

Atrial Fibrillation with No Structural Heart Disease Should Always Undergo Catheter Ablation

Agonist

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BACKGROUND

Approximately 10% to 30% of patients with atrial fibrillation (AF) do not present structural heart disease or have comorbidities such as hypertension. Atrial fibrillation is the most frequent arrhythmia in daily practice that occurs under diverse situations and its treatment should be based on the different scenarios of presentation. Severe population-based studies have found that AF is associated with greater morbidity and mortality and worse quality of life. It is the leading cause of arrhythmia-related hospitalizations with an important impact on medical costs.

Radio-frequency catheter ablation steadily progresses as an option therapy to cure atrial fibrillation. The indications of catheter ablation are increasing due to a greater understanding of the physiopathological mechanisms, technological improvements and better outcomes. The Spanish registry reported that 1 out of 10 catheter ablations were indicated for AF. In the USA, AF is the most frequent condition undergoing catheter ablation in referral centers. How have we reached this point?

THE PROBLEM OF ANTIARRHYTHMIC TREATMENT

Drug therapy has proved to be ineffective to maintain sinus rhythm in patients with AF, with recurrence rates between 40% and 80%. Class I antiarrhythmic drugs are ideal for patients without structural heart disease or with mild conditions due to a lower proarrhythmic risk and better tolerance; yet, the efficacy of these agents is < 40%. In the AFFIRM and RACE studies, the group of patients without structural heart disease was small, and only 30% to 60% were still in sinus rhythm during follow-up. A meta-analysis comparing the efficacy of antiarrhythmic agents to maintain sinus rhythm showed that the proportion of patients in sinus rhythm at follow-up was 35% with placebo and 55% with active treatment and placebo. (2)

Undoubtedly, amiodarone is the most efficient agent used. Yet, 35% of patients receiving amiodarone presented recurrent AF in the CTAF study. The problems of antiarrhythmic drug-related toxicity start with amiodarone. In a study with long-term follow-up of patients with AF more than 30% of patients treated with amiodarone presented severe adverse events:

pulmonary fibrosis (3%), skin discoloration (4.5%) and neurological or ocular abnormalities (2%). (1) Of interest, the AFFIRM study reported that the better survival in patients with sinus rhythm was counterbalanced by the negative effect produced by antiarrhythmic agents (> 60% with amiodarone), specifically due to increased pulmonary death. (3) Dronedarone, a novel non-iodinated amiodarone analogue, seems to have less adverse effects and might be an option to amiodarone, yet its efficacy seems to be limited.

In conclusion, in patients without structural heart disease, especially younger patients, the usefulness of long-term therapy with antiarrhythmic agents, particularly amiodarone, is questionable. Amiodarone provides a partial protection and is associated with high toxicity and treatment discontinuation.

IS RATE CONTROL ENOUGH?

Several studies have reported similar mortality rates with rate control compared to rhythm control. The AFFIRM trial is the most important study that evaluated both strategies, and although this issue is not the aim of this controversy, the questionable aspects of this statement should be remarked.

1) Patients included in the AFFIRM trial had to be eligible for both treatment strategies; in consequence, patients with frequent or severe symptoms might have been considered unsuitable for a rate-control strategy and therefore might not have been enrolled by some investigators. This issue was considered by the authors as about 30% of AF patients have severe symptoms. 2) The incidence of sinus rhythm in the rate-control group was high, as well as the incidence of AF in patients in the rhythm-control group, showing major pitfalls in the effectiveness of both strategies. 3) Subsequent analyses demonstrated that sinus rhythm was associated with greater survival. 4) The authors of the study concluded that antiarrhythmic drugs neutralized this benefit and remarked that a more efficient method to maintain sinus rhythm is needed. 5) Only 12% of AFFIRM patients did not have structural heart disease, constituting a small group that should have undergone long-term follow-up to prove the presence of differences. The low mortality rate observed in patients without

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heart disease, even in the absence of an effective therapy, makes it difficult to show any variation in the prognosis. The basic goal in these patients is to improve symptoms and quality of life, to avoid the adverse effects of antiarrhythmic agents and to cure the arrhythmia to prevent the development of atrial dilation, need for anticoagulant therapy and increased risk. In population-based studies, as the Framingham study, the presence of AF increased long-term mortality 1.5 to 1.9 times.

WHAT ABOUT THE RISK OF EMBOLISM?

The risk of embolism is one of the major problems in patients with AF. The annual risk of stroke in patients with a CHADS score = 0 is low, 0.36%; yet, the risk of stroke exists. Interestingly, patients with persistent or chronic lone AF have a risk of embolism of 1.3% per year, and this percentage may be low but not absent, especially if we bear in mind the cumulative risk. (4) Although this controversy deals with patients without structural heart disease, patients with AF often have hypertension, a condition that increases the risk of embolism (CHADS 1). Oral anticoagulant agents or aspirin are recommended in practice guidelines, yet chronic anticoagulation is preferred over aspirin (Class 1A). (5) The SPAF III trial reported an annual rate of stroke of 2% per year in patients with a history of hypertension.

It is clear that the poor outcomes associated with antiarrhythmic therapy, its adverse effects, recurrent symptoms, and the evidence derived from population-based studies demonstrating greater risk associated with AF, have produced two effects: on the one hand, physicians believe that leaving a young patient with absence of structural heart disease with AF does not have a negative impact on his/her quality of life and prognosis, and on the other hand, they are looking for non-pharmacological strategies that may end this arrhythmia.

WHICH IS THE BASIS FOR CATHETER ABLATION? WHY DOES ATRIAL FIBRILLATION OCCUR?

Undoubtedly, AF is the arrhythmia that has the most complex electrophysiological mechanism. Atrial fibrillation initiates in an ectopic focus that triggers and/or perpetuates the arrhythmia in patients without structural heart disease and in the absence of known conditions (alcohol abuse, hyperthyroidism, Wolff-Parkinson-White syndrome, etc.). These foci are in the pulmonary veins walls, in muscular bands extending from the left atrium into the venous walls. The histological examination has shown the presence of Purkinje cells which might generate abnormal automatism or triggered activity. The ectopic impulse is conducted to the atrial myocardium, initiating AF. Conduction of rapid and sustained impulses will generate AF. Other potential mechanisms have been described: ectopic foci

originating outside the pulmonary veins, the presence of areas in the atrial wall that perpetuate AF (rotors) and the influence of autonomic ganglionated plexi. Interestingly, the latter two mechanisms usually generate in the junction between the pulmonary veins and the atrial wall and are more frequent in persistent and permanent AF.

IS IT POSSIBLE TO CURE ATRIAL FIBRILLATION?

Since first described by Dr. Haissaguerre in 1996, the development of catheter ablation has greatly advanced. Radio-frequency catheter ablation is a high-complexity procedure that requires appropriate technology and specialized staff trained in electrophysiology studies. The left atrium is accessed through trans-septal puncture; the pulmonary vein orifices are encircled and radiofrequency energy is delivered on the atrial tissue. Circumferential pulmonary vein isolation is achieved by delivering radio-frequency energy on the atrial tissue just outside each pulmonary vein ostium, as current guidelines recommend. (6) In this way, catheter ablation blocks pulmonary vein conduction into the left atrium. Radio-frequency energy application in the PV-LA junction eliminates the areas that help to maintain AF. The use of irrigated-tip ablation catheters allows isolation of all the pulmonary veins in more than 90% of cases. In patients with sustained AF, some authors suggest the need of adding linear lesions or ablation of areas showing fractionated electrograms to ensure efficacy.

WHICH ARE THE OUTCOMES?

The outcomes vary according to the population analyzed.

Atrial fibrillation may be cured in 60% to 80% of cases according to the different series. This difference depends on the number of procedures, the definitions used, the use of drugs that were previously not effective and time to follow-up, which is obviously not too long.

The procedure has evolved with the better understanding of the physiopathology of the disease and technical advances, improving the outcomes and reducing the incidence of complications. Table 1 shows the outcomes of the procedure in experienced centers. The best results are achieved in patients without structural heart disease - as those discussed in this controversy - with a success rate of 95% after two procedures in some centers. An international registry performed before 2002 has reported lower success rates (56%), obviously related to the experience of the centers. (12) In general, all studies coincide on the parameters associated with better outcomes: success rate is greater in paroxysmal AF compared with persistent AF; conversely, chronic AF (> 1 or 2 years) is more frequently associated with therapeutic failure. Age < 65 years, a left atrial diameter < 5 cm and the absence of left ventricular dysfunction are related to successful procedure and lower incidence of complications.

Table 1. Outcomes of catheter ablation of AF

Author	Year	N	Afe	SHD (%)	Success (%)	F (m)
Marrouche	2003	259	54±11	21	87	347
Pappone	2003	589	65±9	6	79	861
Oral	2006	755	55±11	4	71	365
Nademanee	2008	674	67±12	60	81	836
Miyazaki	2009	534	61±10	17	84	840

SHD: Structural heart disease N: Patients F: Follow-up.

As it has been mentioned before, controlled trials using antiarrhythmic drugs have shown a clear advantage of catheter ablation over medical therapy, not only to prevent AF recurrences but also to improve the quality of life. There are some encouraging reports about anticoagulant therapy after a successful ablation. Oral et al. reported a low rate of embolic events after successful catheter ablation in a group of 770 patients with risk factors excluding age and previous embolism. In addition, Nademanee et al. studied a population of 674 patients with AF and ≥ 1 risk factor, and found an annual rate of embolic events of 0.4% in patients who maintained sinus rhythm and 2% in patients with permanent AF. It is clear that selected patients may discontinue anticoagulant therapy, yet further controlled studies are needed.

The greatest survival rates in patients who remained in sinus rhythm after catheter ablation were reported by non-randomized studies that included large number of patients. There are few data on mortality in patients without heart disease, or are still pending. For this reason, the immediate goal of catheter ablation is to relieve symptoms, improve quality of life and reduce the future complications of AF.

A study performed in Canada evaluated the costs related to catheter ablation therapy and concluded that it is a valid alternative to medical therapy in atrial fibrillation with cost equivalence after 4 years. This is due to the fact that the favorable outcomes associated with catheter ablation persist one year after ablation and to costs of ongoing medical therapy. (13)

SHOULD ALL PATIENTS UNDERGO CATHETER ABLATION?

I agree with the current practice guidelines recommendation that antiarrhythmic treatment should be the initial therapy and catheter ablation should be indicated for symptomatic recurrences. Other authors even recommend catheter ablation as first-line therapy. (14)

Class IC antiarrhythmic agents should be started in young patients without heart disease, and amiodarone or catheter ablation should be considered in case of failure. Physicians should warn their patients about the potential adverse events of amiodarone *in the same way they would explain the complications of ablation therapy.*

The complications are the Achilles heel of the procedure. Registries including more than 45000 catheter ablations have reported mortality rates of 1/1000, a percentage similar to the 0.8/1000 reported by the Spanish registry for catheter ablation of supraventricular tachycardia due to accessory pathways or to atrioventricular nodal reentry, and even to that reported by previous classic registries. (15 - 17) Cardiac tamponade is the most frequent complication and is successfully treated by pericardiocentesis in most cases; the embolic event ($< 1\%$) is generally transient. Stenosis of a pulmonary vein can occur during late follow-up and may be treated with balloon dilation and *stent* placement. Atrioesophageal fistula is a rare but highly morbid complication that should be operated on immediately.

CONCLUSION

The indication of catheter ablation of atrial fibrillation is a current reality that will increase in the future. The procedure offers the greatest possibilities of cure with the least incidence of complications in patients without structural heart disease who present recurrences.

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Antagonist

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BACKGROUND

Atrial fibrillation (AF) has been and remains the most prevalent arrhythmia in the general population, with a high incidence in healthy subjects. Therefore, we are forced to clarify the appropriate therapy as the impact of using an inadequate strategy might be an expensive mistake. The control of AF remains one of the major problems of modern cardiology, either to terminate an episode or to prevent recurrences. It has been demonstrated that there are no significant differences in mortality between rhythm control or rate control, thus we should not aim for sinus rhythm at all costs. (1) This incomprehensible answer would be related to the fact that, as is necessary to use antiarrhythmic agents with proarrhythmic effects or more than one drug to maintain sinus rhythm, the incidence of adverse effects would increase. This disadvantage of drug therapy is enhanced in patients with complex heart diseases or in those under cardioactive medication that worsens the condition.

Some basic concepts should be considered at the moment of evaluating the importance of catheter ablation of AF in patients without structural heart disease.

We should first define the meaning of "population without structural heart disease", as, in general, this terminology includes patients with normal echocardiogram and functional studies with no evidence of ischemia, or a normal baseline ECG and 24-hour Holter monitoring without major abnormalities. Recent studies have demonstrated that patients with AF have different anatomical findings in the left atrium and pulmonary veins than those without AF (2) and these anatomical changes might be responsible for the arrhythmias. In this way, in these patients it is clear that term "without heart disease" is questionable.

If we want to compare the efficacy of the traditional antiarrhythmic drugs for AF control with an invasive approach as catheter ablation, we should consider several aspects. Undoubtedly, the cost-benefit analysis between both strategies

is the most important issue. In this context, this balance is influenced by two aspects: the impact on health care costs and on patient's quality of life.

COST-BENEFIT EQUATION

The choice of widely known antiarrhythmic drugs seems to be more tempting in patients without heart disease and mild symptoms. The first question we should ask ourselves is whether any kind of treatment is necessary in an AF patient with a healthy heart. We should first evaluate the causes of AF, as there are several conditions that may trigger this arrhythmia (toxicity, endocrine disturbances, autonomic abnormalities) that should be corrected before initiating treatment. When AF presents regularly and in the absence of any trigger, we should use a strategy to control the arrhythmia. Under this circumstance, and according to the type of AF, we may naturally choose a pharmacological strategy. For patients with low risk for embolism presenting brief episodes of lone AF, (3) we shall probably choose a very conservative approach; however, for recurrent, long-lasting episodes that alter patients' quality of life, we shall choose a more radical strategy and, for sure, we shall consider the option discussed in this controversy.

Nobody can ignore there is the general agreement in the published literature that, under these circumstances, one shall consider invasive therapy as a second option once medical treatment has failed. (4) The use of antiarrhythmic drugs is more attractive as first-line therapy as it is cheaper and has lower risks.

Thus, the cost-benefit equation should be carefully analyzed before indicating an invasive and risky procedure.

It is important to know the characteristics of the proposed options before making the right decision. The efficacy and success of catheter ablation of AF depend on complex factors that are difficult to understand.

One of the major problems is related to the variety of methods available, ranging from the simple isolation of only the pulmonary veins with ectopic foci to the use of robot-assisted ablation, and from the creation of simple linear lesions of ablation to more sophisticated systems of navigation. Each novel method or technology emerging from the universe of catheter ablation of atrial fibrillation is rapidly validated by the bibliography, (5-7) probably due to the enthusiasm of the investigators to find an efficient method. These novel methods are rapidly replaced or enriched by other techniques with new disadvantages or complications. In turn, new techniques are necessary to ameliorate these adverse events outcomes, thus creating an endless spiral.

The procedure is focused on different goals: isolation of the pulmonary veins, (8, 9) or the elimination of the nests of AF, as proposed by Dr. Pachón Mateos (10) or of CFE (complex fractionated atrial electrograms). (11) Other authors recommend linear ablation lesions between the left and right atria. The need of maintaining sinus rhythm makes some investigators apply all the methods in one procedure, elevating the costs and complications. On the one hand, the use of anatomic criteria and techniques that ignore the electrophysiological basis, and of electrophysiological methods that neglect the anatomic basis on the other hand, seem to be the unavoidable way in the progress of catheter ablation of FA. Some operators prefer less aggressive strategies with lower success rates. Follow-up of catheter ablation is not standardized yet, and there is no agreement in the definition of therapeutic success. The absence of recurrences? Less recurrences or the same number yet better tolerated? Undoubtedly, such a procedure generates placebo effect, expectation biases on operators and patients that make it difficult to evaluate "quality of life". Finally, the operator preferences will decide the technique to use: the one he feels more comfortable or has more experience with, his progress along the learning curve or the technology available. The use of complementary methods to ensure success (robotic-assisted procedures, special catheters, electroanatomical navigation systems) or to prevent the development of complications (intracardiac echocardiography, esophagoscopy) makes the procedure more expensive than long-term pharmacological treatment.

A particular feature of catheter ablation of AF is the "success rate" of the procedure, as I have mentioned before. The development of recurrences are analyzed from 12 to 18 months after the procedure, and this time interval is sometimes shorter than the interval between two spontaneous episodes in a patient undergoing catheter ablation. Recent studies (12) have demonstrated a success rate of about 86% after the first year and 50% after 60 months. However, additional procedures (one to three) are required to maintain the primary success rate. Thus, costs and complications double or triple.

It is well-known that only a small percentage of patients undergoing catheter ablation for pulmonary vein isolation remain free of symptoms or do not need antiarrhythmic agents or anticoagulant therapy. Thus, an invasive approach must be accompanied by pharmacological support to maintain sinus rhythm, which is evidently more expensive than the simple medical approach. There are not enough arguments to state that the long-term risk of stroke in patients with successful catheter ablation of AF without apparent recurrences is similar to that of patients without AF; for this reason several authors suggest to continue with long-term anticoagulation. (13) This would be a real disadvantage if the goal of the procedure was to avoid drug therapy.

In a same sense, the fact that few trials have demonstrated that the quality of life, the incidence of stroke and survival are not different between patients under medical treatment and those undergoing catheter ablation is quite disappointing. (14) These finding might be related to the fact that these patients are followed-up during short periods of time.

The impact of AF in the quality of life is fundamental to decide the therapeutic strategy. In lone paroxysmal AF with low annual incidence an invasive approach will be immediately rejected. This type of AF has the best outcomes and is well tolerated, even without antiarrhythmic agents, and generally disappears spontaneously. (15) For frequent and badly tolerated recurrences a pharmacological approach is still the first-line therapy; yet, the physician's tolerance to medical failure is lower and the interventional strategy will rapidly emerge. When we refer to quality of life, it is essential to consider the age of the patient. The scourge of AF and its implications in the quality of life seem to be worthier of consideration in younger patients in whom the arrhythmia affects their jobs and professional and social activities. In the elder, physicians consider AF as a natural phenomenon, associated with degenerative causes, or even as an irremediable rhythm in sinus node disease. It should be mentioned that the best outcomes related to invasive procedures are seen in younger subjects. The invasive strategy allows living without chronic medication, yet, there is a little clinical evidence of improved quality of life after catheter ablation. (16) This is due to the need of medical treatment, particularly anticoagulation, after the procedure. Catheter ablation complications, such as pulmonary vein stenosis, brain ischemia, fistula, cardiac tamponade, etc., might limit patients' quality of life more than medical therapy, generating definite lesions which are sometimes difficult to repair. The development of atrial flutter or left atrium reentrant tachycardia generated by ablation lines and lesions is one of the most dreaded complications, as these arrhythmias are more symptomatic than AF and require navigation-guided procedures to be eliminated.

CONCLUSION

Pharmacological treatment has proved to be first-line therapy for AF control in patients without heart disease. Undoubtedly, the variety of antiarrhythmic drugs, the low morbidity and mortality of AF in healthy hearts and the lower costs make medical therapy the best option. Catheter ablation of AF should be recommended only in young patients with frequent and bad tolerated recurrences or with risk of embolism, in whom drug therapy has proved to be inefficient.

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Competing interests

None declared.

ANSWER FROM THE AGONIST

I read with enthusiasm that the conclusions of the excellent approach made by Dr. Zuloaga are finally coincidental with those of my role of agonist: catheter ablation of AF is justified in young patients without structural heart disease with persistent AF despite antiarrhythmic therapy or in the presence of drug-related

adverse effects. This happens precisely very often in the clinical scenario. A less invasive strategy is preferred in elder patients, except in special cases, but in young patients the goal should be to cure AF. I disagree with the lack of changes in quality of life; most studies, even randomized trials comparing catheter ablation with medical therapy have shown that it improves.

Yet, there are many techniques and success rates are lower than those obtained for supraventricular tachycardia or atrial flutter due to the complexity of AF. Indeed, AF occurs in a great diversity of clinical situations and behaves as if it had "a life of its own" as it may shorten the refractory periods and produce atrial electrical remodelling, thus creating new areas that may contribute to the initiation and maintenance of the arrhythmia (AF produces more AF). Therefore, we should not be surprised when an invasive strategy is chosen in the basis of each patient's needs. In cases of chronic AF, generally in the presence of heart disease or marked remodelling, more complex techniques are used due to the high rate of recurrences or complications seen in this group.

Therefore, a success rate of 60% - 70% is acceptable for such a complex and progressive arrhythmia.

I do not believe (and neither does Dr. Zuloaga) that a definite treatment as catheter ablation can be denied to a patient with recurrent AF despite antiarrhythmic therapy or to a young patient that must take amiodarone.

The right selection of patients, the greater knowledge of the physiopathology of the disease and the technological development have made catheter ablation of AF a reality for many patients. Surely the advance of these concepts will raise the indication of the procedure in a near future.

Dr. Carlos Labadet

ANSWER FROM THE ANTAGONIST

It may be risky to try to compare the outcomes of pharmacological therapy with those of catheter ablation of AF at the moment of drawing conclusions. The populations are generally completely different and there are not many trials comparing them. As Dr. Labadet has mentioned, international guidelines recommend medical treatment as first-line therapy. Therefore, the studies evaluating AF control using drug therapy included large populations with diverse types of AF; on the contrary, patients selected for catheter ablation are much selected groups of young subjects, generally without heart disease in whom persistent AF is very rare.

Dr. Labadet also mentioned that the group of patients without heart disease was very small in important trials as AFFIRM and RACE, opposite to patients selected for catheter ablation who are the cases less severe and thus give the greatest benefit from this approach.

In so far as to the cost-benefit equation, the costs after catheter ablation are obviously smaller due to less intensive follow-up after invasive procedures, generally a few months, and longer time intervals between medical visits. Undoubtedly, if follow-up after catheter ablation was longer, the success rate would be markedly lower.

Both therapeutic approaches have complications but with different extents: drug discontinuation reverts the adverse effect of pharmacological treatment, while catheter ablation complications might pose a permanent problem for the patient.

Dr. Labadet asks himself if it is possible to cure AF with catheter ablation. Definitely, the answer is no, as we cannot speak of “curing” such a complex

substrate as AF that involves anatomical, functional and autonomic factors, among others, by destroying a extensive area of the atrium. The production of lesions in a chamber is a palliative therapy rather than a healing method, as it creates a potentially arrhythmogenic substrate and even modifies normal atrial physiology. Finally, I agree with Dr. Labadet that the role of catheter ablation of AF has been clearly growing and we should wait for better outcomes with fewer complications. In the mean time, it will remain as an interesting resource for a selected group of patients in whom traditional medical therapy has failed.

Dr. Claudio De Zuloaga