Is heart rate reduction more important than target dose in chronic heart failure therapy with a beta-blocker?

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1 Introduction

Beta-adrenoceptor blocking agents (beta-blockers) are now well established as cornerstone therapy in patients with systolic chronic heart failure (CHF).^[1] Clinical data have overwhelmingly proven the beneficial effects of beta-blocker therapy in terms of improving patient prognosis, decreasing requirements for hospitalization, and postponing disease progression.^[2–4] However, it remains unclear what the optimal efficacious and safe dose for an individual patient with CHF is, and whether this can simply be inferred from the target dose for each beta-blocking agent as used in the major clinical trials. Beta-blockers are a heterogeneous class of drugs, and due to the polymorphisms of beta-adrenoceptor gene expression, there is marked individual variation in responsiveness to specific agents.^[5] If pharmacodynamic markers of responsiveness to beta-blockade (such as heart rate (HR) reduction) are more important than the achievement of a target dose, could they become another potential therapeutic target in beta-blocker therapy? We provide a discussion of the question in this article.

2 Relationship between heart failure and HR

In left ventricular dysfunction or failure, there is autonomic imbalance with a shift towards dominant sympathetic activity and reduced vagal activity, causing an increase in HR. Under normal physiological conditions, cardiac output is equal to HR multiplied by stroke volume. An increased HR will usually increase cardiac output

through an increased number of beats per minute if the venous return is increased, and by its effect on basal myocardial contractility. The latter effect, often called the force-frequency or strength-interval relation, is known to influence myocardial contractility (inotropic state) in isolated cardiac muscle and in anesthetized animals.^[6] However, in decompensated heart failure the force-frequency relation is inverted, and increasing HR is not concomitant with increased cardiac contractility; on the contrary, an increased HR can worsen cardiac function by increasing the oxygen consumption of the myocardium and by decreasing the diastolic time (thereby decreasing myocardial perfusion during diastole).^[7] The most spectacular example of the detrimental role of a high HR on cardiac function is the cardiomyopathy which develops in patients with rapid atrial fibrillation or prolonged atrial tachycardia, which is reversible with rate and rhythm control.^[8]

3 HR is an independent prognostic factor in heart failure

The association between HR and clinical outcome has also been confirmed in patients with CHF. In a study of 1518 patients with CHF, Fosbøl *et al.*^[9] found that higher resting HR was independently associated with an increased risk of overall mortality. In the Cardiac Insufficiency Bisoprolol Study (CIBIS) II trial, which assessed the effect of bisoprolol therapy in patients with New York Heart Association (NYHA) class III–IV and left ventricular ejection fraction (LVEF) $\leq 35\%$, multivariate analysis showed that higher HR at enrolment was a significant predictor of death, independent of several clinical variables and of beta-blocker therapy.^[10] The association between increased HR and worse outcome in CHF was confirmed in a substudy of the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) trial, which assessed the effect of metoprolol therapy in

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CHF patients with NYHA class II–IV and LVEF < 40%. In this substudy, the risk of outcome events such as all-cause mortality and all-cause hospital admission at follow-up increased significantly in the highest HR quintile (> 90 beats/min).^[11]

4 HR reduction can improve cardiac function and prognosis

Most recent studies of heart failure have found a relationship between HR and mortality. One is the CIBIS trial, in which treatment with bisoprolol reduced HR by approximately 15 beats/min relative to placebo, and HR reduction was the most powerful predictor of survival identified in multivariate analysis.^[12] The relationship between log hazard for mortality and HR change was almost linear over the range –40 to +10 beats/min. In the larger CIBIS II trial, baseline HR and HR change were both significant predictors of mortality. The best prognosis was obtained in patients with the lowest baseline HR and with the greatest HR reduction.^[13] Analysis of data from the Carvedilol or Metoprolol European Trial (COMET) study showed that HR achieved during beta-blocker therapy was a significant independent predictor of mortality.^[14] In a rat model of heart failure, prolonged HR reduction with a HR-lowering agent that has no direct action on myocardial contractility or the autonomic nervous system improves left ventricular function and normalizes structure, including increasing capillary density.^[15]

5 Beta-blockers have no benefit in heart failure outcome if HR is kept constant by atrial pacing

In dogs, left ventricular dysfunction caused by surgically induced mitral regurgitation is substantially ameliorated by beta-blocker treatment, but the amelioration is largely prevented by electrical pacing to the pre-beta-blockade rate.^[16] In patients with heart failure, HR reduction by beta-blockade reduces oxygen requirement and increases mechanical efficiency, benefits that are abolished if HR is kept constant by atrial pacing.^[17] In a recent study of patients with heart failure who were fitted with permanent pacemakers and treated with beta-blockers, pacing at 80 beats/min as opposed to 60 beats/min attenuated or reversed the beneficial effects of beta-blockade on left ventricular volume and systolic function.^[18]

6 HR reduction is more important than target dose in beta-blocker therapy

In the 2005 ACC/AHA guidelines for the diagnosis and

management of chronic heart failure, cardiac specialists advocated that physicians, especially cardiologists and primary care physicians, should make every effort to achieve the target doses of beta-blockers shown to be effective in major clinical trials. However, they pointed out that the dose of beta-blockers in controlled clinical trials was not determined by the patient's therapeutic response, but was increased until the patient received a pre-specified target dose. Lower doses were prescribed only if the target doses were not tolerated, and thus, most trials did not evaluate whether lower doses would be effective.^[1] Even though it is known that considerable heterogeneity exists within the class and that individual patients may exhibit widely differing pharmacodynamic responsiveness to the same dose of a specific drug,^[19] very few systolic CHF studies have sought to examine clinical outcomes by achieved HR reduction rather than achieved dose. In the MERIT-HF, which demonstrated similar HR reductions at doses of extended-release metoprolol above and below the median, similar relative risk reductions in all-cause mortality were observed between patients receiving high and low doses,^[20] supporting the concept that HR reduction that may be more important than absolute (or target) dose in maximizing clinical benefit. Flannery *et al.*^[21] reported a meta-analysis of controlled trials of beta-blockers in systolic CHF. They analyzed 35 trials, which included 22,926 patients with a mean follow-up duration of 9.6 months, for all-cause mortality, LVEF, and HR. There was a close relation between all-cause annualized mortality rate and HR (adjusted R² = 0.51, *P* = 0.004). A strong correlation between change in HR and change in LVEF was also observed (adjusted R² = 0.48, *P* = 0.000), and when only trials with > 100 patients were included an even more significant correlation was found (adjusted R² = 0.60, *P* = 0.0004). This further demonstrated that the HR-lowering effect may be a major contributor to the clinical benefits of beta-blocker therapy in systolic CHF.

In conclusion, HR and HR reduction are at least as important as the target dose in beta-blocker therapy. Understanding the contribution of HR is likely to be particularly useful in managing the large number of patients who might expect to benefit from HR reduction but who do not or cannot receive intensive beta-blocker therapy.

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