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Atrial fibrillation in heart failure with preserved ejection fraction: Insights into mechanisms and therapeutics

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) often coexist, and the outcomes of patients who have both AF and HF are considerably worse than those with either condition in isolation. Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical entity and accounts for approximately one-half of current HF. At least one-third of patients with HFpEF are burdened by comorbid AF. The current understanding of the relationship between AF and HFpEF is limited, but the clinical implications are potentially important. In this review, we explore 1) the pathogenesis that drives AF and HFpEF to coexist; 2) pharmacologic therapies that may attenuate the impact of AF in HFpEF; and 3) future directions in the management of this complex syndrome.

Contents

1. Introduction

Atrial fibrillation (AF) and heart failure (HF) are currently the two most prominent cardiovascular epidemics in the developed world (McCullough, et al., 2002; Miyasaka et al., 2006). Due to advances in various aspects of cardiovascular medicine, including effective treatment of acute coronary syndrome and coronary artery disease (CAD), coupled with an aging global population, we have witnessed a rising prevalence of both AF and HF. Worldwide, over 30 million individuals currently suffer from AF, and the incidence of AF is expected to double

Abbreviations: AAD, anti-arrhythmic drug; AF-HFpEF, atrial fibrillation — heart failure with preserved ejection fraction; AVN, atrio-ventricular node; CAD, coronary artery disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LV, left ventricular; NADPH, nicotinamide adenine dinucleotide phosphate; NOAC, non-vitamin K oral anticoagulant; PUFA, omega-3 polyunsaturated fatty acid; RAAS, renin-angiotensin-aldosterone system; TMC, tachycardia-mediated cardiomyopathy.

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by 2030 (Chugh et al., 2014). Similarly, it is estimated that there are over 25 million HF patients worldwide (Ambrosy et al., 2014). Furthermore, the healthcare cost of each of these disease states in the US alone is over $20 billion and is only expected to increase (M. H. Kim et al., 2011).

Comorbid AF and HF (AF-HF) is common, not only due to the high prevalence of each disease entity, but also secondary to synergistic pathophysiology and shared risk factors (van Deursen et al., 2014). Indeed, AF serves as both a risk factor for and consequence of HF, and AF-HF is associated with worse outcomes than either disease entity in isolation (Stewart et al., 2002; T. J. Wang et al., 2003; Mamas et al., 2009). The majority of our current understanding of AF-HF stems from the relationship between AF and heart failure with reduced ejection fraction (AF-HFrEF). However, heart failure with preserved ejection fraction (HFpEF) accounts for up to half of prevalent HF in contemporary series, and may be more closely related to AF than HFrEF (Vaduganathan et al., 2016). In a recent review of HFpEF trials and registries, comorbid AF was present in one-third of patients (Campbell & McMurray, 2014). In the Framingham Heart Study, over 30% of patients with incident HFpEF had prevalent AF, and the presence of AF was more strongly linked to incident HFpEF than HFrEF (Santhanakrishnan et al., 2016). Overall, 62% of patients with HFpEF had AF at any time, which was significantly higher than the HFrEF cohort in the Framingham cohort (Santhanakrishnan et al., 2016). Indeed, in a separate epidemiological study from Olmstead County, AF was also present in two-thirds of HFpEF patients (Zakeri, Chamberlain, Roger, & Redfield, 2013). With regard to prognosis, AF-HFpEF patients are at an 80% increased risk of mortality compared to patients without either condition (Santhanakrishnan et al., 2016). Given the clinical implications of AF-HFpEF and the complex interplay between these two disease states, there is an increasing need to better define the clinical landscape of this syndrome. In this review, we aim to (1) examine the pathophysiologic mechanisms that drive AF in HFpEF and vice versa, (2) review the available therapies for AF-HFpEF, and (3) explore potential targets for therapy based on the pathophysiologic basis of the AF-HFpEF syndrome.

2. Pathophysiology of heart failure with preserved ejection fraction driving atrial fibrillation

AF and HFpEF possess several common risk factors, including diabetes, obstructive sleep apnea, smoking, CAD, hypertension, and obesity (Ling et al., 2016). Independent of their shared risk factors, however, there appear to be several mechanisms which drive HFpEF patients to develop AF (See Fig. 1) (Kotecha & Piccini, 2015). It is important to note that much of the current understanding of mechanisms behind AF in patients with HFpEF has largely been derived from experimental models of HFrEF. There is currently a need for additional experimental animal models of HFpEF, which may further elucidate the mechanism of AF specific to the HFpEF population.

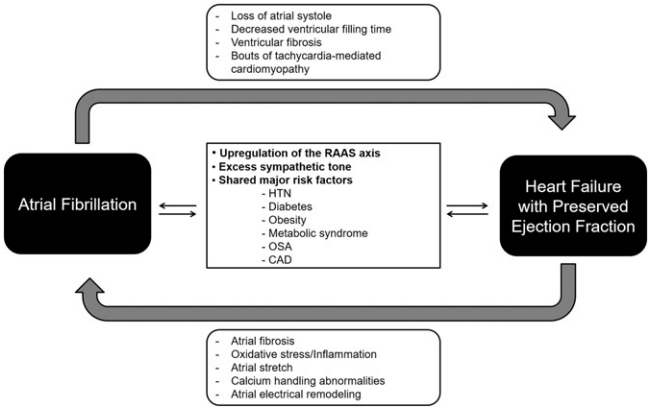

Fig. 1. Mechanistic "cross-talk" between atrial fibrillation and heart failure with preserved ejection fraction. Abbreviations: CAD = coronary artery disease; HTN = hypertension; OSA = obstructive sleep apnea; RAAS = renin-angiotensin-aldosterone system.

2.1. Atrial fibrosis

Atrial fibrosis appears to be a final common step by which HFpEF promotes AF, which ultimately creates heterogeneity of conduction within the atria and thus substrate for reentry (Frustaci et al., 1997; Li et al., 1999; Hanna et al., 2004). The mechanisms by which HFpEF induces atrial fibrosis are multiple, and include renin-angiotensin-aldosterone system (RAAS) activation (Li et al., 2001; Schneider et al., 2010), oxidative stress (Van Wagoner, 2008), inflammatory cascades (Chung et al., 2001; Friedrichs et al., 2011), and mechanical atrial stretch due to pressure and volume overload (Hunter et al., 2012).

HFpEF is potentiated by upregulation of the RAAS axis, a maladaptive neurohormonal state. Angiotensin II has been shown to promote atrial fibrosis through stimulation of cardiac fibroblasts (Li et al., 2001). Angiotensin II appears to activate a specific mitogen-activated protein kinase, known as extracellular signal-related protein kinase, which subsequently results in stimulation of fibroblast proliferation (Pages et al., 1993; Zou et al., 1998; Li et al., 2001). The role of RAAS in fibrosis was confirmed in a study in which dogs with HF were treated with enalapril, which resulted in significantly less atrial fibrosis, heterogeneity in atrial conduction, and burden of AF (Li et al., 2001).

In addition to activation of RAAS, HFpEF is a pro-inflammatory state, which is also a crucial initiator of atrial fibrosis. The activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is increased in HF and appears to be a mediator of inflammation and source of cardiomyocyte superoxide generation (Murdoch et al., 2006; Y. M. Kim et al., 2008; Van Wagoner, 2008). The creation of oxidative species by NADPH oxidase contributes to atrial fibrosis through the activation of matrix metalloprotease enzymes (Chen et al., 2008; Barnes & Gorin, 2011). Alternative inflammatory pathways including secretion of interleukin-6 and tumor necrosis factor-α from neutrophils enhance atrial collagen deposition and matrix metalloprotease activity (Saba et al., 2005). Once atrial fibrosis promotes AF, rapid atrial rates further enhance atrial fibrosis, and thus AF itself potentiates the cycle of fibrosis. Rapid atrial rates stimulate increased nitric oxide synthase, which results in the production of reactive oxidative species and activation of matrix metalloprotease enzymes, both of which in turn may contribute to atrial fibrosis (Friedrichs et al., 2011).

It is well recognized that HFpEF results in increased left ventricular (LV) diastolic pressure, which ultimately promotes left atrial (LA) wall stress. Heterogeneous areas of atrial fibrosis may be secondary to differences in regional LA wall stress. LA scarring on computed tomography imaging has been noted to be highest in areas of peak wall stress (Hunter et al., 2012). These islands of fibrosis may in turn serve as foci for reentry.

2.2. Calcium handling

Experimental models of HF have also implicated abnormalities in calcium handling within the atrial myocyte as important mediators of AF. In dogs with HF, calcium was noted to be overloaded within the sarcoplasmic reticulum (Yeh et al., 2008), which has been associated with increased ectopic triggered activity of atrial myocytes. This process appears to be mediated by prolonged atrial action potential durations, which increase intracellular calcium and reduce inhibition of the sarcoplasmic reticulum calcium-ATPase pump (Yeh et al., 2008). Dysregulation in calcium handling of the failing heart has been proposed as a mechanism for abnormalities in repolarization as well, manifested by variation in action potential duration (Stambler et al., 2003). Action potential duration variability has been associated with AF in patients without clinical HF (Wijffels et al., 1995; Narayan et al., 2011).