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EDITORIAL COMMENT

Catheter ablation of atrial fibrillation: What we can say after more than 20 years of worldwide experience

Ablação por cateter de fibrilhação auricular: o que podemos dizer depois de mais de 20 anos de experiência em todo o mundo

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Since the publication of the first paper describing pulmonary vein isolation (PVI),[1] catheter ablation of atrial fibrillation (AF) in paroxysmal, persistent, or long-standing persistent forms has been one of the most frequently performed procedures worldwide.

Outcomes of the procedure during this experience of over 20 years have been extensively assessed in numerous publications and many prospective and multicenter randomized studies have been published, as well as retrospective and observational studies, but none have been double-blinded.[2,3]

Initial studies showed that ablation is more likely to be successful if the AF triggers originate from the pulmonary veins. Triggers originating from elsewhere are associated with much lower success rates.[2–4]

Persistent forms of AF are probably due to mechanisms other than pulmonary vein triggers, such as fibrosis of the atria (leading to reentry), hypertension, overweight and diabetes, as well as age-related fibrosis.[2–4] The success rate of a PVI-only ablation approach is likely to be much lower in fibrotic atria and particularly in older populations.[2–4]

2012 saw the publication of the first results of MANTRA-PAF,[5] a multicenter trial that randomized patients with paroxysmal AF to PVI (optional mitral and tricuspid lines) versus drugs. The trial failed to demonstrate a difference in AF recurrence after PVI compared to medical therapy in the first 18 months of follow-up.[5]

The CABANA trial[6] (one of the largest multicenter prospective cardiology trials) is also a historical landmark in terms of invasive management of AF. CABANA enrolled 2204 patients with paroxysmal, persistent or long-standing persistent AF. It showed that ablation was not superior to drug therapy for cardiovascular outcomes at five years among patients with new-onset or untreated AF who required therapy, while there was no difference in the primary endpoint of death, disabling stroke, serious bleeding or cardiac arrest at five years for ablation versus drug therapy (8% vs. 9.2%; p=0.3).[6] However, analysis of the primary endpoint based on treatment received (not intention to treat) showed superiority of ablation versus drug treatment (7.0% vs. 10.9%; p=0.006); the same analysis (based on treatment received) showed superiority of ablation over drug treatment for all-cause mortality (4.4% vs. 7.5%; p=0.005) and death or cardiovascular hospitalization (41.2% vs. 74.9%; p=0.002). The trial was only single-blinded (not to intervention received). This may have driven the high crossover rates and may confound assessment of the various endpoints.

Recently, after presentation of data from studies like the RACE trials[3] and from registries such as CARDIO-FIT,[7] attention has increasingly been paid to modifiable (as well as non-modifiable) risk factors in the management of AF, such as age, overweight, hypertension, alcohol intake, excessive exercise and inflammation.

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It is increasingly recognized that AF is a multifactorial arrhythmia and should be managed in a multidisciplinary way.[2,3]

According to current knowledge, it is reasonable to state that if both operator and patient are fully aware of the currently accepted indications, success and complication rates according to the latest guidelines, it is legitimate to perform ablation in all forms of the arrhythmia.

The success rates after 12-month follow-up of catheter ablation of paroxysmal AF based on some major pivotal trials (apart from the above-mentioned results from the MANTRA-PAF and CABANA trials) were 66% (Thermocool AF), 64.1% with radiofrequency ablation (FIRE and ICE),[3] and 65.4% with cryoablation (FIRE and ICE).[2,3]

The main findings of the STAR AF II trial were that the success rate of persistent AF ablation (18-month follow-up)[2,3] was 59% (PVI alone), 49% (PVI plus ablation of complex fractionated atrial electrograms [CFAE]), and 46% (PVI plus linear ablation). These were the main findings of the STAR AF 2[8] trial that led to the conclusion that lesions beyond PVI isolation were of no benefit compared to PVI alone in the population with persistent AF.

CFAE ablation has also been abandoned by most groups due to the lack of reproducibility of the results presented by Nademanee.[2–4]

Real-world rates of success, recurrence and complications are probably worse than those achieved by these high-volume centers and experienced operators. Success rates may increase with repeat procedures but the complication rate must also be taken into consideration.[2,3] AF ablation procedures in general currently have the following complication rates[2,3]:

0.2-5% risk of cardiac tamponade;
0-2% risk of stroke and transient ischemic attack;
2-15% risk of asymptomatic cerebral emboli;
0.02-0.11% risk of esophageal fistula;
0-0.4% risk of permanent phrenic nerve paralysis;
<1% risk of pulmonary stenosis;
0.1-0.4% risk of death;
1-3% risk of potential life-threatening complications.

The incidence of esophageal fistula may be underestimated in many series since it can develop weeks after the procedure.

The study by Freitas et al.[9] in this issue of the *Journal*[9] aims to provide information in a still investigational field, the creation of lesions other than PVI in patients with persistent and long-standing persistent AF.

STAR AF II[8] demonstrated that additional ablation lines (CFAE, roof lines, and a tailored approach) were useless, and additionally reported very modest success rates. Furthermore, care must always be taken when performing ablation lines, especially in the posterior wall (which is so anatomically close to the esophagus), since gaps in these lines may cause reentrant tachycardias (atrial tachycardia/flutter) that can be difficult to manage and to map.

The study by Freitas et al.[9] analyzes a new strategy but has the known limitations of a small retrospective observational study; nevertheless the group have certainly allocated considerable resources in healthcare, logistics, and funding to perform this task.

To best address the benefit or otherwise of ablation in this population and to compare the various strategies, a prospective double-blinded randomized trial would be ideal.

I would point out some well-known but pivotal characteristics that should be taken into consideration when designing such a trial.

(1) The protocol should include a third arm in which no ablation is performed, but only standard medical care (rate or rhythm control), in order to have data matching those from the PVI-only group, PVI plus lines and/or CFAE, and PVI plus a tailored approach.

(2) The trial should be double-blinded, paying particular attention to the need to account for the placebo effect. This may require a sham-controlled trial in which neither the operator nor the patient knows what type of procedure is being performed, which would be challenging to carry out but feasible based on recent experiences from important sham-controlled trials such as SYMPLICITY HTN and ORBITA. CABANA should prompt consideration of a sham-controlled trial, according to the on-line article by Dharam Kumbhani of January 21st, 2022 on the website of the American College of Cardiology. Performing invasive but not active therapy in a group may be hard to accept, but it is probably defensible if it avoids performing procedures in numerous patients who would derive no benefit.

(3) The endpoints should be hard.

(4) Crossovers between group arms should be avoided as far as possible and a detailed description should be given of the types of patient who cross over. This is also the case for dropouts and patients lost to follow-up; these should also be minimized and carefully detailed (particularly when the dropouts occur in the active arm).

(5) An intention-to-treat statistical analysis should be the gold standard.

(6) Success and recurrence should be defined objectively by continuous monitoring (e.g. with subcutaneous loop recorders) which quantifies the variance of AF burden and its correlation with hard endpoints. A reduction of 70% in AF burden correlated better with improved quality of life than variation in the incidence of AF episodes lasting longer than 30 s.[10]

(7) The trial should be sponsored by an independent (public or private) institution. National or governmental health budgets would certainly have difficulty in providing the necessary investment, but could benefit from the establishment of clearer indications and more precise cost-effectiveness of the procedure for millions of patients, leading to better healthcare and optimization of costs.

Unfortunately many of the trials that support current evidence on ablation in the more consensual patient population with AF do not have some of the basic characteristics mentioned above.

Surprisingly a sham trial is already underway, PVI-SHAM-AF, sponsored by the University of Leipzig, and is currently recruiting patients (clinicaltrials.gov identifier: NCT05119231).

I came to contact with pulmonary vein isolation first 22 years ago in Germany; I was naturally excited by the technique and still am. The technique is probably the gold standard of management for a particular subgroup of patients, a subgroup that will likely soon be better defined.

Conflicts of interest

The author has no conflicts of interest to declare.

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