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Atrial Fibrillation Ablation and Left Appendage Closure in Heart Failure Patients

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Abstract

Purpose of Review—Patients with atrial fibrillation (AF) and heart failure (HF) experience an increased morbidity and mortality from the hemodynamic consequences of AF and an increased stroke risk. Consequently, there has been increased attention to procedural alternatives to pharmacologic rhythm control and anticoagulation for stroke prevention. This review aims to evaluate the evidence for AF ablation and left atrial appendage (LAA) closure in HF patients.

Recent Findings—Several randomized control trials and systematic reviews support prior literature demonstrating the safety and efficacy of AF ablation in patients with HF and LV systolic dysfunction. In multiple trials, these patients have shown clinical benefit from AF ablation including improved LV systolic function, quality of life, and clinical HF symptoms. The evidence and clinical benefit of AF ablation in HF patients with preserved ejection fraction remains limited. Only a handful of randomized control trials have been performed evaluating LAA closure and there is insufficient data regarding the safety and efficacy of these procedures in HF patients.

Summary—AF ablation in HF patients remains safe with an overall efficacy comparable to AF ablation in patients without HF. There is consistent evidence for the clinical benefit of AF ablation in HF patients with LV systolic dysfunction and limited evidence for AF ablation in heart failure patients with preserved ejection fraction. Currently there is insufficient data regarding the safety and efficacy of LAA closure devices in HF patients.

Keywords

Atrial Fibrillation; Catheter Ablation; Heart Failure; Left Atrial Appendage Occlusion

Introduction

The estimated prevalence of heart failure (HF) in the United States (US) is 5.7 million people, and unlike other major cardiovascular diseases the prevalence, incidence and mortality from HF are increasing [1–3]. Of particular concern are patients with both heart failure and atrial fibrillation (AF). There is a distinct correlation between these two conditions, with the prevalence of AF rising from 10% in mild cases of heart failure to

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Conflicts of interest

None.

almost 50% in severe heart failure [4]. This correlation has been attributed to an increase in morbidity and mortality among patients with AF and HF [5–6]. While restoration of sinus rhythm could lead to improved left ventricular (LV) systolic and diastolic function [7–9], rhythm control with cardioversion and antiarrhythmic drugs has not been shown to reduce mortality [10]. Consequently, there has been increased use of catheter ablation to restore sinus rhythm in an attempt to ameliorate the effects of AF in HF patients [11].

In addition to the hemodynamic consequences of AF in these patients, the concern for cardioembolic stroke remains. Patients with AF and HF have a 3-fold increased risk of stroke [12]. While anticoagulation has been shown to be effective [13], only 60% of eligible patients receive anticoagulation [14]. As a result, there has been increased attention to procedural alternatives to anticoagulation, such as left atrial appendage (LAA) closure [15–16]. This review aims to evaluate the evidence for AF ablation and LAA closure in these patients.

Early Studies of AF Ablation in HF Patients

Given the challenges of pharmacotherapy for maintaining sinus rhythm in patients with AF [10,17], attention has shifted to ablation therapy for rhythm control. Initial studies evaluating the safety and efficacy of AF ablation in HF patients consisted of small, non-randomized studies [18–25]. With current catheter ablation techniques the risk of major complications from AF ablation in HF patients has been estimated in a recent meta-analysis to be 4.2% (95% CI 3.6%–4.8%) [26**]. This complication rate is similar to that observed in AF ablation performed in patients without heart failure [27].

Early studies demonstrate a wide variation in efficacy of AF ablation in HF patients. The success rate in restoring sinus rhythm following the first procedure ranged from 25%–73% [26**,28]. This range was influenced by the baseline characteristics of the study population, type of AF and ablation protocol. Not surprisingly, aggregated initial efficacy data of AF ablation in HF patients estimates a success rate of 40% in restoring sinus rhythm [26**]. While this rate is lower than initial efficacy rates of AF ablation in patients without HF, after multiple procedures, the overall success rate of AF ablation in patients with HF was found to be 60% in a recent meta-analysis [26**]. To obtain this overall success rate of AF ablation, more repeat procedures were required in patients with HF to maintain sinus rhythm [19,29]. Emerging technology, namely the use of irrigated, contact force sensing ablation catheters may increase the efficacy of AF ablation in patients with HF. Results from several studies in the general population have already shown an increased freedom from AF recurrence when appropriate contact force was maintained during AF ablation [30, 31].

Despite the wide variation in efficacy seen in the early non-randomized trials of AF ablation in HF patients, the clinical impact of restoring sinus rhythm in these patients have been consistently favorable. These studies demonstrate either a significant improvement in left ventricular ejection fraction (LVEF), echocardiographic indices or quality of life scores following ablation [18–23,25]. These studies provide convincing evidence demonstrating the safety & efficacy of AF ablation in this population.

Randomized Trials of AF Ablation in Patients with LV Systolic Dysfunction

To date there have been 4 randomized control trials investigating AF ablation in patients with HF and LV systolic dysfunction (Table 1). The first randomized trial compared AF ablation to atrioventricular node ablation followed by bi-ventricular pacing [32]. Patients with drug resistant AF and LVEF <40% with New York Heart Association (NYHA) Class II or III symptoms were randomized to treatment and followed for 6 months. The study found that patients who underwent AF ablation had better quality of life measurements, better performance on 6-minute walk test, and a higher improvement in LVEF.

These findings were not reproduced in the second randomized control trial by MacDonald et al., which randomized persistent AF patients with NYHA Class II-IV symptoms and LVEF <35% to AF ablation or optimal rate control medications [33]. At 6-month follow up, there was no significant difference between the two groups in LVEF or 2 out of 3 quality of life measurements. Limitations of the study included the fact that sinus rhythm was only achieved in 50% of the patients randomized to AF ablation. Subgroup analysis demonstrated those who maintained sinus rhythm did have an improved LVEF.

In contrast, two recent randomized control trials suggest a clinical benefit to rhythm control with catheter ablation in HF patients and depressed LVEF. The ARC-HF study (A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Heart Failure) analyzed catheter ablation for patients with persistent AF, symptomatic heart failure and LVEF $\geq 35\%$ [34*]. Fifty-two patients were randomized in an intention to treat analysis, to extensive catheter ablation including pulmonary vein isolation, linear ablation lesions along the left atrial roof and mitral isthmus, targeting of complex fractionated atrial electrograms (CFAE) and linear ablation along the cavotricuspid isthmus (CTI). In the patients who underwent ablation, single procedure success was 72% and overall success was 92% off antiarrhythmic drugs. The study demonstrated a significant increase in the primary endpoint of peak oxygen consumption at 12 months in the catheter ablation arm versus the rate control arm by a mean difference of 3.07 ml/kg/min (95% CI 0.56 – 5.59). This difference in peak oxygen consumption between the two groups was not observed at 3 months, suggesting a progressive improvement in peak oxygen consumption following AF ablation. Similar trends favoring ablation occurred in improvements in quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and reduction in B-type natriuretic peptide (BNP). LVEF also significantly increased in the ablation group from $21.5\% \pm 8.3\%$ at baseline to $32.8\% \pm 14.3\%$ at 12 months ($P < 0.001$). However when compared to the rate-control arm these changes only showed a non-significant trend towards improvement. The ARC-HF findings are not trivial. Prior studies have suggested a 7% reduction in all-cause mortality in patients with heart failure with every 6% increase in peak oxygen consumption [36–37]. This study demonstrated a mean improvement in peak oxygen consumption of 19.9% (95% CI 3.9% - 35.9%) in the ablation group compared to the rate control group.

The most recent CAMTAF Trial (A Randomized Controlled Trial of Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure) randomized patients with persistent AF, symptomatic heart failure, and LVEF <50% to AF ablation versus medical

rate control [35*]. The primary endpoint of the study analyzed differences in LVEF between the two groups at 6 months.

Fifty patients comprised the study population, with 26 patients undergoing catheter ablation. Patients underwent a similar ablation protocol to that of the ARC-HF study. The single procedure success rate off antiarrhythmic drugs was 38% at one year. Most patients required more than 1 procedure with an overall success rate of 81% following all procedures at 6 months and 73% at one year. At 6 months, the study demonstrated a significant difference in LVEF between the two groups. The LVEF in the catheter ablation group was 39.9% (95% CI 35.2%–44.7%) versus 31.9% (95% CI 25.5%–36.6%) in the medical group ($P=0.015$). The difference in LVEF between the two groups was evident after 1 month and was sustained at 1 year. Similar statistically significant differences were observed in changes in LV end systolic volume, peak oxygen consumption, plasma BNP, and quality of life as measured with the MLHFQ. The study results suggest a marked benefit in AF ablation in HF patients when compared to medical rate control alone. In fact, 5 of the 26 patients who underwent AF ablation had complete normalization of LVEF and resolution of HF symptoms at 6 months.

The findings in ARC-HF and CAMTAF Trial build on the foundation of the earlier AF and HF ablation studies. The study by MacDonald et al. has been the only randomized control trial which failed to show benefit for AF ablation in HF patients. This study achieved an overall procedural success rate of only 50% with just 6 months of follow up, factors which would have strongly contributed to the observed lack of benefit of AF ablation in HF patients.

Long Term Efficacy of AF Ablation in the Setting of Impaired LV Systolic Function

There are only a handful of recent studies that have looked at the long-term efficacy of AF ablation in patients with LV systolic dysfunction [38**–39*]. In a prospective case-control study, patients with LVEF $\leq 40\%$ underwent AF ablation after which antiarrhythmic drugs were discontinued and serial Holter electrocardiographic and echocardiographic monitoring was performed. The study demonstrated a statistically significant reduction in heart failure symptoms and an increase in LVEF from $33\% \pm 6\%$ at baseline to $48\% \pm 13\%$ at 24 months ($P < 0.001$). In fact, 44% of the study population experienced marked improvements in LVEF $\geq 20\%$ with multivariate regression analysis demonstrating baseline heart rate and rhythm outcome as the only independent predictors of improvement in LVEF.

In subgroup analysis, patients who maintained sinus rhythm following AF ablation had significantly greater improvements in LVEF from baseline compared to those with recurrence of atrial tachycardia/fibrillation. This observation was not observed at 6 months, but only after 12 and 24 months of follow-up, suggesting that the initial LVEF improvement at 6 months was due to changes from baseline heart rate rather than rhythm outcome, while LVEF improvements at 12 and 24 months were due to changes resulting from both baseline heart rate and rhythm outcome. Further supporting this observation is the analysis performed by the study authors which found that only rhythm outcome following AF ablation was

associated with improvements in LVEF at 12 and 24 months after controlling for heart rate at 6 months.

Thus both baseline heart rate and rhythm outcome following ablation appear to be predictors of LVEF improvement in heart failure patients undergoing AF ablation. Interestingly, the relative importance of baseline heart rate and rhythm outcome may vary over time, with the initial improvement in LVEF associated with rate control and later improvements in LVEF associated with sustained rhythm control. This finding supports the hypothesis that restoration of regular atrial contractility and resynchronization of atrioventricular contractions are both important to LV remodeling in AF patients with HF.

These findings have been strengthened by a recently published systematic review and meta-analysis by Anselmino et al. looking at the long-term role of AF ablation in patients with LV systolic dysfunction [26**]. The review included 26 studies published between 2002 and October 2013 of 1,838 patients (45% paroxysmal) with a mean LVEF of 40%. Patients underwent AF ablation with a mean follow-up of 23 months. Patients underwent PVI with additional linear ablation lesions or substrate modification. Re-do procedures were performed in 32% of cases. AF recurrence was consistently defined as atrial fibrillation/tachycardia occurring for at least 30 seconds following an initial blanking period of 3 months post-procedure. Initial procedural efficacy in restoring sinus rhythm ranged from 36% to 44%, while overall procedural efficacy was 60%, consistent with results of AF ablation in the general population [40].

All of the studies in this review demonstrated an improvement in LVEF over the follow up period, with mean LVEF improving from 40% to 53%, with a commensurate decrease in mean N-terminal pro-B-type natriuretic peptide levels from 1,187 pg/ml prior to ablation to 567 pg/ml by the end of the follow-up period ($P<0.001$). This study remains the largest systematic review and meta-analysis of AF ablation in patients with LV systolic dysfunction to date. While these studies show long-term improvements in LVEF and clinical HF symptoms following AF ablation, further benefit with regards to heart failure hospitalization and mortality have not been assessed.

AF Ablation in Patients with HF with Preserved Ejection Fraction

The association between AF and HF is not unique to patients with LV systolic dysfunction. The estimated prevalence of AF among patients with heart failure with preserved ejection fraction (HFpEF) ranges from 20–40% [41–42]. The irregular and rapid ventricular rate with short ventricular filling time has been shown to reduce cardiac output and is implicated in the progression of HFpEF [43]. To date, there has only been one study investigating the efficacy of catheter ablation in patients with AF and preserved ejection fraction [44**].

The prospective, single-center study looked at 74 consecutive patients with HFpEF who underwent AF ablation. Antiarrhythmic drugs were discontinued prior to ablation, during which patients underwent pulmonary vein isolation, linear ablation along the LA roof, isolation of the superior vena cava, targeting of CFAEs and linear ablation along the CTI. If sinus rhythm was not restored with this protocol, DC cardioversion was performed.

Patients were followed at regular intervals with 24-hour Holter monitoring to detect AF recurrence. AF recurrence was defined as any atrial tachyarrhythmia >30s after a 3 month post-procedure blanking period. During a mean follow-up period of 34 ± 16 months, the single procedure success rate was 27% and the multiple procedure success rate was 45% off antiarrhythmic drugs. The multiple procedure success rate with antiarrhythmic drugs was 73%. Subgroup analysis showed that more patients with long-standing persistent AF failed to maintain sinus rhythm after ablation. In multivariate analysis, type of AF [HR=1.81 (95% CI 1.03–3.17, P=0.03)] and lack of hypertension [HR=0.49 (95% CI 0.24–0.96, P=0.04)] were the only two independent predictors of maintaining sinus rhythm following AF ablation.

The study also looked at changes in echocardiographic parameters associated with HFpEF. In patients where sinus rhythm was maintained, LVEF significantly increased and E/E' ratio significantly decreased. There was no change from baseline in LVEF or E/E' ratio in the group with AF recurrence after ablation. Changes from baseline in LV strain and strain rate were also noted in the patients where sinus rhythm was maintained.

The success rate of AF ablation off antiarrhythmic drugs in this study of HFpEF patients was quite low [45–46], which may be due to the role of LV diastolic dysfunction in LA remodeling [47]. This is supported by the findings that AF type and absence of hypertension, both of which relate to diastolic dysfunction were independent predictors of procedural success [48]. Thus, long-term maintenance of sinus rhythm in this population may serve to improve HFpEF by improving LV strain, improved LV diastolic function and LA function.

LAA Closure in HF Patients

Several LAA closure or exclusion devices have been developed as an alternative to anticoagulation in patients with AF. They include the WATCHMAN (Boston Scientific, Natick, MA), LARIAT (SentreHeart, Redwood City, CA), Amplatzer Cardiac Plug (St. Jude Medical, Minneapolis, MN), WaveCrest LAA occluder (Coherex Medical, Salt Lake City, UT) and the LAmbré LAA occluder (Lifetech Scientific Corp, Shenzhen, China) [49]. The data regarding the safety and efficacy of these devices are limited. Most of the published literature has focused on the LARIAT and WATCHMAN devices (Figure 1).

The LARIAT device, a percutaneous epicardial suture delivery device with US Food & Drug Administration (FDA) approval, has been used in almost 2,000 patients in the US [50]. There have been no randomized controlled trials investigating the LARIAT device to date. Recent studies evaluating the safety & efficacy of the LARIAT device have reported acute procedural success rates ranging from 93% to 100% [51–52, 53*–54*]. While studies have claimed low adverse event rates, the true safety profile of the LARIAT device has yet to be fully characterized [51–52]. In the largest multicenter retrospective study of 154 patients, where 34% of the study population had a history of HF, the major complication rate was 9.7% [53*]; death, myocardial infarction, or stroke occurred in 4 patients (2.9%). Further subgroup analysis by LVEF or HF status was not made available. In another recent study of 42 patients who received the LARIAT device, where 29% of the study population was noted

to have a history of HF [54*], 20% of patients required pericardiocentesis due to significant pericardial effusions. None of these studies provided data regarding the safety and efficacy of the LARIAT device specifically in patients with HF.

The WATCHMAN LAA occlusion device has been studied in randomized controlled trials [55–56*]. PROTECT-AF (WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) was a multicenter, unblinded trial of 707 patients conducted at 59 hospitals where patients were randomized to a WATCHMAN device or warfarin therapy. The non-inferiority study recently published longer-term results after 3.8 years of follow up [57**]. In this longer-term follow-up, the WATCHMAN device met criteria for both non-inferiority and superiority when compared with warfarin for preventing the combined outcome of stroke, systemic embolism and cardiovascular/unexplained death. The observed event rate in the Watchmen group was 8.4% versus an event rate of 13.9% in the warfarin group [HR=0.61 (95%CI 0.38–0.97, P=0.04)].

The longer-term follow up study found that the WATCHMAN group had fewer hemorrhagic strokes and fewer cardiovascular deaths when compared to the warfarin group. Rates of all stroke and ischemic stroke did not differ between the two groups. More importantly, the study also met criteria for WATCHMAN superiority with regards to cardiovascular mortality [HR=0.40 (95%CI 0.21–0.75, P=0.005)] and all cause mortality [HR=0.66 (95% CI 0.45–0.98, P=0.040)]. In subgroup analysis differentiated by a median LVEF of 60%, the primary efficacy endpoint was consistent for LVEF ≥60% or <60%.

Concerns remain regarding the paucity of current data that exists for LAA closure/exclusion devices in the heart failure population, especially those with significant LV dysfunction. There is evidence that patients with LV dysfunction are predisposed to left atrial as well as LAA thrombi [50]. This calls into question any strategy that promotes LAA closure without long term anticoagulation in those patients with AF and HF.

Conclusion

AF ablation in HF patients with LV systolic dysfunction has been shown to have a complication rate comparable to AF ablation performed in the general population. The overall efficacy is comparable to that seen in non-HF patients; however studies note increased AF recurrences requiring more repeat procedures. When patients are successfully restored to sinus rhythm, the clinical benefits include improvements in LVEF, peak oxygen consumption, quality of life and overall clinical heart failure symptoms. More randomized studies with long-term follow-up are needed to determine if morbidity and mortality are affected by AF ablation in patients with AF and HF. Two pending trials, both due to complete in 2016, RAAFT AF (A Randomized Ablation-based Atrial Fibrillation Rhythm Control Versus Rate Control Trial in Patients with Heart Failure and High Burden Atrial Fibrillation) and CASTLE-AF (Catheter Ablation Versus Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation), will help answer these questions. There is currently insufficient data to determine the safety and efficacy of LAA closure/exclusion procedures in the HF population. Further trials are required to investigate

the safety as well as overall benefit when compared to warfarin and novel oral anticoagulants.

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* of special interest

** of outstanding interest

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Key Points

1. Safety and overall efficacy of AF ablation in HF patients is comparable to AF ablation performed in non-HF patients, although more repeat procedures are required in HF population.
2. Short term and long term evidence of significant clinical benefit of AF ablation in patients with LV systolic dysfunction.
3. Limited evidence for the role of AF ablation in patients with HFpEF.
4. Insufficient data regarding the safety and efficacy of LAA closure in HF patients.

Figure 1. LARIAT & WATCHMAN LAA Closure Devices

A. The LARIAT device enables ligation of the LAA through the deployment of a 40mm pre-tied suture loop using a combined transseptal approach and subxiphoid pericardial access. [49]

B. WATCHMAN device consisting of a self-expanding nitinol frame with a polyethylene terephthalate fabric cap that is positioned and secured within the LAA. [49]

Randomized Control Trials Investigating AF Ablation in HF Patients with LV Systolic Dysfunction

Table 1

Trial	Number of Patients	Inclusion Criteria	Follow-Up Period	Primary Endpoint	Result	P-Value
Khan et al. PABA-CHF [32] [†]	81	Symptomatic HF LVEF <40% Drug-Resistant AF	6 months	MLHFQ 6 Minute Walk LVEF [^]	Score = 60 vs Score = 82 340m vs 297m 35% vs 28% [*]	P<0.001 [^]
MacDonald et al. [33] ^{††}	41	Symptomatic HF LVEF <35%	6 months	LVEF	+4.5% ± 11.1% [AF Ablation] +2.8 ± 6.7% [Rate Control]	P=0.6
Jones et al. ARC-HF Trial [34] ^{††}	52	Symptomatic HF LVEF 35% Persistent AF	12 months	Peak VO2	+3.07 ml/kg/min (95% CI 0.56–5.59) [‡]	P=0.018
Hunter et al. CAMTAF Trial [35] ^{††}	55	Symptomatic HF LVEF <50% Persistent AF	6 months	LVEF	+8.1% (95% CI 3.0%–13.1%) [AF Ablation] –3.6% (95% CI –7.7%–0.5%) [Rate Control]	P<0.001

[†] = Trial of AF ablation versus atrioventricular node ablation with bi-ventricular pacing.

^{††} = Trial of AF ablation versus medical rate control.

MLHFQ = Minnesota Living with Heart Failure Questionnaire (where lower scores are associated with improved quality of life)
Peak VO2 = Peak oxygen consumption

^{*} = Results showing AF ablation versus atrioventricular node ablation with bi-ventricular pacing favoring patients randomized to AF ablation

[^] = Composite primary endpoint

[‡] = Mean difference in peak oxygen consumption favoring patients randomized to AF ablation