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Efficacy of cryoablation in atrial fibrillation: comparison with antiarrhythmic therapy

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Atrial fibrillation (AF) represents the most common arrhythmia in clinical practice, characterized by irregular atrial electrical activity originating mainly in and around the pulmonary veins. This condition can manifest itself symptomatically or silently but still dangerously. Complications associated with AF include stroke, heart failure, worst clinical outcome in patients with underlying conditions, increased emergency room visits, hospitalizations, and cardiovascular mortality. Currently, according to the main international guidelines, antiarrhythmic therapy is considered the first choice for rhythm control in patients with AF despite modest efficacy and non-negligible side effects. In recent decades, radiofrequency catheter ablation has emerged as an alternative to antiarrhythmic drugs for rhythm control. Cryoablation was developed with the aim of reducing procedural times and reducing complications related to the ablative procedure with radiofrequency without losing efficacy. Recent studies conducted with rigour and scientific solidity have demonstrated on the one hand that the results of this technique are not inferior compare with radiofrequency. This study aims to compare data on the safety and efficacy of cryoablation with those obtained from antiarrhythmic drugs through a review of the most recent scientific evidence.

Introduction

Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice. It is characterized by irregular atrial electrical activity starting from arrhythmogenic foci mainly located at the level of the pulmonary veins.

This arrhythmia can be very symptomatic, significantly impacting the quality of life of affected people or being completely silent, but no less dangerous. Complications related to AF can include stroke and heart failure. Furthermore, it can worsen the outcome of subjects suffering from underlying pathologies, increase the number of emergency room visits, hospitalizations, and cardiovascular mortality.

According to the main guidelines (GLS), antiarrhythmic therapy is still considered the first choice for rhythm control in patients suffering from AF.[1–3]

In recent decades, transcatheter ablation using radiofrequency (RF) emerged as an alternative to antiarrhythmic drugs for rhythm control, although it is not free from complications such as stroke, major bleeding, oesophageal fistula, and cardiac tamponade that can cause the death of the patient.[4]

Although this technique is the most used and has been available for the longest time, there is a limited presence of large prospective randomized studies in the literature and many questions about the optimal management of AF are still unresolved.

Cryoablation was created as an alternative energy source with the aim of reducing procedural times and complications related to the RF ablative procedure without losing effectiveness.[5,6]

Recent studies conducted with rigour and scientific solidity have demonstrated on the one hand that the results of this technique are not inferior to those obtained with RF.[7–9]

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The aim of this review is to provide data on the safety and effectiveness of cryoablation by comparing them with the results obtained from antiarrhythmic drugs through a review of the most recent scientific evidence.

Guidelines

The current GLSs of the main scientific societies recommend pharmacological therapy as the first choice for rhythm control in patients with AF.[1-3]

The European GLS, published in 2020, gives a class I level of evidence A indication to transcatheter ablation of the pulmonary veins in symptomatic patients suffering from paroxysmal AF or persistent AF without risk factors for relapses, in whom at least one antiarrhythmic failed to achieve rhythm control in order to reduce symptoms.[1]

In addition to the failure of medical therapy, emphasis is placed on the concept of AF symptoms and quality of life improvement.[1]

In patients naïve to rhythm control drugs, the indication for ablation is weaker and is considered in class IIa, level of evidence B, in symptomatic patients suffering from paroxysmal AF and in class IIb, level of evidence C, in patients suffering from persistent AF without risk factors for recurrence.[1]

The American GLS, published in 2014, with an update regarding ablation in patients with AF and heart failure in 2019, does not differ significantly from the European GLS regarding the indication for AF ablation as the first choice for rhythm control but they do not stratify patients with persistent AF based on their risk of recurrence.[2]

In the Canadian GLS, published in 2020, the indication for ablation as a first approach is considered weak with a moderate quality of evidence. Attention is placed not only on patient preferences but also on the fact that some patients have relative or absolute contraindications to antiarrhythmic therapy. Unlike the European and American GLSs, no distinction is made between paroxysmal or persistent AF.[3]

A separate chapter is represented by patients with heart failure, for whom, after the publication of the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) study, all three GLSs recognized the beneficial role of ablation compared to antiarrhythmic therapy in term to mortality although with a still low level of evidence.[10]

Drug therapy: risks, and benefits

Antiarrhythmic therapy is indicated by the GLS with the aim of reducing the burden of AF.[1-3] Relapses are reduced by ~50% compared to placebo. Although antiarrhythmic drugs are consolidated as first-line therapy, their effectiveness is overall modest. Furthermore, they are characterized by an intrinsic proarrhythmic effect with a risk of malignant arrhythmias increased by 3–4 times, and by various systemic side effects.[11]

Quinidine and disopyramide, class Ia antiarrhythmics, are generally not recommended as first-line therapy for rhythm control in patients with AF due to their side effects and increased risk of mortality.

Flecainide and propafenone are class Ic antiarrhythmics (sodium channel blockers) and represent the drugs most used in the younger population and with fewer comorbidities. They are contraindicated in patients with advanced atrio-ventricular (AV) block or significant conduction system pathologies (QRS > 120 ms); left ventricular systolic dysfunction (LVEF ≤ 40%), significant hypertrophy of the left ventricle, severe hepatic or renal impairment (creatinine clearance CrCl < 35 mL/min), and acute and chronic ischaemic coronary disease. An increase in mortality has been observed in ischaemic patients treated with flecainide due to the high risk of ventricular arrhythmias.

An increase in QRS duration > 25% from baseline or the appearance of any block with QRS duration > 150 ms increases arrhythmic risk.

Concomitant use of beta-blockers is recommended to reduce atrioventricular conduction due to the potential risk of AF organizing into atrial flutter, with the possibility of 1:1 atrioventricular conduction.

Dronedarone is an amiodarone analogue, created with the aim of reducing its toxicity. Structurally, iodine was replaced with the addition of a methane-sulfonyl group. It appears particularly indicated in patients suffering from dysthyroidism. Dronedarone is the only antiarrhythmic that has showed in to reduce hospitalizations and mortality in the Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter (ATHENA).[12]

It can be used in patients with ischaemic heart disease, valvular heart disease, and in patients heart failure with preserved ejection but it is contraindicated in patients with renal and hepatic dysfunction and specifically in patients with left ventricular dysfunction, unlike amiodarone, as demonstrated in the Dronedarone in high-risk permanent atrial fibrillation study (PALLAS).[13]
Sotalol is a class III antiarrhythmic (Ikr channel inhibitor) which an intrinsic beta-blocker action. At lower doses, the beta-blocker effect prevails while at higher doses (>160 mg/day), the antiarrhythmic effect prevails. The main risk is QT interval prolongation and the appearance of torsades de pointes with a frequency of 2%. Long-term therapy is associated with increased mortality. It can be used in ischaemic patients but is contraindicated in patients with heart failure and renal dysfunction.

Amiodarone is a multichannel blocker and a non-selective beta blocker. It represents the most effective antiarrhythmic drug and can be used both in ischaemic patients and in patients with heart failure. Nonetheless, due to its side effects, it is indicated as a second choice compared to other antiarrhythmics if not otherwise possible.

The incidence of adverse effects is 11–15% during the first year of amiodarone use, increasing up to 50% in the long-term use. Long-term therapy is, in fact, associated with an increase in mortality.

Pulmonary toxicity is one of the serious side effects of amiodarone, with an incidence of ~2% and among those affected, mortality can be up to 10%.

It can cause hypothyroidism since it has a similar structure to the thyroid hormones (triiodothyronine-T3 and thyroxine-T4), and contains high quantities of iodine. However, it can also cause hyperthyroidism. Under that circumstance, it must be suspended

immediately due to the risk of thyrotoxic crises and worsening of the arrhythmic state.

It is contraindicated in patients with severe hepatic dysfunction; pulmonary fibrosis; QTc prolongation; and iodine allergy and concomitant use of cytochrome P450 3A4 (CYP3A4) inhibitors.

Cryoablation: risks and benefits

As regards the comparison with pharmacological therapy, the GLS generically mentions transcatheter ablation, without giving specific indications about the recommended the technique or energy source.[1-3]

Cryoablation involves the insertion of a balloon inside the atrium that will be positioned in succession at the ostium of the pulmonary veins, inflated until complete occlusion is obtained and cooled with nitric oxide, with a target temperature of around −60°C. Electrodes positioned on a circular tip allowing the recording of potentials inside the veins and monitor their disconnection.[14]

Compared to RF ablation, cryoablation showed shorter procedural times but longer fluoroscopic times.

After the publication of several studies including the Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation (FIRE and ICE) and Outcomes of cryoballoon or radiofrequency ablation in symptomatic paroxysmal or persistent atrial fibrillation (FreezeAF), a comparable efficacy between ablation was recognized using RF and cryoablation in terms of reduction of atrial arrhythmia recurrences at 1 year (respectively 70.7% of patients free from AF in the group subjected to RF vs. 73.6% of patients subjected to cryoablation in the FreezeAF and 65.4% of patients free from relapses of atrial tachy-arrhythmias in the group subjected to RF vs. 64.1% of patients subjected to cryoablation in the FIRE and ICE).[5,6]

Over time, various balloons have been develop, designed to increase the effectiveness of the ablation by gradually extending the cooling surface and modifying the tip of the catheter to facilitate the positioning of the balloon at the ostial level of the veins and obtain greater stability.[15]

One shot techniques appear particularly suitable for the isolation of pulmonary veins in patients with paroxysmal AF. In patients with persistent AF, the balloon can be used for the posterior wall isolation and for the left appendage isolation but the effectiveness and safety of these additional lesions are still debated.

The overall incidence of complications between RF ablation and cryoablation is similar with an increased risk of phrenic nerve palsy and a reduced risk of pericardial effusion and cardiac tamponade in patients undergoing cryoablation. The incidence of temporary phrenic nerve palsy is almost 10%. Of those, only 1.5% lasts more than 24 h and only 0.4% lasts more than a year. Contrary to what was expected, rare cases of oesophageal fistula after cryoablation have been reported (1:1000 after RF ablation vs. 1:10 000 after cryoablation). By keeping the extracellular structure intact, the risk of pulmonary vein stenosis is reduced compared to RF with an incidence of ∼0.17%. The incidence of complications relating to vascular access (1.5%) and stroke and TIA (0.2%) is overall comparable.

New evidence

After the publication of major GLSs, several studies provided new evidence to support ablation over drug therapy.

Ablative techniques are increasingly safer and effective, becoming more competitive with antiarrhythmic drugs in terms of risk/benefit ratio.

Previous studies involving radiofrequency ablation, including the Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation trial (MANTRA-PAF), failed to demonstrate the superiority of RF over medical therapy partly due to crossover from the medical therapy group to the ablation group.[16]

The Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST) demonstrated that an early ablative intervention is not only more effective but also capable of impacting the progression of the disease from paroxysmal AF to persistent AF.[17]

These data have paved the way for further studies to evaluate earlier ablative strategy.

Hence, the design of the following studies with the aim of evaluating the benefit of cryoablation as first-line therapy compared to antiarrhythmic therapy.

The Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation (EARLY-AF) is a Canadian multicentre prospective study involving 303 patients randomized to pulmonary vein isolation with cryoablation vs. antiarrhythmic therapy published in 2021. The primary endpoint was the identification of first recurrence of any atrial tachyarrhythmia > 30 s (AF, atrial flutter, or atrial tachycardia) within 3–12 months after ablation documented by loop recorder or the initiation of an antiarrhythmic drug. Secondary endpoints included the assessment of symptomatic atrial fibrillation recurrence, the overall arrhythmic burden, and quality of life.[7]

The Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation (STOP AF First) is an American multicentre prospective study involving 203 patients randomized to pulmonary vein isolation with cryoablation vs. antiarrhythmic therapy published in 2021. The primary endpoint was the identification of the first recurrence of any atrial tachyarrhythmia > 30 s (AF, atrial flutter, or atrial tachycardia) 3–12 months after ablation documented by 12-lead ECG at 1, 3, 6, and 12 months patient-triggered telephone monitoring conducted weekly and when symptoms were present in months 3–12, and 24 h Holter conducted at months 6 and 12 or initiation of an antiarrhythmic drug. An additional primary safety endpoint was evaluated only in the ablation group.[8]

The Cryoballoon ablation vs. antiarrhythmic drugs: first-line therapy for patients with paroxysmal atrial fibrillation study (Cryo-FIRST) is a prospective multicentre study involving 218 patients randomized to pulmonary vein isolation with cryoablation vs. antiarrhythmic therapy published in 2021. Compared to other studies involve a larger geographic area, including Europe, South America, and Australia. The primary endpoint was identification of the first recurrence of any atrial tachyarrhythmia > 30 s (AF, atrial flutter, or atrial tachycardia) 3–12 months after ablation by 12-lead ECG and 7-day Holter ECG at 3, 6, 9, 12 months, or initiation of antiarrhythmic medication. Secondary endpoints

included the rate of serious adverse events in both groups and symptomatic relapses assessed via patient diaries.[9]

Overall, 724 patients were observed, with an average age of 57 years, predominantly male and with low levels of comorbidities. Class Ic antiarrhythmics were the most used drugs (80%).

Andrade *et al.*[14] analysed the results of these studies, highlighting a favourable risk–benefit ratio for cryoablation compared to drug therapy in terms of symptoms, relapses, hospital admissions, and complications.

All three studies demonstrated a reduction in recurrences in patients undergoing cryoablation [relative risk (RR): 0.61; 95% confidence interval (CI): 0.51–0.73], with a risk reduction of 19%.

These patients not only experienced fewer palpitations but also experienced a clinically significant improvement in quality of life, as assessed by the AFEQT (Atrial Fibrillation Effect on QualiTy-of-Life questionnaire) score with an average difference of ∼8 points (95% CI: 5.81–10.82).

Although there was no significant difference in terms of the composite endpoint of major complications (RR: 0.74; 95% CI: 0.35–1.56), there was an overall reduction of cumulative complication in the ablation group (RR: 0.70; 95% CI: 0.54–0.89).

Hospitalizations were significantly lower in patients undergoing ablation (RR: 0.38; 95% CI: 0.23–0.63), as were the visits to healthcare facilities (RR: 0.71; 95% CI: 0. 56–0.90), despite a trend towards more emergency room visits in the group subjected to ablation in the first post-procedural months.

Conclusions

In conclusion, although current GLS recommend the use of antiarrhythmic therapy as the first-line treatment for symptomatic AF in patients with paroxysmal AF with few comorbidities, cryoablation has been proved to be superior to antiarrhythmic therapy in term of efficacy, significantly reducing recurrence of atrial arrhythmias. Furthermore, it showed a reduction of symptoms, an increased quality of life, and a reduction of the hospitalizations.

The risk profile of cryoablation with regard to major complications has proved to be similar to that of medical therapy.

Further prospective randomized studies are needed to evaluate the effects of cryoablation compared to medical therapy in patients with persistent atrial fibrillation, increased risk factors for relapses, and major comorbidities.

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Data availability

No new data were generated or analysed in support of this research.

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