

How effective is cryoablation in the treatment of atrial fibrillation?

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KEYWORDS

Atrial fibrillation;
Cryoablation;
Radiofrequency

Pulmonary vein isolation is the standard for atrial fibrillation ablation. Although the most commonly applied energy source is radiofrequency (RF), cryoablation has rapidly evolved as a powerful one-shot tool, particularly after the introduction of the second-generation catheter, gaining widespread use in recent years. The efficacy in maintaining sinus rhythm after a first ablative procedure is ~70-80%, and the randomization studies comparing cryoablation to RF have not been able to reveal significant differences up to now. Although different baseline characteristics may influence the efficacy of cryoablation, we are not yet able to distinguish which patients may benefit from a personalized choice of ablative source. Regarding safety, cryoballoon ablation appears to be associated with a lower rate of pericardial effusion and cardiac tamponade, mainly due to the lack of risk of overheating. The other side of the coin is a higher incidence of phrenic nerve damage, which occurs in 1-2% of procedures. In conclusion, we do not yet have definitive data to affirm the superiority of the RF technique over that of cryoablation. The choice of energy source currently depends on the availability of the centre and on the experience of the operator.

Introduction

We have known for more than 20 years that the presence of excitable tissues within the pulmonary veins (PVs) and at the left atrium-PV junctions plays a central role in the onset of atrial fibrillation (AF). Disruption of electrical interactions between these areas and the rest of the atrial tissue remains the cornerstone of AF ablation. The pioneering studies have described ablative strategies based on point-to-point radiofrequency (RF) delivery for the disconnection of PVs,^{1,2} with the aim of creating complete and lasting isolation. In the last decade, significant technological improvements have arisen in catheters, such as the introduction of catheters with irrigating tips or with the ability to measure contact force. However, some problems regarding thermal ablation, such as excessive overheating of the tissue or the potential to injure extra cardiac structures, remain an unresolved concern of RF. In this context,

other energy sources have been proposed as an alternative to RF for the isolation of PVs. However, only cryoablation has generated evidence and gained sufficient popularity to be considered a real alternative to RF.

The first steps towards cryoablation were made in 1961 by Irving S. Cooper, a neurosurgeon who developed a probe that used liquid nitrogen circulating through a metal sheath with the aim of creating cryogenic lesions in the brain for the treatment of parkinsonism.³ Half a century of technical improvements led to the contemporary design of the transvenous cryocatheter. Currently, the isolation of PVs is achieved through the use of a deflectable catheter with a cryoballoon positioned distally and designed, contrary to ablation by RF, for 'single-shot' ablation (single energy delivery). The formation of the cryoablative lesion is based on convective cooling, whereby the cryocoolant absorbs heat from the surrounding myocardium, causing cell damage caused by the formation of ice crystals and ischaemic necrosis of the cell. From the initial description of the cryoballoon for the ablation of AF,⁴ cryoablation has benefitted from constant use, especially, though not only, in the centres of medium and low volume. To date, cryoablation is

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the source used in 12–19% of patients undergoing PV isolation in Europe.⁵ Potential arguments in favour of cryoablation include a shorter learning curve and shorter procedural time than the traditional RF thermocoagulation substrate injury technique.

Effectiveness of cryoablation

In 2003 Tse *et al.*⁶ reported a first description of the efficacy of transvenous cryoablation in the treatment of 45 patients with paroxysmal AF and 7 patients with persistent AF. Intra-procedural electrical isolation of PVs was achieved in all but three patients. After a 1-year follow-up, 29 (56%) patients had no AF recurrence while a significant reduction in AF episodes was observed in 71% of patients. A decade after this first description, the second-generation (SG) cryoballoon entered clinical practice. Thanks to the significant improvements in the refrigerant delivery system, the new catheter freezes in a larger and more homogeneous area. A meta-analysis including 15 studies and 2363 patients with AF undergoing SG cryoballoon ablation showed that 82% of patients with paroxysmal AF and 70% of patients with persistent AF were free from arrhythmic relapses in the 12 months after the procedure.⁷ We also have data suggesting that SG's cryoballoon is more effective than its predecessor. A pooled analysis of 10 studies in patients undergoing AF cryoablation [1237 with a first-generation (Arctic Front) cryoballoon and 957 with an Arctic Front Advance (SG) cryoballoon] showed a lower arrhythmia recurrence rate when this last catheter was used.⁸ Furthermore, experience in clinical practice seems to confirm this greater efficacy. The Frankfurt group recently reported their results after 1017 ablation procedures using the SG cryoballoon.⁹ After 12 months, 84% of patients with paroxysmal AF and 75% of patients with persistent AF maintained sinus rhythm. These data seem to confirm the high efficacy of cryoablation in reducing symptomatic relapses. However, when AF relapses are assessed by continuous monitoring, the 1-year patient-free AF rate decreases significantly. The Circa-dose study reported an efficacy of 73–78% for relapse of symptomatic AF, according to the cryoablation regimen employed. However, only 52% of patients were confirmed free from AF recurrence after interrogation of the continuous monitoring device.¹⁰

The results of a randomized multicentre study¹¹ designed to test whether cryoballoon ablation is superior to antiarrhythmic drugs in patients with paroxysmal AF who had not previously received any rhythm control therapy were recently published. This study randomized 203 patients to antiarrhythmic drugs (Class I or III) or cryoballoon ablation (Arctic Front Advance). After 12 months of follow-up, 75% in ablation and 45% in antiarrhythmic drugs group were free from AF recurrence. These findings support the use of cryoablation not only in symptomatic drug-refractory patients, but also as a first-line therapy in patients with paroxysmal AF.

Comparison with radiofrequency

FIRE AND ICE¹² was the first study that randomized patients to RF or cryoballoon therapy with the aim of verifying

whether or not one of the two ablation strategies is superior in patients with drug-refractory paroxysmal AF. A total of 762 patients were randomized. After an average follow-up of 18 months, no differences were found with respect to the efficacy endpoint. Furthermore, both methods were comparable in terms of safety. A subsequent modified intention-to-treat analysis showed that cryoballoon was superior to RF in the rate of repeat ablations, cardioversions, and cardiovascular re-hospitalization during follow-up.¹³ Furthermore, in patients who underwent re-ablation during follow-up, the number of electrical conduction relapses between the PV and the left atrium was significantly lower when the initial isolation was performed with cryoballoon.¹⁴ These results could be explained by the lower stability of the catheter in RF compared to that obtained with the cryoballoon. However, it should be noted that force contact catheters were used in less than one-third of patients in the RF group enrolled in the FIRE AND ICE trial.

In the CIRCA-DOSE study, 346 patients with drug-refractory paroxysmal AF were randomized to cryoballoon or RF ablation.¹⁰ Two main peculiarities distinguish this study from the FIRE AND ICE study. First, both RF and cryoablation were performed with the latest generation catheter (force contact catheters and cryoballoon of SG, respectively). Second, all patients received an implantable loop recorder. The rate of patients who did not suffer from recurrent atrial arrhythmias in the first year was 53%, with no difference between the two different ablation approaches. One of the strengths of continuous heart rhythm monitoring is that the differences between the AF burden can be compared directly before and after the procedure. In this regard, a relevant reduction in arrhythmic load was observed, equal to 98% of the time in AF with no difference between the two ablation techniques in the intention-to-treat analysis.

Two large registers have recently been published comparing the efficacy of cryoablation vs. RF in routine clinical practice. Both show similar results. The first is a Swedish national registry along with an EHRA AF ablation registry that includes 4657 patients, of which a fifth underwent cryoablation. Although there were no differences in the arrhythmic recurrence rate, the number of readmissions after 12 months was significantly lower in the group undergoing cryoablation.¹⁵ The second is a prospective cluster-cohort study, comprising 4189 patients in 42 centres in 8 countries,¹⁶ 2329 (56%) of whom underwent cryoablation and 1860 (44%) RF ablation. Again, there were no differences in the relapse rate, but re-hospitalization due to re-ablations was significantly higher in RF. The outcome of these studies, even if relevant, should be analysed bearing in mind that no randomization was performed and that the difference in baseline characteristics of patients undergoing cryoablation or RF ablation could lead to misinterpretation of the result. Randomized trials evaluating the re-ablation rate as the default endpoint are needed to confirm these results.

The economic aspect of cryoablation was also compared with RF by analysing data from FIRE AND ICE. Cryoablation was associated with a significant reduction in resource consumption, but this difference is mainly attributable to fewer repeat ablations.¹⁶

In conclusion, we do not yet have categorical data to affirm the superiority of one ablation source over the other.

Cryoablation safety

If cryoablation was proposed as an alternative to RF ablation it was partly due to the fact that convective cooling could potentially overcome some still unsolved safety concerns of thermal ablation. Since cryoablation avoids the risk of tissue overheating, a significant reduction in steam pops and cardiac perforation could potentially tip the safety balance in favour of cryoablation. However, after the introduction of cryoballoon ablation into clinical practice, the onset of more specific complications of cryoablation, such as phrenic nerve injury, has rebalanced the balance.

Safety was a predefined endpoint of the main clinical trials comparing cryoablation and RF in patients with AF. In the FIRE AND ICE study, the primary safety endpoint occurred in 40 (11%) and 51 (13%) patients undergoing cryoablation and RF, respectively.¹² While there were no quantitative differences in the complication rate between the groups, these were qualitatively different. Phrenic nerve injury occurred in 10 (2.7%) patients in the cryoablation group but not in patients undergoing RF ablation. On the other hand, cardiac tamponade showed a non-significant tendency to be more frequent in the RF group. In the CIRCA-DOSE study, no differences in the rate of serious adverse events were observed between groups. Again the phrenic nerve injury was observed exclusively in the cryoballoon group, but in this case this complication occurred less frequently, in 1% of patients.

The equivalence in the complication rate between cryoablation and RF appears to be confirmed by two recent meta-analyses. The first included 15 studies and found no significant differences in safety between the two energy sources used for PV isolation.¹⁷ Phrenic nerve injury occurred in 3.3% of patients treated with cryoablation, accounting for 41% of overall adverse events from this source. Similar observations were confirmed in a second meta-analysis,¹⁸ which showed that cryoballoon ablation led to higher rates of persistent phrenic nerve palsy but lower rates of cardiac tamponade.

Although not always covered by large trials, fluoroscopy exposure should be considered when evaluating patient and operator safety. In this regard, the shorter procedure time for cryoablation¹⁵ is largely offset by the superior use of radioscopic control.¹⁰ Fluoroscopy exposure has been estimated to be up to one-third higher using cryoablation.¹⁹

Selection of candidates for cryoablation

The overall effectiveness of cryoablation is in the range of 70-80%, but certain baseline characteristics can increase or decrease the probability of response to therapy in the specific patient. In this regard, it is known that variants of PV anatomy can affect the success of ablation. A left common vein is frequently seen in patients undergoing AF ablation. It has been hypothesized that the mismatch in diameter between the cryoballoon and the more proximal aspect of the left common PV could have a negative impact on the procedure, due to the need for a more distal delivery to

ensure sufficient contact with the tissue. In fact, a complete antral occlusion of the common PV is possible only in half of the patients, while in the remaining patients we usually proceed with an isolation of the first branches of the venous bifurcation. However, the larger series of patients undergoing cryoablation did not revealed difference in the relapse rate between patients with a left common ostium and patients with four independent ostia.^{20,21}

Gender is a prognosis modifier in AF patients. We know that women have a lower prevalence of AF than men. On the other hand, women more often have disabling symptoms and a higher thromboembolic risk. Additionally, procedure-related complications are more common in women undergoing PV isolation. This gender specificity also appears to play a role in the response to cryoablation. A recent meta-analysis of individual patient data including information on 4840 men and 1979 women undergoing pulmonary vein isolation (PVI) concluded that cryoablation is less effective in women.²² The causal mechanism of this observation is not yet fully understood.

A further variable that could influence the effectiveness of cryoablation is the temporal pattern of AF episodes. Pulmonary vein isolation is known to result in less maintenance of sinus rhythms in patients with persistent AF, a phenomenon usually attributed to the presence of extra-PVI triggers and the presence of diffuse fibrosis in a more remodelled left atrium. With the aim of increasing the effectiveness of ablation in these patients, it was proposed to extend the application of RF beyond the PVs. Technical difficulties in performing a linear lesion or ablating fractional electrograms in the left atrium could potentially reduce the efficacy of cryoablation in patients with persistent AF. However, a strategy based on PV isolation with cryoablation as an initial approach for persistent AF was not inferior to either the isolation of the PVs with RF¹⁶ or the combination of PV + additional ablation lines/complex fractionated atrial electrogram (CFAE) with RF.¹⁵ Recently, the creation of additional lesions in the left atrium has been proposed as the concomitant isolation of the posterior wall to increase efficacy in patients with persistent AF undergoing cryoablation.²³ However, further studies are needed to confirm the benefit of this approach.

On the basis of these baseline characteristics, some scores have been proposed to optimize the selection process of candidates for cryoablation.²⁴ However, the accuracy in predicting AF recurrence was suboptimal when tested over an external populations. Nowadays, there is still a long way to go for a personalized approach to the ablation of AF, including the correct selection of ablative energy.

Conclusions

In recent years, AF cryoablation has established itself as a real alternative to RF ablation, to the point that this ablative source is chosen in one out of five European patients undergoing PV isolation. 70-80% of patients maintain sinus rhythm after a first procedure, showing an efficacy rate equivalent to ablation by RF. It is also comparable to RF when it comes to safety. Phrenic nerve palsy remains the

major concern of cryoablation, accounting for 40% of peri-procedural complications. A reduction in total procedure time and less dependence on the operator's experience make cryoablation an attractive choice for centres starting an AF ablation program.

In conclusion, we do not yet have definitive data to affirm the superiority of one energy source over the other. Generally the choice depends on the availability of the centre and on the experience of the operator.

Conflict of interest: none declared.

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