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Relationship between atrial fibrillation and heart failure

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Abstract. – Heart failure (HF) and atrial fibrillation (AF) are major health issues and often co-exist. HF and AF also share common mechanisms, as well as therapies and treatment strategies. The relationship between AF and HF has not been clarified and, therefore, remains an area of research interest. The choice of optimal treatment is a challenge for AF and HF. Control of rate or rhythm is the most important decision for physicians. New tactics for budgeting and centralized monitoring may have an exciting effect on stroke occurrence. Because it is predicted that AF or HF would markedly increase in the next two decades worldwide, a significant burden on the health care systems in multiple countries will occur. It remains imperative that further research about the epidemiology, mechanism, detection, and treatment of AF and HF is urgently promoted. In this paper, we review the recent progress on the relationship between HF and AF.

Key Words:
Atrial fibrillation, Coronary artery disease, Heart failure, Left ventricular, Treatment.

Introduction

Atrial fibrillation (AF) and heart failure (HF) are currently two "epidemics" of cardiovascular disease[1]. Both AF and HF are associated with significant morbidity and mortality and have a poor prognosis[2]. AF and HF have similar risk factors and share the same pathophysiologic mechanisms. Thus, patients with AF or HF present a particular therapeutic challenge for clinicians.

AF is the most common heart disorder, with an overall prevalence of 1%. The occurrence of AF has increased year-by-year. It has been predicted that the current prevalence of AF will double by 2050[3,4]. The Framingham Heart Study suggested that age and gender are risk factors for AF, which further indicates that the risk of AF is enhanced by the presence of rheumatic heart disease, particularly in women[5]. Nevertheless, Zhou[6] reported that the age-standardized prevalence of AF in the Chinese population is 6.5 per 1000 people. It is estimated that at least 4 million adults have AF in the mainland of China and AF is a serious public health problem.

HF affects 2%-3% of the population in developed countries[3], resulting in 12-15 million office visits and 6.5 million hospital days yearly, and is the most common cause of hospitalization[6]. The 5-year mortality is approximately 50%, which is even worse than that of many cancers[7]. Among Medicare patients, the 30-day mortality is 10%-12%[8]and the 30-day readmission rate after hospital discharge is 20%-25%[9].

Relationship between AF and HF

An analysis that included > 30,000 HF patients showed that patients with AF have a 33% increase in mortality[10]. AF and HF often co-exist, and increases in morbidity and mortality are associated with both clinical entities[11,12]. A number of studies have suggested that the presence of AF is associated with increased hospitalization, hospital stay, and mortality in HF patients. Several studies[11-20] have shown that 10%-50% of AF patients with HF have increased morbidity and mortality, partly depending on the age and the severity of HF. Although the causative relationship between AF and HF has not been fully determined, the co-existence may be explained by co-existing risk factors, including hypertension, obesity, diabetes, ischemia, and non-ischemic structural heart disease. Such risk factors are associated with myocardial extracellular alterations and electrophysiologic and neurohormonal changes which predispose the heart to HF and AF[21]. Thus, a worsening prognosis is common in patients with AF and HF.

AF and HF: a Cause or Consequence?

The relationship between AF and HF can partially be explained as follows. AF can facilitate the development and progression of HF. AF can interfere with the pump function of the heart or accommodate the blood, increase the resting heart

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rate, and result in an exaggerated heart rate with a shortened left ventricular (LV) filling time[22], which further leads to reduced cardiac output. The reduction of the LV filling during short cycles is not completely compensated. Also, the loss of effective atrial contractile function is also important in patients with diastolic dysfunction[23], together with the concomitant loss of the effective atrial contraction. In addition, a sustained rapid heart rate can impair systolic function by reducing myocardial contractility[24].

AF can also exacerbate HF symptoms in patients with arrhythmia secondary to other diseases, such as rheumatic valvular heart disease and congenital heart disease. Elevation of atrial pressure is a promoter of AF. In HF patients, the atrial stretch induced by volume overload largely contributes to AF pathophysiology[25]. Atrial stretch results in activation of stretch-activated ionic currents. The neurohormonal activation promotes structural remodeling and atrial fibrosis, thus altering atrial conduction properties and promoting AF[26,27]. Activation of the renin-angiotensin-aldosterone system can enhance downstream pathways of signal transduction, such as mitogen-activated protein kinase (MAPK)[28-30], Janus kinase (JAK)/signal transducers and activators of transcription30, and transforming growth factor-β1[31,32]. Activation of angiotensin II type 1 receptors can activate a family of MAPKs that promote atrial hypertrophy, fibrosis, and apoptosis, which remodels the structure of this heart chamber[33]. Gadolinium, an inhibitor of stretch-activated currents, can reduce the susceptibility to AF in response to atrial pressure overload[34].

Dysregulation of intracellular calcium is an important feature in the pathophysiology of HF. Sarcoplasmic reticulum Ca2+-ATPase and ryanodine receptor are the key regulators of intracellular calcium metabolism and are down-regulated in AF[35,36]. Calcium overload of atrial myocytes occurs early and results in changes of gene expression that down-regulate L-type calcium, which leads to a shortened atrial refractory period to compensate for the calcium overload and promote re-entry37. After depolarization, the sarcoplasmic calcium is recaptured to the sarcoplasmic reticulum through calcium ATPase (SERCA2a), which decreases, leading to high cytosolic and low sarcoplasmic reticulum calcium concentrations in HF38. Persistent and paroxysmal AF is associated with profound impairment in calcium metabolism[39-41].

HF is also characterized by neurohormonal activation, which is important in AF, with increased levels of catecholamine and angiotensin II. The degree of neurohormonal factors, which has become a target of pharmacologic inhibition, correlates with the severity of HF.

Each of these events is associated with loss of myocardial Ca2+ homeostasis. Defective intracellular Ca2+ homeostasis causes contractile dysfunction and arrhythmias in failing myocardium.

Risk Factors of AF or HF

The risk factors for AF and HF are similar, but there are also differences. With the exception of age and gender, associations with a cadre of "pressure" diseases, such as CHF, hypertension, mitral valve regurgitation and stenosis, obstructive sleep apnea, and hypertrophic cardiomyopathy, support this observation. The presence and severity of diastolic dysfunction appear to be a potent precursor of non-valvular atrial fibrillation (NVAF) in the elderly, with an independent, graded relationship between the severity of diastolic dysfunction and the development of NVAF[42]. In a large-scale study that included both outpatients and inpatients from all age groups in an insured population, coronary artery disease (CAD), hypertension[43], diabetes, and valvular heart disease are most frequent in HF patients[44].

Late Clinical Outcomes of AF or HF

As AF becomes more prevalent, the most devastating complication is the increased frequency in embolic stroke[45]. In patients with paroxysmal or permanent AF, systemic embolization becomes more frequent with aging. Guidelines published in Western countries recommend the use of a risk stratification schema, such as the $CHADS_2$ or $CHA2DS_2$-VASc score, for anti-thrombotic therapy in the National Registry of AF (NRAF)[46,47]. However, most guidelines in Asians do not incorporate either $CHADS_2$ or $CHA2DS_2$-VASc scores[48].

Patients < 65 years of age with none of the three risk factors (hypertension, prior cerebral ischemia, and diabetes mellitus[49,50] are at low risk for stroke, averaging 1.0-1.8 strokes per 100 patient-years, and if the patients also lacked two additional stroke risk factors (CAD and CHF), the risk of stroke is 0.0-1.6 per 100 patient-years[49-51].

More recent studies from Asian populations have suggested the risk of stroke to be lower compared to Western populations, even when applying the CHADS-type risk stratification systems [48,52,53]. Lin[53] reported that hypertension plays a more important role in ischemic stroke in Tai-

wanese patients with AF, but the occurrence is lower compared with the Western population. In this study, a total of 7920 patients (3633 women, 4287 men) were investigated. The median follow-up period was 1637 days. Among all subjects, 12.9% had a history of CHF, and 13.1% had cardiovascular diseases. Of the 13.1% subjects with cardiovascular disease, 10.7% had CAD, 2.1% had a myocardial infarction (MI), and 1.7% had peripheral arterial disease. For the cardiovascular diseases, CHF was significantly associated with ischemic stroke, unlike CAD, MI, and the cardiac risk index[53].

Therapeutic Considerations

The treatment of patients with AF and HF currently presents specific challenges. Knowing the importance of AF in patients with HF, the restoration and maintenance of sinus rhythm with electrical cardio version and anti-arrhythmic drugs are often attempted[54-58]. Some reports[59-64] do not support a routine strategy of rhythm control in patients with AF. In some cases, AF patients with LV dysfunction have an increased risk of adverse effects from anti-arrhythmic drugs[65-67]. Only a small minority of patients had impaired LV function, and the lack of benefit from the maintenance of sinus rhythm in such patients may not apply to the general population of patients with HF [68]. Thus, choosing between rate and rhythm control seems to be the most important decision for physicians in the treatment of AF and HF.

Rate or Rhythm

The objective of rhythm control is to restore and maintain sinus rhythm. Rate control is a simpler strategy than rhythm control. Rate control includes the use of less toxic medications and fewer medical procedures, but rate control can result in drug side effects. Rhythm control strategies involve anti-arrhythmic medications or invasive procedures, such as catheter ablation or surgery, which have potential risk, but if successful, these strategies provide the benefits of sinus rhythm. The results of several clinical trials suggest that rhythm control should be routinely favored over rate control in patients with HF and AF[69]. Some data suggest that rhythm control may be the preferred strategy to HF patients with AF[70].

Rate Control

During AF, uncontrolled rapid ventricular rates may cause severe symptoms, and sometimes AF can lead to an association with CHF or tachycardia-induced cardiomyopathy (TICM), which is a causative factor[71]. Patients with TICM do not present with symptoms from AF and only present clinically with systolic HF due to declining ejection fractions from uncontrolled rapid rates that often occur for weeks or months[45], and many patients mistakenly attribute their symptoms to pneumonia or an upper respiratory infection. Thus, for AF patients, rate control sufficient to improve symptoms and prevent the development of CHF and LV dysfunction is of significance. The effect of higher heart rates may be different in patients with systolic dysfunction and CHF[72]. AF patients, particularly with minimal or no symptoms, and in whom there is no evidence of AF-related LV dysfunction, may be well-suited to a rate control strategy[72]. Strict rate control may offer clinical benefit in patients with AF and co-existing CHF. The selection of drugs for rate control is often based on physician preference and also on the basis of patient co-morbidities. For the target rate, Tadros et al[70] suggests that patients with a heart rate < 80 bpm at rest and > 110 bpm during a 6-min walk test (6MWT) should be treated. Tadros[71] generally perform 6MWTs if the patient remains symptomatic, despite an optimal heart rate at rest. Moreover, in patients with non-permanent AF, Tadros et al[70] aim for 60 bpm or the lowest tolerated heart rate in sinus rhythm.

In rate control, most patients with a left ventricular ejection fraction (LVEF) <40% should be prescribed a β-blocker, regardless of the underlying rhythm[73-75]. β-blockers may control the ventricular response to AF and improve survival in patients with HF. Moreover, digoxin may be useful as an adjunct therapy to β-blockers in patients with AF and HF. The conduit artery functional endpoint trial suggested that the combination of digoxin and carvedilol can better reduce symptoms, improve ventricular function, and ventricular rate control in patients with HF and AF than either one alone[76]. In clinical practice, amiodarone may be helpful.

Cardiac resynchronization therapy (CRT) is another consideration for rate control. For patients with CHF due to systolic LV dysfunction and ventricular dyssynchrony with a wide QRS complex, CRT has emerged as an important treatment. When CRT is offered to patients with AF, ventricular rate control with AV nodal-blocking drugs is important to ensure a high percentage of biventricular pacing (in general, > 90% pacing)[72]. Rate control to allow CRT to maximize pacing benefits to systolic CHF patients with rapid AF is also a

desired end point from rate control. In a trial that included patients with pre-existing systolic HF and AF undergoing ablation, the use of CRT versus conventional RV pacing was examined. Some reports have demonstrated that a rate control strategy that uses a resting heart rate <110 BPM as a more strict value of <80 BPM is as effective in terms of death, CHF hospitalization, stroke, embolism, and life-threatening arrhythmic events at a 2-year follow-up[77,78].

Rhythm Control

It should be noted that pharmacologic therapy aims to reduce symptomatic AF[70]. In short, amiodarone is the drug of choice for rhythm control in patients with HF. Dofetilide and sotalol are generally reserved for special circumstances, such as amiodarone intolerance or failure. For patients with AF or CHF, maintaining sinus rhythm with the use of anti-arrhythmic drugs is challenging because of the limited efficacy and potentially deleterious effects of these drugs. In addition, when considering pharmacologic or electrical conversion to sinus rhythm, thromboembolic risk should first be assessed.

Curative catheter ablation is a promising therapeutic option for AF. Also, catheter ablation has been demonstrated to be effective in patients with HF. AF ablation is typically recommended only for symptomatic patients. In patients with AF, catheter ablation is increasingly performed on symptomatic patients as an alternative treatment due to ineffective or intolerance to medical management. For some reports, results and safety profiles of patients, including patients who are obese, have hypertrophic cardiomyopathy or HF[79,80], diastolic dysfunction, and the very elderly, are consistent, suggesting that catheter ablation is effective. Restoration and maintenance of sinus rhythm by catheter ablation without the use of drugs in patients with AF and CHF significantly improves cardiac function, symptoms, exercise capacity, and quality of life. The outcomes of catheter ablation may depend on patient characteristics, such as age, AF type, and the presence of structural heart disease, as well as on the operator, methods, and technologies used during the procedure. The primary reason for considering catheter ablation is relief of symptoms. The target of catheter ablation for treatment of AF is to ablate or isolate triggers that mostly originate in the area of the pulmonary veins. Thus, the most commonly used and recommended catheter ablation procedure is pulmonary vein isolation.

Conclusions

AF and HF are currently the most common cardiac disorders. AF and HF often occur together, and the combination results in increased morbidity and mortality compared with each disorder alone. AF and HF share common mechanisms and treatment strategies. Therapies directed toward HF may protect the heart against the occurrence of AF. Although restoration of sinus rhythm in patients with HF may offer clinical benefits, current trials have failed to demonstrate the clinical advantage of sinus rhythm over optimal rate control. Recent advances in catheter-based ablative therapies for AF have been shown to be efficient in well-selected HF patients, resulting in significant improvements in cardiac function, symptoms, and quality of life. It will be years before sufficient data are collected and generated to specifically guide practice when these two common disease processes interact. New tactics for inexpensive and centralized monitoring may have an exciting effect on stroke occurrence[79,81,82]. Because it is predicted that AF or HF would dramatically increase in the next two decades worldwide, a significant burden on the health care systems in multiple countries will occur. It remains imperative that further research about the epidemiology, mechanism, detection, and treatment of AF and HF is urgently promoted.

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Conflict of Interests

The Authors declare that they have no conflict of interests

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