

The mutual relationship between heart failure and atrial fibrillation

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Abstract

Atrial fibrillation (AF) and Heart Failure (HF) are evolving epidemics, together responsible for substantial human suffering and health-care expenditure. The simultaneous co-existence of the two conditions is associated with higher mortality rates than those observed in individuals with only one or none of them. Patients with concomitant HF and AF suffer from even worse symptoms and poorer prognosis, yet evidence-based evaluation and management of this group of patients is lacking.

In this review, we evaluate the common mechanisms for the development of AF in HF patients and vice versa, focusing on the evidence for potential treatment strategies. Recent data have suggested that these patients may respond differently if compared to those with HF or AF alone. These results highlight the clear clinical need to identify and treat these diseases according to best evidence, in order to prevent adverse outcomes and reduce the huge burden

that HF and AF are expected to have on global healthcare systems in the future.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in general population with higher prevalence in developed countries, in older patients and patients with different co-morbidities such as heart failure (HF) [1,2]. HF prevalence is approximately 1-2% of the adult population in developed countries, rising over 10% in people >70 years old [3].

Both AF and HF are growing problems, and the number of individuals who suffer from the two conditions concurrently is expanding as well. These conditions share common risk factors, and each has a propensity to cause the other [4]. Large HF trials have revealed that the likelihood of AF increases with the severity of HF [5], ranging from 10% in HF with NYHA class I to class II symptoms to 50% in HF with NYHA class IV symptoms.

EORP-AF registry has shown 47.5% of HF with reduced or preserved ejection fraction (HFrEF or HFpEF) in a large European cohort of AF patients [6]. Similarly, large AF trials record high HF prevalence rates, ranging from 21% to 68% [7].

Furthermore, AF is the most common arrhythmia in HFpEF, with a prevalence of 20% to 40% at the time of presentation [8]. It occurs in two-thirds of patients at some point during the course of HFpEF [9]. Patients with HFpEF are more likely to have prevalent AF or AF at any time compared with those with heart failure and reduced ejection fraction [9]. Right ventricular (RV) dysfunction and AF are common in patients with HFpEF; they often coexist and are independently associated with a poor prognosis [10].

Recent studies have indicated a potential relationship between AF and RV dysfunction in HFpEF [11,12]. For example, the prevalence of AF in patients without RV dysfunction ranges from 31% to 53%, while it soars to 6%-73% in HFpEF patients with RV dysfunction [11-13]. Mitral regurgitation (MR) is one of the most common valvular disorders and it is the most common regurgitant disorder in patients with HFrEF and a known risk factor for AF [14].

However, the prevalence and pathophysiology of MR among patients with AF remains unexplored.

Pathophysiology

As highlighted by the epidemiological data, AF and HF tend to share the same population, risk factors and each one can cause

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the development of the other one. The reason of this relationship is explained by the pathophysiology of the two conditions: in fact, each disease condition induces structural, neuro-hormonal, and inflammatory changes that can predispose a patient to the other disease. The acute hemodynamic effects of AF are predominantly loss of atrial systole, which can further reduce cardiac index and acutely decompensate HF.

AF and left atrial function

Loss of reservoir, conduit and booster function of the left atrium (LA) is likely a consequence of the atrial fibrosis secondary to the increased wall stress, the inflammatory cytokines and the circulating neuro-hormonal factors seen in both HFrEF and HFpEF [15,16].

In HF patients, loss of “atrial kick,” changes in LA mechanics, loss of reservoir, conduit, and booster functions may impact on patient functional status as well as adversely affecting outcomes. Loss of atrial systole decreases cardiac output by up to 25% and this plays a significant role, particularly in diastolic dysfunction [17,18].

High ventricular rate and AF-induced heart rate variability

The high ventricular rate in AF reduces the filling time and the end diastolic volume determining a reduction in stroke volume; moreover, the irregularity of cardiac cycles alters the normal filling and emptying timing, contributing to ventricular remodeling and to impairing systolic function [15].

The reduction in stroke volume and the heart rate variability also induce an increase in neuro-humoral activation, with an incremented concentration of cardiovascular markers, for example high-sensitivity troponin T (hsTnT) or N-terminal pro-brain natriuretic peptide (NT-proBNP), that play a prognostic role especially in patients with HF [19,20].

AF and renin-angiotensin-aldosterone system

Upregulation of the renin-angiotensin-aldosterone system (RAAS) axis is thought to promote atrial fibrosis. In particular, Angiotensin II has been shown to stimulate cardiac fibroblast proliferation. This acts synergistically with oxidative stress and cytokines such as interleukin-6 and tumor necrosis factor (TNF) to induce fibrosis.

There can be seen the existence of an imbalance of the RAAS axis with LV dysfunction that promotes physiological maladaptation, increasing filling pressures and afterload. Stretching of the myocardium results in fibrosis and conduction abnormalities [21,22].

AF and arrhythmia-induced cardiomyopathy

Persistent AF can lead to arrhythmia-induced cardiomyopathy (AIC), which is a condition characterized by a dilated cardiomyopathy (increased LV end-diastolic dimension and area) with moderate to severe biventricular systolic dysfunction, normal LV septal and posterior wall thickness (lack of hypertrophy). Mitral insufficiency may be present due to LV and mitral annular dilatation with lack of leaflet coaptation.

The risk of developing AIC depends not only on the type, but also on the duration and rate of tachycardia. It should be suspected in patients with mean heart rate >100 beats/min, atrial fibrillation, and/or premature ventricular contractions burden $\geq 10\%$ [23].

The process is mediated by changes in cellular and neuro-hormonal factors and extracellular remodeling as well. Resting tachycardia, increased HR with exercise, and irregularities in ventricular rhythm result in alterations of myocardial gene and protein expression, calcium handling, and increased sympathetic discharge with

detrimental effects on ventricular function [15,17,18,23]. Recovery of ejection fraction (EF) after cardioversion or rate control confirms AIC.

In the same way enalapril has demonstrated to reduce atrial inflammation, fibrosis, remodeling and mean duration of AF in a similar population [24,25]. Furthermore, atrial scarring and reduced electrical activity can also derive from mechanical stretch of atrial wall, as observed in human patients comparing data from electro-anatomical mapping and CT scan [26].

AF and mitral regurgitation

MR is classified as primary (organic), when the mitral leaflets or the subvalvular apparatus are structurally abnormal causing leaflet malcoaptation, or secondary (functional) when the leaflets and subvalvular apparatus are normal and leaflet malcoaptation is caused by global or regional left ventricular (LV) remodeling that displace the papillary muscles, tethering the mitral leaflets, or by reduction of LV closing forces.

AF is a common sequela of degenerative mitral regurgitation (DMR) and it can lead to progressive left ventricular failure if untreated [27]. DMR may lead to the development of AF via left atrial (LA) volume and pressure overload, progressive atrial fibrosis, LA enlargement, and electroanatomic remodeling [2,27].

Progressive LA enlargement and remodeling – hallmarks of long-standing DMR – promote AF substrate by affecting cell coupling, altering conduction velocity, and promoting reentry [27].

Prognosis

The prognostic implications of AF development in HF is still a controversial subject. Older trials, such as the Vasodilator-Heart Failure Trial (V-HeFT), reported no difference in mortality between patients with mild-to-moderate HF in sinus rhythm (SR) or with the development of AF [28-30].

Retrospective analysis of the data from the Studies of Left Ventricular Dysfunction (SOLVD) trial looking at the association between AF and mortality showed that patients with LV dysfunction and AF at baseline had higher all-cause mortality and death from pump failure. The risk of arrhythmic death was comparable among patients with SR vs AF. Compared to SR, patients with AF were older, more likely to be NYHA functional class III-IV and with a lower mean left ventricular ejection fraction (LVEF) [31].

Similarly, results from the large randomized controlled trial of Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) indicated that baseline AF in patients with symptomatic HF conferred increased morbidity and mortality irrespective of ejection fraction (EF). Furthermore, the development of new-onset AF resulted in increased absolute risk for adverse cardiovascular outcomes in patients with HFrEF and greater relative risk of cardiovascular death and HF hospitalization in those with preserved LV function [32].

An analysis of patients enrolled in the Valsartan in Acute Myocardial Infarction (VALIANT) trial [33] revealed a high mortality rate in patients who developed AF with post-MI cardiac dysfunction. The authors reported occurrence of AF in the peri-infarct period with LV dysfunction ranges from 5%–21% and underlined how these patients tend to have higher mortality and stroke rates, both in-hospital and following discharge. However, limited data are available about a rate or rhythm control strategy in the peri-infarct period as a possible influence factor in-hospital and long-term outcomes [33-35].

A contemporary diagnosis of HF impairs the prognosis of AF patients: in EURObservational Research Programme Pilot survey on atrial fibrillation (EORP-AF Pilot) the thrombo-embolic risk at 1 year was 4% in AF-only patients vs 13.4% in AF with HF patients with non-significant differences between HFrEF vs. HFpEF. In the same way, mortality at 1 year was 3% in AF-only patients vs 10.7% in AF with HF patients, without significant difference between HFrEF and HFpEF [6].

From another prospective, AF predicts a poorer prognosis in HF patients: in a contemporary population of HFrEF from PARADIGM-HF and ATMOSPHERE, 35.6% had history of AF. The risk of primary endpoint (a composite of cardiovascular death, HF hospitalization, all-cause mortality and stroke) was higher in patients with paroxysmal AF than in patients without AF, due to an increased risk of HF hospitalization and stroke.

Furthermore, patients who developed new-onset AF were older, mostly male and were at higher overall risk of cardiovascular mortality and HF hospitalization [35]. Interestingly, the risk of HF hospitalization was not so high in patients with persistent/permanent AF, probably according to the fact that AF paroxysms represent a marker of HF instability or that patients with persistent/permanent AF receive more treatments to control the ventricular rate [35].

Dysfunctions of both ventricles often coexist in CHF patients. LV failure can lead to right ventricular (RV) dysfunction. Ventricular interdependence implies the fact that dysfunctions of both ventricles frequently coexist. Many studies showed that in patients with advanced CHF and LVEF <40% prognosis strongly depends on RV function. RV function influenced the total outcome in these patients more significantly than LV function [36,37].

In patients with AF, LV diastolic function is often worse and may result in deterioration of RV function [38]. In fact, RV function is determined by the heart rhythm, RV filling time, RV systolic synchrony and interdependence between both ventricles. Maintenance of sinus rhythm and atrio-ventricular synchrony is crucial for RV function especially in chronic and acute RV failure. In patients with HFpEF, RV and RA function are more depressed in AF than in sinus rhythm patients. This association was independent from afterload. Moreover, patients in sinus rhythm who had earlier AF also displayed more RV and RA dysfunction than patients without any history of AF. Furthermore, reduced RA function was strongly and independently related to RV dysfunction in HFpEF [12].

Treatment

AF management includes two different aspects: prevention of stroke with anticoagulation therapy and management of cardiac rhythm or ventricular rate.

Anticoagulation therapy

Considering the high risk of stroke in AF population, anticoagulation represents a cornerstone of therapy especially in patients with HF: HF, in fact, increases the risk of stroke in AF, both HFrEF and HFpEF (but the former more than the latter) [39] and it is considered in the CHA₂DS₂-VASc score.

As already seen, Mogensen *et al.* [36] found a higher risk of stroke in patients with paroxysmal AF and less use of anticoagulation despite as high CHA₂DS₂-VASc score versus persistent/permanent AF patients. This observation highlights the importance of adequate anticoagulation in patients with HF and paroxysmal AF.

Rhythm control versus rate control strategy in AF

According to data on prognostic impact of AF in HF, a rhythm control strategy seems intuitively preferable. However, data from the AFFIRM trial [40] demonstrates no difference in survival while using a rhythm control strategy versus a rate control strategy in a non-selected AF population (with appropriate anticoagulation).

Interestingly, neither a better quality of life can be reached using a rhythm control strategy instead of the rate control one [41].

Furthermore, the AF-CHF trial confirms these findings in a selected population with left ventricle systolic dysfunction (EF <35%) [42]. Therefore, we can consider both strategies when we approach a patient with concomitant AF and HF.

Concerning rhythm control strategy, many antiarrhythmic drugs with a good efficacy and low side effects are contraindicated in the setting of HF, but amiodarone can be safely used in these patients to restore sinus rhythm [43]. It can also reduce ventricular rate by 10-12 bpm after 8-12 h [44]. Dofetilide could have the indication for this purpose as well, but it is not available in Europe.

Another strategy to restore acutely sinus rhythm is electrical cardioversion, which is the method of choice in severely hemodynamically compromised patients with paroxysm or new onset AF in order to restore sinus rhythm [1].

Concerning rate control strategy, we have more options for pharmacological therapy. Beta-blockers are standard of care in HFrEF regardless of heart rhythm, for their known effects on reducing mortality and HF hospitalization. In the AF-CHF trials the use of beta-blockers resulted associated with a significant reduction in over-all mortality and cardiovascular mortality [45]. However, in a meta-analysis of 13 studies, the effects of beta-blockers in AF and HFrEF patients was neutral on mortality and cardiovascular mortality [46]. Although this equivocal findings, beta-blockers still remain the first line therapy for rate control as indicated in European guidelines [1]. Non-dihydropyridine calcium channel blockers should be avoided in HFrEF because of their negative inotropic effect [47] but they could be used in HFpEF. Like beta-blockers, digoxin has a role in HFrEF in patients in sinus rhythm [48] but its use in AF is not supported by strong evidence. Moreover, according to the lack of strong evidence and its narrow therapeutic window, digoxin is still used and indicated by European Guidelines but the dosage has to be conservative and followed by plasma levels, especially in elderly and in patients with renal dysfunction [49].

Recent data from an open-label randomized trial of AF ablation in HFrEF patients with EF <35% showed that patients who were assigned to ablation had a reduced incidence of death or HF admissions with a rising trend in EF level post-ablation [50].

The benefit was seen with a decrease in the burden of AF from 60% of time with medical therapy to 25% with ablation, suggesting that a reduction in the amount of time in AF may be sufficient for clinical benefit.

Mitral valve intervention

Mitral valve intervention is indicated for symptomatic severe valvular disease (typically breathlessness and fatigue). It is also indicated for asymptomatic severe valvular disease with evidence of detrimental pathophysiological changes, such as left ventricular systolic dysfunction, pulmonary hypertension, or atrial fibrillation in asymptomatic severe mitral regurgitation. Percutaneous mitral commissurotomy (PMC) is indicated for severe mitral stenosis with favorable anatomical characteristics.

Mitral valve repair is preferred over valve replacement when feasible. Cases for the intervention should be discussed by a Heart

Valve Team in order to recommend the best approach, e.g., PMC, full sternotomy or minimal access valve surgery, or newer less invasive techniques as these become established [51].

Management of concomitant heart failure and reduced ejection fraction and atrial fibrillation

Activation of neurohormonal pathways and RAAS are well described in HF, and the majority of evidence-based therapies target these compensatory mechanisms [52,53]. Angiotensin converting enzyme inhibitors (ACEi) have proven efficacy in HFrEF for significant reduction in mortality, sudden cardiac death, and HF hospitalization, but no trials have examined their benefit in concomitant AF.

Angiotensin receptor blockers (ARBs) are recommended as alternatives to ACEi in cases of intolerance, and there are numerous trials supporting their use in HFrEF [52].

In CHARM, randomization to candesartan significantly reduced CV death or HF hospitalization in HFrEF patients with concomitant AF, similar to that observed in patients without AF at baseline [32].

In contrast, Irbesartan did not reduce the composite outcome of hospitalization due to HF, stroke, myocardial infarction, or death from vascular causes in AF patients enrolled in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events A or W trials [53].

Physical activity and exercise training

Physical activity and exercise training improve symptoms and they can have antiarrhythmic effects in individuals with paroxysmal AF and may be protective against the development of AF [54].

In patients with chronic heart failure with HFrEF, as shown in the “Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study”, exercise training is associated with improved exercise capacity, improved quality of life, and reduced all-cause mortality and hospitalization [54].

Conclusions

AF and HF are increasing in general population and we will find them in the same patient more frequently, especially in elderly. Both conditions together affect the prognosis of patients and complicate the pharmacological management [55].

Despite the possibility of evidence-based therapy for HFrEF, beta-blockers and digoxin probably lose their prognostic effects in AF. However, an adequate therapy is required: it is almost mandatory to have anticoagulation (regarding score risks) also in paroxysmal AF and to reach rate or rhythm control especially in AIC patients who can recover from the ventricular dysfunction.

Exercise training reduced all-cause mortality, hospitalizations, and improve health status in HFrEF patients and permanent AF [54].

Further research is still required to improve treatment of HFpEF and to understand better its relationship with AF.

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