

The ongoing controversy: is rate control or rhythm control the preferred goal in patients with atrial fibrillation?

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Atrial fibrillation (AF) is the most common sustained arrhythmia [1]. It affects an estimated 2 million people in the United States alone, and accounts for over 70,000 cerebrovascular events yearly. With an aging population, the incidence of AF is expected to rise dramatically over the next 2 decades. In addition, two thirds of patients with congestive heart failure (CHF) have AF [2]. These two disease states are closely interrelated, as CHF may promote the development of AF and vice versa. AF is also a marker for increased mortality in patients with LV dysfunction [3].

Atrial fibrillation may potentially worsen CHF by multiple mechanisms, including a direct increase in chronotropy and decrease in filling time; along with a loss of the atrial contribution to filling. Indirectly, there may be adverse effects via the negative inotropic and proarrhythmic effects from medications used to treat AF. Persistent AF may therefore contribute to both LV systolic and diastolic dysfunction in patients.

Several large trials (e.g. AFFIRM, RACE, HOT-CAFÉ) that randomized patients to rhythm versus rate control strategies in AF were recently published [4, 5]. The largest of such trials, the AFFIRM trial, found no survival or events benefit between the two groups. Similarly in a substudy, no differences in functional class (deterioration)

over time or mini-mental status examinations were demonstrated (although a small increase in 6 minute walk test duration was noted to be statistically significant) [6]. An additional prespecified Quality of Life (QOL) substudy of AFFIRM revealed no difference in QOL between the rhythm versus rate control arms; nor was there a difference between those in sinus rhythm versus those in persistent atrial fibrillation (regardless of randomization treatment group) [7].

As pointed out in the current paper by Szulc et al, no large study to date has looked at the important question of serial LV function in a population of AF patients randomized to rate vs. rhythm control. The majority of patients with baseline echocardiographic data in AFFIRM had normal left ventricular ejection fraction (LVEF) at enrollment. However, there was no serial assessment of LV function over time. This leads us to the important question asked in the study of Szulc et al. in a subset of the HOT-CAFÉ trial population of patients: what is the effect of rate versus rhythm control on left ventricular function over time?

In this study, patients with a mean age of 61 years and with persistent AF were randomized to rate control versus rhythm control with DC cardioversion and/or antiarrhythmic medication. After 12 months of follow up, 64% of patients (in the rhythm control group) were deemed to be in sinus rhythm. This, once again, emphasizes the difficulty with attaining and maintaining sinus rhythm over time with conventional treatment. It may also be of importance to note that 21% of the enrolled patients had lone AF and 90% were class I and II NYHA functional class. Thus, this was a relatively young and healthy population at baseline.

Mean left ventricular echocardiographic parameters, which included left ventricular end-diastolic (LVEDD) and systolic dimensions (LVESD) as

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well as fractional shortening (FS), were within normal limits at baseline; indicating further that this cohort was comprised predominantly of those with AF and normal left ventricular systolic function. The conclusion in this study was that LV morphology and LV systolic function (as assessed by LVEDD, LVESD and FS) were not significantly different after 12 months of follow up, irrespective of rate vs. rhythm control treatment strategy.

In their discussion, the authors accurately point out that the “baseline systolic function in the overall study group was relatively preserved”. Also, they state that their population “seemed to be well representative for the average population of patients with AF”. Their findings would seem to correlate with the findings of the large, randomized trials of rate vs. rhythm control. In these trials, there was no advantage amongst treatment groups in survival or event rates; nor was there any appreciable difference in QOL or functional class. Thus, one might expect that LV function would not significantly deteriorate in one treatment group versus the other. However, can these results be extrapolated to a more complex population of patients with significant LV dysfunction at baseline?

A recent French study examining rhythm control in AF (via circumferential pulmonary vein ablation) in patients with significantly reduced LVEF (average LVEF $35 \pm 7\%$) demonstrated significant improvement in LV function, with a $21 \pm 13\%$ increase in LVEF and an $11 \pm 7\%$ increase in fractional shortening in those patients who had baseline LV dysfunction [8]. Further, patients with poor rate control pre-ablation had superior improvements in LV function, compared to those with adequate rate control pre-ablation. Whether this benefit in LV function can be generalized to a subset of the population of patients in the large randomized trials of rate vs. rhythm control is currently unclear. For example, follow-up echocardiograms were not mandated in AFFIRM, and therefore the data is lacking [9].

And, as noted, patients selected for the study by Szulc et al. were a generally younger and healthier cohort with predominantly normal LV systolic function at baseline, in comparison to those recruited for previous rate versus rhythm control trials. In this relatively select population, the primary endpoint (of LV morphology and function) failed to improve significantly in either treatment group.

Given the stated limitations in this well-organized study of Szulc et al, both the HOT CAFÉ trial and this substudy add to the overall knowledge base in AF. However, the ongoing controversy remains

relative to the fundamental question: is it better to attain sinus rhythm or leave the patient in AF and control the rate? In our humble opinion, the studies to date were not designed to answer this fundamental question. Rather these studies determined that, with the current means at hand (including the relative ineffectiveness of conventional antiarrhythmic agents, with high recurrence rates of AF and the potential side-effects) that rhythm control offers no advantage over rate control in the population of AF patients tested.

Further research needs to be performed in order to elucidate whether patients with depressed LV function and AF have improvement in survival, events, QOL, functional class and/or LV function with strategies of rate versus rhythm control. Also, it needs to be determined whether improved methods of attainment and maintenance of sinus rhythm can demonstrate a genuine advantage with rhythm control. Ongoing randomized trials, such as the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial, will attempt to answer some of these questions [10].

Finally, in a cost-effective world, searching for accurate surrogate endpoints (which occur earlier, with higher frequency, and which accurately predict the hard endpoint of interest) may prove to be very beneficial. If true surrogate endpoints can be defined, some of these important questions may be answered without the repeated cost of very large clinical trials [11].

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