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Review Article

Atrial fibrillation with heart failure, Pathophysiology and Management

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Abstract

Atrial fibrillation (AF) and heart failure (HF) are often coexisting, and AF is the most common arrhythmia found in conjunction with HF. Pathophysiologically, these two entities are interlinked. AF in HF presents as a primary cause in the setting of tachycardia-induced cardiomyopathy (TICM) or as secondary AF due to progression of cardiomyopathy. Though earlier clinical trials reported no significant benefit to rhythm control strategy in HF patients, recent data of rhythm control strategy are showing convincing evidence of improved quality of life as well as reduction of cardiovascular death and stroke, particularly if implemented in earlier stages of HF. Over the last decade, there has been significant improvement in ablation techniques, and current data suggest that catheter-ablation is an effective strategy to maintain sinus rhythm in TICM group. However, its efficacy in outcomes of secondary AF in HF patients is still unclear. The majority of AF-ablation trials are of short duration and often require multiple ablations with associated risks to maintain sinus rhythm. Needless to say, AF recurrence is also common after one year of ablation, and a number of patients still require antiarrhythmic drugs (AADs) with their potential side effects. In addition, long-term outcome benefit data of AF ablation in HF patients is still lacking.

Keywords: Atrial fibrillation, heart failure, rate control, rhythm control, ablation.

Introduction

Atrial fibrillation (AF) affects about 1% of the population with a prevalence rate about 25%[1] which increases with age and is associated with higher incidence of heart failure.[2] Though stroke is a known complication of AF, the most common cause of death in AF, in fact, is heart failure (HF), with almost a fourfold increased risk of death compared to stroke.[3] The relationship between AF and HF appears to be complex. Both pathophysiologically and clinically, AF and HF are interlinked and frequently coexist.[4-6] When patients with AF present with HF symptoms, it is often difficult to distinguish whether AF is the primary cause leading to HF or if AF is secondary to long-standing HF. AF-induced HF is primarily diagnosed when improvement of left ventricular (LV) function is documented after HR is controlled.[7] Significant controversies still persist, and therapeutic strategies are still evolving in the management of AF with coexisting HF. Over the last two decades, paradigm has shifted in the treatment of the atrial fibrillation-heart failure (AF-HF) population from rate control to rhythm control strategy with antiarrhythmic drugs (AAD) or AF ablation.

Prevalence of AF and HF

Though likely underestimated, approximately one-third of patients with HF with reduced ejection fraction (HFrEF) will have AF at some point in their disease course.[8, 9] The prevalence of AF is even higher in HF with preserved ejection fraction (HFpEF), seen in up to one-half of patients.[10, 11]

As HF progresses, about 45-50% of patients will develop AF.[12] Patients with HF coexisting with AF have higher mortality and rehospitalization.[13] Results from the Framingham study of patients with newly diagnosed AF, 12% presented with HF, and 16% developed HF after

diagnosis of AF.[14] Results from this study also showed increased mortality when AF and HF coexist. A recently published meta-analysis of 9 major studies showed that patients with AF had almost a fivefold increased risk of HF.[15] Analysis of PARAGON-HF[16] trial also showed that history of AF or flutter in patients with HFpEF was also associated with a significantly higher risk of hospitalization or cardiovascular death.

Pathophysiological relationship of AF and HF

AF can result from high filling pressures, atrial remodeling, and atrial myocardial fibrosis from HF. On the other hand, AF itself can produce severe HF by a mechanism called tachycardia-induced cardiomyopathy (TICM). On presentation, it is often difficult to identify the causal mechanism.

HFrEF and AF

In the setting of LV systolic dysfunction, the hemodynamic and neurohormonal changes induced by HF cause elevated filling pressures with chronic atrial stretch, collagen deposition, atrial myocardial fibrosis, and abnormal subcellular Ca^{2+} handling with disruption of atrial intracellular coupling, which all may predispose atrial fibrillation.[17-19] This kind of atrial remodeling is different from that of electrical remodeling which is seen with rapid heart rate in TICM.[20-23]

Tachycardia induced cardiomyopathy (TICM)

AF-induced TICM (AF-TICM) is a reversible condition upon restoration and maintenance of sinus rhythm.[24,25] It could be overlooked and misdiagnosed as primary HF, which in fact, is caused by AF.[26,27] The diagnosis of TICM is often confirmed after the reversibility of LV systolic function upon restoration of sinus rhythm or controlled heart rate either by electric cardioversion, atrioventricular nodal blockers combined with antiarrhythmic drug (AAD), or by pulmonary vein isolation ablation for AF (AF-ablation).[28] A recent observational study found that 9% of all HF diagnosed as pure TICM were related to AF in 78% of cases and atrial flutter in 15% of cases.[29]

Any persistent tachycardia, like AF or atrial flutter, occurring more than 10-15% of the day may cause TICM.[30] Mechanisms leading to AF-TICM include the following: 1) loss of atrial contraction, 2) irregular heart rate, 3) rapid ventricular rate, 4) worsening of diastolic dysfunction, 5) increase in LV filling pressures, 6) development of functional mitral or tricuspid regurgitation (TR), 7) neurohormonal activation, and 8) structural myocardial changes, including myocardial fibrosis.[31]

It has been shown that irregular ventricular rhythm, independent of heart rate in AF, causes worsening of LV systolic function.[32,33] A beat-to-beat variation causes alteration of Ca^{2+} handling in the myocardium.[34] The shorter cycle lengths affect the sarcoplasmic reticulum Ca^{2+} release more than longer cycle lengths,[35] which compromises myocardial contractility and cardiac output when heart rhythm is irregular.[33]

A reversible rate-related alteration of subcellular Ca^{2+} handling mechanism of LV systolic dysfunction is suggested in TICM.[27] When structural heart disease is already present, the superimposed component of worsening HF due to TICM could still be missed.[36]

AF, right ventricular (RV) failure and TR

AF and RV dysfunction are common in HFpEF. They often coexist and are independently associated with poor prognosis.[37-39] In HFpEF patients with RV dysfunction, the prevalence of AF is much higher (65% to 73%) compared to patients without RV dysfunction (31% to 53%).[40-42] AF may directly contribute to RV dysfunction since cardioversion from AF to sinus rhythm has been shown to improve RV longitudinal contraction.[43]

The TR pressure gradient is also a useful predictor of adverse CV events and all-cause mortality in AF patients.[44] Atrial arrhythmias are associated with atrial remodeling and subsequent mitral regurgitation or TR due to annular dilatation.[45] Presence of TR and RV dysfunction in patients with AF with reduced LVEF

likely indicate that these patients might have had AF for a longer period of time since these changes take time to evolve.

Management Strategies – Rate control vs. Rhythm control

Though earlier treatment strategies were focused on rate control based on trials conducted decades ago,[46-49] recent studies focused on restoration and maintenance of sinus rhythm with AADs or AF ablation. Improved outcomes on death, stroke, progression of HF, AF recurrence, and quality of life as shown by different studies [50,51] have changed the dynamics to rhythm control strategy as a preferred method.[52]

What is the ideal rate control?

Controversy still exists about optimal rate control in AF, lenient (<100 bpm) vs strict (<80 bpm). Analysis of the large dataset from the Get with The Guidelines-HF Program which included 13,981 patients with AF and HF revealed that 9100 (65%) had strict rate control (<80 bpm), 4617 (33%) had lenient rate control (<110 bpm), and 264 (1.9%) had poor rate control as judged by the resting heart rate at discharge.[53] Multivariate analysis of this study clearly showed that lenient rate control compared with strict rate control had higher risk of death (HR 1.21, p<0.001) and all-cause readmission (HR 1.09, p<0.002), irrespective of LVEF.[53] Poor rate control defined as resting HR >80-100 bpm, is fairly common (25-30%) and is associated with adverse heart failure outcomes.[54] Unfortunately, in reality, many more patients would be identified as having poor rate control with continuous monitoring compared to intermittent monitoring.[55]

The results of the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF) showed that optimal ventricular rate control seems to lie around 65 bpm within a range of 60 to 80 bpm, while rates below and above this range may increase mortality risk.[56] With vast evidence of data, recent AF guidelines have adopted a more stricter target heart rate of <80 bpm at rest and <110 bpm during moderate exercise.[57]

Rhythm control

In patients with AF and HF, rhythm control is desirable and can be achieved by cardioversion along with AADs, and by AF-ablation. AADs are widely used to maintain sinus rhythm but have known short- and long-term side effects.[58] The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed that maintaining sinus rhythm could improve survival in AF-HF subgroup of patients.[59] In AF-HF patients, amiodarone and dofetilide are the most widely used AADs. Amiodarone is known to have liver, pulmonary, and thyroid toxicity with long-term use, and dofetilide can cause QT prolongation and ventricular arrythmia. Though AF burden was reduced by these AADs, mortality benefit was not achieved in major trials.[60,61]

Catheter-based pulmonary vein isolation, i.e., AF-ablation offers an appealing alternate way to restore sinus rhythm. Recently, a number of prospective, retrospective, and randomized control trials (RCTs) in patients with AF and HF have shown significant improvement of LV function and clinical symptoms post ablation,[62-67] and in some cases even normalization of LVEF.[6,68] AF-ablation has been very successful in a subgroup of patients presenting with cardiogenic shock secondary to TICM with significant improvement of clinical condition and LVEF.[69] Multiple RCTs have shown improved outcomes in AF-HF patients with AF-ablation when compared to medical therapy.[63,65-67,70] Recently, Romero et al.[71] published a large meta-analysis of eight RCTs showing a 35% relative risk reduction and 4.7% absolute risk reduction in all-cause mortality in the AF-ablation group compared to medical therapy in patients with HF. In this analysis, the AF-ablation group achieved significant improvement of LVEF (9+8%, vs. 3+8%), reduction in AF burden, and improvement in quality of life compared to medical therapy in HF patients. Ideal patient selection strategy for AF ablation in AF and HF patients is still evolving. AF-ablation outcomes in HF may vary considerably depending on types of HF (HFrEF or HFpEF), NYHA class, etiology of cardiomyopathy, and type of AF burden.

A recent study showed that patients with HFrEF and AF had a threefold increased risk in all-cause-mortality, HF hospitalization, and stroke or systemic embolization post AF ablation compared to patients with HFpEF.[72] The best candidates for ablation appears to be those in whom AF has preceded the development of HF and when AF-induced TICM is highly suspected.[36] According to prior studies, advanced HF, ischemic or other structural etiology of HF, significant LA and LV fibrosis as evidenced by LGE (late gadolinium enhancement), high AF burden (>50%), and late timing were considered as unfavorable factors to AF-ablation outcomes.[73] However, the recently published Catheter Ablation versus Standard Conventional Therapy in Patients with LV Dysfunction and AF (CASTLE-AF) trial showed that AF-ablation for patients with HF including all NYHA classes (II-IV), LVEF <35%, and an implanted cardioverter defibrillator, resulted in a significantly lower rate of all-cause mortality or hospitalization for HF exacerbation compared to medical therapy for rate or rhythm control.[63] A recently published meta-analysis also showed that in patients with AF and HFrEF, AF-ablation significantly improved LVEF (6.8%; $p<0.001$) and reduced all-cause mortality (OR 0.49; $p = 0.002$).[74]

Recently, the focus has shifted to earlier intervention for AF ablation in patients with HF. The EAST-AFNET4 (Early Treatment of Atrial Fibrillation for Stroke Prevention)[75] trial showed that early rhythm control improves cardiovascular outcomes by 21% compared to usual care. Recently, ESC guidelines also advised AF ablation as a class I recommendation for patients with AF and HFrEF.[57] Based on the current data, it is becoming clearer that restoration and maintenance of sinus rhythm in HF patients are essential, and the earlier the intervention, the better; ablation is becoming an effective alternative tool in that arsenal.

Recurrence of AF post ablation

A long-term ten-year follow up study by Gaita et al.[76] of AF-ablation patients reported 52% were arrhythmia-free during that time period. Multiple ablation procedures were needed in the vast majority of patients with a success rate up to 61% in paroxysmal AF and 44% in persistent AF. These long-term ten-year success rates are in agreement with five-year success rates reported in earlier studies.[77,78] More than two-thirds of AF recurrence happens in the first year of single or multiple ablations.[79,80] The mechanisms of AF recurrence are unclear, but acute thermal injury, inflammatory response caused by ablation, recovery of electrical connectivity between the pulmonary vein and left atrium, as well as new foci outside the pulmonary vein are all considered to be potential triggering factors for recurrence.

As seen in these studies, almost half of the patients will have recurrence of AF, and a substantial number of patients will require AADs to maintain their rhythm despite being ablated. With these facts in mind, long-term outcome benefits of AF-ablation in HF patients are yet to be determined.

AV Junction (AVJ) ablation

AVJ ablation is often required to control refractory AF. It is more beneficial in HF patients with uncontrolled heart rate despite being on multiple AV nodal blockers, AADs, and failed AF-ablation. Some studies have shown improved clinical and functional outcomes in patients with AF and HF with cardiac resynchronization therapy (CRT),[81-88] while other studies have reported better outcomes with CRT in patients with AF only after atrioventricular junction (AVJ) ablation with effective biventricular (Bi-V) pacing.[89-93] A large meta-analysis by Mustafa et al.[94] studying the impact of CRT in patients with AF and HF showed that AVJ ablation tends to improve all-cause mortality in CRT patients with AF, and there is no difference in all-cause mortality compared to CRT patients in SR. In addition, if CRT is indicated in AF-HF patients, AVJ ablation plus CRT has been shown to be superior to pharmacological therapy in reducing HF hospitalization and mortality in HF patients with permanent AF, irrespective of their baseline LVEF.[95,96] AF was associated with an increased likelihood of lack of response to CRT.[97] Hence, AVJ ablation appears to improve the benefits of CRT in patients with AF.[36]

Conclusion

Whether AF is primary or secondary to HF, it is well known that AF is poorly tolerated by HF patients and is often a precipitating cause of decompensation.

Data from last two decades suggest that patients with AF and HF benefit from rhythm control strategy, and this treatment option should be adopted as early as possible before progression to more advanced stages of HF. AF-TICM is the most prevalent type of a reversible arrhythmia-induced cardiomyopathy. Rhythm control strategy, if feasible, by ablation, should be quickly pursued as AF-TICM might be missed, until proven otherwise. The benefit of AF-ablation in patients with severely reduced LVEF and NYHA class IV has not been clearly established. Large RCTs are still needed to determine which patient population would derive the greatest benefit from AF ablation. Though significant progress has been made over the years in mapping and ablation techniques, most of the recent trials favoring AF-ablation to restore and maintain sinus rhythm are of shorter duration, only for few years, and long-term data are still pending. Atrial flutter ablation is highly successful, but idea of curing AF still appears to be elusive. However, improvement of symptoms and modification of stroke risk and mortality are reasonable targets for AF-ablation, particularly in AF-HF patients if implemented early.

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Declarations

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by the author.

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