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Rhythm control strategy in the transcatheter ablation era

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Abstract

The latest ESC guidelines on atrial fibrillation limit rhythm control to symptomatic cases, continuing on the same line that the Affirm and Race trials traced twenty years ago. There is evidence though that rhythm control, net of the adverse effects of the antiarrhythmic drugs, is useful to improve the prognosis beyond just the reduction of symptoms. With transcatheter ablation we can now finally split the clinical benefit of an antiarrhythmic therapy from the negative impact on prognosis of the medical approach, especially in patients with structural heart disease. We must ask ourselves nowadays, in light of the latest trials analyzed in this review, if there is space for a first line rhythm control strategy, if it should be pursued regardless of symptoms, with what modalities and how much in particular the patient with reduced ejection fraction can benefit from it.

Key words: atrial fibrillation, rhythm control, ablation

A double edged weapon

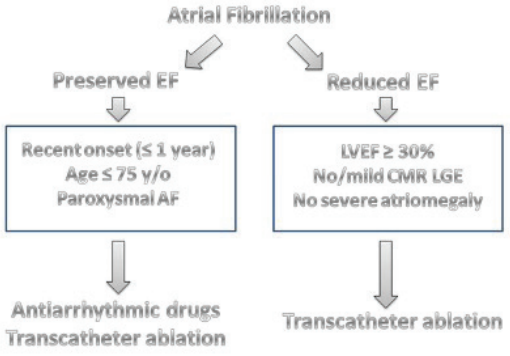
Atria are physiologically responsible for one third of the diastolic ventricular filling and the importance of their mechanical function is bigger in patients with intermediate grades of diastolic dysfunction, in whom the atrial kick is compensatory to the reduced ventricular compliance in order to maintain a valid preload. From these premises it comes natural to consider useful a rhythm control strategy in most of the AF patients, making the atria return to their physiological condition. For decades, however, data suggested the opposite, indicating the simple rate control as non inferior or even better than rhythm control in term of adverse reactions and hospitalizations. On this basis, guidelines recommend sinus rhythm restoration only in AF patients remaining symptomatic despite rate control. Antiarrhythmic drugs have always represented a double edged weapon. If on the one hand they've been shown to prevent arrhythmias, on the other they've sometimes increased all cause mortality and death from arrhythmias. Some of them combine arrhythmogenicity and non cardiac adverse reactions with the antiarrhythmic effect. The CAST trial showed that sodium current inhibition can increase mortality in patients with ischemic cardiopathy [1] and, seven years later, the SWORD trial showed that IKr inhibition can also be dangerous in patients with ischemic cardiopathy and systolic dysfunction [2]. Dronedarone can double mortality in patients with HFrEF NYHA III-IV (ANDROMEDA trial) [3] and in patients with permanent AF (PALLAS trial) [4]. A recent metanalysis by Valembois et al. have shown that sotalol can double the risk of death in patients with atrial fibrillation (NNH 102) [5]. Sotalol use for long-term rhythm control, once recommended as class I, is now a class IIb recommendation. The AFFIRM trial, twenty years ago, showed a trend for increased mortality with rhythm control compared to rate control (HR 1,15 95% CI 0,99-1,34), as well as a significantly greater number of hospitalizations, on a sample of more than 4000 patients with AF (one third of which at the first episode) and a mean LVEF 55% [6]. A subsequent analysis of this trial clearly showed the double face of the antiarrhythmic drugs, which have a useful antiarrhythmic effect but also have a dangerous effect, which increases the risk of adverse clinical events. An as treated analysis of the AFFIRM, after considering the antiarrhythmic therapy and the sinus rhythm as different covariates, revealed that the antiarrhythmic therapy increases significantly the risk of death. Significance which was concealed if sinus rhythm was removed from the multivariate analysis. The rhythm control, even if by drugs, seems then useful clinically, but this usefulness is actually hidden by the other adverse effects that drugs lead to. This concealment seems to be greater in patients with normal systolic function, as outlined by the subgroup analysis of the AFFIRM trial. Also in the RACE, this time in patients with persistent AF only, the rate control approached superiority for the primary efficacy endpoint (HR 0,73 90% CI 0,53-1,01) [7]. It must be said that, in both the trials, anticoagulation therapy was sometimes stopped after some weeks of effective rhythm control, which led to a better rate control than in the rate control arm itself, but which was obtained in a small percentage of patients (62% after 5 years in the AFFIRM and 39% at the end of follow up in the RACE trial).

AF in patients with reduced systolic function

The better performance of antiarrhythmic drugs in patients with reduced systolic function, as outlined by the subgroup analysis of the AFFIRM, led some years later to the AF-CHF, a trial on 1367 AF patients with EF ≤ 35% NYHA II-IV, with a 37 months follow up, which did not show significant differences between rate and rhythm control in the primary endpoint of cardiovascular death (HR 1,06 95% CI 0,86-1,3), [8] but did not show either a trend for greater risk of death or ictus in the rhythm control arm, against what the AFFIRM suggested, according to the concept that a ventricle with systolic dysfunction benefits more from a preserved atrial function. With this in mind, transcatheter ablation of atrial fibrillation, devoid of the clinical adverse effects of antiarrhythmic drugs, can further enhance the benefits of rhythm control in patients with systolic dysfunction. This is what emerged from the ARC-HF trial, on a small sample of patients with persistent AF and severely depressed systolic function (24±8%), in which transcatheter ablation significantly increased the VO2 max during a CPET, a prognostic marker of long term survival, and decreased the left atrium area, compared to a rate control strategy [9]. The exercise tolerance developed progressively during the follow up, indicating a resultant negative ventricular remodeling after sinus rhythm restoration. Similar benefits have been reached in the CAMTAF trial, on patients with persistent AF and reduced EF, in which ablation significantly increased LVEF compared to rate control (8,1% vs -3,6% p<0,001) during a six months follow up, with a negative LV remodeling totally absent in the rate control arm (ΔLVESV -14,2% vs 4,7% p=0,03), in which a positive remodelling has been noted instead [10]. This was the first trial to show ablation superiority, compared to rate control, even in patients with systolic dysfunction and asymptomatic AF. According to these results, transcatheter ablation resulted superior than amiodarone in the AATAC trial, in patients with persistent AF and systolic dysfunction, both in reducing relapses (70% vs 34% in sinus rhythm after 2 years, 95% CI 25-44%, p<0,001) and in decreasing mortality (8% vs 18% p=0,037) or hospitalization for AF or heart failure (31% vs 57% p<0,001), with a low NNT moreover (10 for mortality and 3,8 for hospitalizations), even if the trial was not designed to test such endpoints [11]. The superiority of ablation in reducing relapses, compared to antiarrhythmic drugs, was already been shown by the MANTRA PAF trial in patients with preserved ejection fraction [12].

Regarding hard clinical endpoints like death or hospitalizations for heart failure, in 2018 the CASTLE-AF trial, on a sample of 363 patients with symptomatic AF and LVEF < 35%, showed that ablation is superior than standard medical therapy, which consisted of rate control associated with antiarrhythmic drugs in 30% of patients [13]. Ablation reduced by 38% the risk of death or HF hospitalization compared to medical therapy (HR 0,62 95% CI 0,43-0,87), with a NNT of only 8 and similar NNT for each component of the composite outcome. The reduction of all cause death became significant after 3 years of follow up, according to the concept that rhythm control has a positive effect on ventricular remodeling and on the clinical history of heart failure patients. It must be said that the CASTLE recruited patients unsuccessfully treated with antiarrhythmic drugs, selecting a subgroup partially resistant to a rhythm control approach and making it impossible to draw conclusions about a first line ablative approach, which may be even more useful in more responsive patients. In the subgroup analysis of the CASTLE it came out that a severely depressed systolic function (EF < 25%) affects significantly (p value for interaction = 0,01) the benefit of ablation compared to medical therapy (HR 1,36 95% CI 0,69-2,65). The little effectiveness of ablation in patients with severely impaired systolic function has been confirmed later by the AMICA trial, in which ablation did not improved EF compared to optimal medical therapy (ΔLVEF 8,8% vs 7,3% p=0,36) on a sample of 140 patients with non paroxysmal AF and a median EF of 27,6% (compared to 32,5% in CASTLE-AF), even if rhythm control was more efficacious in the ablation arm (73,5% of patients in sinus rhythm after 1 years compared to 50% in the OMT arm) [14]. In the CASTLE, ablation was compared to a control arm in which rhythm control was possible by drugs. We should ask ourselves if ablation would be also superior, in patients with systolic dysfunction, to rate control only. It's what shown by the CAMERA MRI trial indeed, which recruited patients with tachycardiomyopathy (LVEF ≤45%) due to persistent AF [15]. In these patients, ablation significantly increased EF compared to the rate control arm (+18±13% vs +4,4±13% after 6 months, p<0,0001), with smaller advantages if MRI showed ventricular late enhancement after gadolinium injection. These data, besides those showed by the AMICA trial, suggest that the more a ventricle is remodeled and structurally altered, the less it benefits from a restored atrial function. A rhythm control strategy is therefore the more effective in heart failure the more AF is responsible for the failure itself. The CAMERA MRI trial showed that AF, which increases the risk of death, ictus and HF progression in patients with reduced systolic function, does not find in the increased heart rate the only mechanism for worsening the prognosis. In fact, the ablation arm achieved superiority over the primary efficacy endpoint despite a good rate control in the rate control arm. Transcatheter ablation, net of the adverse effects of the antiarrhythmic drugs in patients with structural heart disease, not only decreases heart rate, but also resolves the irregularity of the ventricular response and it restores the presystolic filling due to the atrial contraction, two factors promoting ventricular remodeling when altered. If the CASTLE trial compared ablation with medical therapy (which included rhythm control by drugs in one third of the patients), the RAFT-AF, currently in progress, is comparing ablation therapy with the rate control only on a sample of 411 patients with high burden AF and heart failure NYHA II-III, on a primary outcome composite of death and heart failure exacerbation [16]. The CONTRA-HF will evaluate the benefits of cryoablation compared to optimal medical therapy in patients with severe heart failure [17].

Figure 1 - Algorithm for AF rhythm control in the transcatheter ablation era



AF in patients with preserved systolic function

We should ask if ablation may also be useful in symptomatic AF patients with preserved systolic function. The CABANA trial compared ablation with medical therapy (rhythm or rate

control) on a sample of 2204 patients, with a EF greater than 35% in more than 95% of cases, on a follow up of five years [18]. In the intention to treat analysis, ablation did not achieve superiority for the primary efficacy outcome, probably due to the low frequency of events and a crossover as high as 30% from the medical therapy to the ablation arm, but it achieved superiority in the as treated analysis (HR 0,67 p=0,006), which is not altered by crossover, with a significant reduction of all cause death (HR 0,6 p=0,005). In the intention to treat analysis, by the way, ablation significantly reduced cardiovascular death and hospitalizations (HR 0,83 p=0,001). The EAST AFNET 4 trial, in the transcatheter ablation era, showed that a rhythm control strategy may be better than a rate control one, despite what the AFFIRM showed two decades ago [19]. The EAST studied a sample of 2789 patients under 75 y/o, with AF since less than one year, mostly with preserved systolic function, during a follow up of five years, comparing an early rhythm control strategy (both by ablation or by drugs) with usual therapy (rhythm control in symptomatic patients only). Early rhythm control achieved superiority in the primary composite outcome of cardiovascular death, stroke and hospitalizations for cardiovascular causes (HR 0,79 p=0,005), even if there was a NNT of just 91. There were no differences between the arms in the nights spent in the hospital or in the systolic function changes. In the subgroup analysis of the EAST, the early rhythm control strategy was superior in patients with heart failure too.

Conclusion

In conclusion, nowadays, the early rhythm control seems prognostically useful in patients with impaired systolic function, probably also in asymptomatic ones, preferably by transcatheter ablation, which not so infrequently has to be redone a second time. Out of this rule there are patients with severely impaired systolic function or with marked structural alterations of the ventricles, in which remodeling progression has gone too far to benefit from a restored sinus rhythm, and patients with severe atriomegaly (left atrium anteroposterior diameter greater than 6 cm), excluded from the most of the aforementioned trials, in which a rhythm control strategy would be of little benefit cause of a high number of relapses. An early rhythm control strategy should also be considered, according to the EAST-AFNET 4 trial, in asymptomatic patients younger than 75 with recent onset AF (diagnosed since less than one year), whatever the systolic function. We still have to understand, in these patients, if a transcatheter ablation should be done as a first line step or after an ineffective attempt at rhythm control by drugs. The ATHENA and the PALLAS trials showed that a rhythm control strategy by drugs can be clinically useful , decreasing hard endpoints like cardiovascular death, if patients have a recent onset AF, mostly in sinus rhythm (ATHENA) [20], being harmful instead, doubling mortality, in patients with AF since more than two years or with long-standing persistent AF (PALLAS). Finally, we still have to understand the optimal transcatheter ablation strategy, beyond the simple pulmonary vein isolation.

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