Atrial fibrillation ablation

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Mapping systems.

Radiofrequency catheter ablation is currently used widely and successfully to treat a variety of arrhythmias, and ablation for atrial fibrillation represents the frontier of arrhythmia research. Development in many areas will offer to the electrophysiologic community a more rational and effective background upon which select patients for ablation and identify the optimal ablative strategy. Among mechanisms recognized for having a role in atrial fibrillation stay pulmonary vein focal triggers, rotor at the pulmonary vein-left atrial junction, a critical mass to sustain fibrillatory conduction and vagal ganglia. The latter represents the frontier of research as with new technologies based on magnetic resonance imaging they could be easily and specifically identified and targeted for ablation. It is fundamental that both CARTO and NavX systems are currently investigating integration with magnetic resonance imaging to reconstruct the left atrium. Furthermore a learning curve effect can be abated with the use of new systems for the remote control of the catheter such as stereotaxis. In the last decade, we empirically devised a technique that is both safe and effective for curing atrial fibrillation. Briefly, using a three-dimensional mapping system, either CARTO or NavX system, we reconstruct the left atrium and the pulmonary ostia; thereafter circumferential ablation lines are normally created starting at the lateral mitral annulus and withdrawing posterior then anterior to the left-sided pulmonary veins, passing between the left superior pulmonary vein and the left atrial appendage before completing the circumferential line on the posterior wall of the left atrium. The right pulmonary veins are isolated in a similar fashion, and then a posterior line connecting the two circumferential lines on the roof is performed to reduce the risk of macroreentrant atrial tachycardias. The endpoint for circumferential ablation is a > 70-90% reduction in voltage within the isolated regions.

In this article we sought to describe critical methodological aspects of our techniques along with future implementation with new technologies and to summarize our published clinical experience on the most prestigious journals.

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Circumferential pulmonary vein ablation (CPVA) for patients with atrial fibrillation (AF) is an effective treatment and is becoming more widely practiced and accepted[1]. In this article we sought to describe critical methodological aspects of our techniques along with future implementation with new technologies and to summarize our published clinical experience on the most prestigious journals.

Patient selection

Inclusion and exclusion criteria are reported in table I[2].

Technical aspects

Three catheters are usually used: a standard bi- or quadripolar catheter in the right ventricular apex to provide back-up pacing; a quadripolar catheter in the coronary sinus (CS) to allow pacing of the left atrium (LA); and the ablation catheter which is passed into the LA following transseptal puncture with a standard Mullins sheath[2].

During navigation and ablation power and impedance as well as electrical activity are continuously monitored. We use 8 mm tipped catheters to avoid thrombus formation particularly as we use higher power (100 W) and temperature settings (65°C). If thrombus forms on the catheter tip, the impedance may suddenly increase, however in our experience, a much more useful indicator is a reduction of 40-50% in the power being delivered to reach target temperature[2]. Alternatively we can also use a 3.5 mm irrigated-tip catheter with continuous saline infusion at a rate of 20 ml/min. Indeed, active cooling of the electrode with saline during ablation allows the delivery of energy while minimizing the risk of overheating the electrode tip. Lesion sizes are consistent irrespective of catheter tip orientation with a larger proportion of the

Table I. Patient selection criteria.

Inclusion criteria
At least one monthly episode of persistent symptomatic AF
At least one weekly episode of paroxysmal AF
Permanent AF
At least one failed trial of antiarrhythmic drugs
More than one antiarrhythmic drug to control symptoms
Exclusion criteria
NYHA functional class IV
Age > 80 years
Contraindications to anticoagulation
Presence of cardiac thrombus
Left atrial diameter ≥ 65 mm
Life expectancy < 1 year
Thyroid dysfunction
Recent updates
Patients with mitral and/or aortic metallic prosthetic valves are not excluded
Previous repair of atrial septal defects is not an absolute contraindication

AF = atrial fibrillation.

catheter electrode in contact with the tissue and a more predictable lesion size as well as more uniform lesion shape result[3].

Mapping systems

The CARTO system. The CARTO system (Biosense-Webster, Diamond Bar, CA, USA) correlates electrophysiologic characteristics with endocardial anatomy by continuously recording mapping catheter location[4]. With this system, a mapping catheter with tip and proximal electrodes to record unipolar and bipolar signals is advanced percutaneously to the chamber of interest. Catheter position is recorded relative to the location of a reference back patch, thus compensating for subject motion within the coils' fields. The mapping procedure involves positioning the mapping catheter at sequential points along the endocardium. Catheter tip location and electrograms are simultaneously acquired while the catheter remains in stable contact with the endocardium. Local activation times are calculated relative to the body surface ECG or to a fixed (reference) intracardiac electrode. The system continuously monitors the quality of catheter-tissue contact and local activation time stability to ensure validity and reproducibility of each local measurement. The acquired information is then color-coded and displayed. As each new site is acquired, the reconstruction is updated in real time to progressively create a three-dimensional chamber geometry color encoded with activation times. In addition to activation time maps, dynamic propagation maps displayed as movies of sequential activation on the computer workstation can be created. Moreover, the collected data can be displayed as voltage maps (substrate maps) depicting the magnitude of the local peak voltage in a three-dimensional model (Fig. 1). These can be useful to define scare areas and electrically diseased tissue. This system allows precise positioning of the catheter tip at a site of interest that was previously sampled, tagging of regions of interest such as ablation points, and marking positions of veins and valves, with high spatial resolution (< 1 mm). The three-dimensional electroanatomic reconstruction of the targeted atrium and catheter navigation facilitate linear lesion creation by "tagging" ablation sites on the map, but catheter "reach" remains challenging. Another technical challenge is assuring the "completeness" of ablation lines, because gaps that permit impulse conduction often are proarrhythmic and lead to incisional flutters. Electroanatomic mapping can confirm line integrity, but the entire length of the linear lesion must be retraced with the mapping catheter while pacing from a second site.

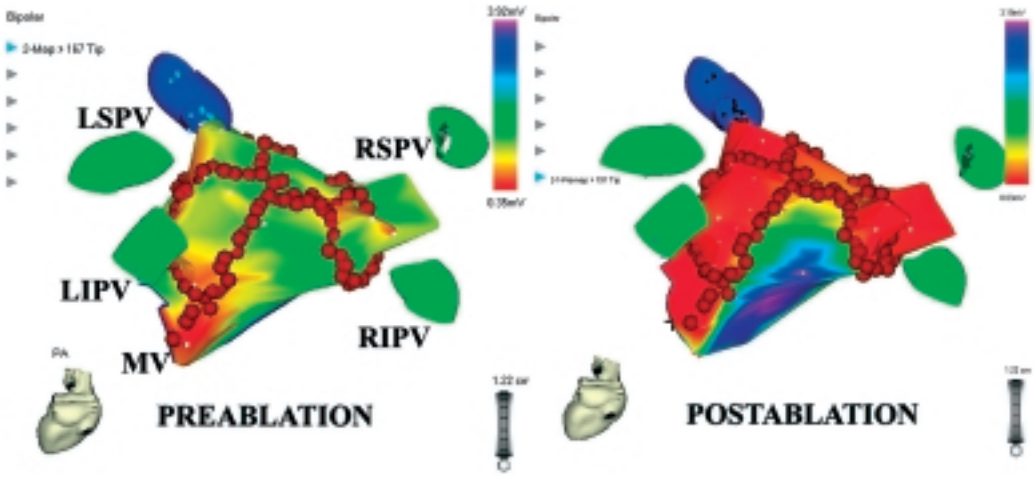

Figure 1. *Three-dimensional left atrial voltage maps (postero-anterior view:* left, *pre-ablation;* right, *post-ablation), depicting peak-to-peak bipolar electrogram amplitude obtained with the CARTO system. Color red represents the lowest voltage, and purple the highest voltage. Claret red spheres represent radiofrequency lesions. Post-ablation: areas within and around the ablation lines, involving to some extent the left atrial posterior wall, show low-amplitude (≤ 0.1 mV) electrograms. LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; MV = mitral valve; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.*

The mapping and ablation procedures are performed by using the CS atrial signal if the patient is in sinus rhythm or the right ventricular signal if the patient is in AF, as the synchronization trigger for CARTO. If spontaneous ventricular rates during AF are too low, we usually pace the right ventricle at higher rates to increase the CARTO system sampling rates. If the patient is in sinus rhythm we map during continuous CS pacing to increase the refresh rate.

Among advantages of the CARTO system lye the accurate anatomic reconstruction, the validation in several published reports showing safety and efficacy, the possibility of magnetic resonance imaging (MRI) anatomy merging into CARTO maps and the ongoing integration with stereotaxis technology (see below). A new evolution of the CARTO system is *CARTOMerge*. This system includes acquisition on real anatomy on MRI or computed tomography (CT) and after a phase of registration, the navigation within the MRI or CT with simultaneous display of voltage and activation maps.

The NavX system. Recently we started using a new system for left atrial mapping, the NavX system (Endocardial Solutions Inc., St. Paul, MN, USA) to facilitate pulmonary vein (PV) ablation[5]. This system utilizes regular mapping and ablation catheters to sense a 5.6-kHz, low-current electrical field generated in the thorax by externally placed electrodes. It has the ability to generate an anatomic map and superimpose in real time the precise locations of up to 64 catheter electrodes upon the map. The three-dimensional computer model of the LA depicted in this image is created by tagging point-by-point the endocardial surface of the LA and in each of the PVs. The precise anatomic location of the PV-LA junction is identified by dragging the ablation catheter from the PV to the LA and marking the point of drop-off with the mapping system. This is confirmed electrophysiologically by recording the location of change from PV potentials to atrial signals only. The anatomic landmarks identified include the four PVs, left atrial appendage (LAA), and annulus of the mitral valve. Once completed, the three-dimensional model can be manipulated and visualized in any view during a PV ablation procedure and is shown here in the four different projections (Fig. 2). Simultaneously displayed is usually a quadripolar catheter in the CS used for compensate heart motion. Among advantages of this mapping system lay the possibility of using all ablation catheters including those with bidirectional bending capability; patient motion is allowed, without the need for anesthesiological assistance; finally this system may be cost-saving as it avoids the need for an external magnetic field. Among limitations, lay the dependence on baseline impedance, although a specific algorithm is currently under development, the improvable accuracy of the anatomic reconstruction and a limited body of published evidence supporting the use of this technology. One of the previous limitations, the inability to obtain activation and voltage maps has been solved with the new version of the software (Fig. 3). Finally, also for the NavX system the development of integration with MRI or CT is ongoing so as to navigate in a real anatomy, and this technology is called DIF (digital image fusion).

Mapping process

We normally start by acquiring the location of all four major PVs and the mitral annulus as anatomical landmarks for the CARTO or NavX navigation systems

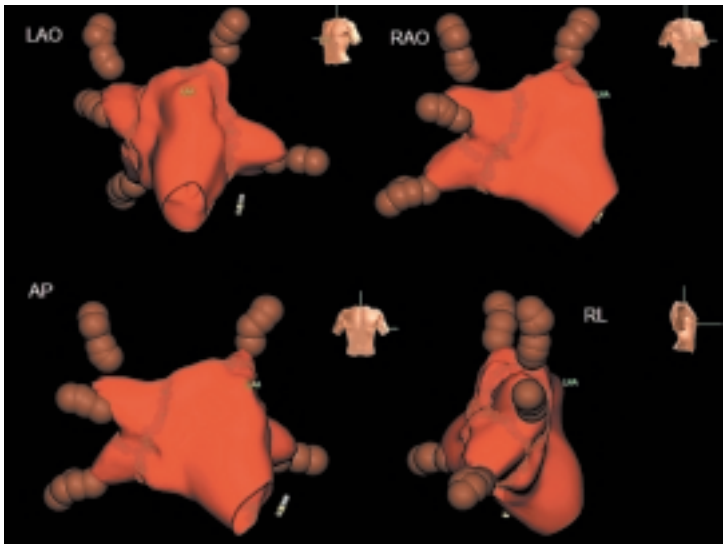

Figure 2. *Three-dimensional left atrial maps obtained with the NavX system. Brown spheres represent radiofrequency lesions. AP = antero-posterior; LAA = left atrial appendage; LAO = left anterior oblique; RAO = right anterior oblique; RL = right-lateral.*

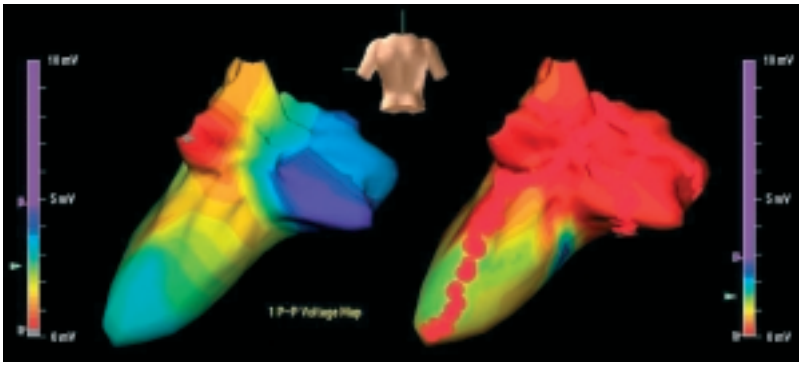

Figure 3. *Three-dimensional left atrial voltage maps (postero-anterior view:* left, *pre-ablation;* right, post-ablation*), depicting peak-to-peak bipolar electrogram amplitude obtained with the NavX system. Color red represents the lowest voltage, and purple the highest voltage. Claret red spheres represent radiofrequency lesions. Post-ablation: areas within and around the ablation lines, involving to some extent the left atrial posterior wall, show low-amplitude (≤ 0.1 mV) electrograms.*

and we create the map by entering each PV in turn; to acquire PVs we use three criteria based on 1) fluoroscopy; 2) impedance; and 3) electrical activity.[2] Entry into the vein is clearly identified as the catheter leaves the cardiac shadow on fluoroscopy, the impedance usually rises above 140-150 Ω, and the electrical activity disappears. Due to the orientation of some veins and the limitations of catheter shape, it can be difficult to enter deep into some veins, but the impedance still rises when it is in the mouth of the vein. In order to better differentiate between PVs and LA, we use voltage criteria (fractionation of local bipolar electrogram) and impedance (a rise of > 4 Ω above mean left atrial impedance) to define PV ostium. The chamber geometry is reconstructed in real time by interpolation techniques of the acquired points. Usually, 100 points are required to create adequate maps of the LA and PVs and up to 200 points for accurate mapping of left atrial tachycardia (AT). Local activation times can be used to create activation maps with CARTO and NavX, which are of enormous importance when attempting to map and ablate focal or macroreentrant AT.

Radiofrequency ablation

Once the main PVs and LA have been adequately reconstructed, radiofrequency (RF) energy is delivered to the atrial endocardium with generator settings of 55-65°C and a power limit of 100 W when using standard 8-mm catheter; this is reduced in the posterior wall to 50 W and 55°C to reduce the risk of injury to the surrounding structures[2]; 45°C and 40 W are corresponding values for cooled-tip catheter. RF energy is applied continuously on the planned circumferential lines, as the catheter is gradually dragged along the line. Continuous catheter movement, often in a to and fro fashion over a point helps keep catheter tip temperature down due to passive cooling. Successful lesion creation at each point is considered to have taken place when the local bipolar voltage has decreased by 80% or to < 0.1 mV. On average, a total of 5 to 15 s non-continuously applications of RF are required. If the catheter position deviates significantly from the planned line, or falls into a PV (usually associated with a sudden rise in impedance of > 4 Ω), RF application is immediately terminated until the catheter is returned to a suitable location. Circumferential ablation lines are normally created starting at the lateral mitral annulus and withdrawing posterior then anterior to the left-sided PVs, passing between the left superior PV (LSPV) and the LAA before completing the circumferential line on the posterior wall of the LA. The "ridge" between the LSPV and LAA can be identified by fragmented electrograms due to collision of activity from the LAA and LSPV/LA. The appendage is identifiable by a significantly higher impedance (> 4 Ω above LA mean), a high-voltage local bipolar electrogram, with characteristically organized activity in fibrillating patients. The right PVs are isolated in a similar fashion, and then a posterior line connecting the two circumferential lines on the roof is performed to reduce the risk of macroreentrant AT[6]. The endpoint for circumferential ablation is a > 70-90% reduction in voltage within the isolated regions[2]. Gaps are defined as breakthroughs in an ablated area, and identified by sites with single potentials and by early local activation. Usually, we do not validate circumferential lesions around PVs by pacing maneuvers, but validate the bipolar voltage abatement within the encircled areas by performing a voltage remap by acquiring new points on the existing geometry to give voltage measurements[2]. This should characteristically show low voltage with the PV encircling lines. Completeness of lesion lines, particularly at the mitral isthmus, are critical in preventing post-ablation macroreentrant left AT, which in the majority of cases are mitral-isthmus-dependent and incessant[6]. The completeness of the mitral isthmus line is demonstrated during CS pacing by endocardial mapping looking for widely spaced double potentials across the line of block and confirmed by differential pacing. In our experience, the minimum double potential interval at the mi-

tral isthmus during CS pacing after block is achieved is > 150 ms, depending on the atrial dimensions and the extent of scarring and lesion creation[6]. After the planned lines of block have been created, the LA is remapped, and the pre-ablation and post-ablation activation maps are compared. Incomplete block is revealed by impulse propagation across the line; in such a case, further RF applications are given to complete the line of block.

Assessment of pulmonary vein innervation

Potential vagal target sites are identified during the procedure in at least one third of patients[7]. Vagal reflexes are considered sinus bradycardia (< 40 b/min) or asystole, atrioventricular block, or hypotension occurring within a few seconds of the onset of RF application (Fig. 4). If a reflex is elicited, RF energy is delivered until such reflexes are abolished, or for up to 30 s. The endpoint for ablation at these sites is termination of the reflex, followed by sinus tachycardia or AF[7]. Failure to reproduce the reflexes with repeat RF is considered confirmation of denervation. Complete local vagal denervation is defined by the abolition of all vagal reflexes.

Remap process and lesion validation

In patients in sinus rhythm, post-ablation remap is performed utilizing the pre-ablation map for the acquisition of new points to allow accurate comparison of pre- and post-RF bipolar voltage (Figs. 1 and 3). We found a small intrapatient difference between the anatomic map of a fibrillating, non-contracting atrium and the map during pacing, in which locations are recorded at end diastole. This is validated by measuring the distance between corresponding locations acquired during AF and pacing. Lesion validation requires acquisition of two maps during CS and right atrial pacing for the lateral and septal PVs, respectively. The rationale behind this setting is to pace from a site close to the lesions and shorten conduction time to the ablation site, thereby allowing detection of delayed activation inside the circular line[2].

Repeat ablation procedure

If there is a recurrence of persistent AF or monthly episodes of symptomatic paroxysmal AF beyond the first month after ablation or there is incessant highly symptomatic left or right atrial flutter then a redo procedure is scheduled at 6 months after the index procedure if the patient wishes. During the repeat ablation procedure, an isthmus line for typical atrial flutter, left atrial mapping and ablation for left atrial flutter or a touch up of the prior ablation lines is usually performed[2].

The stereotaxis technology

We are currently setting our electrophysiology lab to start using a new technology enabling remote control of the mapping-ablation catheter[8] on a variety of mapping

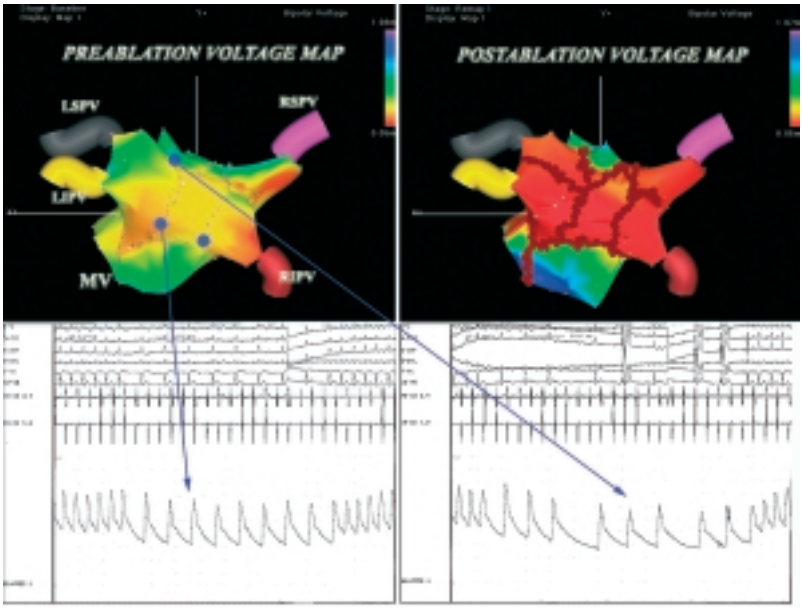

Figure 4. *Pre-and post-ablation three-dimensional left atrial voltage maps in a patient with a vagal reflex evoked and abolished around the left superior (LSPV) and left inferior (LIPV) pulmonary veins* (arrow). *Red represents low voltage and purple high voltage. The reflex site is depicted as blue spot. Red circles represent ablation lines.* Bottom: *surface, intracardiac and arterial pressure tracings during radiofrequency application at the two reflexes sites. MV = mitral valve; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.*

system such as CARTO, NavX or MRI. In this system, a fixed magnet system is used to orient (steer) the tip of the catheter or wire and a catheter advancer system for advance and retract the catheter. Indeed, an external magnetic field of a specified direction and magnitude is used to orient the tiny magnet in the tip of the catheter without any pull or push effect as far as tip-endocardium contact[8]. Obviously no device torque is required and navigation and ablation are independent from manual dexterity. Navistar catheter can be already used with this system. Steep learning curve with potential for inefficacy and unsafety are with this system obviated. Among other applications of this system lay coronary angioplasty/stenting and the placement of left ventricular lead for cardiac resynchronization purposes. For AF ablation, integration with the CARTO system is ready (Fig. 5), and with NavX under development. Included in the CARTO-Niobe integration will be the ability to register CARTO on X-ray, and after generation of CARTO map and definition of lesion set, the software will guide remote ablation automatically. The final evolution will be target navigation with computerized CardioDrive for semi-automated CARTO map generation.

Open issues

Among open issues due to limitations of current technology lay:
• virtual anatomy. Our preliminary data indicate a left atrial volume overestimated up to 40% due to catheter pushing on the endocardial surface to keep contact with the endocardium;

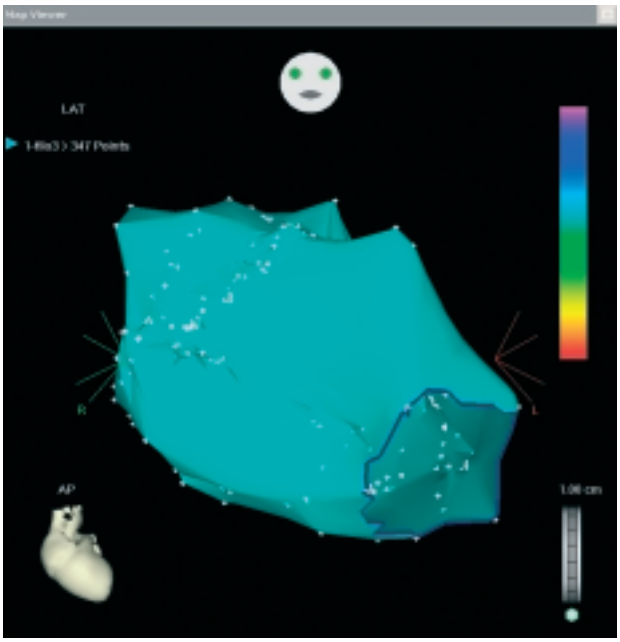

Figure 5. *Our first case of a CARTO map acquired using stereotaxis technology. Note the good detail of the map. AP = antero-posterior; LAT = lateral.*

• need for a long learning curve. A steep learning curve for catheter ablation of AF is a fundamental issue, also considering the warning reports of cases of left atrial-esophageal fistula at the beginning of the learning curve[9];
• catheter drift during RF delivery;
• difficult catheter manipulation at few but critical regions such as septal aspect of right-sided PVs and the channel between LAA and LSPV;
• virtual impedance and voltage due to catheter pushing. These parameters could be used to estimate transmurality if stable contact without pushing was feasible;
• not efficient catheter design. We are currently investigating the role of irrigated-tip catheter for a more effective transfer of RF energy from tip to tissue without undue overheating;
• need for simpler and cheaper systems for wider application of these procedures beyond tertiary centers.

The implementation of MRI or CT into CARTO and NavX systems and their integration with stereotaxis will surely represent relevant solutions.

Clinical outcomes

Herewith, we report on the clinical course over 2 years (29 ± 7 months) of 1171 consecutive patients with symptomatic AF who were referred to us between January 1998 and March 2001[10]. CPVA was performed in 589 patients, who were compared with 582 control subjects treated with antiarrhythmic medications for sinus rhythm control throughout the follow-up period; 1.5% of them had previously undergone an unsuccessful focal and/or segmental PV ablation. A total of 519 procedures were performed because of recurrences prompting repeat ablation in 30 patients. Procedural and mapping times were 162 ± 32 and 75 ± 27 min, respectively, with 29 ± 11 min of fluoroscopy. Thus, procedure duration was quite acceptable, as most cases required ≤ 2 hours, with fluoroscopy times < 30 min in all cases. The extent of the ablated area was 4.9 ± 0.5 cm^2, accounting for 28 ± 9% of the total left atrial map surface. RF delivery acutely restored sinus rhythm in 32% of patients with the arrhythmia during the procedure. Successful ablation was achieved in 98.5% of patients. No major complication, including death, stroke or other thromboembolic events occurred in our series. The rate of minor pericardial effusion (4%) was similar to that in previous transseptal studies. Five patients required pericardiocentesis for cardiac tamponade. No high-velocity turbulence near the ostia suggestive of PV stenosis was detected at transesophageal echocardiography performed within 3 days and 1 to 3 months after ablation, probably because lesions are deployed at more than 5 mm apart from each PV ostium thereby avoiding scarring and contraction of the venous wall resulting from thermal injury. Moreover, to further minimize any risk of PV injury, we carefully avoid RF applications at points where a definite atrial potential was not recorded.

Survival

Thirty-eight (6%) ablated patients and 83 (14%) in the medical group had died. Cardiovascular deaths occurred less frequently in the ablation group with lower number of fatalities due to heart failure and ischemic strokes and no sudden death, although non-cardiovascular mortality was comparable between the two groups. Of the total 77 patients who died of cardiovascular reasons, 58 (75%) had concurrent AF at time of death. Of note, 23 (74%) and 11 (61%) of the 31 and 18 deaths due to heart failure and myocardial infarction occurred in subjects with AF. Observed survival for ablated patients was longer than among medically treated patients and not different from that expected for age- and gender-matched persons of the Italian population. A reduction of 54% occurred in the risk of death for ablated patients. Among the baseline characteristics, history of ischemic heart disease, ejection fraction < 45%, a left ventricular mass index > 125 g/m^2 resulted independent predictors of death.

Recurrences and predictors

After a mean follow-up of 29 months, overall freedom from AF was 80% with not significant difference between paroxysmal (81%) and chronic (76%) arrhythmia. The arrhythmic burden was approximately 3-fold as low as in medically treated patients. The difference in the Kaplan-Meier probability of freedom from arrhythmia for the paroxysmal and chronic types of AF was maximal at 6 months (97% for permanent and 87% for paroxysmal), and minimal at one (84 and 83%) and 2 years (75 and 82%). Recurrences responded to antiarrhythmics in 78% of cases, with no difference between AF types and no relation to the time of relapse. Early (within 2 weeks) recurrences of AF, occurred in 15% of our patients, with 78% of these subjects free from relapses with no antiarrhythmics during long-term follow-up. Patients with chronic AF have a higher probability of early recurrences (22 vs 11%). Nevertheless relapses occurring in this temporal window were not predictive of long-term outcome after ablation in either chronic or paroxysmal AF, and 77% of these patients had no further symptomatic AF during long-term follow-up. Among univariate predictors, independent predictors of a higher likelihood of sinus rhythm restoration were left atrial dilation and post-ablation low-voltage area, suggesting that patients with an enlarged LA may require wider lesions to achieve AF suppression. A left atrial size reduction (mean -11.5 mm) was detected in ablated patients with no recurrences during follow-up. During follow-up, all patients without AF recurrence showed preserved and/or improved LA contraction, as assessed by mitral inflow Doppler tracings. Attention to these endpoints (vigor of atrial contraction) is critical if this procedure is to be truly an improvement upon the vastly simpler technique of ablate and pace.

New mechanisms are currently investigated as potential target for catheter ablation. That autonomic nervous system could play a role in triggering and maintaining AF is clinically known from a long time, but no ablative strategy had included vagal ganglia ablation among ablation endpoints. For the first time we tried to identify vagal ganglia by eliciting parasympathetic reflexes in the LA and subsequently delivery RF energy until complete denervation, i.e. reflex abolition[7]. At 12-month follow-up, 85% of patients without vagal reflexes were free of symptomatic AF, compared with 99% of patients with vagal reflexes and complete vagal denervation. At multivariate analysis, only a larger percentage of left atrial isolation and complete vagal denervation were independent predictors of AF recurrence. This study indicates that parasympathetic attenuation by PV denervation confers added benefit in patients undergoing CPVA for paroxysmal AF. Patients free of recurrent AF were characterized by marked and prolonged heart rate variability changes consistent with vagal withdrawal which were more pronounced in those in whom vagal reflexes were elicited and abolished. In this study also we provided, for the first time, maps localizing parasympathetic innervation around and outside PV areas: the roof junction of the LSPV as well as the postero-inferior junction of the left and the right inferior PVs are the optimal sites for eliciting and eliminating vagal reflexes. Vagal attenuation is an additional mechanism of the antiarrhythmic action of CPVA. Thus, vagal reflexes can be elicited in several specific sites around all PV ostia and should be specifically targeted to cure paroxysmal AF[7].

Finally, we recently investigated the role of adjunctive linear lesions in the posterior left atrial wall and at the mitral isthmus for the prevention of post-ablation AT; with this modified CPVA approach no incremental benefit was observed as for AF freedom during follow-up[6].

Safety

Complications rates are reported in table II.

Atrio-esophageal fistula is very rare but its occurrence is dramatic and devastating. We now recommend

Table II. Complication rates following circumferential pulmonary vein ablation.

Death	0%
Pericardial effusion	0.1%
Stroke	0.03%
Transient ischemic attack	0.2%
Tamponade	0.1%
Atrio-esophageal fistula	0.03%
Pulmonary vein stenosis	0%
Incisional left atrial tachycardia	6%

lower RF energy applications when ablating on the left atrial posterior wall, and to make the line on the posterior wall near to the roof of the LA, where the LA is not in direct contact with the esophagus[9].

The more frequent complication of CPVA is represented by incisional left AT[6]. Indeed, CPVA procedure requires multiple lesions that, if non-transmural, may predispose to proarrhythmias such as left atrial macroreentrant tachycardia. Different line designs have recently been reported in a small series of patients to better prevent either recurrent AF or new-onset AT. We recently reported randomized data on prevalence, mechanisms and clinical significance of new-onset AT in patients with AF who were undergoing CPVA alone (group 1) or a modified CPVA (CPVA-M) approach (group 2). The latter approach included two additional ablation lines in the posterior LA connecting the contralateral superior and inferior PVs and along the mitral isthmus between the inferior aspect of the left-sided encircling ablation line and the mitral annulus. Gaps in a single PV were arbitrarily defined as single gap and as multiple gaps if > 1 PV. During the 6-week blanking period, 19 and 9% patients in group 1 and 2 respectively had episodes of AT. Beyond this blanking period, AT spontaneously resolved in 48 and 56% patients in group 1 and 2, respectively. As a result, 10% in group 1 and 3.9% in group 2 continued to experience AT.

In this study, patients with new-onset incessant AT all underwent a repeat procedure. Only multiple gaps were found in the 82% of group 1 and 73% of group 2 patients at the second procedure, whereas at the end of the first procedure single gaps were present in 46 and 9% respectively, and multiple in 25 and 64%, suggesting that recovery of conduction was an important factor in the occurrence of AT. Gaps were also detected on additional lines in 2 patients. Among patients with macroreentrant AT, the critical isthmus was localized to the area between the mitral annulus and the left inferior PV in 16 patients after CPVA and in 2 after CPVA-M, the area between the right PVs (8 patients, 5 after CPVA) or between the left PVs (5 patients, 2 after CPVA) with the circuit passing between the two ipsilateral veins at the site where previous intervenous lines were performed. In less than one third of patients AT was focal. Among the clinical and procedural variables, the strongest predictors of AT were multiple gaps and chronic AF. To summarize, AT are characterized by multiple gaps in several areas, particularly around the right superior PV and between the LSPV and appendage, where only single gaps had been found at the initial procedure, suggesting that these are points where recovery of conduction can easily occur. These data suggest an important role for the ablation lines between the ipsilateral PVs, not only for preventing recurrent AF, but also in preventing macroreentrant AT. The aforementioned caveat of completeness of lines remains and the width of tissue between the veins is often reduced to a narrow ridge making complete ablation extremely difficult[6]. Whether using irrigated tip catheter may increase transmurality and reduce the incidence of gaps remains to be investigated.

Feasibility and learning curve effect

Anatomical-guided and electrophysiological-guided ablation procedures have been shown to be effective for curing AF. However, long durations and large amounts of radiation exposure may currently limit the widespread application of this therapy that shows a primary effect of operator experience. Recently, it has been reported that after > 75 cases, segmental ablation to isolate the PVs using fluoroscopy and conventional RF ablation usually is feasible in < 3 hours[11]. With the purpose to determine the effects of operator experience on the outcome and duration of CPVA procedures for AF, we measured the learning curve effect on the outcome and duration of the procedure on 267 consecutive patients with AF who underwent CPVA with non-fluoroscopic CARTO guidance for curing AF. The mean procedure duration was 212 ± 60 min (range 41-560 min). We observed an indirect linear relation between the total procedure time and the number of procedures performed (r = -0.59), and between the non-fluoroscopic mapping time and the number of procedures performed (r = -0.80). We failed to find a relation between fluoroscopic time and operator experience. We found RF energy delivered during the procedures slightly increased as operator experience increased, as did the low-voltage encircled area. On univariate analysis, operator experience slightly predicted recurrent AF in patients with persistent (hazard ratio 1.56), but not in those with paroxysmal AF. Thus, a clear learning curve effect exists for the CPVA, and as operator experience increases, it can be expected a marked reduction in mapping duration. Thus, a careful sizing of the encircled area is mandatory for the procedure to be effective, in patients with predominant substrate-dependent AF. Last but not least, we recently found in an analysis on 6442 patients that complications are predicted by an operator caseload of < 150 procedures.

Pulmonary vein stenosis: questioning on anachronistics?

PV stenosis has been reported in < 2% of patients treated but in > 20% of PVs treated with ablation[12]. In addition, the risk of PV stenosis during long-term follow-up is not known. PV stenosis, as a typical complication of techniques delivering RF energy within PV tissue, can be partly explained by the anatomical and histological characteristics of the junction between the PV vasculature and LA; myocardial sleeves are always found in the outer layer of PVs, with myocardial cells embedded in a dense collageneous matrix, with fibro-

cytes and smooth muscle cells – cellular types well known to have a potential for a strong proliferative response to injury, including RF energy-related injury. No histopathophysiologic studies of PV stenosis in humans have been reported; however, in dogs, the pathophysiologic mechanisms of PV stenosis produced by RF delivery include fibrocellular intimal proliferation, endoluminal thrombus formation, endocardial contraction, and proliferation of elastic lamina; intimal proliferation is observed in all stenotic PVs and is responsible for much of the narrowing. The risk of PV injury can be easily overwhelmed by RF energy delivering at a safety distance around each PV ostia, with relatively low risk, although, the initial data usually are reported from highly experienced centers, and the risk-to-benefit profile of the same procedure may be different in other institutions[2,12].

Pulmonary vein ablation: not for all patients?

At the present time, there is no universal consensus as to which subset of AF patients should be ablated as first-line approach. However, the presence of specific myocardial diseases, the size of the LA, the type of AF, comorbidities and the need for long-term anticoagulant and antiarrhythmic therapy, may determine the type and role of the PV ablation strategy[13].

Recent-onset atrial fibrillation. After the first documented episode it may be not necessary to prescribe either long-term antiarrhythmic therapy or anticoagulation for all patients. However, if cardioversions fail to restore sinus rhythm or AF early recurs (i.e., arrhythmia becomes sustained or recurrent), and/or long-term antiarrhythmic and anticoagulant therapy is deemed necessary, consider ablation.

Recurrent paroxysmal and persistent atrial fibrillation. Again, patients for whom long-term (> 1 year) antiarrhythmic and anticoagulant therapy is deemed necessary, are good candidates to PV ablation regardless of symptoms and cardiac concomitant conditions. The combination of paroxysmal or persistent AF and systolic dysfunction poses a challenge for both rhythm and ventricular rate control, since digoxin is often ineffective and other agents may have a negative inotropic and/or proarrhythmic effect. Thus, if heart failure, left ventricular dysfunction or coronary artery disease are present PV ablation can be considered as a first therapeutic choice.

Permanent atrial fibrillation. Patients with permanent AF have been traditionally managed with some digoxin or calcium-channel blockers, but this approach has proved as harmful as rhythm control by drugs. His-bundle ablation and permanent pacemaker implantation must be considered only as an expensive palliative approach as swings between thromboembolic and bleeding risk are unchanged, and atrial systole not restored. Interestingly, circular PV ostial lesions can be tailored for each of such patients, in order to proportion to the individual left atrial size the amount of encircled "electrically inactive" area, thus, increasing the likelihood of a successful sinus rhythm maintenance. Moreover, in this setting patients can benefit from concomitant transcatheter occlusion of the LAA for purpose of stroke secondary prevention.

Conclusions

RF catheter ablation currently is used widely and successfully to treat a variety of arrhythmias, and AF ablation represents the frontier of arrhythmia research[14,15]. Development in many areas will offer to the electrophysiologic community a more rational and effective background upon which select patients for ablation and identify the optimal ablative strategy. Among mechanisms recognized for having a role in AF stay PV focal triggers[16], rotor at the PV-LA junction[17], a critical mass to sustain fibrillatory conduction[18] and vagal ganglia[7,19]. The latter represents the frontier of research as with new technologies based on MRI they could be easily and specifically identified and targeted for ablation. It is fundamental that both CARTO and NavX systems are currently investigating integration with MRI to reconstruct the LA. Finally a learning curve effect can be abated with the use of new systems for the remote control of the catheter such as stereotaxis.

In summary, catheter ablation procedures to cure AF patients are still in a continuing phase of development. The electrophysiologic community has to face to the warning trend toward a higher risk of death in the rhythm-control groups in both RACE[20] and AFFIRM[21] studies. As it is intrinsically unlikely that sinus rhythm is *per se* harmful to the patient's life, we believe that the quest for safer and more effective catheter ablation techniques for curing AF will, and should, continue[1].

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