesion. A standard multipolar circular mapping catheter (Lasso, Biosense-Webster Inc, Diamond Bar, Calif) was used to record PV electrograms before and after ablation. Both entrance block and exit block were required to consider a vein electrically isolated. For those animals slated to survive the procedure and undergo long-term testing, additional measurements of the targeted PV were obtained with contrast angiography before ablation.

Follow-Up

In the short-term phase (n=9), animals were killed 30 minutes after the delivery of the last ablation lesion, and pathological examination was performed. Long-term–phase animals (n=11) were allowed to recover after the initial procedure and underwent a repeat procedure either 4 (n=4) or 8 (n=7) weeks later using the technique outlined above. Long-term electric PV isolation was assessed with the Lasso catheter, and the presence of PV stenosis was evaluated with contrast venography with multiple imaging angulations. Significant PV stenosis was defined as a >50% narrowing compared with baseline measurements.

Pathological Examination

The explanted heart and lungs were subjected to gross examination; any abnormal tissue was set aside for histological analysis. In all cases, the LA with attached PVs and adjacent tissue was fixed in 5% buffered formalin for a minimum of 48 hours and submitted for histological analysis. The samples were sectioned, paraffin embedded, and stained with either hematoxylin and eosin or Masson’s trichrome stain. Gross pathological examination was performed to assess for evidence of appropriate placement of the circumferential lesions along the PV ostia. A total of 4 histology samples were generated from each targeted PV spaced at ~90° degrees around the vein and were assessed for transmurality, lesion width, and the extent of collateral damage to surrounding tissue.

Clinical Phase

Study Design

The study was a prospective, open-label, nonrandomized, 3-center study of patients with symptomatic, recurrent, paroxysmal AF who had previously failed at least one class I or III antiarrhythmic drug. Patients were included if they met the following criteria: between 18 and 75 years of age, ECG documentation of AF in the prior year, and 30 mm, PVs >27 mm in diameter were excluded. In this study, 1 common PV was <27 mm and therefore ablated. We attempted to treat a total of 116 PVs; thus, 3 additional PVs were not attempted for ablation (because of being either too small or difficult to access).

The primary end point was freedom from symptomatic sustained AF (lasting at least 1 minute) at 12 months. A blanking period of 30 days after index or repeat ablation procedure was used; all antiarrhythmic drugs were discontinued after this period. Prespecified secondary end points included partial clinical success for patients experiencing AF recurrence after the initial 30-day blanking period, followed by subsequent freedom from AF after reinstitution of a previously ineffective antiarrhythmic drug, and the number of PVs successfully isolated as measured 30 minutes after the last energy delivery. End points were analyzed on an intention-to-treat basis.

Postablation follow-up included clinic visits at 1, 3, 6, and 12 months; 12-lead ECGs at 1, 3, and 6 months; and CT or MRI at 3 and 6 months to assess for PV stenosis. A repeat imaging study (CT/MRI and/or Ventilation-Perfusion scan) was performed if a patient experienced any symptoms compatible with PV stenosis. Holter monitoring was performed at 1, 3, and 6 months and for symptoms. Each participant also was given an event recorder for weekly and symptom-driven transmissions for 180 days after the index procedure. All patients were discharged on coumadin for a target international normalized ratio of 2.0 to 3.0 for at least 6 months; low-molecular-weight heparin was used to bridge patients with nontherapeutic international normalized ratio at the time of discharge.

Procedure

The use of intracardiac echocardiography for the procedure was encouraged (Figure 3). Two transseptal punctures were performed for the ablation catheter and multipolar mapping catheter. After the deflatable sheath was placed in the LA, the balloon catheter was inserted, inflated within the LA, and sequentially positioned at each PV ostium. Energy delivery was performed with a power density of 6.3, 6.9, or 7.6 W/cm² for 60 seconds. The arc size was 150° for the first 20 patients and 90° for the last 10. Before delivery of energy to the right superior PV, a pacing catheter was positioned within the superior vena cava above the level of the balloon catheter, and phrenic nerve pacing was performed to minimize the risk of phrenic nerve palsy. A Lasso catheter was used to interrogate each PV before prior PV ablation, AF secondary to a reversible cause, known presence of an intracardiac thrombus, cardiac surgery within the prior 3 months, New York Heart Association class III or IV, left ventricular ejection fraction <30%, moderate to severe valvular heart disease or previous valve replacement, an implanted defibrillator, pacemaker placement in the prior 3 months, a history of stroke or transient ischemic attack, PV diameters >80% of the largest available balloon diameter based on preprocedural CT or MRI, and an LA >5 cm based on echocardiography.

Because the maximal balloon diameter available in this study was 30 mm, PVs >27 mm in diameter were excluded. In this study, 1 common PV was <27 mm and therefore ablated. We attempted to treat a total of 116 PVs; thus, 3 additional PVs were not attempted for ablation (because of being either too small or difficult to access).

The primary end point was freedom from symptomatic sustained AF (lasting at least 1 minute) at 12 months. A blanking period of 30 days after index or repeat ablation procedure was used; all antiarrhythmic drugs were discontinued after this period. Prespecified secondary end points included partial clinical success for patients experiencing AF recurrence after the initial 30-day blanking period, followed by subsequent freedom from AF after reinstitution of a previously ineffective antiarrhythmic drug, and the number of PVs successfully isolated as measured 30 minutes after the last energy delivery. End points were analyzed on an intention-to-treat basis.

Postablation follow-up included clinic visits at 1, 3, 6, and 12 months; 12-lead ECGs at 1, 3, and 6 months; and CT or MRI at 3 and 6 months to assess for PV stenosis. A repeat imaging study (CT/MRI and/or Ventilation-Perfusion scan) was performed if a patient experienced any symptoms compatible with PV stenosis. Holter monitoring was performed at 1, 3, and 6 months and for symptoms. Each participant also was given an event recorder for weekly and symptom-driven transmissions for 180 days after the index procedure. All patients were discharged on coumadin for a target international normalized ratio of 2.0 to 3.0 for at least 6 months; low-molecular-weight heparin was used to bridge patients with nontherapeutic international normalized ratio at the time of discharge.

Procedure

The use of intracardiac echocardiography for the procedure was encouraged (Figure 3). Two transseptal punctures were performed for the ablation catheter and multipolar mapping catheter. After the deflatable sheath was placed in the LA, the balloon catheter was inserted, inflated within the LA, and sequentially positioned at each PV ostium. Energy delivery was performed with a power density of 6.3, 6.9, or 7.6 W/cm² for 60 seconds. The arc size was 150° for the first 20 patients and 90° for the last 10. Before delivery of energy to the right superior PV, a pacing catheter was positioned within the superior vena cava above the level of the balloon catheter, and phrenic nerve pacing was performed to minimize the risk of phrenic nerve palsy. A Lasso catheter was used to interrogate each PV before prior PV ablation, AF secondary to a reversible cause, known presence of an intracardiac thrombus, cardiac surgery within the prior 3 months, New York Heart Association class III or IV, left ventricular ejection fraction <30%, moderate to severe valvular heart disease or previous valve replacement, an implanted defibrillator, pacemaker placement in the prior 3 months, a history of stroke or transient ischemic attack, PV diameters >80% of the largest available balloon diameter based on preprocedural CT or MRI, and an LA >5 cm based on echocardiography.

Because the maximal balloon diameter available in this study was 30 mm, PVs >27 mm in diameter were excluded. In this study, 1 common PV was <27 mm and therefore ablated. We attempted to treat a total of 116 PVs; thus, 3 additional PVs were not attempted for ablation (because of being either too small or difficult to access).

The primary end point was freedom from symptomatic sustained AF (lasting at least 1 minute) at 12 months. A blanking period of 30 days after index or repeat ablation procedure was used; all antiarrhythmic drugs were discontinued after this period. Prespecified secondary end points included partial clinical success for patients experiencing AF recurrence after the initial 30-day blanking period, followed by subsequent freedom from AF after reinstitution of a previously ineffective antiarrhythmic drug, and the number of PVs successfully isolated as measured 30 minutes after the last energy delivery. End points were analyzed on an intention-to-treat basis.

Postablation follow-up included clinic visits at 1, 3, 6, and 12 months; 12-lead ECGs at 1, 3, and 6 months; and CT or MRI at 3 and 6 months to assess for PV stenosis. A repeat imaging study (CT/MRI and/or Ventilation-Perfusion scan) was performed if a patient experienced any symptoms compatible with PV stenosis. Holter monitoring was performed at 1, 3, and 6 months and for symptoms. Each participant also was given an event recorder for weekly and symptom-driven transmissions for 180 days after the index procedure. All patients were discharged on coumadin for a target international normalized ratio of 2.0 to 3.0 for at least 6 months; low-molecular-weight heparin was used to bridge patients with nontherapeutic international normalized ratio at the time of discharge.

Procedure

The use of intracardiac echocardiography for the procedure was encouraged (Figure 3). Two transseptal punctures were performed for the ablation catheter and multipolar mapping catheter. After the deflatable sheath was placed in the LA, the balloon catheter was inserted, inflated within the LA, and sequentially positioned at each PV ostium. Energy delivery was performed with a power density of 6.3, 6.9, or 7.6 W/cm² for 60 seconds. The arc size was 150° for the first 20 patients and 90° for the last 10. Before delivery of energy to the right superior PV, a pacing catheter was positioned within the superior vena cava above the level of the balloon catheter, and phrenic nerve pacing was performed to minimize the risk of phrenic nerve palsy. A Lasso catheter was used to interrogate each PV before
and after ablation to assess whether electric isolation was achieved. PV isolation was reassessed 30 minutes after delivery of the last ablation lesion. As per operator preference, an esophageal temperature probe was used to monitor esophageal heating during energy delivery; when used, the probe was advanced or retracted under fluoroscopic guidance to ensure vertical alignment with the balloon catheter. Energy delivery was terminated if the esophageal temperature exceeded 39°C. Also per operator preference, selected patients underwent preablation and postablation high-density electroanatomic mapping with a circular mapping catheter and the NavX electroanatomic mapping system (St Jude Medical, Inc, Minnetonka, Minn). This was not prespecified 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

#### Preclinical Short-Term Phase

In a total of 17 PVs targeted for ablation, a matrix of various doses/durations of energy was evaluated. As shown in Table 1, titration to a power of 6.3 W/cm for at least 45 seconds was required to achieve isolation. In toto, short-term PV isolation was achieved in 15 of 17 PVs (88%). The total duration of energy delivery per isolated PV averaged 277 seconds (range, 135 to 720 seconds). As shown in Table 2, the mean number of energy deliveries per vein to achieve isolation was 4.1 (range, 2 to 9). The target PV was mapped 1.7 times (range, 1 to 3) with the circular mapping catheter before isolation was achieved. When the energy was transmitted with the full 360° ring (n = 9 PVs), an average of 2.7 energy deliveries (range, 2 to 4) were applied. When the 150° arc was used, an average of 4.8 deliveries (range, 3 to 9) were required.

Gross pathological examination revealed evidence of circumferential lesion placement at the LA-PV junction without evidence of atrial endocardial charring (Figure 4). There was no evidence of acute PV stenosis. There also was no evidence of pericardial damage or perforation. On histological analysis, there was no evidence of endocardial destruction such as surface pitting, granulation, or cartilage formation. There was minimal disruption of the endothelial and epithelial cell layers on the respective atrial endocardial and epicardial surfaces. The lesions themselves were homogeneous with well-demarcated borders. Histological analyses revealed that the mean lesion depth and width were 1.8 mm (range, 0.5 to 5.0 mm) and 8 mm (range, 1 to 20 mm), respectively; 85% of the lesions were histologically transmural.

#### Preclinical Long-Term Phase

As shown in Table 3, a total of 12 PVs (11 right superior PVs, 1 left superior PV) were targeted with the 150° arc, and animal follow-up studies occurred at either 4 (n = 4 PVs) or 8 (n = 7 PVs) weeks. In these experiments, the left superior PV was not targeted if the PV muscular sleeves were too short

### Table 1. Preclinical Acute Phase: Dose Effectiveness

<table>
<thead>
<tr>
<th>Power, W/cm</th>
<th>Time, s*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3, % (n/N)</td>
<td>45  60  90</td>
</tr>
<tr>
<td>6.9, % (n/N)</td>
<td>0 (0/2)  ···  ···</td>
</tr>
<tr>
<td>7.6, % (n/N)</td>
<td>···  ···  100 (8/8)</td>
</tr>
</tbody>
</table>

*One PV was targeted twice: first at 6.3 W/cm for 45 seconds and again at 6.9 W/cm for 45 seconds.

### Table 2. Preclinical Acute Phase: Procedural Effectiveness

<table>
<thead>
<tr>
<th>Vein</th>
<th>PVs Targeted, n</th>
<th>Isolation Achieved, n (%)</th>
<th>Lesions Delivered, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSPV</td>
<td>10</td>
<td>9 (90)</td>
<td>4.7 (2–9) 47</td>
</tr>
<tr>
<td>LSPV</td>
<td>6</td>
<td>5 (83)</td>
<td>3.3 (2–4) 20</td>
</tr>
<tr>
<td>LIPV</td>
<td>1</td>
<td>1 (100)</td>
<td>3.0 3</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>15 (88)</td>
<td>4.1 (2–9) 70</td>
</tr>
</tbody>
</table>

**RSPV** indicates right superior PV; **LSPV**, left superior PV; and **LIPV**, left inferior PV.

### Table 3. Preclinical Chronic Phase: Procedural Effectiveness

<table>
<thead>
<tr>
<th>Duration of Follow-Up, wk</th>
<th>PVs Targeted, n</th>
<th>RSPV</th>
<th>LSPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>4</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Assessment for block</td>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>PVs not accessed, n</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>PVs accessed, n</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Electrical isolation, n (%)</td>
<td>9 (90)</td>
<td>5 (100)</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Stenosis (≥50%), n (%)</td>
<td>3 (25)</td>
<td>0</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

**RSPV** indicates right superior PV; **LSPV**, left superior PV.
The total procedure time was 334 ± 112 minutes, of which 278 ± 91 minutes involved deployment and use of the EAS. (n = 5), the animal’s health status was concerning (n = 3), or the vein was too small for balloon placement (n = 2). For each application, a dose of 6.9 W/cm² was delivered for 60 seconds per lesion, with an average of 6.2 energy deliveries per vein (range, 4 to 9). Short-term isolation occurred successfully in all veins; no acute adverse events were observed, and all animals survived both the initial and follow-up procedures.

At the time of follow-up, 9 of the 10 PVs (90%) that could be assessed with the Lasso catheter were still isolated (Table 3). One vein could not be assessed because we were unable to position the multipolar catheter at the os and another because of the presence of a transseptal scar (flap) that prevented access to the previously ablated vein. Pulmonary vein stenosis (>50% narrowing) was detected in 3 of 12 veins (25%). Posthoc analysis revealed that because of the small size of the targeted PVs relative to the balloon ablation catheter, the actual location of the delivered lesions was further within the PVs. Gross pathological examination revealed no evidence of collateral damage to the atria, lung parenchyma, pericardium, pulmonary artery, esophagus, phrenic nerve, or other adjacent structures. Histological analysis again revealed homogeneous lesions with well-demarcated borders.

### Clinical Phase: Baseline

A total of 30 subjects were enrolled in this study; all completed follow-up through the 12-month period. As shown in Table 4, most patients were young (mean age, 53 years), without structural heart disease, and with preserved ventricular function. The mean AF duration was 6.0 ± 4.9 years, and all patients had failed at least 1 class I or III antiarrhythmic medication. As demonstrated by preprocedural CT/MRI, there was significant interpatient and intrapatient variability in the PV sizes: left inferior PV, 12.5 to 23.0 mm (mean, 17.2 ± 2.7 mm); left superior PV, 13.0 to 23.0 mm (17.8 ± 2.4 mm); right inferior PV, 14.0 to 24.0 mm (17.9 ± 2.1 mm); right superior PV, 13.8 to 24.0 mm (19.8 ± 3.1 mm); and left common PV, 23.0 mm.

### Clinical Phase: Treatment Parameters

The total procedure time was 334 ± 112 minutes, of which 278 ± 91 minutes involved deployment and use of the EAS. Although the procedure time was considerable, it is of note that there was a clear learning curve: The procedure duration decreased from a mean of 386 to 283 minutes from the first 10 to the last 10 procedures. The mean fluoroscopy time was 53 ± 23 minutes. A total of 51 balloon catheters were used (1.7 catheters per patient), of which 12 (23.5%) were 20 mm, 32 (62.7%) were 25 mm, and 7 (13.7%) were 30 mm in diameter. No study participant underwent any repeat procedures or additional ablations. Intracardiac echocardiography and esophageal temperature monitoring were each used in 28 of 30 of cases (93%). Examples of visually guided PV isolation are shown in Figures 5 through 8.

A total of 105 of 116 PVs (91%) were electrically isolated successfully, requiring a mean of 13.9 energy deliveries per vein. The mean number of energy deliveries per vein for the first 20 participants treated with the 150° arc (77 attempted veins) was 12.1 (range, 2 to 19), whereas the mean number of energy deliveries per vein for the last 10 participants treated with the 90° arc (39 attempted veins) was 31% greater (17.5; range, 6 to 40). This is consistent with the fact that the 150° arc covers 66% more circumferential distance than the 90° arc. On a per-vein basis, electric PV isolation was achieved in 89%, 100%, 93%, and 86% of the left superior PV, left inferior PV, right superior PV, and right inferior PVs, respectively.

### Clinical Phase: Efficacy

With an initial 30-day blanking period, the single-procedure success rate for freedom from symptomatic AF over a 12-month follow-up period was 67% (20 of 30 patients without recurrences). Two of these patients remained on antiarrhythmic medications for non-AF indications: 1 for atrial flutter and the other for premature ventricular contractions; accordingly, the drug-free single-procedure success rate was 18 of 20 (60%). Twenty (67%) and 21 (70%) patients were free of postprocedural AF using a 60- and 90-day blanking period, respectively.

Examination of the treatment failures revealed no differences between long-term treatment successes and failures as

<table>
<thead>
<tr>
<th>Clinical Phase: Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>A total of 30 subjects were enrolled in this study; all completed follow-up through the 12-month period. As shown in Table 4, most patients were young (mean age, 53 years), without structural heart disease, and with preserved ventricular function. The mean AF duration was 6.0 ± 4.9 years, and all patients had failed at least 1 class I or III antiarrhythmic medication. As demonstrated by preprocedural CT/MRI, there was significant interpatient and intrapatient variability in the PV sizes: left inferior PV, 12.5 to 23.0 mm (mean, 17.2 ± 2.7 mm); left superior PV, 13.0 to 23.0 mm (17.8 ± 2.4 mm); right inferior PV, 14.0 to 24.0 mm (17.9 ± 2.1 mm); right superior PV, 13.8 to 24.0 mm (19.8 ± 3.1 mm); and left common PV, 23.0 mm.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Phase: Treatment Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>The total procedure time was 334 ± 112 minutes, of which 278 ± 91 minutes involved deployment and use of the EAS. Although the procedure time was considerable, it is of note that there was a clear learning curve: The procedure duration decreased from a mean of 386 to 283 minutes from the first 10 to the last 10 procedures. The mean fluoroscopy time was 53 ± 23 minutes. A total of 51 balloon catheters were used (1.7 catheters per patient), of which 12 (23.5%) were 20 mm, 32 (62.7%) were 25 mm, and 7 (13.7%) were 30 mm in diameter. No study participant underwent any repeat procedures or additional ablations. Intracardiac echocardiography and esophageal temperature monitoring were each used in 28 of 30 of cases (93%). Examples of visually guided PV isolation are shown in Figures 5 through 8. A total of 105 of 116 PVs (91%) were electrically isolated successfully, requiring a mean of 13.9 energy deliveries per vein. The mean number of energy deliveries per vein for the first 20 participants treated with the 150° arc (77 attempted veins) was 12.1 (range, 2 to 19), whereas the mean number of energy deliveries per vein for the last 10 participants treated with the 90° arc (39 attempted veins) was 31% greater (17.5; range, 6 to 40). This is consistent with the fact that the 150° arc covers 66% more circumferential distance than the 90° arc. On a per-vein basis, electric PV isolation was achieved in 89%, 100%, 93%, and 86% of the left superior PV, left inferior PV, right superior PV, and right inferior PVs, respectively.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Phase: Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>With an initial 30-day blanking period, the single-procedure success rate for freedom from symptomatic AF over a 12-month follow-up period was 67% (20 of 30 patients without recurrences). Two of these patients remained on antiarrhythmic medications for non-AF indications: 1 for atrial flutter and the other for premature ventricular contractions; accordingly, the drug-free single-procedure success rate was 18 of 20 (60%). Twenty (67%) and 21 (70%) patients were free of postprocedural AF using a 60- and 90-day blanking period, respectively. Examination of the treatment failures revealed no differences between long-term treatment successes and failures as</td>
</tr>
</tbody>
</table>
stratified by sex ($P=0.56$), age ($P=0.22$), left ventricular ejection fraction ($P=1.0$), LA diameter ($P=0.70$), duration of AF ($P=0.30$), or short-term PV isolation of all versus some PVs ($P=0.66$). The majority of treatment “failures” did not require repeat AF ablation because of minimal symptoms. However, 1 patient did undergo a subsequent ablation procedure using a standard radiofrequency ablation catheter. PV reconnections were noted, and after simple reisolation of the PVs, this patient was free of further arrhythmias.

**Clinical Phase: Safety**

Three patients (10%) met the predefined primary safety end point. One patient experienced a cerebrovascular event (prolonged reversible ischemic neurological deficit) 1 day after the procedure that presented as dysphasia and malcoordination of the right hand; CT and MRI of the brain revealed the presence of a partial median infarction. Complete resolution of this deficit occurred after several weeks. There was 1 episode of cardiac tamponade during the procedure that was treated successfully with pericardiocectomy; this complication was related to the transeptal puncture and not the ablation catheter itself. Finally, 1 episode of right phrenic nerve palsy was discovered on a routine postprocedure chest x-ray. Of note, phrenic nerve pacing from the superior vena cava had not been performed in this patient during ablation of the right superior PV. The patient did report mild shortness of breath, but the palsy resolved completely by the 6-month follow-up visit.

Relative to the secondary end point of the effect of the laser ablation system on PV caliber, no significant PV stenosis (ie, $<50\%$ decrease in PV diameter) was observed in any participants during follow-up CT imaging. As shown in Table 5, although PV narrowing (defined as a $20\%$ to $50\%$ decrease in the PV caliber) was noted in up to 13% of PVs at the 3- and 6-month imaging, increases in the PV diameter were similarly seen. For those patients with PV narrowing, repeat 12-month PV imaging did not reveal any significant PV stenosis.

**Discussion**

This study revealed that visually guided PV isolation with laser is both technically feasible in the canine experimental and human clinical scenarios and clinically effective in a series of patients with paroxysmal AF.

**Technical Feasibility of PV Isolation**

The short-term experimental phase of the study helped establish the technical aspects of visually guided ablation...
with the EAS. It became apparent that the deflection capability of the transseptal sheath was instrumental in ensuring access to the various PVs. The demonstrated ease of accessing the canine PVs was borne out in the clinical experience; of particular note is that even the right inferior PV was easily accessed. Although not evaluated systematically, the optimal location for the transseptal puncture to facilitate PV access appeared to be the posterior and inferior aspects of the atrial septum; this facilitated good apposition to the ostium of the right inferior PV. Once in position at the LA-PV junction, the balloon acted as workspace to enable facile peristial ablation; the operator could easily manipulate the “aiming” beam/arc under direct visualization of the target tissue.

There are 2 major aspects to the visual guidance potential of this system: balloon positioning relative to the LA-PV anatomy and positioning the aiming arc to target the appropriate locations during laser energy delivery. For the former, because the endoscopic view is limited to what can be seen and is dependent on the amount of tissue contact, the relative balloon location in the LA cannot be based on the endoscopic image alone. Accordingly, balloon positioning is largely dependent on fluoroscopy and intracardiac echocardiography. One caveat noted in the long-term animal study is that when tissue contact is extensive enough to be seen proximal to the diameter of the balloon (indicating deep balloon seating inside the PV), the risk of PV stenosis is high; this was avoided in the clinical cases, resulting in no significant stenoses. On the other hand, the endoscopic image proved critical for laser energy delivery to the proper location. Without endoscopy, the energy could easily be delivered inappropriately into the blood, and the various arcs might not “connect” together to achieve a contiguous circumferential lesion.

After the safety and effectiveness of various power levels in the canine model were demonstrated, the EAS was evaluated in a series of patients with paroxysmal AF. One important clinical observation was that the balloon could not typically be positioned coaxial with the long axis of the target PV. Despite this skewed angle of approach, however, short-term PV isolation was achieved in 91% of the 30 participants enrolled in the trial. For those patients in whom it was used, intracardiac echocardiography was helpful in identifying atrial and PV anatomy, evaluating the position of the balloon in relation to the target PV, and assessing for possible complications. It is likely that intracardiac echocardiography also decreased fluoroscopy exposure.

Clinical Efficacy of Balloon Isolation
When patients with paroxysmal AF have clinical recurrences after radiofrequency catheter ablation, the most common cause is PV reconnection.13–16 That is, reproducible long-term PV isolation remains an elusive goal. In this study, the long-term freedom from AF recurrences after a single ablation procedure was 67%, a rate comparable to that achieved with radiofrequency ablation. In the only patient with AF recurrences symptomatic enough to warrant reablation, PV reconnections were observed. After point ablation to reisolate the PVs, this patient experienced no additional AF episodes. These data suggest that to improve the clinical success rate of this laser balloon procedure, the power levels used may need to be increased to achieve uniform, permanent isolation of the diseased human PVs.

Safety of Balloon Isolation: PV Stenosis
The long-term phase of the experimental study revealed that significant PV stenosis can occur when ablation energy is delivered deeper within the PV. The major reason for the inappropriate location of energy administration is the small distance between the transseptal puncture and the right superior PV in the canine model. Combined with a relatively large balloon size for the canine PVs, this resulted in inadvertent seating of the balloon inside the vein, culminating in PV stenosis. These results underscore the importance of ensuring that the balloon is outside the PV during ablation. In the patient experience, however, the balloon sizes were more appropriate, and no such abbreviated distance existed. Accordingly, significant PV stenoses were not observed.

The clinical significance of the PV diameter changes seen in the clinical cases is not known. In addition to PV narrowing, a significant number of PVs measured larger than baseline. It is possible that variability is due to the respiratory or cardiac phase of CT acquisition or to technical variation in identifying and measuring the PV ostia.

Safety of Balloon Isolation: Thromboembolism
There are 2 major possibilities as to the cause of the single embolic event in this study. First, although the risk of thrombus formation is low when laser energy is delivered into atrial tissue, the risk of thrombus formation is high if the arc inadvertently overlaps any stagnant blood distal to the face of the balloon.17 Second, the sheath used in this study has a relatively large “dead space” that has the potential to harbor significant amounts of air or clot; atrial dislodgement of either could result in an embolic neurological event. Thus, careful sheath management, including a constant flush and careful attention to prevent inadvertent entry of air into the sheath, is vital.

Safety of Balloon Isolation: Esophageal Injury
There were no instances of atrial-esophageal fistula formation. Although comforting, one must recall that thousands of patients were treated with radiofrequency energy before the first fistula was observed. Esophageal temperature monitor-

### Table 5. PV Diameters by CT Imaging

<table>
<thead>
<tr>
<th>PV diameter decrease, %</th>
<th>3-Month Follow-Up, n (%)</th>
<th>6-Month Follow-Up, n (%)</th>
<th>12-Month Follow-Up, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–20</td>
<td>54 (45)</td>
<td>50 (42)</td>
<td>13 (54)</td>
</tr>
<tr>
<td>21–50</td>
<td>15 (13)</td>
<td>13 (11)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PV diameter increase, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–20</td>
<td>46 (38)</td>
<td>46 (39)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>21–50</td>
<td>5 (4)</td>
<td>9 (8)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ing was used in the majority of the clinical cases, and it is possible that this was operative in preventing fistula formation. The arcs of energy can be manipulated to variable locations of tissue contact, and it was thus possible to redirect the energy when esophageal heating was observed. For example, with esophageal temperature rises, the arc was repositioned either closer to or further from the vein—presumably farther from the esophagus—to permit reaplication of energy and PV isolation. Incidentally, this is an important advantage of the EAS because it permits the delivery of nonuniform circumferential energy titration. This also permitted the operator to directly visualize the tissue being targeted for ablation, an approach moving ever so closer to approximating the surgical experience.

Safety of Balloon Isolation: Pericardial Effusion/Tamponade
With radiofrequency energy, inadvertent delivery of excess power can result in tissue superheating, steam pops, and perforation. These complications are less likely to occur with volumetric heating associated with laser energy. Indeed, atrial perforation was not observed in any of the preclinical or clinical experience. The episode of cardiac tamponade was related to the transeptal puncture procedure.

Safety of Balloon Isolation: Phrenic Nerve Injury
There was 1 instance of asymptomatic right phrenic nerve palsy after right superior PV ablation. Although not used in this particular case, a phrenic nerve pacing protocol was used during the procedures to mitigate this possibility. Briefly, phrenic nerve capture was achieved by a pacing catheter high in the superior vena cava. This provided an online means to assess the integrity of phrenic nerve conduction during ablation. Again, avoiding this complication is facilitated by the ability to tailor the amount, duration, and location of laser energy application anteriorly versus posteriorly.

Study Limitations
Procedure times were relatively long (334±112 minutes, 278±91 of which was for the use of the ablation system). However, there was a clear learning curve, and it is expected that the mean procedure time will decrease further with increasing operator experience.

Given the relatively small number of patients, it is premature to opine whether this system is indeed a “one-size-fits-all” ablation technology. But, it is likely that this visually guided ablation system would be best served by the use of a compliant balloon able to better conform to the atrial anatomy. This could result in a greater safety margin between the point of energy delivery and the stagnant distal blood pool, as well as the ability to ablate more proximally in the PV antrum. In addition, it is possible that arcs shorter than 90° to 150° may provide greater flexibility of lesion delivery. It is also possible that other wavelengths of laser energy may prove more efficacious.

Conclusions
This study introduces experimental feasibility and early clinical experience for a novel paradigm to AF catheter ablation: direct endoscopic visualization. Instead of relying on indirect cues to the location of the ablation catheter in relation to the LA-PV anatomy, endoscopic visualization permits the operator to directly visualize the tissue being targeted for ablation, an approach moving ever so closer to approximating the surgical experience.

Source of Funding
This study was supported by CardioFocus Inc.

Disclosures
Drs Reddy, Neuzil, Themistoclakis, Bonso, Rossillo, and Raviele have received research grant support from CardioFocus Inc. Dr Schweikert has received honoraria from CardioFocus Inc. The other authors report no conflicts.

References

Reddy et al Visually Guided AF Ablation


**CLINICAL PERSPECTIVE**

Catheter-based electric isolation of the pulmonary veins can successfully treat patients with paroxysmal atrial fibrillation. Although conceptually straightforward, its clinical application has been hindered by important technical hurdles related to the complexity and patient-to-patient variability of pulmonary venous anatomy, as well as the difficulty in sequentially positioning the ablation catheter in a point-by-point contiguous fashion to isolate the veins. These considerations have led to the development of a balloon ablation catheter equipped with an endoscope that allows direct visualization of the atrial-venous junction and an easily maneuverable optical fiber that projects an arc of ablative laser energy (980 nm) onto the tissue in contact with the balloon face. This novel endoscopic ablation system was used in a series of preclinical porcine experiments and a first-in-human multicenter clinical study. The former demonstrated the feasibility to electrically isolate the pulmonary veins both immediately and persistently. In the clinical phase, a total of 30 patients with paroxysmal atrial fibrillation were treated. In the short term, >90% of the veins were successfully isolated with the balloon system. Long term, the 12-month drug-free freedom from atrial fibrillation after a single procedure was 60%. This study establishes the feasibility for this novel paradigm of catheter ablation of atrial fibrillation. Instead of relying on indirect cues to the location of the ablation catheter in relation to the pulmonary venous anatomy, endoscopic visualization permits the operator to directly visualize the tissue being targeted for ablation, an approach moving ever so closer to approximating the surgical experience.
Visually-Guided Balloon Catheter Ablation of Atrial Fibrillation: Experimental Feasibility and First-in-Human Multicenter Clinical Outcome

Circulation. 2009;120:12-20; originally published online June 22, 2009;
doi: 10.1161/CIRCULATIONAHA.108.840587

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/1/12

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2009/06/19/CIRCULATIONAHA.108.840587.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/