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Pharmacologic and Nonpharmacologic Therapeutic Approaches of Atrial Fibrillation in Patients With Congestive Heart Failure

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ABSTRACT

Atrial fibrillation (AF) and congestive heart failure (CHF) constitute the two “epidemics” of cardiovascular disease that often coexist and result in significant morbidity and mortality. Due to the complex interaction between AF and CHF, neither can be treated optimally without treating both. Despite an extensive amount of research and literature about each of these disorders separately, there is a paucity of controlled clinical trial data for the management of AF among patients with CHF. Consequently, the optimal therapy of these patients remains controversial. New treatment approaches, both pharmacologic and nonpharmacologic, including catheter ablation techniques, as well as the results of ongoing clinical trials are likely to alter future AF management in CHF patients.

Atrial fibrillation (AF) and congestive heart failure (CHF) are the two “epidemics” of cardiovascular disease that often coexist and result in considerable morbidity and mortality. A causal reciprocal relation exists between AF and CHF. The prevalence of AF has been observed to increase in proportion to the severity of CHF [1].

The objectives of AF treatment include rate control, cardioversion and maintenance of sinus rhythm, and prevention of thromboembolism. In patients with recent-onset AF, anticoagulation and rate control should be used as front-line therapy before cardioversion is considered. If the patient is hemodynamically unstable, urgent cardioversion is clinically mandatory. For both acute and chronic AF it is clear that effective treatment of the arrhythmia depends on optimal management of CHF. It is essential not to overlook the treatment of precipitating factors and of the underlying etiology. A decrease in filling pressures and reduction of neuroendocrine activation will enhance spontaneous conversion to sinus rhythm in acute AF and help reduce ventricular rate in both acute and chronic AF. On the other hand, effective treatment of CHF may not be possible until ventricular rate is controlled or sinus rhythm restored. Angiotensin-converting enzyme inhibition and AT1 receptor blockade may prevent or delay the development of AF in patients with CHF by unloading the left atrium and inhibiting atrial fibrosis [2-9]. Anticoagulation with warfarin is imperative in patients with AF and CHF, even if sinus rhythm is maintained.

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RHYTHM VERSUS RATE CONTROL

The issue of rhythm control versus rate control for long-term therapy of AF in CHF represents a challenging therapeutic dilemma and an object of intense debate. A subgroup analysis of the AFFIRM trial [10] showed a trend toward better survival associated with rhythm control among patients with CHF. However, AFFIRM was not adequately designed to assess treatment strategies in this subset of patients because only 23% of patients in this study had a history of CHF. A recent retrospective analysis [11] showed that there was no difference in mortality after 2 years of rate control or rhythm control treatments in patients with CHF in predominantly New York Heart Association (NYHA) functional classes III and IV. A recently published prespecified substudy of the RACE trial [12] demonstrated that in patients with mild to moderate CHF (NYHA II and III), cardiovascular morbidity and mortality were comparable between those treated with rate control and those treated with rhythm control. However, there was a trend for higher mortality and major bleeding in the rate control group. The primary objective of the ongoing AF-CHF trial [13] is to determine whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared to a rate control strategy in patients with AF and CHF.

RHYTHM CONTROL (RESTORATION AND MAINTENANCE OF SINUS RHYTHM)

Because of the high risk of proarrhythmia and the danger of exacerbating heart failure of class I antiarrhythmic drugs [14,15], IV ibutilide, IV or oral amiodarone, oral dofetilide, or direct current cardioversion are the preferred approaches to convert AF in patients with CHF. Although ibutilide is hemodynamically well tolerated in patients with left ventricular (LV) dysfunction [16], the incidence of torsade de pointes (TdP) is increased in patients with a LV ejection fraction (LVEF) of <35% and therefore should be used with caution in this setting. The recurrence rate of AF after cardioversion in CHF is high. Prevention of AF with antiarrhythmic drugs is suboptimal. Oral amiodarone [17] or dofetilide [18,19] are the drugs of choice for maintenance of sinus rhythm. The use of amiodarone in patients with CHF and AF is not without risk. This population is very prone to the development of bradyarrhythmias requiring pacemaker implantation [20]. Amiodarone may increase the risk of sudden death in CHF patients with a history of previous TdP [21]. The rate of discontinuation due to noncardiac adverse effects is high. Additionally, amiodarone increases the plasma levels of warfarin.

RATE CONTROL

Current ACC/AHA/ESC guidelines [22] consider the ventricular rate controlled when the ventricular response ranges between 60 and 80 bpm at rest and between 90 and 115 bpm during moderate exercise. However, no study has validated these criteria. Rate control in AF is mainly based on pharmacological depression of atrioventricular (AV) nodal conduction.

There are no data on the safety and efficacy of β -blockers in acute AF and CHF. Esmolol, an intravenous, ultra-short acting β -blocker, may be a useful therapeutic option in the acute clinical setting due to its ability to be titrated according to changing circumstances. Moreover, despite the fact that β -blocker therapy is considered the standard of care in chronic heart failure, it is uncertain whether β -blockade provides a similar degree of clinical benefit for CHF patients with AF. A retrospective analysis, which assessed the use of metoprolol or carvedilol in patients with CHF and sinus rhythm or AF, demonstrated a significant improvement in LVEF in both groups [23]. A retrospective analysis of the US Carvedilol Heart Failure Trials Project showed a significant improvement in LVEF and a trend towards reduced mortality and CHF hospitalization [24]. Bisoprolol failed to show a survival benefit in patients with AF in a retrospective analysis of CIBIS II [25]. Prospective trials to clarify the impact of β -blocker therapy and the optimal therapeutic strategy in this group of patients are warranted.

In acute AF, digoxin is relatively slow and ineffective in controlling heart rate. Digoxin may also be ineffective in controlling heart rate in chronic AF when sympathetic tone is increased, as occurs in worsening CHF and during exercise [26-28]. However, in the context of chronic heart failure, digoxin may improve symptoms and reduce hospitalization [29,30]. Additionally, digoxin and β -blockers produce a synergistic effect on the AV node [31]. A retrospective analysis of the US Carvedilol Heart Failure Trials Project demonstrated a better survival benefit of carvedilol in patients with CHF treated with digoxin [24]. In a group of 47 patients with predominantly NYHA II CHF, the combination of carvedilol and digoxin was superior to either carvedilol or digoxin alone in controlling ventricular rate and reducing symptoms [33].

Amiodarone is an interesting alternative in patients in whom both rapid rate control and cardioversion are considered appropriate [33]. Verapamil and diltiazem should be avoided in the acute setting as they may worsen CHF. For long-term rate control of chronic AF, diltiazem is a controversial alternative [34-36].

NONPHARMACOLOGIC THERAPY

In 10% to 15% of patients with AF ventricular rate cannot be controlled sufficiently by pharmacologic means [37]. In such cases, radiofrequency catheter ablation of the AV node with permanent pacemaker implantation (“ablate and pace” strategy) is a useful alternative. The only randomized controlled study comparing pharmacological rate control versus AV node ablation and VVIR pacing in AF patients with CHF demonstrated an improvement in symptoms in the “ablate and pace” group [38]. The choice of pacing site appears crucial in the setting of CHF. The PAVE trial [39] prospectively compared chronic biventricular pacing to right ventricular pacing in patients undergoing ablation of the AV node for management of AF with rapid ventricular rates and demonstrated that biventricular pacing provides a significant improvement in the 6-min walk test and in LVEF compared to right ventricular pacing. These beneficial effects of cardiac resynchronization appear to be greater in patients with impaired systolic function or with symptomatic heart failure.

Limited available evidence suggests a beneficial effect of cardiac resynchronization therapy (CRT) in patients with chronic AF, although larger studies are needed. Several single-center studies with a relatively small number of patients have demonstrated acute hemodynamic improvement in patients with chronic AF receiving CRT [40,41], as well as improvement in echocardiographic parameters [42]. Two studies reported comparable benefit of CRT in patients with AF as compared to patients with sinus rhythm [43,44]. To date, only one prospective randomized and controlled trial designed to assess the efficacy of CRT in AF patients with severe CHF has been published [45]. It showed a significant improvement in NYHA functional class, 6-min walking distance and quality of life with effective CRT therapy (>85% of time). In addition, LV reverse remodeling was observed with a reduction in hospitalization rate for CHF. It was subsequently demonstrated that the benefit of CRT was sustained at 12 months [46]. An important issue remains whether CRT in patients with chronic AF should be accompanied by AV nodal ablation in order to avoid inhibition of resynchronization therapy by the rapid intrinsic AV nodal conduction.

Curative catheter ablation for atrial fibrillation, currently effected with pulmonary vein isolation procedures, has been established as an effective therapeutic option mainly for patients without significant heart disease. A recent retrospective study examined the effect of catheter ablation of AF on LV function in 94 patients with LV dysfunction [47]. The study showed a nonsignificant overall increase of 5% in LVEF after ablation. However, a recently published study [48], which prospectively evaluated the effect of catheter ablation for AF on LV function in patients with CHF, showed that restoration and maintenance of sinus rhythm by catheter ablation without the

use of drugs significantly improve cardiac function, symptoms, exercise capacity, and quality of life.

CONCLUSION

Because of the complex interaction between AF and CHF, neither can be treated optimally without treating both. Despite the extensive amount of research and literature about each of these disorders separately, there is a paucity of controlled clinical trial data for the management of AF among patients with CHF. Consequently, the optimal therapy of these patients remains controversial. New treatment approaches, both pharmacologic and nonpharmacologic, as well as the results of ongoing clinical trials are likely to alter AF management in CHF patients in the near future.

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