Rate versus Rhythm Control – An Open and Shut Case?

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Atrial fibrillation (AF) and heart failure (HF) are the cardiovascular epidemics of the 21st century. AF is the most common sustained arrhythmia in man and is a significant cause of health care expenditure in the industrialized world. Although predominantly an arrhythmia of the aged (>10% of individuals over the age of 65 years will experience AF), both the AF itself and the clinical context in which it occurs are very heterogeneous. The prevalence and persistence of AF and the relative inefficacy of pharmacotherapy have complicated the management of this rhythm disturbance and have motivated the search for alternative methods to manage patients. Catheter-based techniques are increasingly utilized rhythm and rate control therapeutic modalities in patients with AF [e.g. 1, 2]. Finally, the risk of thromboembolism adds to the complexity and patient dissatisfaction associated with treatment of AF.

In the past several years four randomized clinical trials (AFFIRM, Dutch RACE, PIAF and STAF) have been published that demonstrate the equivalence (or noninferiority) of rate versus rhythm control strategies on mortality and other major trial endpoints [3–6]. In general the rate control therapeutic approaches were associated with a trend toward lower mortality, a reduced frequency of hospitalization and a lower incidence of drug-associated side effects.

Case closed, right? Not so fast. The populations in these trials share a number of demographic features that

may limit the generalizability of these data to all patients with AF. First, the mean age of patients in all of these trials exceeded 65 years. Second, patients in AF with their ventricular rate controlled were minimally symptomatic. Third, in most cases, patients had a prior clinically recognized episode of AF. Fourth, the efficacy of pharmacological rhythm control was at best marginal, thus patients were subjected to the risk of antiarrhythmic drugs with only marginal therapeutic benefit. As a corollary it is not surprising that patients in the rhythm control arms of these trials suffered thromboembolic complications at rates comparable to patients managed with rate control strategies. The limited efficacy of rhythm control strategies is in part responsible for the increased hospitalization rate in this group; patients were admitted to hospital for antiarrhythmic drug therapy, cardioversion and decompensation of underlying structural heart disease. Contemporary methods such as radiofrequency catheter ablation may afford improved rhythm control [1, 2] allowing for the constitution of a true rhythm control group.

Landolina et al. [7] nicely summarize the limitations of a broad general application of rate control as a first-line management approach to AF. In addition they report a small prospective nonrandomized study of younger patients with advanced HF that suggests that a rhythm control strategy has a reasonable chance of success and may have a salutary effect on left ventricular function. It is important to note that in addition to the atrial remodeling

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that is associated with AF, a different type of structural and electrical atrial remodeling may occur in patients with HF that may exaggerate the predisposition to AF in patients with HF. There are a number of reasons to believe that AF might lead to the development or exacerbation of HF. Certainly, tachycardia-induced cardiomyopathy is a well-recognized phenomenon that may complicate AF. Other features of AF such as irregularity of ventricular rate and the absence of synchronized atrial and ventricular activation may be associated with symptoms of HF and/or produce progression in left ventricular dysfunction. However, the mechanism and indeed the hypothesis that AF promotes the progression of the HF phenotype are not proven. The AF-CHF trial [8] is a randomized trial of rate versus rhythm control strategies of AF in patients with CHF, a left ventricular ejection fraction $\leq 35\%$ with cardiovascular mortality as the primary end-

point and an intention-to-treat approach as the primary method of analysis. The rhythm control arm will include the use of electrical cardioversion combined with antiarrhythmic drugs (amiodarone or other class III agents) and the rate control arm will employ β -blockers, digoxin, or pacemaker and AV nodal ablation. It will be interesting to see if the study by Landolina et al. [7] foreshadows the results of this larger trial. However, the time appears to be right for larger clinical trials that examine the difference between rate and rhythm control using contemporary treatment strategies (e.g. ablation, newer atrial-selective pharmacotherapeutics) that more effectively reduce the AF burden in the rhythm control groups. Such studies in patients with left ventricular dysfunction should attempt to address the issue of whether AF itself even with controlled ventricular response promotes progression of the HF phenotype.

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