What is the Latest on Catheter Ablation of Atrial Fibrillation?

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Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia observed in clinical practice, affecting 1–2% of the general population. AF is associated with reductions in quality of life, functional status, cardiac performance, and survival.¹ In addition, AF accounts for 1.0–2.7% of total annual healthcare expenditures, with a sizeable proportion of these expenses attributed to direct costs associated with emergency department visits and acute care hospitalization.^{2–5}

The contemporary management of AF is centred on symptomatic improvement, reduction in healthcare utilization, and reduction in AF-associated morbidity and mortality (in particular the prevention of stroke or systemic thromboembolism).⁶ While ventricular rate control can be effective, many patients remain symptomatic despite optimal rate control. For these patients, restoration and maintenance of sinus rhythm can alleviate symptoms, and improve quality of life. Oral antiarrhythmic drug (AAD) therapy, which remains the “first-line” therapy for the maintenance of sinus rhythm, has only modest efficacy at maintaining sinus rhythm over the long term and can be associated with significant side-effects such as pro-arrhythmia, heart failure, and organ toxicity.^{7–12}

For many patients, catheter ablation offers an alternative for maintaining sinus rhythm when AADs have been ineffective or cannot be tolerated. While catheter ablation has not been proven to improve mortality, it has been shown to be universally superior to AADs for the maintenance of sinus rhythm (AF elimination in 66–89% with catheter ablation vs. 9–58% with AAD). In addition, catheter ablation significantly improves symptoms, exercise capacity, and quality of life.^{13–23}

The focus of this article will be a brief review of the history of AF ablation, followed by a discussion of four areas where significant recent developments have occurred.

Evolution of Current Ablation Strategies and Techniques

Up until the mid to late 1980s the “multiple wavelet hypothesis” was the dominant mechanistic theory of AF pathophysiology. This theory postulated that AF results from the presence of multiple independent coexisting wavelets that are occurring simultaneously and propagating randomly throughout the atria. This hypothesis postulated that AF could be initiated and then perpetuated indefinitely as long as the atrium had a sufficient area with adequately short refractory periods. As such, the early surgical and percutaneous interventions aimed to decrease arrhythmia perpetuation by compartmentalizing the atrium into smaller regions. It was thought that reducing the excitable mass of atrial tissue would render the atria incapable of sustaining the critical number of circulating wavelets. The approach was associated with only moderate success.

In the late 1990s Haïssaguerre and colleagues demonstrated that AF was a triggered arrhythmia initiated by rapidly repetitive discharges predominantly originating from the pulmonary veins (PVs). This led to the development of percutaneous procedures designed to electrically isolate the PV from the left atrium. Over the past 20 years the technique of PV isolation (PVI) has evolved significantly from focal ablation of discrete triggers within the PV, to circumferential ablation of the left atrial myocardium outside of the tubular veins with a goal of large circumferential

Figure 1. Example of AF ablation with point-by-point contact force radiofrequency (bottom left) and cryoballoon ablation (bottom right).

electrical PVI (i.e., electrical conduction block into and out of the PVs). This contemporary approach not only targets the initiating triggers of AF (the PVs) but also the mass of electrically active LA tissue capable of perpetuating AF (Figure 1).

Unfortunately, although the results of catheter ablation are unequivocally superior to antiarrhythmic drug therapy, they are not perfect. It can be anticipated that only approximately 70% of paroxysmal AF patients will remain arrhythmia- and AAD-free after a single ablation procedure. For persistent AF patients the progressive pathoanatomical changes in the atria result in a further reduced procedural efficacy (50–60% vs. 66–89% in paroxysmal AF), but additional ablation strategies targeting the substrate outside the PVs (linear ablation or ablation of complex atrial fractionated electrograms) are not superior to PVI alone.²⁴ Therefore, PVI remains the cornerstone of catheter ablation for paroxysmal and persistent AF.²⁵

However, it is important to realize that even in the face of arrhythmia recurrence a clinical improvement can be obtained. Recent studies have suggested that complete elimination of AF may not be necessary, and that significant clinical benefit can be obtained if the overall arrhythmia burden (i.e. time in AF) is reduced. For example, a recent analysis from the CASTLE-AF trial demonstrated that a 50% reduction in AF burden was associated with a significant reduction in the risk of death (HR 0.30), or

heart failure hospitalization (HR 0.43). Therefore, although the arrhythmia might not be considered “cured” in all patients, a significant proportion of patients derive meaningful clinical benefit.

Novel Technologies to Ensure Durable Pulmonary Vein Isolation

While electrical PVI may be achieved acutely, the creation of durable scar around the PVs with a percutaneous procedure is challenging. With time, inadequate ablation leads to recovery of electrical conduction between the PV and LA, which may trigger recurrent arrhythmia episodes. In this regard several novel ablation technologies have been designed in an effort to improve ablation lesion creation.

Contact Force Sensing Catheters

Contact force (CF) sensing is a newly developed technology embedded within the radiofrequency ablation catheter that allows for the real-time estimation of the contact between the tip of the catheter and the target myocardium. Durable lesion formation in the atrium requires adequate catheter electrode-tissue contact. Insufficient tissue contact can result in edema with only transient loss of conduction. Available data suggests that incorporating real-time CF assessment into the ablation procedure results in a reduction in procedure time, ablation time, and total energy delivery.^{26,27} Recent studies suggested improved arrhythmia outcomes when the procedure was performed with adequate CF parameters (84% one-year freedom from AF in the 47% of patients in whom ablation was in the target range $\geq 80\%$ of the time in SMART-AF, and 76% one-year freedom from AF in the 57% of patients in whom $\geq 90\%$ of the lesions were $>10\text{g}$ in TOCCASTAR).^{28,29}

Balloon-Based Technologies

While focal point-by-point radiofrequency catheter ablation has shown considerable success, the procedure is time-consuming and dependent on operator competency.³⁰ In response considerable effort has been directed towards the development of technologies that are less reliant on operator dexterity. The most mature of these balloon-based technologies is the Cryoballoon (Medtronic, Minneapolis, MN), a purpose-built ablation catheter specifically designed for PVI. Instead of the “heat” utilized with radiofrequency ablation, the cryoballoon employs freezing inside the balloon to destroy the atrial tissue. When compared to radiofrequency cryothermal energy offers several potential advantages, including improved catheter stability (due to tissue adherence at freezing temperatures), minimal endocardial surface disruption, reduced thrombogenicity, and preserved ultrastructural tissue integrity leading to a lower perforation risk.³¹ Balloon-based technologies

continue to evolve and recent studies have demonstrated improved arrhythmia-free survival with the second-generation cryoballoon compared to the first generation cryoballoon (OR of arrhythmia recurrence 0.34 [0.26–0.45]; 10 studies, 2310 patients).^{32,33} While these outcomes are comparable to standard radiofrequency ablation,^{34,35} ongoing studies are evaluating the effectiveness of 2nd generation cryoballoon ablation compared to CF sensing radiofrequency ablation.³⁶

Other balloon-based technologies include: (1) the HeartLight laser balloon (CardioFocus, Marlborough, MA), which is an endoscopic laser ablation catheter that allows direct visualization of the endocardial surface of the PV during infrared light energy ablation; (2) The multi-electrode Helios radiofrequency balloon (Biosense); and (3) The Apama radiofrequency Balloon (Boston Scientific, Marlborough, USA). Each of these technologies have recently published encouraging short-term safety and efficacy outcomes, with large randomized multicenter studies ongoing.

Ablation as a First-Line Treatment

The ideal management of patients with newly diagnosed symptomatic AF remains unknown. Current practice guidelines recommend a trial of antiarrhythmic drugs prior to considering an invasive ablation procedure. However, the universal superiority of ablation over antiarrhythmic drug therapy suggests that performing catheter ablation earlier may offer an opportunity not only for better symptom control but also to halt the progressive pathophysiological and anatomical changes associated with AF.³⁷ So far the evidence supporting “first-line” catheter ablation (i.e., as an initial therapy prior to AAD) is promising, but far from definitive. The MANTRA-PAF Study and the RAAFT studies randomized patients to either first-line ablation or first-line AADs.^{14,38,39} Despite disparate ablation techniques, these studies collectively demonstrated an improved freedom from recurrent arrhythmia (37% reduction in AF recurrence vs. AAD therapy), an improved freedom from symptomatic AF (43% reduction in symptomatic AF vs. AAD therapy), and a reduction in the overall AF burden (50% reduction over AAD therapy). While the results of these studies suggest that ablation is more effective than AAD therapy as first-line treatment, a significant proportion of patients in the intervention group experienced arrhythmia recurrence. Thus, the issue of first-line ablation remains an open question, where further research is required before first-line catheter ablation can be considered routine for most patients with symptomatic paroxysmal AF.

Ablation in Patients with Heart Failure

AF and heart failure (HF) are global cardiovascular epidemics. These conditions frequently coexist, and are both increasing in

prevalence.^{40,41} AF is an independent predictor of progression, hospitalization and death in the HF population.^{42–46} While restoring and maintaining sinus rhythm may be a therapeutic target to improve outcomes, large randomized controlled trials of antiarrhythmic drugs (AAD) have failed to support this hypothesis.^{47–51} It is postulated that the attenuated benefit observed with AADs therapy is related to cardiac and non-cardiac toxicities (e.g., pro-arrhythmia, conduction block, negative inotropy), and ablation may be a more efficacious means to improve outcomes.

To date seven randomized trials have been performed, in addition to an observational meta-analysis, and an observational multi-centre cohort study. Collectively these studies have demonstrated a single procedure success (e.g., elimination of any AF episodes >30 seconds) in the range of 40–69%, with multiple procedures improving the success up to 88%. Beyond arrhythmia recurrence, catheter ablation of AF in HF patients with LV systolic dysfunction appears to be associated with improvement in left ventricular ejection fraction (LVEF improvement of 4.5–18%), exercise performance (VO₂ max improvement of 3 mL/kg/min vs. comparator; and 6-minute walk improvement of 20–70 meters from baseline), and quality of life (33% average improvement in Minnesota Living with HF Questionnaire score).^{52–58}

However, a truer measure of the utility of catheter ablation in patients with AF and HF with reduced systolic function is the objective outcomes, such as mortality and hospitalization. While a recent large RCT failed to demonstrate significant mortality benefit in unselected populations, two recent randomized trials have demonstrated that catheter ablation of AF in HF patients with reduced systolic function population results in significant improvement in all-cause mortality as well as fewer HF hospitalizations.^{52,58,59} The first of these studies was the AATAC study, which randomized 203 patients with New York Heart Association functional class II to III HF and an LVEF <40% to catheter ablation (n=102) or amiodarone rhythm control (n=101).⁵² After 24–27 months of follow-up patients in the ablation group had a significantly greater freedom from recurrent AF (70% vs. 34%; *P*<0.001). In addition, the secondary endpoints of unplanned hospitalization and all-cause mortality were both significantly reduced (45% and 56% respectively), corresponding to a NNT of 3.8 for unplanned hospitalization and 10 for all-cause mortality. The second study, CASTLE-AF, randomized patients with symptomatic paroxysmal or persistent AF, New York Heart Association class II–IV HF, and an LVEF ≤35% to catheter ablation (179 patients) or medical therapy (184 patients).⁵⁸ All patients had a cardiac implantable device (ICD or CRT-ICD). After a median follow-up of 37.8 months, patients in the ablation group were significantly less likely to meet the primary composite end point of all-cause mortality or HF

admission (16.1% absolute reduction; HR 0.62; 95% CI 0.43–0.87; $p=0.006$). Similar to AATAC, there was a 47% relative reduction in all-cause mortality (HR 0.53; 95% CI 0.32–0.86) and a 44% reduction in HF hospitalization (HR 0.56; 95% CI 0.37–0.83).

The third study was CAMERA-MRI, which evaluated catheter ablation vs. medical rate control in 68 patients with persistent AF and left ventricular systolic dysfunction (LVEF $\leq 45\%$).⁵⁷ AF burden was assessed in ablation patients via implanted loop recorder, and serial holter monitors in the medical rate control patients. The primary endpoint was change in the LVEF on magnetic resonance imaging (MRI) at six months. The authors observed an $18 \pm 13\%$ absolute improvement in the ablation arm vs. $4.4 \pm 13\%$ in the rate control arm ($P < 0.0001$). The absence of ventricular scar, as defined by late gadolinium enhancement on cardiac MRI, predicted greater improvement in LVEF (22.3% vs. 11.6% in those with scar, $p=0.0069$), and a greater likelihood of LVEF normalization (73% vs. 21% in those with scar, $P=0.009$). As such, it is possible that MRI may be used to prospectively identify HF patients with reduced systolic function who may benefit from catheter ablation of AF.

Taken together these studies demonstrate that catheter ablation is associated with an improvement in ejection fraction and clinical outcomes when compared to medical therapy. Most striking is the observation that these adverse outcomes seem to be more linked to the overall AF burden. Specifically, the clinical benefit observed in CASTLE-AF was not dependent on the complete elimination of AF. Notably, while 63.1% of patients in the ablation group and 21.7% of patients in the medical therapy group were free of recurrence at the 60-month follow-up visit, the time in AF was reduced to $\sim 25\%$ in the ablation group compared to $\sim 60\%$ in the medical therapy group. A subsequent analysis of these patients demonstrated an AF burden $< 5\%$ was associated with a more than 3 times significantly greater freedom from all-cause mortality or HF hospitalization at 1 year, when compared to greater burdens of AF. It is hypothesized that the reduction in AF burden facilitates improvement in cardiac hemodynamic function (including cardiac output), autonomic nervous system performance, and reverse remodeling, which could also explain the lack of benefit observed in the rate control group in CAMERA-MRI.

Lifestyle Intervention to Target AF Perpetuating Substrate

AF is a complex chronic cardiovascular condition, with modifiable lifestyle and cardiovascular risk factors impacting the risk for AF development, AF progression, and AF recurrence after cardioversion and catheter ablation. Modifiable risk factors such as hypertension, obstructive sleep apnea, obesity, physical

Figure 2. Risk factor management targets and strategies from the ARREST-AF cohort study. (ACEI - angiotensin converting enzyme inhibitor; AHI - apnea-hypopnea index; ARB - angiotensin receptor blocker; BP - blood pressure; CPAP - continuous positive airway pressure; LDL - low density lipoprotein; TG - triglycerides). Reproduced with permission from Lau et al.⁶⁰

inactivity, alcohol and tobacco use, and diabetes mellitus have all been shown to significantly contribute to AF frequency, duration, and symptom severity. As such, interventions to optimally manage these comorbidities have been postulated to improve outcomes.

The ARREST-AF cohort study examined 149 patients with a body mass index $\geq 27 \text{ kg/m}^2$ and ≥ 1 cardiac risk factors, dividing them into 61 patients who opted for risk factor management (RFM) and 88 control subjects (Figure 2). In the RFM group: blood pressure was treated to a target of $< 130/80 \text{ mmHg}$ (ACEI/ARB preferred), weight management targeted a $> 10\%$ weight loss to a BMI $< 27 \text{ kg/m}^2$, exercise was targeted to start at 90 minutes per week increasing to 250 minutes per week, obstructive sleep apnea (AHI ≥ 30) was treated with CPAP therapy, lipids were treated to contemporary targets, with elevated fasting blood sugar/HbA1c treated with metformin to target an HbA1c $< 7\%$. At a mean follow-up of ~ 42 months post ablation the RFM groups achieved greater reductions in weight ($-13.2 \pm 5.4 \text{ kg}$ vs. $-1.5 \pm 5.1 \text{ kg}$; $p=0.002$), blood pressure ($34.1 \pm 7.5 \text{ mmHg}$ vs. $20.6 \pm 3.2 \text{ mmHg}$; $p=0.003$), glycemic control (HbA1c levels $< 7\%$ in 100% vs. 29%; $p=0.001$), and lipid values (controlled in 46.2% vs. 17%; $p=0.01$). Arrhythmia-free survival rates after catheter ablation were 87% with RFM compared with 18% for the control group ($p < 0.001$), with a significantly greater reduction in symptom scores and global well-being ($p < 0.001$).

Conclusion

Catheter ablation is an effective treatment for AF. Pulmonary vein isolation remains the cornerstone of AF ablation procedures, with considerable effort having been directed towards developing technologies to achieve safer and more durable lesions. Ongoing research is being invested in studying ablation strategies to improve outcomes in various AF populations.

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