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Atrial fibrillation ablation in patients with heart failure review

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ABSTRACT

Atrial fibrillation and heart failure often coexist in patients with advanced heart failure symptoms. The result, in addition to a significant impact on quality of life, is an increase in the risk of a adverse clinical outcomes including stroke, hospitalization and overall mortality. Pharmacological therapy for atrial fibrillation in the heart failure population remains limited due to sub-optimal drug efficacy and a likely increased mortality due to pro-arrhythmia. Atrial fibrillation ablation, since it allows for therapy without the need for toxic medication, has the potential to become mainstream treatment in patients with drug refractory, symptomatic atrial fibrillation and heart failure. Randomized studies and observational data suggest that atrial fibrillation ablation provides superior rhythm control to anti-arrhythmic drugs. Atrial fibrillation ablation is relatively safe and may result in improvement of left ventricular function and quality of life. Ongoing studies are attempting to assess a number of outcome measures to help define its role in the heart failure patient population. This review focuses on atrial fibrillation ablation in patients with congestive heart failure, and summarizes the results of available literature.

Keywords: Atrial Fibrillation; Ablation; Heart Failure

1. INTRODUCTION

Atrial Fibrillation (AF) and Heart Failure (HF) are major, and often coexisting, public health burdens, which are increasing in prevalence and incidence [1-3] and affect equally patients with impaired and preserved Left Ventricular (LV) function [4,5].

Atrial fibrillation, which affects 1% - 2% of the population of the western world [6], is associated with increased risk of stroke, hospitalization and overall mortality and has a significant impact on quality of life [7-12]. The prevalence of AF increases in patients with more advanced HF symptoms [13]. Heart failure was present in 34% of AF patients, and atrial fibrillation in 42% of HF patients according to The European Heart Surveys [14,15]. There is a direct relationship between New York Heart Association (NYHA) functional class and the presence of AF. Atrial fibrillation prevalence increases from 4 to 40 percent as the NYHA functional class increases from I to IV [16-23]. This association of AF and HF exists also in those with isolated diastolic dysfunction with preserved LV function [24].

Different mechanisms could explain the co-existence of atrial fibrillation and heart failure including: 1) rapid ventricular response leading to rate-related cardiomyopathy [24]; 2) reduced cardiac output from loss of atrial transport [25,26]; 3) heart failure causing increased atrial filling pressure and atrial dilatation promoting atrial fibrillation by ionic remodeling and atrial fibrosis [27]; and 4) atrial stretch-related effects on atrial electrophysiologic properties such as refractoriness and triggered activity [28]. In fact, treatment to relieve chronic stretch has been demonstrated to reverse this remodeling process [29,30].

Treatment to eliminate AF in patients with impaired LV function improves LV function [31,32]. Several studies addressed the prognostic influence of the presence of AF in HF. Mamas *et al*., in a systematic review of 53,969 patients [33], showed that AF is associated with worse prognosis in HF patients whether (OR 1.49) or not (OR 2.0) LV function was impaired.

2. PHARMACOLOGICAL THERAPY FOR ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE

Pharmacologic therapy of AF in heart failure is challenging in symptomatic patients despite conventional HF therapy. Drug-based AF rhythm control strategy in HF

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patients has failed to show any survival benefit compared with a rate control strategy in randomized studies such as RACE [34] AF-CHF [35] and ANDROMEDA [36]. This may be because of potential pro-arrhythmia with all anti-arrhythmic drugs, including amiodarone [37-40]. In addition, in these rate vs. rhythm control studies, which are intention to treat, there is a significant number of rate control patients who achieve sinus rhythm and conversely a significant number of rhythm control patients in whom AF persists. The somewhat similar rhythm outcomes in the two treatment arms, though valid within the intention to treat, undoubtedly affects the veracity of the results if survival in sinus rhythm vs AF is the desired end point.

Data from AFFIRM [41,42], DIAMOND [43] and other studies [44] suggests that patients maintaining sinus rhythm may have better survival, but the benefit may be offset by the adverse effects of anti-arrhythmic drugs. CAFÉ II study supports this further by showing improved LV function and NT-pro BNP in patients assigned to rhythm control [45].

3. CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH HEART FAILURE

Since the initial reports of catheter ablation for AF rhythm control in 1998 [46], there has been substantial progress in the understanding, technique and technology of catheter ablation such that the procedure is becoming mainstream treatment in patients with drug refractory symptomatic AF. Catheter ablation for AF rhythm control has been found to be a relatively safe, effective and cost-effective therapy in both clinical trials and in a worldwide survey [47,48] and has superior efficacy compared to anti-arrhythmic drugs [49,50].

The improvement of LV function, following catheter ablation for AF, may be due to restoration of atrial transport, better ventricular filling and enhanced contractility through Starling mechanism. Sinus rhythm also usually results in better rate control.

Extending this therapy to patients with LV systolic dysfunction is appealing, because of the multiple potential effects of AF on the multiple pathophysiologic mechanisms of HF [51]. However, because of differences in atrial substrate and co-morbidities, ablation in these important patients may be associated with higher risk for recurrent AF or complications.

Despite encouraging reported results for catheter ablation in patients with HF, ablation is not widely used in this substantial patient population. Even in experienced high-volume centers, HF is present in only a small proportion of patients undergoing ablation [52-54]. In this review we summarize all the data available from recent AF ablation publication enrolling patients with HF

4. CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH IMPAIRED LV FUNCTION

4.1. Observational Data

Several studies [55-64] assessed outcome of AF ablation in patients with impaired LV function (**Table 1**). The maintenance of sinus rhythm free of anti-arrhythmic drugs post ablation ranged from 50% up to 87% (**Figure 1**). The risk of recurrence was higher in this population with more repeat procedures required, although some studies showed no significant difference compared to the control group and concluded that LV systolic dysfunction by itself is not a predictor of outcome after AF ablation. The patients who underwent AF ablation showed significant improvement in LV Ejection Fraction (EF) ranging from 4.6% increase in ejection fraction, up to normalization of LVEF suggesting the presence of a reverseble atrial fibrillation-induced ventricular cardiomyopathy in many patients with AF and depressed LV function. This was associated with significant improvement in remodeling, exercise capacity, symptoms, and quality of life. This effect was not observed to the same extent in the medically treated group. The improvement was observed regardless of concurrent structural heart disease and adequacy of rate control before ablation. Performing catheter ablation in patients with LV dysfunction was found to be feasible and not associated with higher procedural complications.

Table 1. Summery of observational and randomized studies of AF ablation in patients with heart failure.

Author/study	Publication year	Patient number	Age (y)	Cutoff (or highest) LVEF (%)	Mean LVEF (%)	Patients with CAD (%)	Type of AF	Follow-up (months)	Outcome
Impaired LV function									
Observational studies									
Chen [55]	2004	94	57 ± 8	40	36 ± 8	78	Paroxysmal and persistent	6	- Recurrence related to LVEF, and pulmonary vein size. - PVI may be a feasible therapeutic option

Continued

Hsu [56]	2004	58	56 ± 10	45	35 ± 7	21	Paroxysmal and persistent	12	- Significant improvement in LVEF, symptoms, exercise capacity, and QoL.
Tondo [57]	2006	40	57 ± 10	40	33 ± 2	25	Paroxysmal and persistent	14	- Ablation is feasible, not associated with higher procedural complications, - Significant improvement in LVEF, symptoms, and QoL.
Gentlesk [58]	2007	67	54 ± 9	50	42 ± 9	18	Paroxysmal and persistent	6	Maintenance of SR associated with more LVEF improvement
Efremidis [59]	2007	13	54 ± 12	40	36 ± 5	23	Paroxysmal and persistent	9	- AF ablation is effective method of maintaining sinus rhythm - Improvement in LVEF, and reversing atrial and ventricular remodelling
Nademanee [60]	2008	129	67 ± 12	40	31 ± 7	21	Paroxysmal and persistent	27	- Duration of AF, LA size > 50 mm are associated with recurrence - Maintenance of SR predicts survival
Lutomsky [61]	2008	18	56 ± 11	50	41 ± 6	17	Paroxysmal	6	Pulmonary vein isolation improves cardiac function
De Potter [62]	2010	36	49 ± 10	50	43 ± 7	19	Paroxysmal and persistent	6	- LA size, not LVEF or AF duration, predicts recurrence - Similar improvement in LVEF in both ischemic and nonischemic
Choi [63]	2010	15	56 ± 11	45	37 ± 6	33	Paroxysmal and persistent	16	PVI significantly improved LVEF and NYHA class
Cha [64]	2011	111	55 ± 6	40	35 ± 5	13	Paroxysmal and persistent	13	Increased risk of arrhythmia recurrence compared with normal function.
Randomized studies									
Khan (PABACHF) [65]	2008	41	60 ± 8	40	27 ± 8	73	Paroxysmal and persistent	6	PVI superior to atrioventricular-node ablation with biventricular pacing in patients with heart failure
MacDonald [66]	2011	22	62 ± 7	35	36 ± 12	50	Persistent	10	- Ablation resulted in long-term restoration of sinus rhythm in only 50% of patients. - RFA did improve radionuclide LVEF - Associated with a significant rate of serious complications.
Preserved LV function									
Cha [64]	2011	157	62 ± 2	≥50	62 ± 2	17	Paroxysmal and persistent	13	Ablation associated with improvement in QoL and LV functional benefit.

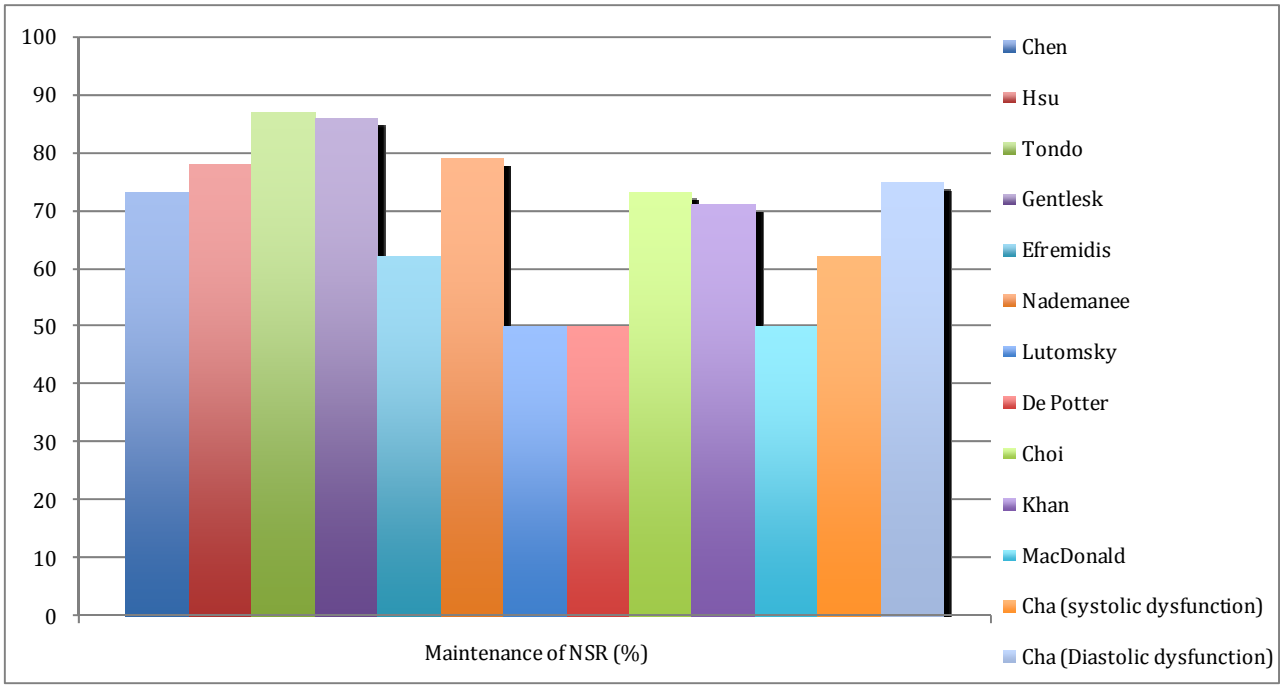

Figure 1. Rate of maintenance of NSR without AADs post AF ablation in patients with heart failure.

4.2. Randomised Controlled Trials

Khan *et al.* [65] randomized 81 patients with symptomatic drug-resistant AF, an EF of 40% or less, and NYHA class II or III heart failure to either pulmonary vein isolation or atrio-ventricular nodal ablation with biventricular pacing. Out of 41 patients in the pulmonary vein isolation arm, 71% were free of AF without anti-arrhythmic drugs at 6 months follow-up. Catheter ablation for AF/HF patients with impaired LV resulted in improvements in LVEF (35% vs 28%, $P < 0.001$), quality of life (60 vs 82 on questionnaire score, $P < 0.001$) and 6-minute walk distance (340 m vs 297 m, $P < 0.001$) compared to patients treated with rate control by AV nodal ablation and biventricular pacing.

MacDonald *et al.* [66] randomised 41 patients with persistent AF, advanced HF and severe LV dysfunction to AF ablation (rhythm control) or continued medical treatment (rate control). Patients were followed up for a minimum of 6 months. In the ablation group, 50% of patients were in sinus rhythm at the end of the study. The ablation group had a greater increase in LVEF (using either cardiovascular magnetic resonance or radionuclide determinations) than patients in the medical treatment group although this did not reach statistical significance. AF ablation did not improve N-terminal pro-BNP, 6 min walk distance or quality of life. The rate of serious complications related to ablation was 15% (1 stroke, 2 tamponade recovered after emergency pericardiocentesis without long-term complications, 3 worsening heart failure requiring adjustment of diuretic therapy/hospitalization). There are several limitations to this study including small sample size with lower than predicted success rate and baseline imbalances between the treatment groups. As well, this was a single centre study with a single operator performing the ablation procedures.

4.3. Metanalysis

Wilton *et al.* [67] performed a systematic review and metaanalysis of 7 randomized and observational studies including 1851 patients, comparing the rates of recurrent AF, atrial tachycardia and complications after AF catheter ablation in patients with normal compared to impaired LV systolic function. Sixty-four percent to 96% of patients with LV dysfunction were free of AF or atrial tachycardia after a mean of 1.4 procedures. There were no differences in complication rates. After catheter ablation, patients with systolic LV dysfunction experienced a pooled absolute improvement in the LVEF of 11%.

Dagres *et al.* [68] performed meta-analysis on 9studies involving 354 patients with LV dysfunction to assess change in LVEF after catheter ablation of AF. A similar 11.1% LVEF improvement post ablation was reported. The presence of coronary artery disease predicted failure of LVEF improvement. There was no association between LVEF change and AF recurrence during follow-up.

5. CATHETER ABLATION OF ATRIAL FIBRILLATION IN PATIENTS WITH PRESEVED LV FUNCTION

Cha *et al.* [64] assessed catheter ablation for anti-arrhy-

thmic drug-refractory AF in 368 patients with HF. They compared 3 groups prospectively: 111 HF patients with systolic dysfunction, defined as LVEF ≤ 40%; 157 HF patients with isolated diastolic dysfunction but preserved LVEF ≥ 50%; and 100 control patients without HF and with normal LV function. The primary end point was freedom from AF and anti-arrhythmic drugs at one year post ablation. This end point was achieved in 62% of patients with systolic dysfunction, 75% of those with diastolic dysfunction, and 84% of controls (P = 0.007). AF control on or off drug was achieved in 76% of patients with systolic dysfunction, 85% of those with diastolic dysfunction, and 89% of controls (P = 0.08). In the systolic dysfunction group, 49% experienced an increase in LVEF by ≥5% after ablation. Of these, 64% achieved normalization of LVEF. In the diastolic dysfunction group, 30% of patients demonstrated at least one grade improvement in diastolic dysfunction. They concluded that an ablation approach for AF has the potential for substantial quality-of-life improvement and LV functional benefit.

6. ONGOING STUDIES

To date, published, randomized trials involve only small numbers of patients but suggest benefit of catheter ablation for rhythm control for atrial fibrillation patients with heart failure whether or not LV function is preserved. Larger scale, randomized studies assessing a number of endpoints, including hard endpoints, are needed and indeed there are multiple ongoing studies looking into outcomes, predictors of success, and safety in this high risk population.

Pulmonary Vein Isolation for Rhythm Control in Patients with Atrial Fibrillation and Left Ventricular Dysfunction (Catheter Ablation for AF & HF) [69] is an observational study enrolling patients with NYHA I-III CHF on optimal medical therapy with planned catheter ablation for paroxysmal or persistent AF. Primary endpoint is improvement in LV end systolic volume by 15% or more frombaseline at 6 months. Secondary endpoints include remodeling as demonstrated by atrial and ventricular dimensions on echocardiography, NYHA class, quality of life and six minute hall walk test. Composites of hospitalization for heart failure, thrombo-embolism, major bleeding or all cause mortality, as well as absence of AF will also be assessed. This study was withdrawn prior to enrollment.

Catheter Ablation Versus Medical Treatment of AF in Heart Failure (CAMTAF) [70] is an open label, parallel assignment study randomizing patients with HF and persistent AF to medical treatment or catheter ablation to restore sinus rhythm. The primary end point is the difference in LVEF between groups. Secondary outcomes include differences in peak VO_2, NYHA class, BNP, quality of life, reduction in end systolic volume, and difference in HF symptoms. The study is complete but not yet published.

Catheter Ablation Versus Medical Rate Control for Atrial Fibrillation in Patients with Heart Failure (ARC-HF) [71] is a prospective study enrolling HF patients on optimal therapy, with documented persistent AF, and comparing the strategies of catheter-ablation and medical rate control in a 1:1 randomized fashion. The primary end point is difference in peak oxygen consumption at cardiopulmonary exercise test. Secondary endpoints includes changes in LVEF, quality of life score, 6 minutes walk test, BNP levels, and freedom from AF. The study is complete but not yet published

AMICA Atrial Fibrillation Management in Congestive Heart Failure with Ablation [72] is a randomized, open label study in symptomatic AF patients comparing the effect of AF ablation plus ICD/CRT implant to best medical treatment plus ICD/CRT implant in patients with reduced EF of less than 35% who are felt to require ICD or CRT-D implantation. Primary endpoint is LVEF improvement as determined by echocardiography. This study is estimated to complete in 2013.

CASTLE-AF Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation [73] is a prospective, open label, randomized, multicenter study comparing the effect of catheter ablation to conventional treatment in HF patients with AF. Eligible patients are those with LV dysfunction (LVEF ≤ 35%) and NYHA class ≥ II who have already been implanted with a dual chamber ICD with Home Monitoring® capabilities. The primary endpoint is the composite of all-cause mortality or worsening of heart failure requiring unplanned hospitalization using a time to first event analysis. Secondary endpoints are all-cause mortality, cardiovascular mortality, cerebrovascular accidents, worsening of HF requiring unplanned hospitalization, unplanned hospitalization due to cardiovascular reason, all-cause hospitalization, quality of life, number of therapies (shock and anti-tachycardia pacing) delivered by the ICD, time to first ICD therapy, number of device-detected ventricular tachycardia and ventricular fibrillation episodes, AF burden, AF-free interval, LVEF, exercise tolerance, and percentage of right ventricular pacing. This study should be completed in 2015.

Rate Versus Catheter Ablation Rhythm Control in Patients With Heart Failure and High Burden Atrial Fibrillation (RAFT-AF) [74] is a large multicentre, randomized, open label study comparing catheter ablation for AF rhythm control to rate control in patients with HF (NYHA II-III, on optimal medical therapy, and elevated NT-pro BNP) and high burden AF. Primary end point will be cardiovascular mortality. Cost-effectiveness and

quality of life will be secondary end points. The study is currently recruiting, and anticipated completion is 2016.

7. CONCLUSIONS

AF and HF with impaired or preserved LV function coexist with increasing prevalence. AF in such patients is associated with increased mortality as well as deterioration of LV function, NYHA class, exercise tolerance, and quality of life. Pharmacological therapy of AF in this population is limited due somewhat to suboptimal efficacy and increased risk of pro-arrhythmia.

Observational data suggests AF ablation is a superior modality for rhythm control with significant improvement in LVEF, symptomatic state, and quality of life. This is further supported by data from small size randomized studies showing feasibility and safety of AF ablation with improved outcome in patients with HF.

Ongoing studies will hopefully shed light on a multitude of endpoints, particularly hard endpoints such as mortality and hospitalizations and further characterize the optimal heart failure patient subgroups.

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