Ablation of long-standing AF. Is it wise to pursue it?

Carlo Pappone, MD and Vincenzo Santinelli, MD

From: Department of Arrhythmology, GVM Care and Research, Cotignola, Ravenna, ITALY

Address for correspondence:
Carlo Pappone, MD
Department of Arrhythmology,
Villa Maria Cecilia Hospital,
Via Corriera 1
48010 Cotignola, Ravenna, ITALY
E-mail: cpappone@gvm-vmc.it
vsantinelli@gvm-vmc.it
Catheter ablation techniques for PVs isolation are effective in patients with paroxysmal atrial fibrillation AF (1-9). However, extension of the technique of PVI alone from patients with paroxysmal to long-standing persistent AF (> 1 year), in which several areas are characterized by disorganized atrial activity with marked regional differences, is inadequate (10,11). Indeed, the mechanisms underlying long-lasting persistent AF are more complex and multifactorial. Long-standing persistent AF also includes a broad spectrum of patients with moderate-to-severe left ventricular dysfunction. Structures annexed to the left atrium such as the coronary sinus or left atrial appendage frequently show continuous or prolonged complex fractionation and rapid activity while the remaining structures may be still organized (11). The addition of left atrial substrate modification at these sites has a significant impact on AF cycle length, more organized atrial activity, which may lead to an organized atrial tachycardia or sinus rhythm, all of which improve the outcomes in patients with long-lasting persistent AF (10). Therefore, it is not surprising that further linear lesions not limited to PV ostia alone, as initially performed in Circumferential Pulmonary Vein Ablation (CPVA) using an electroanatomic mapping technique, had been more effective in patients with both paroxysmal and chronic AF (2-6). This better outcome, largely reported many years ago in patients undergoing CPVA (2), may be explained by the fact that sequential multiple atrial sites critical for maintenance of the arrhythmia are targeted for ablation. In our previous experience published in the NEJM, about 75% of patients with chronic AF, most of whom without enlarged atria, maintained the sinus rhythm at 1 year after CPVA (12). However, patients with long-standing AF who remain in AT/AF after standard CPVA approach need more extensive ablation sequentially targeting other atrial structures showing complex and disorganized activity. Currently, step-by-step linear lesions throughout the atria guided by non-inducibility are sequentially performed in order to interrupt multiple re-entrant wavelets usually guided by ablation of continuous complex fractionated atrial potentials, ablation of areas with short cycle length activity, focal sources, or ablation of sites of dominant frequency. Patients with long-standing persistent AF are considered for catheter ablation if they are
symptomatic and have already failed at least 2 conventional antiarrhythmic drugs, electrical cardioversion, or both. In many patients with long-standing persistent AF, a redo procedure is required to maintain sinus rhythm and there is no predetermined limit of number of procedures per patient. As catheter ablation is a safe and effective treatment among patients with both paroxysmal or persistent AF and heart failure, we perform this alternative to patients with left ventricular dysfunction, NYHA II or more. Preliminary results have reported excellent long-term results in almost all patients, but in many cases (about a half) multiple procedures are required after the index ablation (10). In our experience, this extensive ablation approach is required among patients with enlarged atria and persistent long-standing AF and consists in a sequential ablation of structures which are empirically identified by the effect of their ablation on the AF cycle length.

Circumferential Pulmonary Vein Ablation (CPVA)

The standard CPVA lesion set is considered as the initial ablation step in patients with long-standing persistent AF (Figure 1). The ablation procedure is usually performed by manual tip-irrigated catheters or remotely by magnetic tip-irrigated catheters. The lesion set consists of large circumferential ablation lines in order to perform a point-by-point tailored distal disconnection of all PVs ostia, vagal denervation, as well as additional linear lesion lines with validation of the mitral isthmus line. Non-inducibility of both AF and AT at the end of the procedure is performed in all patients. Accumulating data from our laboratory indicate that among patients with paroxysmal/persistent AF without enlarged atria standard CPVA alone is associated with an excellent outcome (2,3,5,6,9). However, in patients with enlarged atria and long-lasting persistent AF, the addition of left or right atrial substrate by further lesions in a stepwise fashion using the least amount of ablation results in an incremental benefit achieving a stable sinus rhythm and noninducibility of AF, off all antiarrhythmic drugs at 1 year.
**End Points of CPVA**

*Restoration of sinus rhythm.* In our experience achievement of sinus rhythm is the main endpoint in patients with both paroxysmal and persistent AF since it is usually associated with a better clinical outcome. However, multiple steps are required to achieve sinus rhythm in patients with persistent long-standing AF (about 60% of patients are in sinus rhythm). The standard set of lesions, as performed in the CPVA approach, may be insufficient to achieve a stable sinus rhythm in patients with persistent long-lasting AF and then, time consuming step-by-step addition of left atrial substrate modification using electrogram-based or linear lesions is necessary. In these cases, usually sinus rhythm is restored by an intermediate step of one or multiple ATs, which are then mapped conventionally and ablated. However, all atrial regions represent potential ablation targets and distinguishing passive from active sites is time consuming and probably this is the most challenging aspect of catheter ablation in patients with long-standing AF. If sinus rhythm is not still achieved, any effort is made to further slow and organize local atrial activity. If AF becomes an organized AT, activation mapping and entrainment are used to evaluate the circuit; and in case of transition to another AT, further activation maps are generated until sinus rhythm restoration is achieved.
Fig 1 A voltage map of the left atrium has been generated using the CARTO system after AF termination; the red area indicates left atrial regions without electrical activity.

Noninducibility. After restoration of sinus rhythm, AF/AT inducibility is assessed by programmed extrastimuli using up to 3 extrastimuli at twice diastolic threshold and then by burst atrial pacing (10-second bursts at an output of 20 mA) from the proximal coronary sinus and the right atrium (CS ostium or right atrial
free wall) beginning at a cycle length of 350 ms and reducing by 10-ms intervals until atrial refractoriness. Sustained AT/AF is considered as inducible if the arrhythmia persists for >1 minute; induction is repeated at least 3 times from each site. In contrast to paroxysmal AF, where noninducibility of AF may be achieved in the majority of patients, in long-lasting persistent AF, AF/AT may be induced in about a half of patients at the end of the index procedure.

**Radiofrequency setting.** Radiofrequency applications are usually deployed with an open irrigated tip catheter (40W, 40°C with an irrigation rate of 17-25 mL/min except for ablation within the CS ablation in which the setting are 25W, 40°C with an irrigation rate of 30-40 mL/min).

**Step-by-step ablation in long-standing persistent atrial fibrillation**

**Step 1-** Standard CPVA is performed as the initial ablation step in all patients with long-lasting persistent AF in our electrophysiology laboratory. Circumferential and multiple sequential linear lesions with validation, as performed in the modified CPVA, are useful not only to completely disconnect PV ostia, but, particularly in patients with persistent long-lasting AF, by altering the substrate for AF by defragmentation or disrupting macroreentrant circuits capable of sustaining AF. The benefit of linear lesions is also extended to the attenuation of parasympathetic tone which plays an important role in the generation of AF by shortening the atrial refractory period.

**PV disconnection.** Circumferential lines are aimed at PV-atrial junction outside the ostia, an area considered as the antrum (Figure 1). The lesions are performed to encircle the left and right PVs individually or as ipsilateral pairs in accordance with the venous anatomy and operator’s preference to electrically disconnect all PVs (Figures 1-2). We have recently demonstrated that complete distal electrical isolation can be safely obtained by potential abatement (>90% reduction of electrogram amplitude) and electrogram amplitude decrease of <0.1 mV around and within the encircled areas (13). Rapid PV isolation is achieved by good catheter stability and optimal wall contact which results in rapid attenuation of atrial electrograms during each
RF energy application up to complete elimination for up to 50 seconds, usually within a few seconds depending on the local effect (Figure 2). Partially ablated signals require further RF applications before moving on the next ablation site. **Vagal denervation.** During the procedure we attempt to eliminate all potential vagal reflexes (Figure 3), which enhances the efficacy of the procedure in the long-term outcome (3).

**Figure 2.** The figure shows complete PV isolation after CPVA. A careful mapping of the PV ostia by the ablation catheter (green tip) demonstrates disappearance of electrical activity inside the lesion set. Note that pre-ablation high amplitude signals in the left PVs (panels A and B) are eliminated after ablation (panels C and D).
**Posterior and mitral isthmus ablation.** Additional ablation lines are performed point-by-point along the back and the roof of LA between the two sets of PVs connecting the superior and inferior PVs and the mitral valve annulus (Figures 1-2). The mitral isthmus line is deployed to further reduce the substrate as well as to prevent postablation macroreentrant left atrial tachycardias (Figure 1). Completeness of the mitral isthmus line is an important electrophysiological end point and it is validated during CS pacing by endocardial and coronary sinus mapping, looking for widely spaced double potentials across the line of block, and confirmed by differential pacing (5). The minimum double-potential interval at the mitral isthmus during CS pacing is between 80 and 150 ms depending on the atrial dimensions and the extent of scarring and lesion creation (5). Achievement of 80 ms delay may be clinically sufficient in many patients for prevention of left atrial tachycardias, thus avoiding further and long RF applications within the CS to achieve a complete bidirectional conduction block. Ablation of the mitral isthmus may be difficult and may lead to periprocedural tamponade if “complete” mitral isthmus block is attempted.
Figure 3. Vagal reflexes are elicited during RF applications; continuous RF delivery eventually abolishes the vagal reflex.

Step 2- Endocardial coronary sinus ablation. Point-by-point ablation of the coronary sinus begins along the endocardial aspect and is usually completed from within the vessel (Figure 4). The map/ablation catheter is dragged along the endocardium of the inferior LA after looping the catheter in such a way as to position it parallel to the coronary sinus catheter. After achieving a 270-360 loop in the left atrium, RF applications are started at the inferior LA along the posterior mitral annulus from a site adjacent to the coronary sinus ostium up to the lateral left atrium (4 o’clock in the left anterior oblique projection). The endpoint is abolition of local endocardial electrograms bordering the mitral annulus in order to prolong the cycle length of or eliminate the sharp potentials within the coronary sinus.
Step 3- Endocardial septum ablation. Ablation of the interatrial septum is performed starting from the anterior aspect of lesion encircling the right superior PV up to the anterior mitral annulus. Ablation is sequentially point-by-point performed with the aim of transecting areas of complex fractionated electrograms.

As with coronary sinus ablation, the endpoint is abatement of local endocardial electrograms to eliminate or prolong the cycle length of sharp potentials in this region; assessment of complete conduction block across this lesion is not routinely performed. During ablation of the anterior septum, areas facing the His bundle were avoided.

Step 4- Left atrial ablation. Ablation is typically performed beginning from the lesion encircling the left superior PV and then, it is extended inferiorly and superiorly. The endpoint is elimination of local endocardial electrograms bordering the left atrial appendage posteriorly, inferiorly and anteriorly in an attempt to prolong
the CL of sharp potentials present within the left atrial appendage; complete isolation of the left atrial appendage is intentionally avoided.

**Step 5- Epicardial coronary sinus ablation (Figure 4).** Ablation within the coronary sinus is performed in case of persistent coronary sinus potentials and usually it starts distally (4 o’clock in left anterior oblique position) and pursued along the vein up to the ostium simply by targeting local sharp potentials. Finally, additional radiofrequency applications are continued around the coronary ostium from the right atrium. Coronary sinus disconnection is validated by the dissociation or abolition of sharp potentials in its first 3 cm.

**Step 6- Right atrium ablation.** In our laboratory, all patients with persistent AF undergo ablation of the cavotricuspid isthmus. After ablation around coronary sinus ostium, a linear lesion is deployed between the inferior vena cava and the tricuspid annulus isthmus to create a conduction block across the isthmus. Validation of bidirectional block is always done in sinus rhythm. Superior vena cava isolation is not routinely performed, but only when there is presence of an arrhythmogenic source in this vessel.

**Step 7- Atrial Ablation.** Atrial ablation is performed at sites showing continuous electrical activity, complex fractionated potentials, sites with a gradient of activation (significant electrogram offset between the distal and proximal recording bipoles on the map electrode), or regions with a CL shorter than the mean left atrial appendage AF cycle length. Ablation at these sites is performed to achieve local prolongation of CL, with synchronous activation at distal and proximal bipoles indicating passive activation of this local area. At each site, 20–60 seconds of RF is delivered before moving.

**AFCL as a monitoring tool**
A cumulative increase of AF cycle length leading to termination is achieved by sequentially targeting left atrial targets in a stepwise manner. Therefore, the effect of RF applications is continuously monitored by
assessing potential changes of AF cycle length (AFCL) before and after each ablation step by averaging 10 consecutive cycles and at the time of AF termination. The AFCL is determined within the coronary sinus and the right and left atrial appendage. At each time point, annotation is manually done using online calipers at a paper speed of 100 mm/sec. An individual site is considered to have a significant impact if its ablation results in termination of AF or prolongation of the AFCL (evaluated in the LAA except if specified otherwise) by 10 msec or more, when compared to the highest AFCL during the previous steps. Termination of AF is defined as a transition directly to SR or conversion to AT. The LAA, CS, and interatrial septum were identified as key areas, suggesting that their inclusion in ablation strategies to prevent recurrent paroxysmal AF after CPVA or persistent AF needs to be evaluated in order to improve the clinical outcome in these patients as well.

Intermediate Atrial Tachycardias (Figures 6-7)

In many cases of long-standing AF, termination of AF is followed by intermediate atrial tachycardias, all of which require accurate mapping (usually by Carto or NavX systems) and ablation for achievement of sinus rhythm. AF is defined by beat-to-beat variability in CL and morphology, while AT is defined as an organized atrial activity with stable CL, morphology, and activation sequence in both atria. Focal AT is defined by centrifugal activation from a localized region. A macroreentrant mechanism is defined by demonstrating the entire CL of activity (>70%) in a chamber with entrainment at ≥2 sites displaying a postpacing interval of <20 msec longer than the tachycardia CL. When AF converts to a regular arrhythmia, conventional activation and entrainment mapping are performed to differentiate a focal from a macroreentrant mechanism (Figure 5).
In focal AT, the catheter is moved gradually in the direction of earliest activity until we reach a site showing the earliest possible activity relative to the reference electrogram in the CS or RAA or LAA; ablation at the site of earliest activity usually requires 1–2 minutes of RF application. When a macroreentrant mechanism is diagnosed, entrainment is initially performed at the roof and the mitral isthmus to identify reentry utilizing these regions. In our experience, prolongation of AFCL occurs gradually with the largest increments being in the interatrial septum, CS region, and LAA region which results in the conversion to SR with or without intermediate an organized tachycardia. After conversion, multiple ATs may develop, but conventional mapping techniques usually show a limited number of critical structures from which they arose. Focal ATs are frequently located at the PVs, LAA, and CS regions originating at any part of their (circumferential or longitudinal) connection with the LA; some of them have narrow isthmuses with fractionation suggesting a localized reentry. Macroreentrant ATs are usually perimetal or roofline and rarely the cavotricuspid isthmus.

**Figure 5.** AF cycle length is continuously monitored to evaluate the effect of RF application.
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At present, catheter ablation is effective in the treatment of all forms of AF including long-standing persistent AF. However, many patients after the stepwise procedure may experience episodes of atrial tachycardias, most of which are due to macro or microreentry due to incomplete linear lesions. Microreentry or localized reentry is defined when the circuit is contained within an area <2 cm, which can be easily eliminated by ablation. Therefore, development of postablation ATs represents the future challenge of electrophysiologists requiring improved mapping tools with improved ablation technologies and alternative energy sources to RF energy.

Figure 6. Ablation of the left atrial isthmus results in an organized left atrial electrical activity, which is associated with a simultaneous increase of the AF cycle length
Figure 7. During rf application within the coronary sinus (CS Disconnection), sinus rhythm is restored. On the left side a left lateral oblique projection is showed. Note that the ablation catheter is parallel to the catheter inside the coronary sinus. RF application begins distally.

It will be necessary to accurately identify selective areas, which are actively participating in the AF generation in the single patient to minimize the ablation amount. Important measures need to be taken to prevent potential complications; in particular, the power used for ablation should be limited inside the CS, isolating the LAA should be avoided and continuous RF applications should be shortened (20 seconds) in the same point on the posterior wall to minimize the complication rate despite the achievement of complete lesions. This strategy may be a major reason for the absence of major complications. In addition, ablation at some sites may be avoided or minimized possibly without compromising efficacy, for example, the SVC or extensive CS ablation to produce disconnection. Despite the large amount of energy delivery required to cure AF in our
experience, the procedure is well tolerated and associated with an acceptable risk–benefit ratio. Anyway, further studies are needed to identify the atrial regions that can be spared ablation because they are not involved in the AF process in a particular individual or because they play an important role in ventricular filling. Initially, the majority of patients undergoing AF ablation were affected by paroxysmal AF and many of them had no enlarged left atrium. The excellent results obtained in such selected patient population have encouraged electrophysiologists to include patients with persistent AF and recently even patients with long-lasting persistent AF and enlarged left atria. As a result, many patients with enlarged atria and persistent long-lasting AF are referred for potential ablation of their arrhythmia. With this approach, in our laboratory termination of AF and maintainance of sinus rhythm occurs in almost all patients after 2 procedures with an unprecedented rate of elimination of chronic AF by catheter ablation. In agreement with our data, Haisssaguerre et al. have recently described an ablation method targeting multiple LA sites to cure long-lasting persistent AF (10).

**Conclusions**

We believe that in well trained electrophysiologic centers, catheter ablation of long-standing persistent AF can be safely and effectively performed by a step-wise approach which currently is focused to organize left atrial activity using mapping and ablation of intermediate atrial tachycardias. Preliminary findings from our laboratory provide evidence for future larger studies to confirm the high efficacy of such approach. Despite initial encouraging results among patients with persistent long-standing AF, it may be reasonable to pursue a strategy of early catheter ablation among patients with AF who are at risk to rapidly progress to persistent AF in order to prevent symptomatic or asymptomatic transition from paroxysmal to persistent AF, which is associated with higher morbidity and mortality risk (14).
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