Atrial Fibrillation: Unanswered Questions and Future Directions

Vivek Y. Reddy, MD

KEYWORDS

• Atrial fibrillation • Ablation • New technology

Just over a decade ago, Haissaguerre and colleagues[1] provided the seminal demonstration of the role of pulmonary vein (PV) triggers in the pathogenesis of atrial fibrillation (AF) and the potential therapeutic role of catheter ablation to treat patients who have paroxysmal AF. This initial observation ushered in the modern era of catheter ablation to treat patients who have AF, and tremendous progress has been made in understanding its pathogenesis and the catheter approaches to treating this rhythm. Although the current state of AF catheter ablation is well described elsewhere in this issue, this article reflects on some of the major unanswered questions about AF management, and the future technologic and investigational directions being explored in the nonpharmacologic management of AF.

CATHETER ABLATION OF PAROXYSMAL ATRIAL FIBRILLATION

After the initial demonstration that the PVs harbor most of the triggers for paroxysmal AF, the approach to catheter ablation in this patient population evolved considerably. The initial approaches centered on inducing and identifying the specific AF triggering sites within the PVs and targeting these for catheter ablation.[1,2] From a safety and efficacy perspective, empiric isolation of all PVs was clearly a much more suitable strategy.[3–6]

The poor efficacy of ablating AF triggers stems from the difficulty in inducing these initiating foci during any given electrophysiology ablation procedure. During these early procedures, electrophysiologists often spent many hours with multiple catheters positioned in various PVs waiting for AF-initiating premature ectopic depolarizations to occur. Beyond this prolonged case duration, these procedures were often followed by clinical recurrences related to additional initiating foci at sites completely unelicited during the index ablation procedure. By empirically ablating around the PV ostia to isolate all veins electrically, however, one could ensure that no PV triggers would affect the left atrium, proper.

Empiric PV isolation also has one very important safety advantage compared with focal ablation of AF triggers. Briefly, ablation deep within the PVs can result in PV stenosis, a dreaded complication that has a strong tendency to recur as restenosis after balloon venoplasty. If the circumferential isolating ablation lesion set is placed outside the PVs, however, the risk for stenosis is minimized.

Based on the improved efficacy and safety of empiric PV isolation, several approaches have been forwarded to achieve this electrophysiologic end point. These approaches include using contrast angiography to identify and target the PV ostia; targeting the ostia using electroanatomic mapping systems to localize the catheter tip

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University of Miami Hospital Cardiovascular Clinic, Electrophysiology, So. Building, 1295 NW 14th Street, Miami, FL 33125, USA
E-mail address: v.reddy@miami.edu

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(with or without the incorporation of preacquired three-dimensional CT scans or MRIs); and using intracardiac echocardiography to position a circular mapping catheter at the PV ostia and target the electrograms for ablation. Regardless of the approach used during the index procedure, the mechanism of arrhythmia recurrence is virtually always caused by electrical PV reconnection.[7] That is, point-to-point ablation lesions are placed completely to encircle the PVs during the initial ablation procedure. Because the ablation lesions cannot be directly visualized, however, a surrogate marker for lesion integrity is used: the lack of electrical conduction across the ablation lesions at the end of the procedure. If the tissue at one of these sites is damaged but not fully necrotic from the ablation, however, PV to left atrial conduction can recur several weeks later after tissue healing is complete, leading to clinical AF recurrences. The difference in clinical outcome after ablation of paroxysmal AF is very likely related directly to the ability of the operator to manipulate and stably position the ablation catheter with the requisite force to generate effective ablation lesions.

The most important goal during catheter ablation of paroxysmal AF is to achieve permanent PV isolation. To improve the technical feasibility of the procedure and thereby improve the continuity of the isolating ablation lesion sets, extensive effort has been made to improve the ablation technology. These various technologic advances can be broadly separated into two groups: remote navigation technology to provide for precise navigation with the hope that this translates to improved lesion contiguity, and balloon ablation catheter technology using various ablation energy sources designed to isolate the PVs in a facile manner.

REMOTE NAVIGATION TECHNOLOGY

Currently, two remote navigation systems are available for clinical use: a magnetic navigation system (Niobe II system, Stereotaxis, St. Louis, Missouri) and a robotic navigation system (Sensei system, Hansen Medical, Mountain View, California).

Remote Magnetic Navigation

The magnetic navigation system (**Fig. 1**) uses two large external magnets positioned on either side of the fluoroscopy table to generate a uniform magnetic field (0.08 T) of approximately 15-cm diameter within the patient's chest.[8] Specialized ablation catheters are used with this system; briefly, these catheters are extremely floppy along their distal end, and have magnets embedded at the tip of the catheter. When placed within the patient's heart, the catheter tip aligns with the orientation of the generated magnetic field. The operator uses a software interface to manipulate the magnetic field, and by extension, the tip of the ablation catheter. This ability to manipulate the magnetic field provides the first level of freedom of movement with this system. The other level of freedom

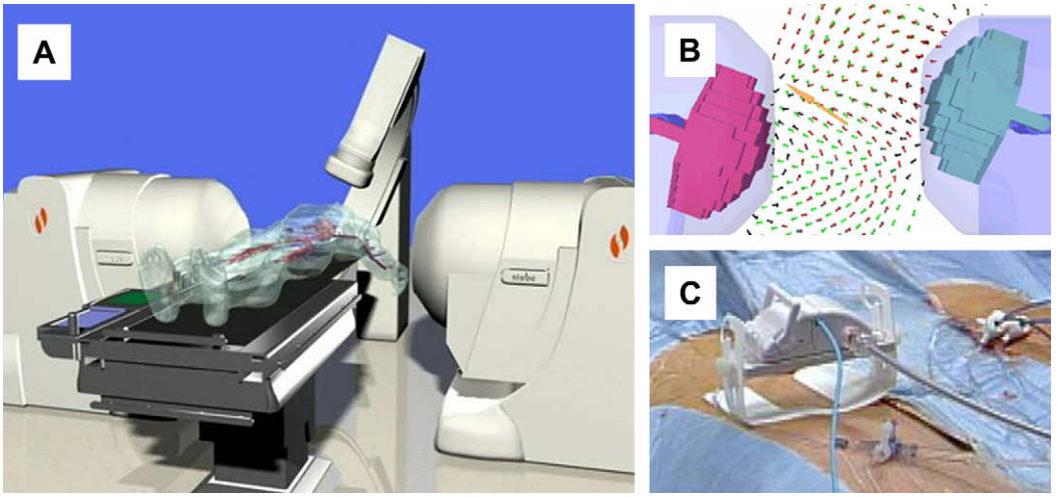

Fig. 1. (*A*) The magnetic navigation system uses two large magnets positioned on either side of the fluoroscopy table. (*B*) These magnets can generate a uniform magnetic field in virtually any direction so that magnetically enabled catheters orient in the same direction as the field. (*C*) A disposable catheter advancement system is positioned at the femoral puncture site to advance or retract the catheter remotely. (*Courtesy of* Stereotaxis, St. Louis, Missouri; with permission.)

of movement is the ability remotely to advance or retract the catheter tip. This function is possible using a computer-controlled catheter advancer system consisting of a disposable plastic unit positioned at the femoral catheter insertion site. The catheter shaft is affixed to this unit where it enters the sheath, and can transduce the remote operator instructions to advance or retract the catheter appropriately. This combination of remote catheter advancement-retraction and magnetic field manipulation allows the operator a great deal of flexibility in intracardiac catheter manipulation.

This magnetic navigation system is now integrated with one of the electroanatomic mapping systems (CARTO RMT, Biosense Webster, Diamond Bar, CA). The mapping system can precisely localize the catheter tip in space to a submillimeter resolution (**Fig. 2**A). Through precisely tracking the catheter location, this combination of mapping and navigation systems allows for a novel capability: automated chamber mapping. Briefly, the operator remotely manipulates the catheter within the left atrium to a few defined anatomic locations (eg, the ostia of the various PVs, the mitral valve annulus) and, based on these parameters, the system automatically manipulates the catheter throughout the chamber to facilitate the creation of an electroanatomic map. Future iterations of the software are planned to allow the system automatically to manipulate the catheter tip to create linear ablation lesions with the chamber as per the operator's wishes. The efficiency and accuracy of these automatic software solutions, however, remain to be determined. The other significant advance is the ability to incorporate preacquired three-dimensional MRIs or CT scans into the system to allow mapping on a realistic model of the heart.

With the current generation software, some clinical data are available on its efficacy for AF ablation. In a consecutive series of 40 patients, Pappone and colleagues[9] used the mapping and navigation systems in tandem to determine the feasibility of circumferential PV ablation in patients undergoing catheter ablation of AF. Using a 4-mm tip ablation catheter (with the requisite embedded magnets), they showed that the left atrium and PVs could be successfully mapped in 38 of 40 patients. Ablation lesions were placed in a circumferential fashion for a maximum of 15 seconds at any endocardial ablation site. They reported that procedure times decreased significantly with increased operator experience. Although this study clearly showed the feasibility of remote mapping of the left atrium and PVs, the procedural end point was not electrical PV isolation in the standard electrophysiologic sense. Instead, the end point was "$>$90% reduction in the bipolar electrogram amplitude, and/or peak-to-peak bipolar electrogram amplitude $<$0.1 mV inside the line."[9] The significance of this end point is unclear.

To address some of these uncertainties, DiBiase and colleagues[10] examined the efficacy of PV isolation using this remote navigation system in

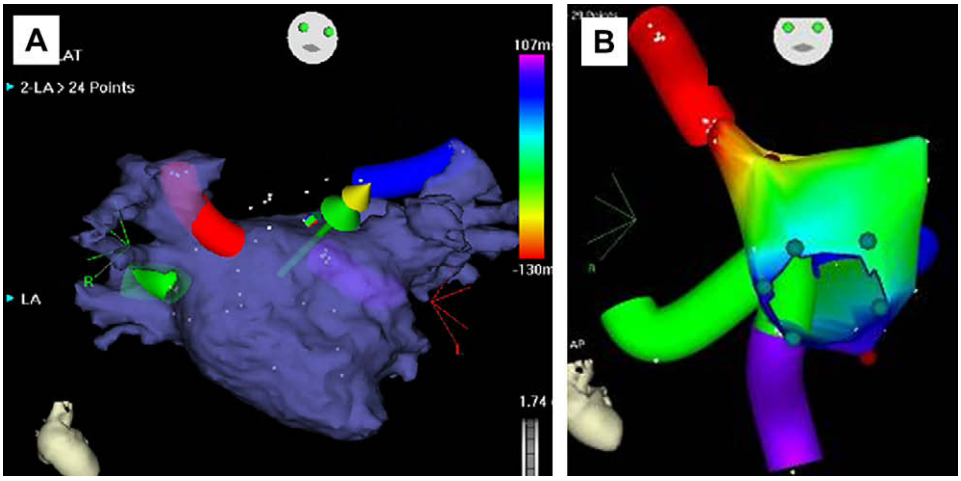

Fig. 2. (*A*) The magnetic navigation system is integrated with an electroanatomic mapping system that also permits integration of three-dimensional CT or MRI models. Once integrated, the magnetic field can be directly controlled with the computer mouse to the desired direction. The yellow arrow represents the current direction of magnetic field and the green arrow represents the desired direction of the field. Note that the catheter is oriented in the same direction as the field. (*B*) Magnetically enabled irrigated ablation catheters are not currently available for clinical use. As shown in this anterior view of the left atrial anatomic map, however, this catheter has been used in experimental protocols to show the ability to map the porcine left atrium and pulmonary veins.

a series of 45 patients using a stepwise approach. First, the ability remotely to map the chamber was again confirmed in this study. Second, these investigators performed circumferential ablation using the same 4-mm tip radiofrequency ablation catheter as described in the initial paper by Pappone and colleagues.[9] When a circular mapping catheter was deployed into the PVs to assess more precisely for vein isolation, no veins in any patient were shown to be electrically isolated. The operators then used the circular mapping catheter to guide the ablation catheter remotely to isolate the vein antra, but electrical disconnection was attained in only four veins in four different patients (8%). In the remaining 41 patients (92%), no evidence was found of disconnection in any of the veins. When the operators then targeted a portion of the veins using a standard manual radiofrequency ablation catheter (ie, not using the remote navigation system), however, they were able to achieve electrical isolation in all attempted veins.

Despite the sharply improved procedural outcome with manual catheter manipulation, concluding that PV isolation is not possible using the magnetic navigation system is inappropriate. Unlike with remote navigation, manual ablation in this study was performed using an irrigated radiofrequency ablation catheter. Unlike with standard radiofrequency ablation, irrigated ablation allows the operator safely to deliver more energy into the tissue, thereby achieving deeper ablation lesions. Significant charring on the ablation catheter tip was seen in 15 (33%) of 45 procedures when using the standard remote 4-mm tip ablation catheter. The critical information that remains to be determined is whether remote PV isolation can be reproducibly achieved using an irrigated ablation catheter. An irrigated ablation catheter with the requisite embedded magnets to permit remote navigation exists but, at the time of this writing, has not been used clinically. In the experimental animal setting, however, the author has shown that this catheter can be remotely manipulated to map all chambers of the porcine heart (**Fig. 2**B), and can deliver ablation lesions of similar quality to those seen using a manual irrigated ablation catheter (Vivek Y. Reddy, unpublished data, 2006). How this finding translates during clinical use of this remote irrigated catheter will not be known until the ongoing studies are completed.

Remote Robotic Navigation

The remote navigation capability of the robotic system (Sensei) is based on multiple pullwires that control the deflection capability of two steerable sheaths.[11,12] Briefly, this is a ''master-slave'' electromechanical system that controls an internal steerable guide sheath and an external steerable sheath (**Fig. 3**). The internal sheath contains four

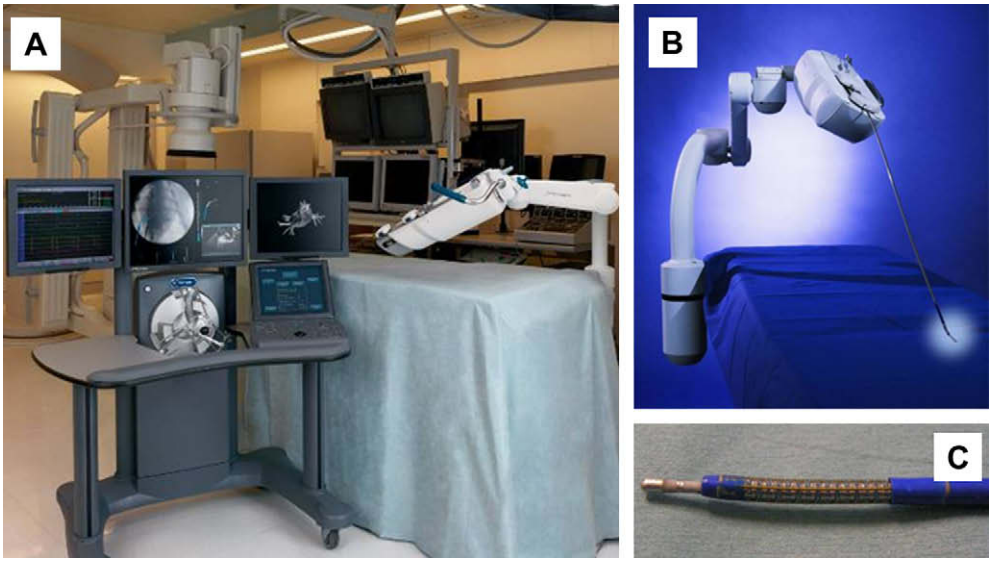

Fig. 3. The primary components of the robotic navigation system are shown (*A*) including the workstation and the robotic arm (*B*), which can be mounted at the foot of any standard fluoroscopy table. The two-piece sheath system extends from this robotic arm and is inserted through the femoral venous puncture site. (*C*) Any standard ablation catheter can be manipulated within the heart by simply placing the catheter within the sheath system so that the tip of the catheter is protruding just beyond the tip of the inner sheath. (*Courtesy of* Hansen Medical, Mountain View, California; with permission.)

pullwires located at each quadrant; the range of motion includes deflection in 360 degrees and the ability to insert and withdraw. The external sheath has a single pullwire to permit deflection, and can rotate and insert and withdraw. This combination of movements allows for a broad range of motion in virtually any direction. Unlike the magnetic navigation system, most standard ablation catheters can be used with this system, because the inner steerable sheath can accommodate any catheter up to 8.3-French catheter diameter. By fixing the mapping-ablation catheter so that it is just protruding beyond the tip of the inner system, remotely driving these steerable sheaths translates to remote navigation of the catheter tip. The steerable sheaths are attached to the remote robotic arm unit, which can be mounted to any standard radiography procedure table. Using a software interface, a three-dimensional joystick allows the operator remotely to drive the catheter tip. Movements of the joystick are translated into a complex series of manipulations by the pullwires governing sheath motion.

The author examined the feasibility of synchronizing this robotic navigation system with electroanatomic mapping and three-dimensional CT imaging to perform view-synchronized left atrial ablation (**Fig. 4**).[13] The mapping catheter was remotely manipulated with the robotic navigation system within the registered three-dimensional CT image of the left atrial PVs. The initial porcine experimental phase (N = 9) validated the ability of view-synchronized robotic navigation to guide atrial mapping and ablation. An irrigated radiofrequency ablation catheter was able to be navigated remotely into all of the PVs, the left atrial appendage, and circumferentially along the mitral valve annulus. In addition, circumferential radiofrequency ablation lesions were applied periosteally to ablate 11 porcine PVs. The consequent clinical phase (N = 9 patients who had AF) established that this paradigm could be successfully applied for all of the major aspects of catheter ablation of paroxysmal or chronic AF: electrical PV isolation in an extraostial fashion, isolation of the superior vena cava, and linear atrial ablation of typical and atypical atrial flutters. The electrophysiologic end point of electrical PV isolation, as verified using a circular mapping catheter, was achieved in all patients. This study showed the safety and feasibility of an emerging paradigm for AF ablation involving the confluence of three technologies: (1) three-dimensional imaging, (2) electroanatomic mapping, and (3) remote navigation. This study involved a minimal number of patients, however, treated by a single center. The long-term safety and efficacy of PV isolation performed by multiple operators in a larger patient cohort using this robotic navigation system remains to be established.

Image Guidance

Three-dimensional imaging is playing an increasingly important role in guiding ablation procedures. It is now standard to integrate patient-specific preacquired three-dimensional models of the left atrium and PVs (generated using either contrast-enhanced CT or MRI) with mapping systems to guide better the ablation procedure (**Fig. 5**).[14–19] This approach is somewhat limited, however, by the variable chamber geometry and size that can

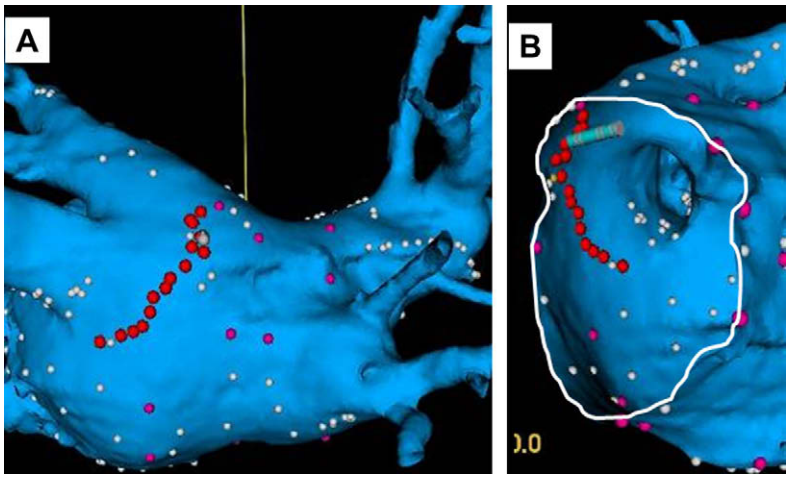

Fig. 4. View-synchronized robotic ablation was performed to treat atrial fibrillation. In this paradigm, the mapping system provided the location of the catheter tip, the CT scan identified where the catheter should be positioned, and the robotic navigation system was used to manipulate the catheter to each location. Shown are an external posterior view (*A*) and a left-sided endoluminal view showing the left pulmonary veins (*B*).

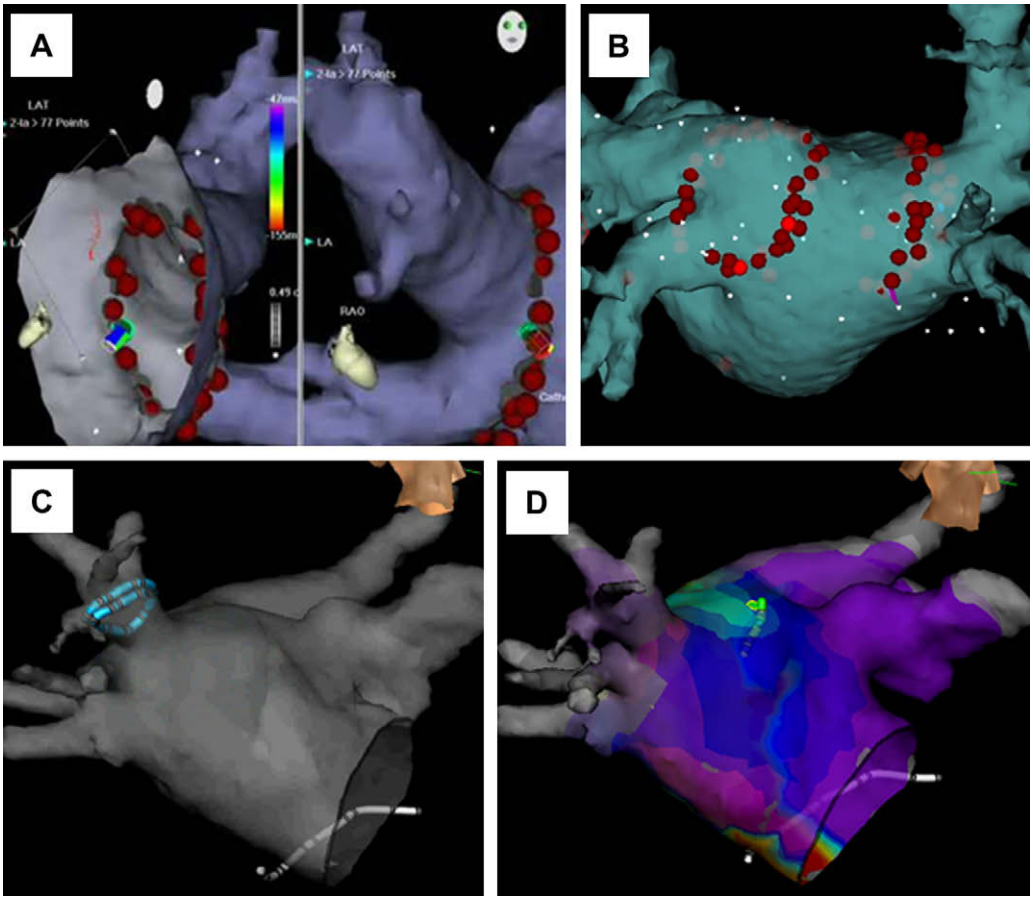

Fig. 5. Three-dimensional CT-MRI integration with electroanatomic mapping systems is now a standard procedure. Once the three-dimensional image is integrated, the ablation catheter can be manipulated to encircle the pulmonary veins with ablation lesions. Shown is integration with either the CARTO RMT (*A*, *B*) or NavX (*C*, *D*) systems.

occur as a result of various physiologic factors, such as heart rate, rhythm, and volume state. Accordingly, a significant amount of effort is being devoted to real-time or near real-time imaging of the three-dimensional chamber anatomy during the ablation procedure. The modalities being explored include ultrasound imaging, three-dimensional rotational angiography, and MRI. Although three-dimensional surface transducers are already available for ultrasound imaging, obtaining accurate images of the left atrium and PVs through surface thoracic imaging can be difficult. Three-dimensional intracardiac ultrasound imaging probes do not currently exist; however, localized three-dimensional intracardiac ultrasound probes exist and can be used to generate three-dimensional images. Briefly, this consists of an intracardiac ultrasound catheter with a localization sensor that precisely provides the location and direction of the catheter. Accordingly, a series of high-resolution two-dimensional images can be "stitched" together to generate a near real-time three-dimensional image.

Rotational angiography consists of the injection of contrast followed by rotation of the x-ray fluoroscopy head around the patient to generate a three-dimensional image.[20,21] For example, the contrast can be injected directly into the pulmonary artery, and imaging can be performed during the levo-phase after the contrast traverses the pulmonary vascular bed and flows back through the PVs into the left atrium. As shown in **Fig. 6**, a volumetric three-dimensional image of the left atrium and PVs can be generated through properly timing the rotation of the x-ray fluoroscopy unit. The quality of these three-dimensional rotational angiography images was compared with the gold standard, preacquired, three-dimensional CT scans or MRIs in a consecutive series of 42 patients undergoing AF ablation procedures.[21]

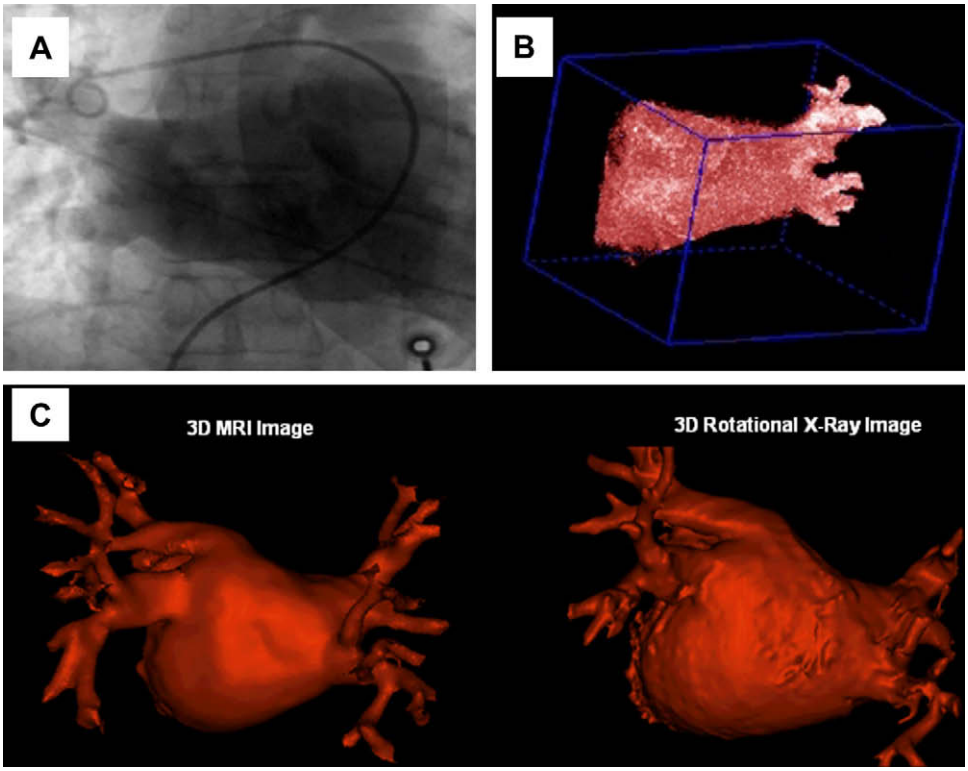

Fig. 6. Rotational angiography imaging can be used to generate volumetric images of the left atrium and pulmonary veins. Contrast is injected from a pigtail catheter positioned in the pulmonary artery, and rotational imaging is performed during the levo phase as the contrast courses back into the left atrium from the pulmonary veins (*A*) to generate a volumetric image of this anatomy (*B*). (*C*) These intraprocedural rotational images are of comparable quality to preacquired three-dimensional MRIs or CT scans.

In this series, most of the three-dimensional rotational angiography acquisitions (71%) were qualitatively sufficient in delineating the left atrial and PV anatomy. A blinded quantitative comparison of PV ostial diameters resulted in an absolute difference of only 2.7 $\pm$ 2.3 mm, 2.2 $\pm$ 1.8 mm, 2.4 $\pm$ 2.2 mm, and 2.2 $\pm$ 2.3 mm for the left-superior, left-inferior, right-superior, and right-inferior PVs, respectively. In addition, the feasibility for registering the three-dimensional rotational angiography image with real-time electroanatomic mapping was also shown. More recent reconstruction algorithms that can resolve soft tissue structures are likely further to increase the capability of three-dimensional rotational angiography through improving the image quality of data obtained with the current strategy (of intracardiac contrast injection) and potentially allowing for CT-like imaging of the left atrium and PVs using a peripheral intravenous injection of contrast.

Real-time interventional MRI involves the concept of performing the entire procedure in the MRI environment.[22] In this paradigm, various MRI-compatible catheters are continuously imaged as they are positioned within the patient anatomy. MRI has the advantage of using nonionizing radiation, the ability to resolve soft tissue with high resolution, and the potential for physiologic imaging; for example, during liver tumor ablation, MRI-based thermal imaging has been used directly to image ablation lesion formation. Although this modality is in some respects the most powerful, it is also the one furthest away from clinical practice. A significant amount of research and development is required in the MRI scanning equipment and protocols and MRI-compatible equipment (eg, catheters, patient monitoring equipment). Each of these three-dimensional imaging modalities will likely show a tremendous amount of progress.

BALLOON ABLATION CATHETERS

A significant effort has been put into developing balloon ablation catheter designs quickly, easily, and effectively to isolate the PVs. The first device

tested clinically was an ultrasound balloon ablation catheter that delivered energy in a radial fashion at the level of the diameter of the balloon, hence necessitating that the balloon catheter be placed within the PV when delivering energy.[23] This balloon design was suboptimal because the level of electrical isolation typically excluded the proximal portions of the vein, and PV triggers of AF located at this region are not included in the ablation lesion.[24] From a safety perspective, the intravenous location of the energy delivery resulted in PV stenosis. Since this first-generation device, balloon ablation catheters have evolved considerably. Four major balloon-based ablation devices are now used at various stages of clinical evaluation: (1) cryoballoon ablation, (2) endoscopic laser ablation, (3) high-intensity focused ultrasound, and (4) balloon-based radiofrequency ablation (**Fig. 7**). Each of these devices was fashioned to be placed at the PV ostia theoretically to isolate the veins outside their tubular portion.

Balloon Cryoablation

The cryoballoon system is a deflectable catheter (manufactured by Cryocath Technologies, Montreal, Quebec, Canada) with a balloon-within-a-balloon design wherein the cryo refrigerant (N_2O) is delivered within the inner balloon. A constant vacuum is applied between the inner and outer balloons to ensure the absence of refrigerant leakage into the systemic circulation in the event of a breach in the integrity of the inner balloon. The cryoballoon catheter is manufactured in two sizes: 23 mm and 28 mm in diameter. After transseptal puncture, the deflated balloon catheter is deployed through a 12-French catheter deflectable sheath. Once within the left atrium, the inflated balloon is positioned at each respective PV ostium to occlude blood flow temporarily from the targeted vein. Each balloon-based cryoablation lesion lasts 4 minutes. Because the cyrorefrigerant is delivered to the whole face of the balloon, any tissue in contact with the balloon is ablated. This function can be safely performed because the experimental results have shown that cryothermal ablation is associated with a minimal risk of PV stenosis.[25,26] Similarly, no evidence of stenosis has been seen in the clinical experience, perhaps because at the temperatures achieved with this system, the cryoablative energy is selective toward the cellular elements of the tissue and leaves the connective tissue matrix intact. Accordingly, cryothermy as an energy source seems to have a good safety profile. The long-term efficacy of achieving permanent PV isolation, however, has not been established.

Balloon-Based Visually Guided Laser Ablation

The most unique aspect of this system is the capability for endoscopic visualization using a 2-French catheter endoscope positioned at a proximal location in the balloon. This 12-French catheter laser ablation catheter system (CardioFocus, Marlborough, MA) is delivered using a deflectable sheath. Once in the left atrium, a 20-mm, 25-mm, or 30-mm diameter balloon is inflated and positioned at the PV ostia. The endoscope allows the operator to visualize the internal face of the balloon and identify areas of balloon-tissue contact (blanched white) versus blood (red).[27] An optical fiber that projects a 90-degree to 150-degree arc is advanced and rotated to the desired location for energy delivery. Once the proper location is identified, a diode laser is used to deliver laser energy at 980 nm to isolate electrically the PV. This endoscopic laser balloon catheter provides greater flexibility to the location of energy

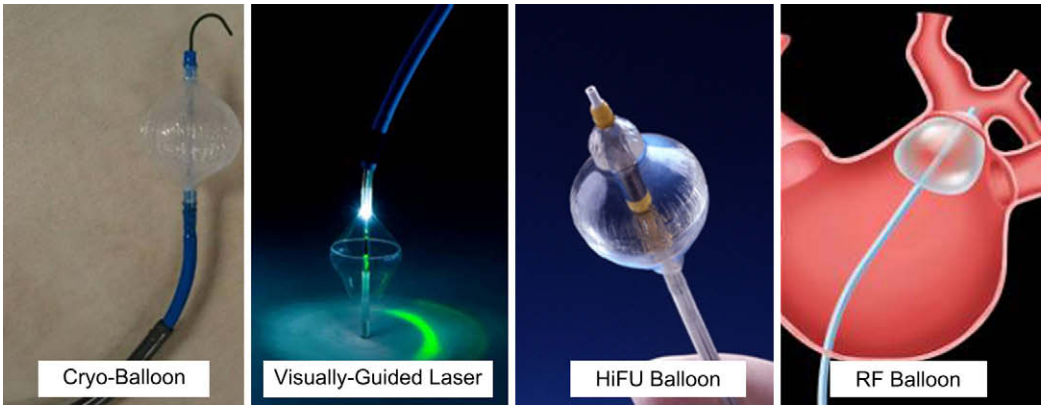

Fig. 7. Four major balloon ablation catheter technologies are currently in clinical trials to assess their safety and efficacy in treating patients who have paroxysmal AF.

deposition and the total amount of energy applied to each site. For example, a greater amount and duration of energy may be applied anteriorly along the ridge between the left-sided PVs and left atrial appendage than that applied along the thinner posterior wall near the course of the esophagus.

Balloon-Based High-Intensity Focused Ultrasound Ablation

The high-intensity focused ultrasound catheter (ProRhythm, Ronkonkoma, NY) is a 14-French catheter system that, once inflated, consists of a fluid-filled balloon in front of a smaller carbon dioxide–filled balloon.[28] The ultrasound transducer delivers energy in a radially directed fashion; this energy reflects off the air-fluid interface to project forward and deposit and concentrate just beyond the face of the balloon. Because of the minimal chance of clot formation when sonicating through blood, contact with the atrial tissue is not necessary for ablation with this catheter. This deflectable catheter is delivered using a nondeflectable 14-French catheter sheath. Lesions are delivered using either a 20-mm or 25-mm diameter balloon catheter for 40 to 60 seconds per lesion. To use this technology to ablate the PVs, a series of partially encircling ablation lesions sometimes must be stitched together as the balloon is precessed about the orifice of each vein.

Balloon-Based Radiofrequency Ablation

This elastic balloon ablation catheter (Toray Industries, Tokyo, Japan) is made of a heat-resistant, antithrombotic resin. Inside the fluid-filled balloon are a coil electrode for the delivery of radiofrequency energy and a thermocouple to monitor the electrode temperature.[29] The radiofrequency generator delivers a high-frequency current (13.56 MHz) to induce capacitive-type heating of the tissue in contact with the balloon. The energy output is modulated to maintain the temperature in the balloon at 60°C to 75°C. During each application of energy, the venous blood is continuously suctioned through the central lumen of the catheter to protect the PV blood from excessive heating, preventing thrombus formation beyond the face of the balloon.

Clinical Overview of Balloon-Based Pulmonary Vein Isolation

Analysis of three-dimensional left atrial–PV surface reconstructions from MRI datasets on patients who had paroxysmal AF showed a marked intrapatient and interpatient variability in PV ostial size and geometry.[30] The challenge to each of the balloon ablation catheters is to negotiate this venous anatomy so that the lesions are proximal enough to include all of the potentially arrhythmogenic periostial tissue and minimize the risk for PV stenosis. The energy source used also has important implications on the ablation strategy. For example, cryothermal ablation is believed to portend minimal risk for PV stenosis. A balloon cryoablation catheter may be used safely even deep within large common PVs (ie, within the common truck separately to isolate the individual superior and inferior PVs). The adjustable lasing element of the endoscopic balloon catheter, however, allows the operator to vary the circumference and location of the ablative beam. This catheter design may be considerably useful in patients who have veins with marked variability in size and shape. Alternatively, because high-intensity focused ultrasound energy can be delivered through blood with minimal risk, this energy modality might be efficacious in isolating large PV ostial or antral regions through delivering a series of sequential lesions as it is precessed about the long axis of the targeted vein.

Although the clinical experience is still very early, the results from nonrandomized feasibility studies suggest that most patients who have paroxysmal AF can be treated successfully with these balloon devices. Several balloon ablation catheters have received regulatory approval for clinical use in Europe, but none have been approved for general clinical use in the United States. Most of these devices are being studied in a randomized fashion versus antiarrhythmic medications in the United States. These investigations should determine conclusively whether all or any of these catheters can provide facile, safe, and reproducibly effective PV isolation.

CATHETER ABLATION OF NONPAROXYSMAL ATRIAL FIBRILLATION

Unlike catheter ablation of paroxysmal AF, considerably less consensus exists as to the proper approach to catheter ablation of chronic AF. There is a growing understanding that as the pathophysiology of AF progresses from the paroxysmal to the persistent and eventual permanent state, significant electrophysiologic and structural changes occur. These changes in ion channel physiology and increased extracellular fibrosis are believed to potentiate atrial myocardial substrate-driven reentry. When progressing on the continuum from paroxysmal to permanent AF, the pathophysiologic importance of focal triggers diminishes and the importance of substrate-driven reentry increases. Furthermore, because the latter perpetuating sources of AF are typically located

outside the PVs in the atrial tissue itself, the efficacy of PV isolation alone is believed to decline in nonparoxysmal AF. This hypothesis has never been addressed conclusively, however, because of the clinical difficulty in achieving permanent PV isolation. That is, because permanent vein isolation is difficult to achieve reproducibly, whether the cause of clinical arrhythmia recurrence is resumption of PV conduction or from the extravenous perpetuators of AF cannot be determined. If one or more of the balloon ablation catheters can consistently achieve permanent PV isolation, this cause can be determined. Because of the limitations of current technology, however, a PV isolation-alone strategy is ineffective in many patients who have nonparoxysmal AF.

Intraoperative mapping studies of AF suggested the role of perpetuators of AF. These studies showed that complex fractionated atrial electrograms (CFAEs) were observed mostly in areas of slow conduction or at pivot points where the wavelets turn around at the end of the arcs of functional blocks (**Fig. 8**).[31] These areas of fractionated electrograms during AF represent either continuous reentry of the fibrillation waves into the same area, or overlap of different wavelets entering the same area at different times. This complex electrical activity was characterized by a short cycle length and heterogeneous temporal and spatial distribution in humans. This observation led Nademanee and colleagues[32] to hypothesize that, if the areas of CFAEs could be identified through catheter mapping during AF, locating the areas where the wavelets reenter would be possible. They showed that they could terminate AF in 95% of patients, and reported that most patients were free of arrhythmia symptoms after these CFAE sites were ablated. These investigators concluded from this experience that CFAE sites represent the electrophysiologic substrate for AF and can be effectively targeted for ablation to achieve normal sinus rhythm.

Despite these encouraging clinical results, one of the difficulties other investigators have encountered in attempting to reproduce these results is the relative subjectivity inherent in defining whether a particular electrogram is complex enough to warrant ablation. To standardize the definition of a CFAE site, signal processing software to analyze atrial electrograms during AF is being developed. Several mapping systems now contain signal processing software to quantify the degree of electrogram complexity. Further clinical work is necessary, however, to determine whether catheter ablation of the sites identified by these software algorithms can truly convert AF into sinus rhythm.

Given the current clinical data, catheter ablation of chronic AF has evolved into an approach that incorporates strategies to address the AF triggers and perpetuators (ie, electrical isolation of the PVs to isolate the former, and ablation within the atria to eliminate the latter). Specifically, this stepwise approach initially involves electrical PV isolation and then targeting of CFAE sites within the left atrium, particularly the interatrial septum, the base of the left atrial appendage, and the inferior left atrium along the coronary sinus.[33] During this progressive ablation strategy, the rhythm often converts from AF to organized macroreentrant or microreentrant atrial tachycardias. These organized atrial tachycardias are then targeted for ablation to terminate the rhythm to sinus. Although feasible, this approach is limited by the long procedural duration and the extremely high rate of atrial tachycardia recurrence mandating second, and even third, ablation procedures.[34]

Further technical and scientific advances are required to refine the ablation approach to overcome these limitations. One promising approach to these reentrant atrial tachycardias is to use multielectrode mapping catheters in conjunction with advanced mapping systems rapidly to map these complex tachycardias (**Fig. 9**). In conclusion, although many questions are unanswered regarding ablation of nonparoxysmal AF, many patients at this end of the disease spectrum clearly require a more extensive procedure that is still being defined.

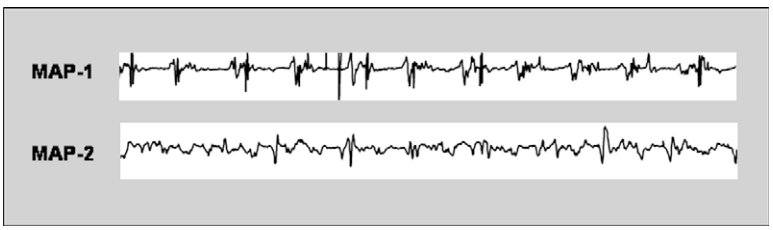

Fig. 8. Shown are two electrograms during AF. MAP-1 is a site with the usual degree of complexity (likely a passive site that would not be targeted for ablation), whereas MAP-2 is a site of complex fractionated activity (this site would be targeted for ablation). Note the continuous nature of electrogram activity in the latter.

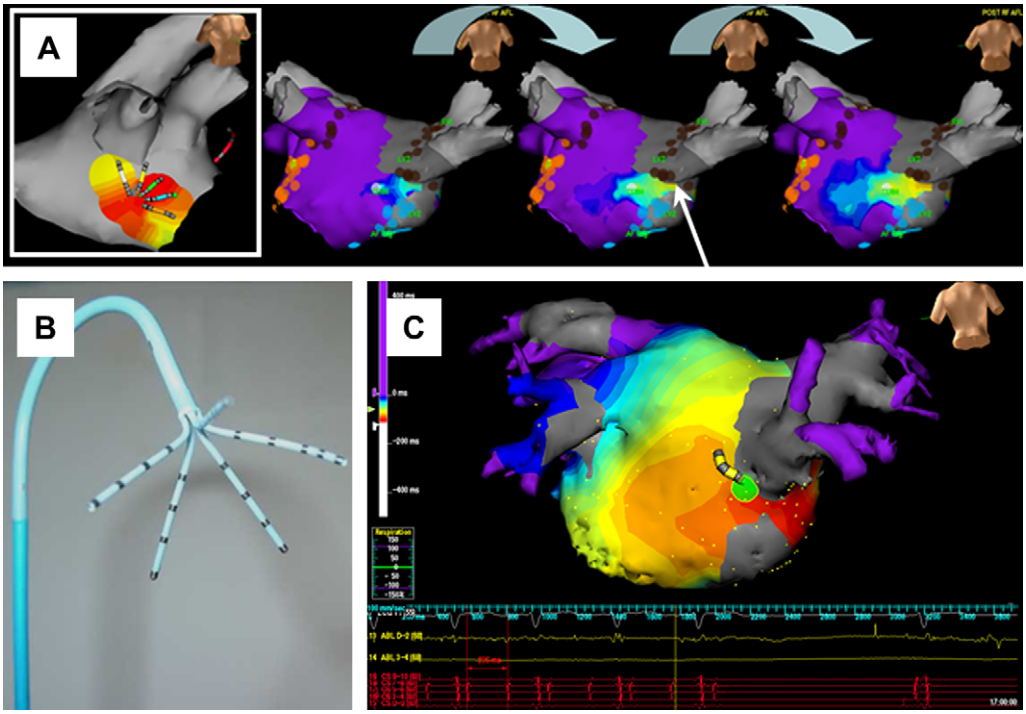

Fig. 9. (*A*) One paradigm for rapid mapping of an atypical atrial flutter seen during an ablation procedure for nonparoxysmal AF. After isolating the pulmonary veins and placing additional lesions at sites of CFAEs, the rhythm had organized to the atypical flutter. (*B*) Using a penta-array catheter in conjunction with an electroanatomic mapping system (NavX), the atrium was rapidly mapped. Activation mapping showed an area of percolation of activity (*A, arrow*) between the previously placed ablation lesions isolating the right inferior pulmonary vein and the inferior left atrium region below the right inferior pulmonary vein. Entrainment of the flutter from this site showed a postpacing interval–tachycardia cycle length. (*C*) As shown on the activation map projected onto a three-dimensional CT image, an ablation lesion placed at this location terminated and eliminated the flutter.

THE SAFETY OF ATRIAL FIBRILLATION ABLATION

When performed by experienced operators, catheter ablation of AF is not a very high-risk procedure. As with all procedures, however, several potential complications are associated with ablation. Accordingly, improving the safety of the procedure has been and continues to be an important area of investigation. Several complications are associated with AF ablation, but the most important are PV stenosis, thromboembolism and stroke, perforation with cardiac tamponade, phrenic nerve injury, and atrioesophageal fistula.

It is now well established that if too much radiofrequency energy is applied within a PV, stenosis can occur.[35,36] Although this complication was common early in the ablation experience, symptomatic PV stenosis is now uncommon, with a frequency of approximately 1%. This decreased incidence is partly a result of the more careful use of various imaging modalities (eg, intracardiac ultrasound, three-dimensional CT and MRI) to prevent inadvertent ablation deep within a PV (**Fig. 10**). Future developments include continued refinements in real-time imaging, such as three-dimensional ultrasound imaging or direct visual guidance (eg, endoscopic visualization using the laser balloon catheter), and the use of alternative energy modalities, such as cryothermal energy, that seem to have minimal risk for PV stenosis.[37]

During radiofrequency energy delivery, the temperature of the catheter tip increases when in contact with the tissue being ablated. When this temperature exceeds approximately 50°C, however, coagulum can accumulate and embolize to cause a stroke. The simple solution has been to irrigate the tip of the ablation catheter with saline to prevent overheating. Future approaches include the use of other ablation technologies that either work by generating more volumetric heating (eg, focused ultrasound, laser energy) or have an inherently low thrombogenic potential (eg, cryothermal energy).

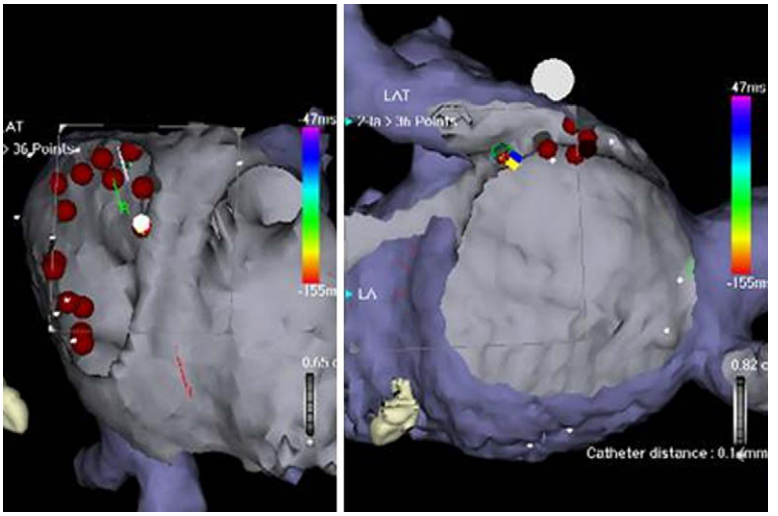

Fig. 10. Using a properly registered CT image, the ablation catheter is precisely positioned at the ridge, separating the left pulmonary veins and left atrial appendage. In avoiding placing the catheter deep inside the pulmonary vein, the risk for pulmonary vein stenosis can be minimized. An endoluminal image of the left pulmonary veins (*left*) and a posterior view with the posterior atrial wall clipped away to show the relative incursion of the ablation catheter into the pulmonary vein (*right*).

When too much radiofrequency energy is delivered into the tissue, steam formation can rapidly occur, culminating in a "pop." Although some of these pops are clinically insignificant, others can result in cardiac perforation and pericardial effusion with tamponade physiology. The amount of power that qualifies as too much varies significantly, however, according to the catheter tip–tissue contact force. That is, mild contact may require 35 W of energy to generate an adequate lesion, but forceful contact with the tissue may require only 15 W, with 35 W causing a pop. One of the important areas of active investigation is the development of a force-sensing mechanism on the catheter tip to optimize energy delivery.

The right phrenic nerve is typically located just lateral to the superior vena cava in proximity to the right superior PV but several centimeters distal to the vein ostium. Phrenic nerve injury can occur if radiofrequency energy is delivered at this location.[38] From a practical perspective, this complication is now uncommon during radiofrequency ablation, because ablation is now typically delivered at the vein ostium and not within the vein. Because of the typical funnel-shaped morphology of the right superior PV, however, balloon ablation catheters tend to lodge further inside the vein. Accordingly, phrenic nerve injury has been a more common issue associated with these devices. One of the important goals in the further development of these balloon catheters is either to minimize the impact of this complication or to avoid this complication altogether.

Although certainly one of the most infrequent complications associated with AF ablation (estimated at less than 1:10,000), atrioesophageal fistula formation remains the most feared because of its high mortality. This complication occurs from inadvertent damage to the esophagus as ablation energy is applied to the posterior left atrium.[39–41] Although the exact pathophysiology of atrioesophageal fistula formation is unknown, the outcome is dismal.[42] Recent experience suggests that early recognition and treatment may prevent a fatal outcome. With an esophageal ulcer, mild interventions may be required, such as treatment with proton-pump inhibiting medications and not giving patients anything by mouth. Esophageal stent placement has been used successfully, however, in a patient who had a transmural esophageal ulcer, without a frank fistula to the atrium.[43] Furthermore, with prompt recognition that an atrioesophageal fistula has already formed, cardiac surgery can correct the defect.

Although the best strategy is prevention, further work is needed to define best the most appropriate means to avoid esophageal injury. The strategies that are currently being used include minimizing the overall amount of energy delivered to the posterior wall, visualizing the real-time position of the esophagus during catheter ablation with either intracardiac ultrasound or fluoroscopy, and esophageal temperature monitoring to help titrate the magnitude and duration of energy delivery. Two other concepts being explored are the use of a cooling balloon catheter placed inside the esophagus to counteract the thermal effect of the ablation energy, and deflecting an endoscope positioned within the esophagus to deviate it away from the ablation catheter.[44,45] Further work is required to determine fully the usefulness of these various maneuvers. This investigation is particularly important as the ablation energy sources become progressively more powerful (eg, balloon ablation catheters).

STROKE PROPHYLAXIS IN PATIENTS WHO HAVE ATRIAL FIBRILLATION

Little doubt exists that warfarin treatment should be instituted in patients who have AF and additional risk factors (eg, advanced age, hypertension, congestive heart failure, diabetes, prior personal history of thromboembolism). Less well-understood, however, is whether successful catheter ablation can substantially and favorably modify this risk to obviate the need for oral anticoagulation treatment. Some data suggest that catheter ablation can favorably modify the risk to a level safe without warfarin.[46] One very important observation from the Atrial Fibrillation Follow-up Investigation of Rhythm Management study, however, was that patients who were believed to be treated successfully with antiarrhythmic medications still developed strokes as a result of asymptomatic AF.[47] Although catheter ablation can treat symptoms of AF, further studies are required to assess fully the effect of ablation on the long-term risk for thromboembolism and stroke.

Several other oral anticoagulant medications are being investigated as alternatives to warfarin (discussed elsewhere in this issue), but none has gained clinical approval. One nonpharmacologic approach is currently being investigated, however, as an alternative to warfarin: the Watchman device. This device consists of a nitinol spline and is covered by a 120-μm pore filter made of polytetrafluoroethylene. When delivered through a long transseptal sheath, it can be placed at the ostium of the left atrial appendage to cause permanent occlusion (**Fig. 11**). After undergoing significant evolution in a preliminary safety study, the device is now being studied in the pivotal phase in the United States.[48] In this US Food and Drug Administration study, patients who have AF and at least one other risk factor for stroke are randomized to treatment with either the Watchman device or continued usual therapy (warfarin), with stroke as the primary end point.[49] This noninferiority study is designed to determine whether the Watchman device can replace warfarin for treating patients who have AF. In addition to assessing the safety of the Watchman device, this study directly assesses the true import of the left atrial appendage in the pathogenesis of stroke in patients who have AF. If positive, the Watchman device may be relevant in managing patients who have asymptomatic AF who do not want to

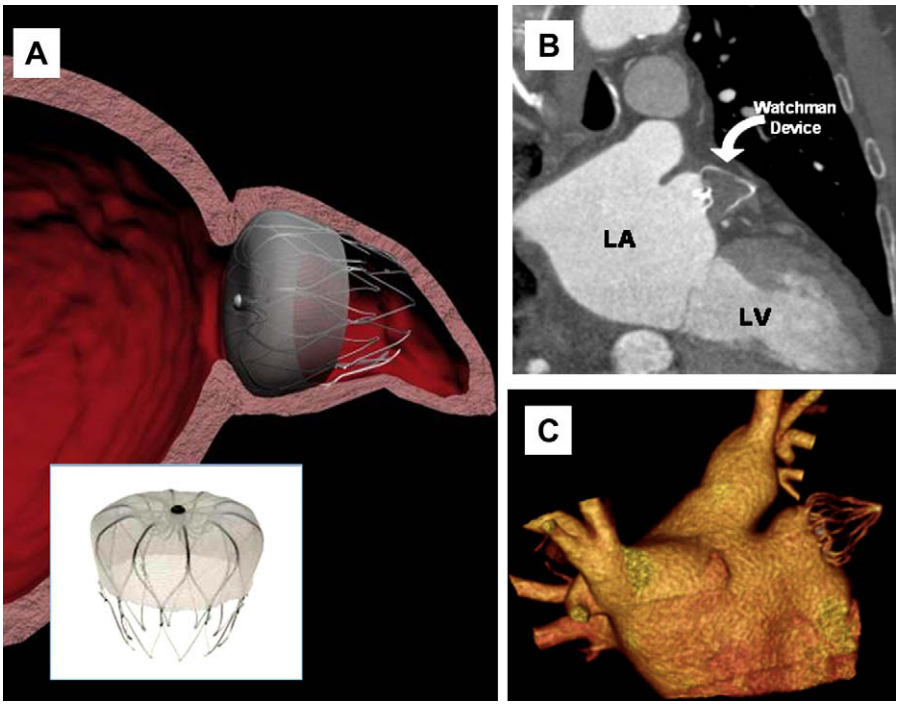

Fig. 11. The Watchman device (*A*, *inset*) is designed to occlude the left atrial appendage at its ostium. In a patient treated with this device, two-dimensional (*B*) and three-dimensional (*C*) CT images of the left atrium were obtained 1 year after implantation. Note the location of the Watchman device and the absence of contrast in the left atrial appendage, indicating its successful exclusion from the systemic circulation. (Part A *Courtesy of* Atritech, Plymouth, Minnesota; with permission.)

take warfarin and those who undergo catheter ablation (as concomitant therapy).

SUMMARY

Considerable progress has been made in understanding the pathogenesis of and approaches to the treatment of AF. More unanswered questions than answered questions remain, however, including the following:

- What is the best approach to achieve permanent PV isolation?
- Which patients who have nonparoxysmal AF can be treated with PV isolation alone?
- What is the proper follow-up for patients who have undergone AF ablation?
- How much ablation should be performed during catheter-based substrate modification of nonparoxysmal AF?
- Which energy sources are the best for achieving long-term safety while maintaining an acceptable level of efficacy?
- What are the precise electrogram characteristics during AF that best identify an active source of AF as opposed to irrelevant areas of passive activation?
- In which patients can warfarin treatment be stopped after catheter ablation?

Further studies are required to answer these questions.

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