



## Clinical update

# Catheter ablation of atrial fibrillation: an update

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Catheter ablation of atrial fibrillation (AF) is now an important therapeutic modality for patients with AF. There is considerable evidence available from several prospective randomized trials demonstrating that catheter ablation of AF is superior to antiarrhythmic drug therapy in controlling AF and that AF ablation improves quality of life substantially. This is especially true for patients with paroxysmal AF without other severe comorbidities. Catheter ablation is indicated for treatment of patients with symptomatic AF in whom one or more attempts at class 1 or 3 antiarrhythmic drug therapy have failed. Although current guidelines state that is appropriate to perform catheter ablation as a first-line therapy in selected patients, in our clinical practice this is rare. This reflects a number of important realities concerning the field of AF ablation. Catheter ablation of AF is a challenging and complex procedure, which is not free of the risk of potentially life-threatening complications, such as an atrio-oesophageal fistula, stroke, and cardiac tamponade. Although these major complications are rare and their rate is falling, they must be considered by both patients and physicians. The progress made and the new developments on the horizon in the field of AF catheter ablation are remarkable. When radiofrequency catheter ablation was first introduced in the late 1980s, few would have predicted that catheter ablation of AF would emerge as the most commonly performed ablation procedure in most major hospitals.

## Keywords

Atrial fibrillation • Catheter ablation

## Introduction

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered in clinical practice and affects ~1% of the general population with increased incidences in the elderly population. Currently ~5 million people are affected in Europe.<sup>1</sup> About 6% of the population group aged 60 years or more has AF. Atrial fibrillation has an important impact on morbidity and mortality in these patients. Pharmacological therapy to suppress arrhythmia is frequently unsuccessful due to low efficacy and/or side effects. Catheter ablation of AF has advanced since 15 years to a well established and widely performed interventional therapy for many patients with symptomatic AF.<sup>2–4</sup> Several prospective randomized trials have demonstrated the superiority of catheter ablation over antiarrhythmic drug therapy in patients with paroxysmal AF and structurally normal hearts.

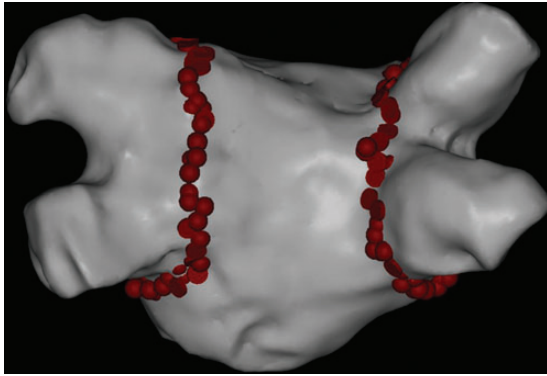
## Current techniques of atrial fibrillation ablation

More than 15 years ago, the basis for the development of catheter ablation of AF was established when foci of ectopic beats originating

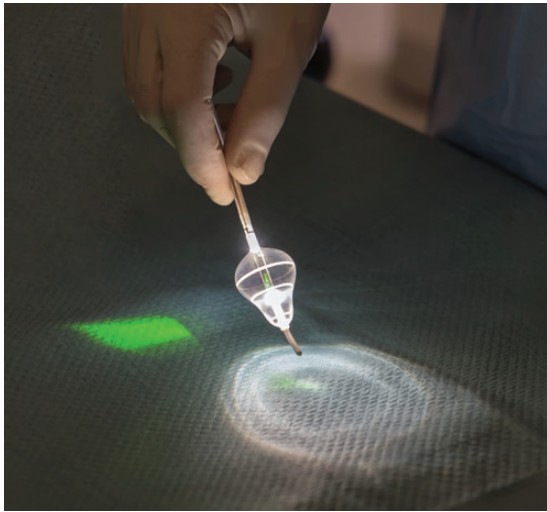
from the pulmonary veins were observed to be capable to trigger AF.<sup>5,6</sup> Sincethem, circumferential ablation around the orifices of the pulmonary veins with the procedural endpoint of electrical disconnection of the pulmonary vein from the left atrium has become the cornerstone of catheter ablation of AF. The ablation consists of a series of point-by-point radiofrequency lesions encircling each or both ipsilateral ostia of the pulmonary veins (*Figure 1*). Most centres perform this ablation lesions set using a transvenous irrigated radiofrequency ablation catheter inserted through the femoral vein.<sup>7–9</sup> Cryoenergy or laser light is used as alternatives to conventional radiofrequency energy applied through balloon-tipped catheters (*Figure 2*). The anatomical variation of the pulmonary vein ostia presents important hurdles for the one-size-fits-all balloon-based catheters. High-intensity focused ultrasound energy was removed from the market because of high incidence of a left atrio-oesophageal fistula.

Pulmonary vein isolation is confirmed by a circular multipolar mapping catheter placed into the pulmonary vein showing entrance block (*Figures 3 and 4*). In addition, pulmonary vein isolation can be proved by pacing inside the pulmonary vein and documentation of an exit block out of the pulmonary vein.<sup>10</sup> Residual gaps in the ablation line can be rapidly identified by pacing from the tip of the

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**Figure 1** Three-dimensional electroanatomical map of the left atrium and the pulmonary vein ostia in a posterior projection with circumferential ablation lesions (red points) around ipsilateral pulmonary veins.



**Figure 2** The laser balloon ablation catheter consists of a variable diameter and compliant balloon, and an atraumatic and flexible tip.

mapping catheter and ablating to obtain conduction block and isolation of the pulmonary veins, proposed as the pace-and-ablate approach.<sup>11</sup>

The procedure is carried out with fluoroscopy and a three-dimensional electroanatomical mapping system, which also allows the integration of pre-acquired MRI or CT images. The ablation is performed either with deep conscious sedation or with general anaesthesia depending on patient's condition and centre's preference. Patients who present in AF and have not been continuously anticoagulated with warfarin undergo a transoesophageal echocardiogram to rule out thrombus formation in the left atrium prior to ablation. The presence of a left atrial thrombus precludes a left atrial ablation procedure. Patients are commonly admitted on a short-stay basis.<sup>12</sup>

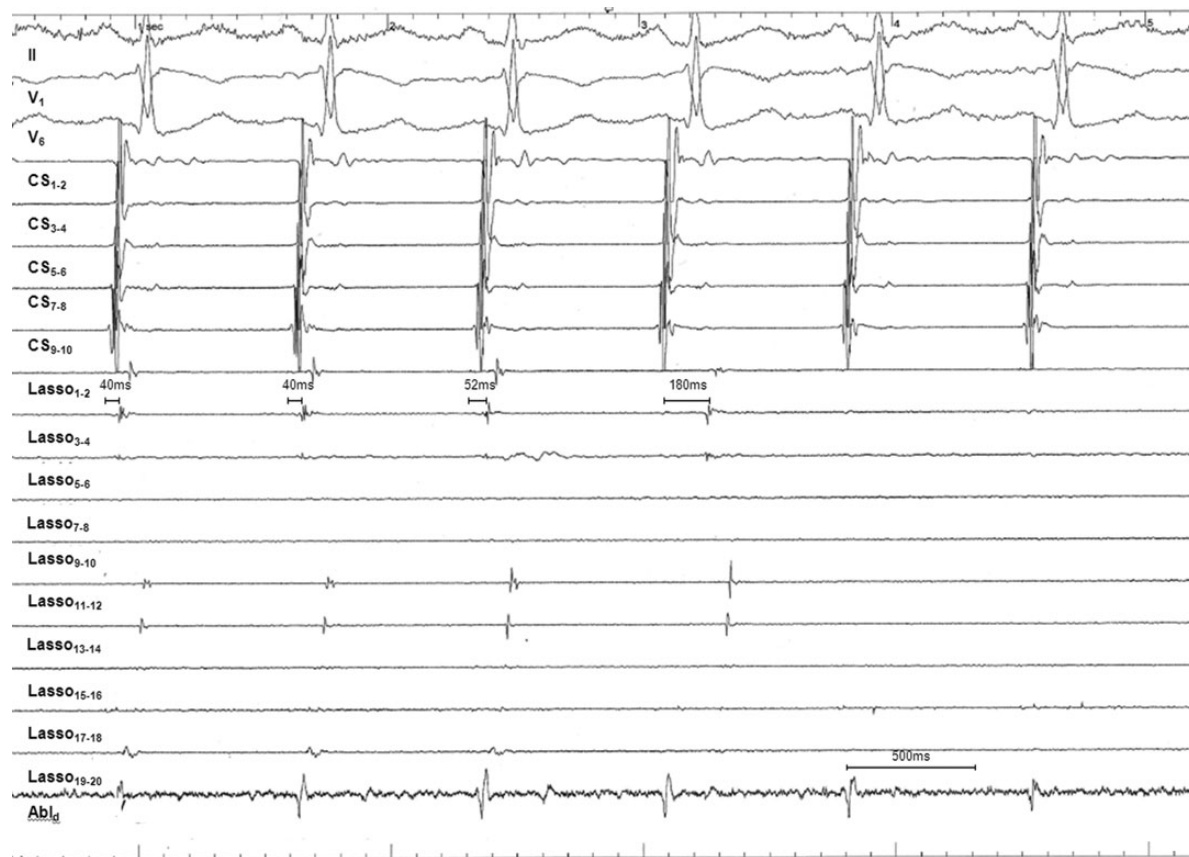
Atrial fibrillation ablation procedures are routinely performed on anticoagulated patients with warfarin or phenprocoumon who

have a therapeutic INR. Novel oral anticoagulation agents, such as thrombin inhibitors (dabigatran) or factor Xa inhibitors (rivaroxaban, apixaban), are now increasingly used in the pre- and post-procedural anticoagulation regimen of patients undergoing AF ablation.<sup>13</sup> Fast onset of action and pharmacodynamic elimination make these novel oral anticoagulants especially attractive in this patients group. Conversely, an important limitation of these new anticoagulant agents is the absence of a reversal agent. Because of this, most centres will hold these novel anticoagulants for 1 to 2 days prior to an AF ablation procedure and resume them 3–4 h after the procedure is completed.

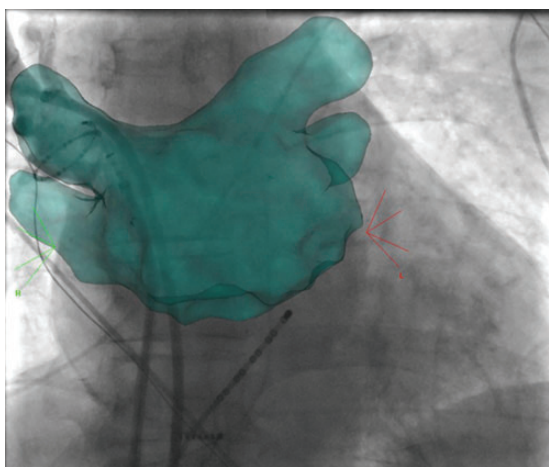
## Success rates of atrial fibrillation ablation

Success rates of catheter ablation of AF depend mainly on three variables: the patient, the electrophysiologist, and the definition of success. The type of AF (paroxysmal, persistent, or long-standing persistent AF), concomitant structural heart disease, comorbidities such as obesity and sleep apnoea determine the success rates. Furthermore, high-success rates and low-complication rates are achieved in high-volume and experienced centres. Results from various centres differ greatly because of divergent ablation techniques, reporting and follow-up protocols. Standardization of practice is required to obtain consistent and comparable outcome data in this field. The HRS/ EHRA/ ECAS (Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society) Consensus Document on AF ablation recommends that success should be defined as freedom from symptomatic or asymptomatic AF, atrial tachycardia, or atrial flutter lasting  $\geq 30$  s at a 12-month follow-up after AF ablation.<sup>2</sup> It is recognized that this definition of success is very strict and best used for clinical trials. A 3-month-blanking period after AF ablation, in which recurrences of atrial arrhythmia are not considered as failure of the procedure, is recommended because a majority of patients develops temporary AF or atrial flutter shortly after the ablation procedure, in part due to transient myo- and pericardial inflammation. From a clinical perspective, a marked reduction of symptomatic AF is considered as a successful result from a patient's and a physician's perspective.

Two recent meta-analyses involving 63 AF ablation studies reported that the single-procedure success of ablation with no antiarrhythmic drug therapy was 57%, the multiple-procedure success rate with no antiarrhythmic drug therapy was 71%, and the multiple-procedure success rate with antiarrhythmic drugs was 77%. In comparison, the success rate for antiarrhythmic drug therapy was 52%.<sup>14</sup> There have been at least 12 prospective, randomized clinical trials comparing the results of AF ablation with antiarrhythmic drug therapy.<sup>15–22</sup> A meta-analysis of four of these studies reported that 76% of patients treated with catheter ablation were free of AF compared with 19% of patients randomized to antiarrhythmic drugs.<sup>23</sup> The authors concluded that there was a  $>3.7$ -fold probability of remaining in sinus rhythm with catheter ablation than with antiarrhythmic drug therapy. MANTRA-PAF (Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation) compared first-line catheter ablation of AF to antiarrhythmic drugs in 294 patients. At 2 years, significantly more patients in the



**Figure 3** The recordings from the circular multipolar mapping catheter placed in a pulmonary vein are shown during ablation (Lasso<sub>1-2</sub> – Lasso<sub>19-20</sub>). On Lasso<sub>1-2</sub> prolongation of conduction delay from the atrium into the pulmonary vein is seen on the first four beats before the sharp local pulmonary vein potential finally disappears on beat 5 and 6 as a result of successful pulmonary vein isolation. CS, coronary sinus; Abl<sub>d</sub>, distal ablation catheter.



**Figure 4** Image integration technology combines the electroanatomical reconstruction of the left atrium (green) and the fluoroscopy image into a single overlapping image aiming to reduce radiation exposure for both the patient and the operator. The circular multipolar mapping catheter is placed in the right upper pulmonary vein which is filled with a contrast dye.

ablation group were free from any AF (85 vs. 71%) and symptomatic AF (93 vs. 84%).<sup>21</sup> Quality of life was significantly better in the catheter ablation arm. In RAAFT-2 (Radiofrequency Ablation vs. Antiarrhythmic Drugs as First-Line Treatment of Paroxysmal Atrial Fibrillation), the recurrence rate of AF was significantly lower after ablation compared with antiarrhythmic drugs after 2 years among 127 patients with paroxysmal AF without previous antiarrhythmic drug treatment. Quality of life improved in both treatment groups.<sup>22</sup> Similar results were found if cryoenergy was used for ablation of AF for treatment-naïve patients in STOP AF (Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front pivotal trial).<sup>19</sup>

There is only little evidence from prospective, randomized, multi-centre clinical trials in patients with chronic AF, both persistent (>1 week) and long-standing persistent (>12 months of continuous AF). However, the recently published prospective randomized TTOP-AF trial (Tailored Treatment of Persistent Atrial Fibrillation) in patients with persistent and long-standing persistent AF demonstrated a significant greater reduction of AF at 6 months after ablation compared with medical treatment (56 vs. 26%).<sup>24</sup> While the primary goal of most electrophysiologists performing an ablation in patients with paroxysmal AF will be the pulmonary vein isolation using a circumferential ablation approach, the strategies used for ablation of patients

with non-paroxysmal AF are far more varied and less well supported by evidence.<sup>2,25–28</sup> Currently, there is a lack of evidence and a large debate among electrophysiologists as to what is the optimal ablation strategy in patients with non-paroxysmal AF.<sup>27,28</sup> A meta-analysis of studies reporting the results of catheter ablation of persistent and long-standing persistent (> 12 months of continuous AF) concluded that the success rate of different strategies is similar, provided that pulmonary vein isolation was performed.<sup>29</sup>

The role of the left atrium as a substrate in the progression of paroxysmal to chronic AF is still not fully understood. Some patients having the same characteristics stay in paroxysmal AF for years, while others develop persistent AF within few months after the first episode of AF. Therefore, the phenotypical classification into paroxysmal vs. persistent AF is frequently not directly related to the degree of atrial fibrosis in this heterogeneous patient group.

Based on the review of the literature and in our experience, we would estimate the single-procedure efficacy of AF ablation in an optimal candidate for AF ablation with paroxysmal AF to be between 60 and 80%. The efficacy of a single procedure in a less optimal patient, such as a patient with persistent AF, lies between 50 and 70%.

A large number of studies concerning the long-term efficacy of AF ablation have been published.<sup>30–32</sup> In a series of 264 patients, late recurrence after 5 years was reported more likely in patients with hypertension and hyperlipidaemia.<sup>30</sup> A recent large study reported long-term freedom from AF in 47% of patients after 4.8 years of follow-up.<sup>31</sup> If a patient is brought back to the electrophysiology laboratory with recurrent AF, recurrence of pulmonary vein conduction is almost universally observed. This finding highlights the difficulty in performing permanent pulmonary vein isolation with current ablation techniques. Furthermore, iatrogenic organized left atrial tachycardias after AF ablation are reported with an incidence of 1.2–40%. The frequency of occurrence appears to depend on the type of ablation strategy and the extent of underlying atrial disease. Ablation strategies combining pulmonary vein isolation with extensive left ablation using linear lesions and targeting complex fractionated atrial electrograms (CFAEs) will facilitate the occurrence of the secondary atrial tachycardia mechanisms due to slow conduction induced by incomplete linear lesions. These arrhythmias are frequently very symptomatic because of rapid ventricular rate response with commonly 2:1 AV conduction. They respond poorly to drug therapy and require further ablation procedures.

There is a lot of evidence that ablation is superior to antiarrhythmic drugs, especially in patients with paroxysmal AF and structurally normal hearts, which is reflected in current guidelines and accepted in clinical practice.

## Complications of atrial fibrillation ablation

Catheter ablation of AF is a challenging and complex invasive procedure, which is associated with a risk of major complications. An international survey in 2005 reported a 6% incidence of major complications (tamponade, stroke, pulmonary vein stenosis, or death).<sup>33</sup> A recent update of this survey reported a 4.5% complication rate.<sup>34</sup> Another report from an international survey of AF ablation of 162 centres

provided details on 32 deaths that occurred during or after AF ablation procedures in 32 569 patients (0.1%).<sup>35</sup> Death was due to tamponade in eight patients (25% of deaths), to stroke in five (16%), to atrio-oesophageal fistula in five (16%), and pneumonia in two (6%). There is more recent data suggesting that the complication rate of AF ablation is decreasing.<sup>36,37</sup> A recent consecutive series of patients undergoing AF ablation reported a major complication rate of 0.8%, with no instances of death, stroke, atrio-oesophageal fistula, or pulmonary vein stenosis.<sup>36</sup>

Oesophageal injury due to tissue heating at the posterior wall of the left atrium ranges from frequent mild ulceration to very rare fatal left atrio-oesophageal fistula. Limitation of power applied to the posterior left atrial wall, especially while ablating close to the oesophagus, visualized by a contrast-media filled gastric-oesophageal tube or by image integration of CT or MRI, as well as luminal temperature monitoring to identify potentially dangerous heating of the oesophagus during ablation and the treatment with proton pump inhibitors may prevent a left atrio-oesophageal fistula. However, there are no evidence-based data available demonstrating that these measures reduce the incidence of this very rare complication which is estimated <0.1%.<sup>38</sup>

On the basis of our review, as well as our clinical experience, we would estimate that the current incidence of major complications lies between 1 and 5%. The incidence is 0.5–2% for tamponade, 0.3–1% for stroke, 0.5–2% for vascular injury, and <1% for pulmonary vein stenosis, and the risk for development of an atrio-oesophageal fistula and/or death is <0.1%. Further developments of the technique are required to improve the safety of an AF ablation procedure.

## Unanswered questions concerning the outcome of atrial fibrillation ablation

Several prospective randomized trials have demonstrated that catheter ablation is superior to antiarrhythmic drug therapy in patients with paroxysmal AF and structurally normal hearts. However, there are many important unanswered questions. More information is needed on the impact of AF ablation on mortality and stroke risk beyond rhythm and symptom control. Although patients with AF have an increased risk of stroke and increased mortality, it is unclear whether AF ablation reduces the risk of stroke and improves survival. There are some large case series that have reported a low risk of stroke after AF ablation.<sup>39</sup> Although the stroke rate is low in these series, few patients at high risk of stroke were monitored after anticoagulation was stopped for a significant period of time. It is for this reason that the HRS Consensus Document concluded that a desire to discontinue anticoagulation therapy is not an appropriate indication for AF ablation and that the patient's CHA<sub>2</sub>DS<sub>2</sub>-VASc score [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–75, and sex category (female)], rather than the presence or absence of AF, should be used to determine the appropriate anticoagulation approach after an AF ablation procedure.<sup>2</sup>

The impact of AF ablation on both stroke and survival is currently being evaluated in the CABANA trial (Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation) and the EAST



study (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial).<sup>40–42</sup>

Most AF ablation trials enrolled white male patients <70 years of age.<sup>43–45</sup> It, therefore, remains uncertain what the safety and efficacy of AF ablation are in elderly patients. No difference in the success and complication rates was observed in a study comparing the outcome of three subsets of patients (patients <65 years of age, patients between the ages 65 and 74 years, and patients older than 75 years).<sup>30</sup> However, patients >75 years old were less likely to undergo repeated procedures and preferred to continue antiarrhythmic drug therapy.

A number of clinical trials have addressed the role of catheter ablation of AF in patients with heart failure. The first study addressing this topic examined the impact of AF ablation in 58 patients with heart failure with an ejection fraction <45% and in 58 control subjects. During a follow-up of 1 year, 78% of patients with heart failure and 84% of control subjects remained in sinus rhythm. Of particular note is that the ejection fraction improved by  $21 \pm 13\%$ . Improvements were also seen in exercise capacity and quality of life. Another study, the PABA-CHF study (Pulmonary Vein Antrum Isolation vs. AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure) compared the outcome of AF ablation with the ablation of the atrioventricular node after pacemaker implantation.<sup>46</sup> The trial showed an overall superiority of pulmonary vein antrum isolation to atrioventricular node ablation, as evidenced by an increase in quality of life, longer walking distance (340 vs. 297 m), and a higher ejection fraction (35 vs. 28%). Only few data are available on cost-effectiveness of AF ablation. A successful catheter ablation of AF would potentially significantly reduce healthcare resource utilization, especially if large randomized prospective trials will demonstrate that successful AF ablation reduces the risk of stroke. A decision analytic model using data from a randomized study comparing first-line catheter ablation to antiarrhythmic drug therapy showed that the costs of ablation were neutralized in patients with paroxysmal symptomatic AF 2 years after an initial procedure compared with drug therapy.<sup>47</sup>

## Guidelines for the catheter ablation of atrial fibrillation

The Consensus Statement on catheter and surgical ablation of atrial fibrillation of the HRS/ EHRA/ECAS and the Guidelines for the management of patients with atrial fibrillation of the ESC (European Society of Cardiology), the AHA (American Heart Association), the ACC (American College of Cardiology), and the HRS recommend the catheter ablation of symptomatic paroxysmal AF after failure of at least one class 1 or 3 antiarrhythmic agent.<sup>2–4</sup> This indication is stratified as class I and level A. Catheter ablation as a first-line therapy is considered as reasonable (class IIa, level B indication) in selected patients with paroxysmal AF without structural heart disease. The same level of indication accounts for patients with persistent AF after failed antiarrhythmic drug therapy. Currently, the primary goal of catheter ablation of AF is control of symptoms and improvement of quality of life.<sup>40–42</sup>

## New techniques and future perspectives

Ongoing developments of new ablation tools will improve safety and efficacy of AF ablation. They will shorten procedure time and learning curve allowing the procedure to be performed by less skilled operators, resulting in an opening of this therapeutic modality to a higher proportion of patients with AF.

An alternative to radiofrequency energy for lesion creation is cryoenergy, which is available in a cryoballoon ablation system for the clinical use for treatment of patients with paroxysmal AF. This balloon-based ablation system isolates each pulmonary vein by freezing the tissue below  $-80^{\circ}\text{C}$ .<sup>19</sup> It appears that cryoballoon ablation is best suited for patients with paroxysmal AF with comparable efficacy and safety to conventional ablation with radiofrequency.

Another alternative energy is laser light which is also applied through a balloon-based ablation system that enables direct visualization of the pulmonary vein ostium (Figure 2). In 200 patients electrical isolation was achieved in 99% of the targeted pulmonary veins. At 12 months, 60% of patients were in sinus rhythm without antiarrhythmic drugs.<sup>48</sup>

A recent study showed that remaining pulmonary vein activity after ablation was an independent predictor of AF recurrence and recommend additional ablation for spontaneous dissociated pulmonary vein activity after pulmonary vein isolation.<sup>49</sup>

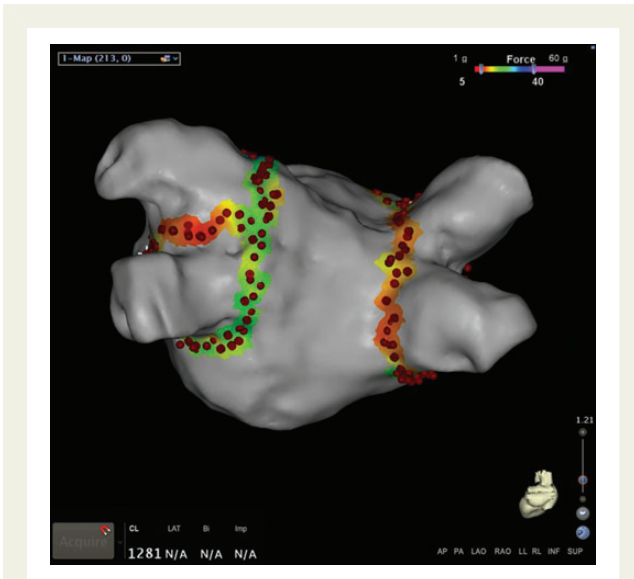
Another novel approach, referred to as pulmonary antrum radial-linear ablation, consists of creating six to eight short ablation lines starting from the pulmonary vein ostium. The endpoint was not electrical isolation, but completion of the ablation lines, conversion into sinus rhythm and non-inducibility of AF.<sup>50</sup> At 14 months, 74% of patients treated with pulmonary antrum radial-linear ablation were free from AF compared with 50% of patients treated by pulmonary vein isolation.

Contact force determines the size of ablation lesions. Novel ablation catheters have been developed that provide instantaneous feedback on the degree and orientation of force with which the ablation catheter is contacting the atrial wall (Figure 5).<sup>51</sup> Initial experiences are encouraging; however, definitive outcome data are not yet available.

Other ablation strategies than aiming pulmonary vein isolation are being developed, such as ablation of CFAEs. In a single-centre study, 81% of 674 patients were in sinus rhythm at 5 year after ablation of CFAEs.<sup>26,52</sup> However, other groups could not replicate these impressive results likely due to the subjective nature of defining CFAEs by visual inspection.

One-third of patients develop a vagal reflex during AF ablation and this group have a 99% success rate as compared with a 85% success rate among patients without vagal reflex during ablation.<sup>53</sup> However, the findings are somewhat controversial and the role of ablation of autonomic ganglia remains to be better defined.

Another recent and novel approach consists of mapping and ablating localized areas other than pulmonary veins, referred to as electrical rotors.<sup>54</sup> Contact mapping using a 64-polar basket catheter and computational mapping identify localized sources for AF. At a follow-up of 273 days and after a single-procedure, patients treated with an additional ablation of localized electrical rotors were



**Figure 5** Three-dimensional electroanatomical map of the left atrium with the circumferential ablation lesion points (red points) around ipsilateral pulmonary veins and additional lesions between left superior and inferior pulmonary vein created by a novel ablation catheter which measures in real-time contact force and direction of the catheter tip. The amount of contact force applied for each ablation lesion is displayed in this 'force map' with a specific colour.

significantly more frequently free from AF (82%) compared with patients treated by pulmonary vein isolation alone (45%).

There are two ablation tools available that allow remote and robotic ablation. The first is a robotic magnetic navigation system that consists of two permanent magnets placed on either side of the patient, and the second is a remote navigation system that uses a robotically steerable sheath.<sup>55,56</sup> As of today, the goals of improved efficacy and safety and shortening of procedure times have not been met yet and few electrophysiologists worldwide rely on these robotic systems.

Recently, a number of studies have demonstrated the value of using magnetic resonance imaging (MR) to image myocardial scar, both before ablation as a predictor of success and after ablation.<sup>57</sup> Moreover, substantial progress has been made on developing the tools to allow electrophysiology studies and catheter ablation procedures to be performed in a MR scanner.<sup>58</sup> Magnetic resonance imaging is radiation free, allows imaging of myocardial tissue and structures and ablation lesions, and is similar in cost to a biplane fluoroscopy system. Despite these theoretical advantages, the obstacles to performing catheter ablation in an MR environment are considerable. Research on developing MR-based ablation is ongoing.

## Conclusions

Catheter ablation of AF is now an important therapeutic modality for patients with AF. There is considerable evidence available from several prospective randomized trials demonstrating that catheter ablation of AF is superior to antiarrhythmic drug therapy in controlling AF and that AF ablation improves quality of life substantially. This

is especially true for patients with paroxysmal AF without other severe comorbidities. Catheter ablation is indicated for treatment of patients with symptomatic AF in whom one or more attempts at class 1 or 3 antiarrhythmic drug therapy have failed. Although current guidelines state that it is appropriate to perform catheter ablation as a first-line therapy in selected patients, in our clinical practice this is rare. This reflects a number of important realities concerning the field of AF ablation. Catheter ablation of AF is a challenging and complex procedure, which is not free of the risk of potentially life-threatening complications, such as an atrio-oesophageal fistula, stroke, and cardiac tamponade. Although these major complications are rare and their rate is falling, they must be considered by both patients and physicians. The progress made and the new developments on the horizon in the field of AF catheter ablation are remarkable. When radiofrequency catheter ablation was first introduced in the late 1980s, few would have predicted that catheter ablation of AF would emerge as the most commonly performed ablation procedure in most major hospitals.

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