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Editorial

Atrial Fibrillation in Congestive Heart Failure: Two Winding Roads Leading to a Profound Precipice

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Atrial fibrillation (AF) and heart failure (HF) are two common winding roads in the cardiovascular field that share high comorbidities and mortality and severe prognostic implications. Their association worsens the clinical outcomes and the prognosis accounting for an enormous economic burden on healthcare [1-5]. The developing of AF during the course of the evolution of HF complicates the clinical outcome and adds complexity and difficulties to the therapeutic management. AF generates a profound hemodynamic alteration through a number of different mechanisms, namely, fast ventricular rate, irregularity of ventricular rhythm, loss of atrial kick and organized atrial contribution to cardiac output, and in some cases, tachycardia-induced cardiomyopathy [6-11]. Due to an increase in the proportion of elderly population, there are more people with increased risk of developing HF and AF. It has been demonstrated an increasing prevalence of left ventricular wall hypertrophy in aging population [12]. The resulting left ventricular diastolic dysfunction with advanced age may increase the size of the left atrium predisposing elderly patients to develop AF [13-17]. It is well known that AF has an incidence that rises sharply with advancing age. Indeed, aging alters the histological and thus, electrophysiological properties of the human atrial myocardium which contribute to the higher prevalence of AF in the elderly [18-24]. The histological modifications observed include a reduction in the number of myocytes within the sinus node, a generalized loss of atrial myocardial fibers in the surroundings of the internodal tracts, as well as an increase in fibrosis which leads to an apparent loss of myocardial fiber continuity [18-20]. The prevalence of AF in patients with HF increases with the severity of the disease reaching up to 40% in advanced cases. AF is considered to be an independent predictor of morbidity and mortality increasing the risk of death and hospitalization in 76% in HF patients [11-13].

There has been a notorious technical improvement in the diagnosis and treatment of cardiovascular diseases in recent years. New advances and sophisticated technology has offered quantitative and qualitative improvements in pharmacological agents in the armamentarium of the medical management of HF patients. It was demonstrated that the ACE inhibitors produce a decrease in atrial pressure and in left ventricular end diastolic pressure in patients with HF [25,26]. In this regard, these agents may decrease the susceptibility to develop AF in HF patients simply by decreasing atrial pressure and atrial wall stress and consequently by attenuation of atrial enlargement. Another beneficial mechanism of ACE inhibition may be a direct antiarrhythmic effect. Even in the absence of heart failure, it seems that angiotensin II directly contributes to atrial electrical remodeling. The shortening of the atrial refractoriness during rapid atrial pacing is more pronounced in the presence of angiotensin II [25-28]. It was demonstrated a 78% reduction of new onset AF with enalapril [26]. In addition, there was a beneficial effect on AF recurrence with irbesartan in patients with persistent AF who underwent electrical cardioversion [27]. Losartan was found to reduce the incidence of new onset AF in 33% compared to atenolol despite a similar blood pressure control in both treated groups [29]. The clinical relevance of preventing new onset AF in HF patients was clearly demonstrated, since AF was associated with a 2 to 5 fold greater cardiovascular morbidity and mortality, cerebrovascular accidents and hospitalization due to heart failure. New onset AF was also reduced by 45% with trandolapril [30]. It is important to note that these were placebo con-

trolled studies. Therefore, it is probable that the antihypertensive effect of the pharmacological agent contributed to the less incidence of AF decreasing atrial pressure and left ventricular end diastolic pressure. This was further corroborated since the LIFE study showed that high systolic pressure is an independent predictor of the development of new onset AF [29]. The LIFE study showed that patients with AF history had a reduction of 42% in combined end point and cardiovascular morbidity and mortality, with a 45% reduction in the risk of cerebrovascular accidents [31]. Recently, the Ca^{2+}-calmodulin dependent protein kinase II was reported to be an established central mediator of electrophysiological and contractile responses to cardiac stress, and its hyper-activation in cardiac diseases has been linked to HF and atrial arrhythmias. The utilization of appropriate inhibitors with specific selectivity might represent a novel therapeutic approach for HF and AF [14].

There is no doubt about the beneficial effects of pharmacological agents on the clinical outcome, morbidity and survival of HF patients. However, despite the good clinical results obtained with different new drugs, the optimal medical treatment can fail in the intention to improve symptoms and quality of life of HF patients with severe left ventricular dysfunction. Therefore, the necessity to utilize cardiac devices to perform biventricular pacing emerges facing the failure of optimal medical treatment in order to achieve hemodynamic improvement and correction of the physio-pathological alterations. Patients with HF and complete left bundle branch block commonly have an abnormal movement of the interventricular septum that is related with inter-ventricular dis-synchrony and the resultant abnormal pressure gradient between the two ventricles [32]. There is an inhomogeneous and altered depolarization of the ventricles because of the disturbance of the conduction system. Due to this abnormal septal movement, there is an increase in the end systolic diameter of the left ventricle and a decrease in regional septal ejection fraction. Therefore, ventricular dis-synchrony in HF patients puts the failing heart in further jeopardy and additional mechanical disadvantage. In this context, the simultaneous electric stimulation of both ventricles with cardiac resynchronization therapy (CRT) results in a significant hemodynamic improvement restoring a more homogeneous contraction pattern. CRT can reduce the inter-ventricular and intra-ventricular mechanical dis-synchrony. CRT exerts a number of beneficial effects in HF patients with severely depressed ventricular function through several mechanisms. For example, CRT increases the left ventricular filling time, decreases septal dyskinesia, decreases mitral regurgitation, allowing a hemodynamic improvement [33-35]. These beneficial hemodynamic changes are already seen during the first week post-implantation of the device, and are followed by chronic adaptations that allow long term benefits. Several longitudinal clinical studies demonstrated structural and functional ventricular improvement, and beneficial effects of CRT in left ventricular remodeling [15,35,36]. There was a significant improvement in left ventricular ejection fraction, and a significant decrease in end systolic and end diastolic volumes at 3 months of follow-up [33,34]. These beneficial effects are dependent on continuous bi-ventricular stimulation since it was observed that interruption of electric stimulation produce a progressive but not immediate loss of effect. However, a well-functioning CRT may lose synchronization when sinus rhythm is lost. Indeed, CRT may be interrupted in over one-third of patients after successful implantation of a device and the most common reasons for CRT interruption is the development of AF (18%). Almost one fifth of patients who undergo successful implantation of a defibrillator capable of delivering CRT experience an AF with a rapid ventricular response, which at least temporarily results in the inability to deliver CRT and sometimes in inappropriate shocks [33-35]. However, CRT can be re-instituted in a high proportion of patients so that only 5% of patients who successfully undergo implantation of a CRT device permanently lose CRT. Predictors of this therapy interruption as the result of the development of AF in the HF population include a previous history of AF, a relatively slow resting heart rate, and the absence of therapy with both beta-blockers and angiotensin converting enzyme inhibitors [35].

There is a strong necessity to find better ways of prevention of AF since this will improve outcomes and the ability to deliver CRT in HF patients. In this context, it is very useful the AF suppression algorithm in dual-chamber permanent pacemakers which is a stimulation parameter designed specifically to suppress AF. It eliminates the unnecessary rapid stimulation produced by the pacemaker associated to the fixed overdrive stimulation when the patient is at rest. It even performs the overdrive stimulation when the intrinsic atrial rate of the patient increases in response to physical activity [37]. The benefits of the AF suppression algorithm are: 1) automatically suppression of paroxysmal and persistent AF, 2) significant decrease in symptomatic episodes of AF, 3) decrease in the need for painful electric cardioversion, 4) improvement in the quality of life of the patients, 5) effective and safety, 6) well tolerated by 97% of the patients [37].

The maintenance of sinus rhythm in HF patient is paramount. Therefore, the findings of several AF ablation studies are very interesting and important. For example, it was observed an improvement of left ventricular function following AF ablation [38]. These authors studied 69 AF patients with HF with a mean ejection fraction of 31% who underwent AF radiofrequency ablation [38]. Most of their patients had persistent AF. 65% of the patients were free of AF at a mean follow-up of 28 months. Interestingly, in patients who remained in sinus rhythm after AF ablation the ejection fraction improved by 15% at 6 months and continued to improve reaching a mean of 53% increase at 28 months. Sinus rhythm, but not hear rate, was found to be an independent predictor of improvement in ejection fraction at 24 months post-AF ablation [38]. The authors concluded that sinus rhythm is associated with a long-term improvement in left ventricular systolic function after AF ablation. The implication is that AF ablation may improve the systolic function in HF patients even when there was already a good heart rate control [38]. On the other hand, it was demonstrated in another study that there is an incomplete cure of the tachycardia-induced cardiomyopathy secondary to rapid AF in HF patients by the rate control strategy without sinus conversion [39]. These studies clearly suggest that AF ablation has a primary role as a rhythm control strategy in the definite treatment of AF in patients with HF.

In conclusion, there should be a strong effort to prevent AF, since it would significantly improve outcomes and the ability to deliver CRT in HF patients. The search for better pharmacological agents should continue to provide the help needed to decrease the incidence of AF and to improve performance of cardiac devices. Dual-chamber rate-modulated pacing mode, and the AF suppression algorithm, may reduce interruptions of CRT in certain patients with bradycardia. Sinus rhythm is associated with a long-term improvement in left ventricular systolic function after AF ablation. Therefore, AF catheter ablation may have a primary role as a rhythm control strategy in the definite treatment of AF in HF patients. In the therapeutic management of these two common cardiovascular diseases, we should keep on driving carefully through these two winding roads towards a safer pathway in order to accomplish better clinical outcomes and search for new advances in treatment.

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