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EDITOR'S FORUM

Should cryoballoon ablation of paroxysmal atrial fibrillation be proposed as a first-line treatment?

Alexis Hermida[1] · **Jean-Sylvain Hermida**[2]

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Atrial fibrillation (AF) is the most frequent heart rhythm disorder, affecting 33.5 million people worldwide in 2010. The incidence of AF increased to a greater extent in developed than in developing countries between 1990 and 2010. AF increases the risks of stroke and heart failure and the rates of hospitalization and mortality. The estimated age-adjusted incidence per 100,000 inhabitants is higher for men than for women: 77.5 (95% CI, 65.2–95.4) versus 59.5 (95% CI, 49.9–74.9) in 2010 [1].

The first-line treatment of symptomatic paroxysmal AF is based on antiarrhythmic drugs. In accordance with the European Society of Cardiology (ESC) recommendations, percutaneous catheter ablation is reserved for patients with symptomatic episodes despite treatment with antiarrhythmic drugs (class I indication). Several randomized studies have demonstrated its efficacy in this context [2].

Catheter ablation of symptomatic paroxysmal AF in first line is only a class IIa indication [2]. This recommendation resulted from the publication of the RAAFT 1 and 2 and MANTRA PAF studies, which found a high rate of recurrences in the two groups and a worrying number of complications in the ablation group. In addition, the results of the MANTRA PAF study, despite indicating a trend towards lower rates of recurrence with ablation, did not reach statistical significance. It is only by compiling the data from these 3 studies, corresponding to a total of 491 patients, that a meta-analysis showed that catheter ablation appeared to be superior [3]. Three new randomized trials comparing first-line ablation, this time by cryoballoon, with antiarrhythmic drugs, were published in 2021.

✉ Alexis Hermida
a.hermida.jarry@gmail.com

[1] Service de Cardiologie, Rythmologie Et Stimulation Cardiaque CHU Amiens-Picardie, 1, rond-point du Professeur Christian Cabrol, 80054 Amiens Cedex, France

[2] Service de Cardiologie, Clinique de l'Europe, Amiens, France

1 Rationale for first-line ablation

There are many arguments for early treatment of AF. AF is a disease that progresses over time. The rapid occurrence of atrial myocardium conduction disorders and irreversible fibrosis was demonstrated as early as 2002, in a dog model of AF and heart failure. It was thus argued that early treatment was desirable to prevent the atrial remodeling associated with AF [4]. In some patients, AF is initially paroxysmal, subsequently becoming persistent over a period of months or years. For example, in the Canadian CARAF registry, including patients recently diagnosed with paroxysmal AF, the percentage of progression to persistent AF was 8.6% after 1 year, 24.3% after 5 years, and 36.3% after 10 years [5]. The very recent randomized EAST study comparing early heart rhythm to heart rate control showed lower rates of cardiovascular mortality, stroke, and hospitalization, with no increase in complications, for the early control of heart rhythm [6].

Longer intervals between AF onset and interventional treatment are associated with a higher risk of recurrence, for both paroxysmal and persistent AF [7]. Mortality and the risk of stroke are higher in persistent or permanent AF than in paroxysmal AF [8].

Antiarrhythmic drugs also have a more limited efficacy than ablation for preventing AF recurrence and may be associated with serious side effects. Efficacy is even lower for asymptomatic episodes. Atrial remodeling, as assessed by measurements of atrial strain on echocardiography, worsens in patients on antiarrhythmic drugs, whereas recovers in patients who have undergone ablation [9]. The rate of progression to persistent AF is markedly lower after ablation than with antiarrhythmic drugs, at 2.4 to 2.7%, and it remains stable. With conventional treatment, progression to the persistent AF is 10 to 20% after 1 year and reaches 50 to 77% after 12 years [10].

2 Results of the three new studies: EARLY-AF [11], STOP AF First [12], and Cryo-FIRST [13]

2.1 Recurrences of atrial arrhythmia

The three new studies demonstrate the superiority of pulmonary vein isolation by cryoablation over antiarrhythmic drugs for preventing recurrences of atrial arrhythmia. The rate of atrial arrhythmia recurrences at 1 year was between 17.8 and 42.9% for patients treated by cryoablation and 32.4 and 67.8% for those on antiarrhythmic drugs (Table 1). This difference was statistically significant in the three studies. However, the differences in the results between these three trials, testing the same hypothesis, are striking. The reasons for differences in the rate of symptomatic AF recurrence or AF burden may be due to several points.

First, the types of patients included differed between the studies, in terms of age, exclusion criteria, associated heart disease, and comorbidities. In particular, the patients in the STOP AF First study were older and had a higher frequency of hypertension. Furthermore, this study, unlike Cryo-FIRST, did not exclude patients with a history of coronary artery disease. A considerable number of patients had already undergone electrical or pharmacological cardioversion in EARLY-AF (30 to 40%) and STOP AF First (25 to 30%), suggesting a longer disease duration, than for the Cryo-FIRST study in which cardioversion was an exclusion criterion. CHA2DS2-VASc score for the patients also differed between the three studies, at 1.9 for EARLY-AF, 1.6 for STOP AF First, but only 0.7 for Cryo-FIRST.

The method used for the detection of recurrent atrial arrhythmia also differed between studies. For example, the method used in EARLY-AF, based on the use of an implantable loop recorder, was much more sensitive than the methods used in STOP AF First and Cryo-FIRST. Relative to the use of an implantable loop recorder, the monitoring used in STOP-AF would be expected to have a sensitivity of 40.9% for the detection of recurrence and that used in Cryo-FIRST, 58.4% [14]. With a sensitivity of 100%, it is not surprising that the rate of recurrent atrial arrhythmia was highest in EARLY-AF, particularly for asymptomatic episodes. However, within each study, the same monitoring method was used for the two randomized groups, and the relative recurrence rates are therefore comparable. It is notable that the relative benefit of first-line cryoablation was remarkably consistent between the three studies.

Overall, the patients included in Cryo-FIRST were younger and had no underlying heart disease. [15] Recurrence rates were lowest in this population, particularly as ECG monitoring was not rendered continuous using an implantable device.

Table 1 Studies assessing cryoballoon pulmonary vein isolation to antiarrhythmic drugs, in first-line therapy, in patients with symptomatic paroxysmal atrial fibrillation

Study name Inclusion criteria	Endpoints		Cryoablation	Antiarrhythmic drugs	Method used to detect recurrences
EARLY-AF [11] At least one episode of symptomatic AF > 18 years old. Authorized episodic use of antiarrhythmic drugs	Recurrence of symptomatic or non-symptomatic atrial tachyarrhythmia after the blanking period	No. of patients Age (years) All recurrences Symptomatic recurrences Cryoballoon procedure Antiarrhythmic drugs SAE	154 57.7 42.9% 11.0% 100% success - - 3.2%	149 59.5 67.8%, $p < 0.001$ 26.2% - Class Ic: 81.2% Class III: 18.8% 4.0%	Implantable loop recorder with AF detection algorithm
STOP AF First [12] Symptomatic AF episodes Patients aged 18 to 80 years with no prior AA	Recurrent atrial arrhythmia, use of AA in the cryoballoon arm, ablation after the blanking period	No. of patients Age All recurrences Cryoballoon procedure Antiarrhythmic drugs SAE	104 60.4 25.4% 97% success - - 14%	99 61.6 55.0%, $p < 0.0001$ - Class Ic: 69% Class III: 21% 14%	24-h Holter monitoring Trans-Telephonic monitoring weekly and in the event of symptoms
Cryo-FIRST [13] At least 2 episodes of symptomatic AF in the last 6 months No prior AA	Atrial arrhythmia for more than 30 s after the blanking period	No. of patients Age All recurrences Cryoballoon procedure Antiarrhythmic drugs SAE	107 50.5 17.8% 100% success - - 9%	111 54.0 32.4%, $p = 0.013$ - Class Ic: 92.2% Class III: 7.7% 4%	7-day Holter monitoring before and at 1 month and then every 3 months thereafter

SAE serious adverse event

2.2 Symptomatic AF burden

In EARLY-AF, the AF burden was reduced by 3.3 ± 1.0% in the ablation group. The recurrence rate was low if only symptomatic episodes were considered: 11.0% for cryoablation and 26.2% for antiarrhythmic drugs. The recorded rates were, however, much higher if the asymptomatic episodes detected with the implantable loop recorder were considered: 42.9% for cryoablation and 67.8% for antiarrhythmic drugs. These findings highlight the frequent association of asymptomatic AF with symptomatic AF, both in patients treated with antiarrhythmic agents or undergoing ablations. In both cases, the symptoms may be masked by treatment. It is therefore important to perform close ECG monitoring, to prevent the progression of AF and the constitution of atrial cardiopathy.

The intensity of ECG monitoring differed between the three studies: full monitoring with an implantable loop recorder in EARLY-AF, a loop recorder and systematic transmission by telephone and during symptoms in STOP AF First, and a loop recorder for 7 days in Cryo-FIRST, before and 1 month after randomization and then every 3 months thereafter. In Cryo-FIRST, data for the percent of time in atrial fibrillation during the 7-day Holter monitoring were therefore available for the baseline and then after randomization. This parameter, which cannot truly be called the AF burden, decreased significantly relative to baseline in the cryoablation arm, and to a lesser extent in the antiarrhythmic drug arm.

2.3 Quality of life

Scores were used to assess quality of life in all three studies. The most frequently used score was the AFEQT score, which is a specific score for patients with AF. The evaluation includes symptoms, everyday activities, and anxiety about AF treatment, each of which is scored on a scale of 1 to 7. Consistent results were obtained in all three trials, with a statistically significant improvement of the AFEQT and EQ5D scores from baseline to 12 months in STOP AF First and EARLY-AF. The magnitude of improvement was clinically meaningful. For example, the incidence rate of patient-reported days with symptomatic palpitations was lower in the cryoballoon group ($P < 0.001$) in Cryo-FIRST, and EARLY-AF reported no symptoms for 85.1% of patients of the cryoablation group (vs. 73.2%, HR = 1.17).

This result is important because it indicates that a greater improvement in quality of life was obtained with first-line ablation, even for patients with symptoms presumed to be recent and not necessarily already disabling.

We observed a trend toward less healthcare utilization with first-line cryoballoon ablation in the three studies, but the differences did not reach significance. In CRYO-FIRST, the annualized rate of hospital or emergency service access due to symptoms caused by atrial arrhythmia recurrence was 0.23 in the cryoballoon and 0.35 in the AAD group (IRR 0.67, 95% CI 0.41–1.10; $P = 0.11$). In EARLY-AF, emergency department visits were 18.2% in the ablation group vs. 20.1% in the antiarrhythmic drug group (HR = 0.90 (0.57–1.44)). Similarly, in STOP AF first, the authors found no significant differences at 12 months between the two groups in the percentage of patients free from a cardiovascular healthcare utilization event (69.9% in the ablation group and 53.5% in the antiarrhythmic drug group).

2.4 Complications

Severe adverse events occurred with a similar frequency in the two treatment arms. Serious procedural complications were very rare, with no tamponade. This is a key advantage of cryoablation, given the rate of tamponade collected in radiofrequency ablation studies. Only one stroke in each treatment arm was observed for the three studies combined.

3 Conclusion

First-line cryoablation is superior to drug therapy in terms of preventing the recurrence of symptomatic episodes, decreasing AF burden, and improving quality of life in symptomatic paroxysmal AF. The rate of serious procedural complications is low. All three studies gave identical results at 1 year of follow-up. A longer period of follow-up will be required to confirm these good results in the long term.

Declarations

Conflict of interest The authors declare no competing interests.

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