Introduction to atrial fibrillation and heart failure: a mutually noxious association

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The complex interactions between atrial fibrillation (AF) and congestive heart failure (CHF) have been long and vigorously debated, with few firm conclusions reached. Several unresolved issues persist, beginning with epidemiology. The only reliable data pertain to permanent or chronic AF, which, within equivalent age groups, is markedly more prevalent among patients with CHF than in the general population [1]. This prevalence increases in parallel with the New York Heart Association (NYHA) CHF functional class and disease progression, from 10–26% among patients suffering from mild to moderate CHF (NYHA functional class II and III), to 30–50% among patients in NYHA class IV [2]. In contrast, no reliable data are available regarding the prevalence and incidence of paroxysmal AF, which should be one of the first questions addressed with the support of new implantable devices with powerful diagnostic functions. These devices, whether pacemakers or cardioverter defibrillators (ICD), are implanted at rapidly increasing rates in patients suffering from CHF without indications for treatment of bradycardia. Observational studies should be conducted with the assistance of these invaluable diagnostic tools, not only to measure the prevalence of paroxysmal AF at various stages of CHF, but also to define better its characteristics, including frequency of episodes, triggering mechanisms, circumstances surrounding its development, and spontaneous evolution. Numerous experimental and clinical observations suggest that both the triggers and electrophysiological substrates of AF in patients with CHF are different from those present in patients without structural heart disease [3]. The diagnostic functions of implanted devices offer a unique opportunity to confirm these observations, and to sharpen the focus on effective preventive therapies.

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Besides its epidemiology, the prognostic significance of AF in CHF remains poorly understood. Subgroup analyses of large clinical trials, such as SOLVD [4] or VAL-HeFT [5], and the recent report from the population-based Framingham Heart Study [6] support the long-held notion that the presence or development of AF in patients suffering from CHF is associated with a higher mortality. However, the independent predictive value of AF remains debated. The recent publication of the results of the "Italian Network on Congestive Heart Failure" has made an important contribution to this debate [7]. In that large cohort study, chronic AF was an independent predictor of death from all-causes and of sudden death, with a hazard ratio (HR) = 1.32, 95% confidence interval 1.09–1.59, and \( P = 0.0046 \), values similar to those associated with previously identified factors, including age, NYHA functional class, systolic blood pressure, history of ventricular tachycardia, or presence of left bundle branch block (LBBB) on the surface electrocardiogram. It is noteworthy that, in that study, the combination of AF and LBBB [8] present in 3.3% of the entire cohort, was associated with particularly high risks of deaths from all-causes (HR = 1.88), sudden death (HR = 1.89), and rehospitalisation for management of CHF (HR = 1.83). This population at inordinately high risk of adverse events should be the object of particularly close surveillance during long-term follow-up, and may represent an appropriate target for a trial on non-pharmacological interventions, especially cardiac resynchronisation therapy.

Tachycardia-induced cardiomyopathy is one other aspect of the complex interaction between AF and CHF. This disorder, originally described in children and adolescents suffering from atrial or the permanent form of junctional tachycardia [9], was more recently extended to adult populations presenting with very frequent paroxysmal AF, or permanent AF with a rapid ventricular response [10]. It is likely that the irregularity of the cardiac cycles is the cause of further left ventricular (LV) systolic or diastolic dysfunction beyond that due to the rapid heart rate. While total or partial regression of cardiac mechanical dysfunction has undoubtedly been observed after control of the heart rhythm or rate, this outcome is far from predictable. Within a population of patients with AF, LV systolic dysfunction and CHF, those likely to respond to rhythm or rate control remain difficult to identify. Prospective studies are needed to define markers of a positive response, and more accurately select patients who may benefit from these forms of management.

The choice of long-term therapy of AF in CHF is also the object of intense debate. Whether to control rate versus rhythm is unclear, despite the subgroups analysis of AFFIRM [11], and RACE [12] which tend to support rhythm control. The results of studies specifically designed to examine populations of patients with CHF, such as AF-CHF [13], are needed to draw more definitive conclusions. If rhythm control were the preferred strategy, its safety and efficacy remain a challenge. The article by Savalieva and Camm, in this Supplement, is a reminder of the narrow scope of antiarrhythmic drug therapy, currently limited mostly to amiodarone and new class III agents, until the availability of more effective and safer compounds has become a reality.

Non-pharmacological therapies may play a growing role, though their merit in patients with CHF cannot currently be accurately measured. It is unlikely that the results of surgical or non-surgical ablation, defibrillation or preventive pacing observed in patients with lone AF can be extrapolated to patients with CHF, considering the marked differences in substrates, which, in the latter condition, represents a true atrial myopathy, requiring specific investigations.

With respect to preventive atrial pacing, particular attention will have to be paid to the site of stimulation. The high prevalence and diffuse nature of abnormal intra-atrial conduction in the hearts of patients with CHF, their possible accentuation by stimulation at an inappropriate site, and the importance of optimising the left atrial contribution to ventricular filling, may determine a choice of non-conventional sites, particularly the septum, or of multiple simultaneous sites [14–16]. The tolerance of overdrive pacing algorithms will also need to be scrutinised. In an era when life-saving beta-adrenergic blocking drugs are regularly included in the management of CHF, it may seem paradoxical to introduce pacing algorithms with a view to maintain a relatively high heart rate, as well as cause its inappropriate, albeit transient, acceleration.

If, on the other hand, the optimal strategy were rate control, drug therapy would be simplified, based mostly on beta-adrenergic blockade and digoxin, two types of pharmaceuticals which slow the heart rate and exert positive effects on cardiac mechanical function in patients with CHF.

The indications for radiofrequency ablation of the atrioventricular junction must be weighed carefully, since this treatment is inescapably followed by permanent pacing, with the potential adverse mechanical effects of complete ventricular capture. The choice of pacing site appears crucial in presence of CHF. Numerous case reports
or observational studies, and a few controlled trials like DAVID [17] (though in DAVID, the majority of patients were asymptomatic or only had mild heart failure) suggest that right ventricular (RV) apical pacing may cause or worsen heart failure particularly in the setting of post-myocardial infarction left ventricular systolic dysfunction. The prevention of such adverse effects may mandate the choice of other RV pacing sites, or of biventricular pacing. A randomised study in patients suffering from chronic AF and with a LV ejection fraction (EF) <40%, conducted at our institution, showed better preservation of ventricular function after ablation of the AV junction followed by RV septal compared with RV apical pacing [18]. Preliminary results of the PAVE trial presented at the 2004 American College of Cardiology Scientific Sessions (Late-Breaking Trials) indicated that, after ablation of the AV junction, biventricular pacing was associated with better preservation of LV systolic function than single-site RV pacing. However, these results must be interpreted cautiously since neither CHF nor a low LVEF were criteria of inclusion into the trial. The only trustworthy comparison available thus, far, between biventricular and single-site RV stimulation in patients with moderate or severe CHF and an LVEF <35% is from the MUSTIC-AF trial [19]. However, the results were disappointing. A statistically borderline significant improvement in functional capacity was observed during the crossover phase with biventricular stimulation; this must be considered inconclusive. The most important information derived from this study was the inordinately high dropout rate during a long observation before randomisation, attributed to single-site RV stimulation imposed on all patients during that phase of the trial. This observation suggests that it might no longer be ethical to conduct a MUSTIC-like comparative trial in this patient population.

On the other hand, a pragmatic study should be designed to answer questions asked by the community of heart failure specialists pertaining to patients in chronic CHF and AF, questions probably different from those asked by arrhythmia experts. A prolonged morbidity/mortality trial should be conducted in a large patient population, to compare, in a parallel design, a) optimal medical treatment of CHF + rate control versus b) optimal medical treatment + cardiac resynchronization + ICD therapy, to ascertain the efficacy of complete electrical therapy. Radiofrequency AV junctional ablation could be added for patients whose ventricular rate remained uncontrollable.

This introduction was written to open a discussion as well as to ask several questions which will only be answered by the design and conduct of additional appropriate studies.

References:


