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Catheter ablation of atrial fibrillation in patients with heart failure:

can we break the vicious circle?

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Heart failure (HF) management should aim to symptoms relief, exercise tolerance increase, reduction of disease-related morbidities and mortality. Since atrial fibrillation (AF) relates to worsening of symptoms and increased risk of mortality¹, it warrants maximum consideration. However, despite HF and AF are two strongly correlated emerging epidemics, the approach to patients presenting these cardiovascular diseases together remains, to date, challenging and cause of concerns.

AF and HF often coexist in the same patients, as they share several pathophysiological links. Patients with AF, due to the deleterious hemodynamic effects of atrial contraction loss and ventricular systoles irregularity, are more prone to develop HF compared to patients in sinus rhythm (SR)^{2, 3}. On the other side, patients with HF present incident AF more frequently than patients with normal ventricular function, being increased left ventricular filling pressures, and left atrial dilation and fibrosis, the ideal substrate for AF onset and perpetuation. Noteworthy, this link is relevant both in case of reduced left ventricular ejection fraction (LVEF) than in patients with preserved LVEF HF.

Therefore, AF and HF can perpetuate each other in a vicious circle, and this mechanism mutually contributes to worsen prognosis when compared to that of a similar patient affected by only one of the two pathologies at a time. In fact, higher mortality was reported among HF patients with AF compared to those in SR, and especially patients with preserved LVEF HF suffer an even worse negative prognostic effect of AF compared to those with HF and reduced LVEF⁴. Additionally, patients with AF and concomitant HF present higher mortality and thromboembolic events compared to patients with AF without HF⁵.

No direct evidences favor rhythm by antiarrhythmic drugs compared to rate control. In fact, rhythm control by antiarrhythmic drugs achieves poor results and exposes patients to side effects. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial observed no difference in cardiovascular mortality, death from any cause, and worsening of heart failure between patients

with LVEF \leq 5% and symptoms of HF randomized to rate or rhythm control⁶. For this reason guidelines recommend, as in patients without HF, that management of AF should start with rate control and, only in case of persistent symptoms, rhythm control. On the other side, a substudy of the AFFIRM trial suggested that the benefit in terms of survival deriving from SR maintenance (HR 0.53, 99%CI 0.39-0.72) was neutralized by the detrimental effects of antiarrhythmic drugs (HR 1.49, 99%CI 1.11-2.01)⁷. In addition, recent observational studies broaden the possibility that rhythm may better perform than rate control, being related to longer survival⁸ and decreased stroke incidence⁹. Eventually, although in the general population, AF duration has related to cerebral lesions detected by MR scans and cognitive performance¹⁰.

Given these presumptions, AF catheter ablation, as rhythm control strategy, has been increasingly proposed over the last decade. Despite the epidemics of HF and AF, however, few patients presenting both these diseases are managed by AF catheter ablation. Catheter ablation of AF in HF patients should be considered when amiodarone fails to control symptoms. Bearing in mind that assessment of AF-related symptoms may be challenging with overlapping HF symptoms, and that more extensive left atrium ablation may be needed in addition to isolation of the sole pulmonary veins (PV)¹¹, emphasizes the need for an individual and informed decision for catheter ablation in HF patients. However, previous statements suggesting a lower likelihood of SR maintenance following AF catheter ablation and higher procedure-related risk in HF patients, do not seem to be confirmed in several recently published experiences.

Given the paucity of data focusing on this subgroup of patients recommendations derive mostly from the three meta-analyses available that have differently pooled data on AF catheter ablation in HF patients. The first meta-analysis¹² included seven observational studies and one randomized trial (n=1,851). Follow-up ranged from 6 to 27 months. In patients with HF 28-55% were free from AF at follow-up after 1 AF catheter ablation, increasing to 64-96% after a mean of 1.4 procedures. The relative risk for recurrent AF in those with versus without HF was 1.5 (95%CI 1.2 to 1.8, p <0.001)

after 1 procedure and 1.2 (95%CI 0.9 to 1.5, $p=0.2$) after multiple procedures. No difference in complications was observed in patients with (3.5%) versus without (2.5%) HF ($p=0.55$). The second meta-analysis¹³ focused, instead, on LVEF changes following the ablation procedure. A total of 354 patients, mean age 49 to 62 years, with LVEF ranging from 35% to 43%, were included. LVEF improved after ablation by 11.1% (95%CI 7.1 to 15.2, $p < 0.001$). The proportion of patients with coronary artery disease was inversely related with LVEF improvement ($p < 0.0001$). Eventually, in the largest meta-analysis available on this topic, AF catheter ablation outcome improves especially when performed early in the natural history of both AF ($p=0.030$) and HF ($p=0.045$), providing long-term benefits on LVEF and reducing the proportion of patients who would subsequently maintain a LVEF $< 35\%$ ($p < 0.001$)¹⁴. Supporting these data, one long-term multicenter study¹⁵ performed on 196 patients with impaired LVEF has reported, following PV isolation and, in 85% of the cases, additional ablation lines in the left atrium, that 62% of the patients were arrhythmia free after about 4 years, a percentage equivalent to that reported in similarly long follow-up studies in patients without HF¹⁶. Overall, the strongest predictors of rhythm control failure are enlarged left atrium and arrhythmia duration. This finding is not surprising, as these parameters reflect an advanced structural disease involving both left atrium and left ventricle, characterized by greater fibrosis extent and lower recovery capabilities.

To date only one randomized controlled trial has directly compared, specifically in HF patients, the ideal rate control strategy (and not standard care), AV node ablation preceded by cardiac resynchronization therapy (CRT), to rhythm control by AF ablation. The PABA-CHF¹⁷ trial enrolled 81 patients with symptomatic refractory AF, LVEF $< 40\%$ and NYHA class II-III. One arm of the study underwent PV isolation, the second AV node ablation preceded by CRT. After 6 months follow-up, rhythm control patients reported higher LVEF (35% vs. 28%, $P < 0.001$), 6-minute walking test distance ($p < 0.001$), and Minnesota Living with HF questionnaire increase ($p < 0.001$) compared to patient undergoing AV node ablation and CRT. These findings indeed support the beneficial role of SR among these patients, deriving not only from regularization of the

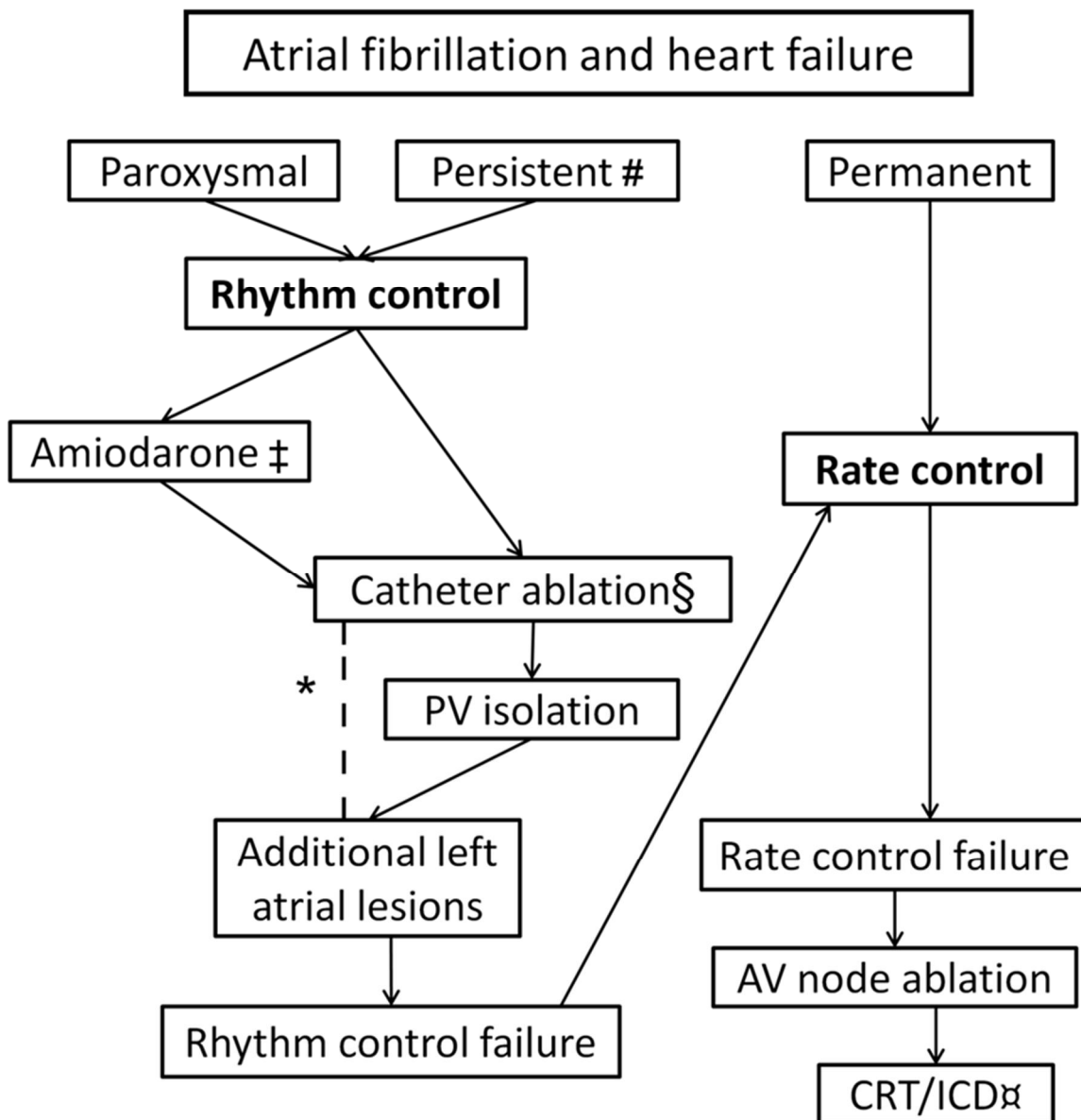
ventricular systoles (that also CRT provides¹⁸) but also from the maintained atrial mechanical function (also, perhaps, reducing the risk of thromboembolic events).

Awaiting currently ongoing randomized controlled trials specifically investigating the role of AF catheter ablation in the setting of HF (e.g. Catheter Ablation versus Standard conventional treatment in patients with LV dysfunction and Atrial Fibrillation [CASTLE-AF]; AF Management In Congestive heart failure with Ablation [AMICA]; Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD [AATAC-AF in Heart Failure]), it can, indeed, be stated that AF catheter ablation presents the potential to gain a significant role in HF management for the following reasons. First, AF and HF are two emerging epidemics that often coexist. Based on the extremely scarce literature focusing on this topic it is clear that, to date, the treatment of AF and HF do not consider their intrinsic links and this, in any case, is limiting. Second, AF catheter ablation is a safe procedure and can be performed with low complications rate in patients with complex atrial substrate, comorbidities and frailty such as patients with HF. Third, AF catheter ablation, by maintaining SR, increases LVEF over both short and long term follow-up. This finding is not surprising: interruption of the vicious circle between AF and HF, by restoration of regular cardiac cycles and normal atrial mechanical function are likely to slow or even interrupt the negative electrical and structural remodeling of the failing heart. Fourth, AF catheter ablation is related to significant improvement in quality of life, functional class and exercise tolerance.

In conclusion, bearing in mind that AF ablation should be recommended to candidates with the highest hypothetical procedural success (enlarged left atrium, arrhythmia and HF duration strongly influence outcome), the flow chart proposed by our group and based on a multidisciplinary approach involving physicians evaluating HF patients and interventional electrophysiologists, is reported in the Figure.

Eventually the following points are lacking clinical evidences and are still under debate. First, ablation protocol. PV isolation alone and/or additional non-PV targets, as in the general population, need to be tested in prospective randomized trials on HF patients. Second, randomized studies are encouraged to precisely define the optimal timing of AF ablation during natural HF course, especially in vision this may impact on the long-term prognosis of these patients, potentially influencing referral for device implantations, such as ICDs and CRTs.

Figure 1. Proposed flow-chart for optimal atrial fibrillation treatment in patients with heart failure



Legend.

long-standing persistent AF to approach as persistent AF, except in case of severe left atrial dilation (volume > 150 ml).

§Ablation as first-line rhythm control therapy for patients intolerant to or that reject antiarrhythmic drug therapy;

*More extensive left atrial ablation may be needed in addition to pulmonary vein isolation in patients with enlarged left atrium or long history of AF

αAs recommended by current guidelines

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