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Heart rate-guided, but not dose-guided titration of beta blockers stabilizes ventricular repolarization in patients with chronic heart failure☆

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Abstract

Aims: We compared the effects of heart rate-guided and dose-guided beta-blocker titration strategies on QT variability in patients with chronic heart failure (CHF).

Methods: In a prospective study we recorded 5-minute resting high-resolution ECGs (HRECG) in 100 patients with CHF and measured heart rate (HR) and ventricular repolarization by QT variability index (QTVI). In a subgroup of patients not reaching target HR (<70 bpm) we uptitrated beta blockers and repeated HRECG measurements 3 months thereafter.

Results: Target HR was present in 46 patients (group A), and in 54 patients HR was above target (group B). The groups did not differ in age, gender, NYHA class, NT pro-BNP, creatinine, or beta blocker dose. Patients in group A displayed significantly lower QTVI than patients in group B (−1.25 ± 0.55 vs. −1.52 ± 0.42, P = 0.013). When uptitrating beta-blockers we found a decrease in HR (from 91 ± 15 bpm to 71 ± 15 bpm, P < 0.001), NTpro BNP levels (from 4474 ± 3878 pg/ml to 3042 ± 2566 pg/ml, P = 0.024), and NYHA class (from 3.0 ± 0.8 to 2.5 ± 0.7, P = 0.006). With beta-blocker uptitration QTVI decreased in 10 of 24 patients (42%). In these patients HR decreased more than in the remaining cohort (−25 ± 20 bpm vs. −15 ± 17 bpm, P = 0.017). On multivariate analysis, the presence of target HR was a predictor of QTVI decrease (P = 0.017), but beta-blocker dose was not.

Conclusions: In patients with CHF treated by beta-blockers, changes in QT variability appear to occur in parallel with changes of heart rate. This suggests that heart rate-guided titration of beta-blockers may be associated with decreased risk of sudden cardiac death.

Keywords: Chronic heart failure; Beta blockers; QT variability; Heart rate

Introduction

Sudden cardiac death (SCD) remains one of the important factors limiting the long-term survival in patients with chronic heart failure. Although the use of implantable cardioverter-defibrillators (ICDs) has been shown to be very effective in SCD prevention [1], the use of this therapy is limited to a specific subgroup of patients. On the other hand, although inferior to ICD therapy, treatment with beta-blockers has also been associated with a significant reduction in SCD in patients with chronic heart failure [2]. However, the association between beta blocking therapy and SCD reduction appears to be variable, possibly reflecting the differences in beta-blocker up-titration regimens. Typically, beta-blocker uptitration is based on a strategy aiming to achieve the target doses used in large clinical trials [3]. In chronic heart failure patients with ICDs, such maximization of beta-blocker dose was associated with fewer ventricular arrhythmic events [4]. On the contrary, the results of recent meta-analysis suggest that the survival benefits of beta-blocker therapy in chronic heart failure are related to heart rate reduction, and not to the dose of beta-blocking agent [5]. Thus, it remains unclear whether in an attempt to maximize the anti-arrhythmic effects of beta-blocker therapy in everyday clinical setting one should focus on achieving a target heart rate or a target dose of a beta-blocking agent.

SCD in heart failure results from malignant ventricular arrhythmias, which are thought to be a consequence of spatial and temporal dispersion of ventricular repolarization

☆ Disclosures: None.

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[6]. Using high-resolution electrocardiography (hrECG), temporal repolarization dynamics of the ventricular myocardium can be measured by QT interval variability index (QTVI) [6]. When compared to healthy controls, QTVI in patients with chronic heart failure is significantly increased [7]. Since an increase in QTVI has been repeatedly associated with higher likelihood of SCD, it can be used as a surrogate marker of pro-arrhythmic potential in patients with chronic heart failure [7]. By measuring QTVI, the aim of the present study is to compare the effects of heart rate-guided and dose-guided beta-blocker therapy on QT variability in patients with chronic heart failure.

Materials and methods

Patients

All patients with chronic heart failure referred to Advanced Heart Failure and Transplantation Center at University Medical Center Ljubljana from March 2010 to March 2012, were considered for inclusion in the study. Inclusion criteria consisted of the following: age 18–65 years old, diagnosis of chronic heart failure according to European Society of Cardiology Guidelines [8], left ventricular ejection fraction (LVEF) <40%, and presence of beta blocker therapy (stable dose for at least 3 months before referral). Patients with acute heart failure, acute exacerbations of chronic heart failure, or coronary interventions in the previous 6 months were not included. Informed consent was obtained in all patients before participation in the study; the study protocol was registered with Slovenian Drug Agency and approved by the National Medical Ethics Committee.

Study design

For the purpose of this study, target heart rate was defined as resting heart rate <70 bpm, and target daily doses of beta blockers were defined as 50 mg for carvedilol, 10 mg for bisoprolol and 10 mg for nebivolol [8]. Flow chart of the study design is presented in Fig. 1. In phase 1 we stratified the patients according to the presence of target heart rate and target beta-blocker dose and compared QTVI values between the groups. In phase 2, we selected patients from phase 1 without evidence of decompensated heart failure in who had heart rates above 70 bpm and had sub-therapeutic beta-blocker dose. In this group we uptitrated beta-blockers to the target dose in a 3-month period and compared QTVI values at baseline and 3 months thereafter. At each time point we also collected clinical and laboratory data, and performed standard 2D and Doppler echocardiography.

High-resolution electrocardiography

Electrodes with soft cloth tape and solid gel were used to obtain a 5-minute recording of a standard electrocardiogram with the patient in a supine position. In all subjects, high-fidelity (12 bit resolution, 1000 samples/sec/channel) ECG recordings were performed to get a minimum of 256 waveforms acceptable for both signal averaging and

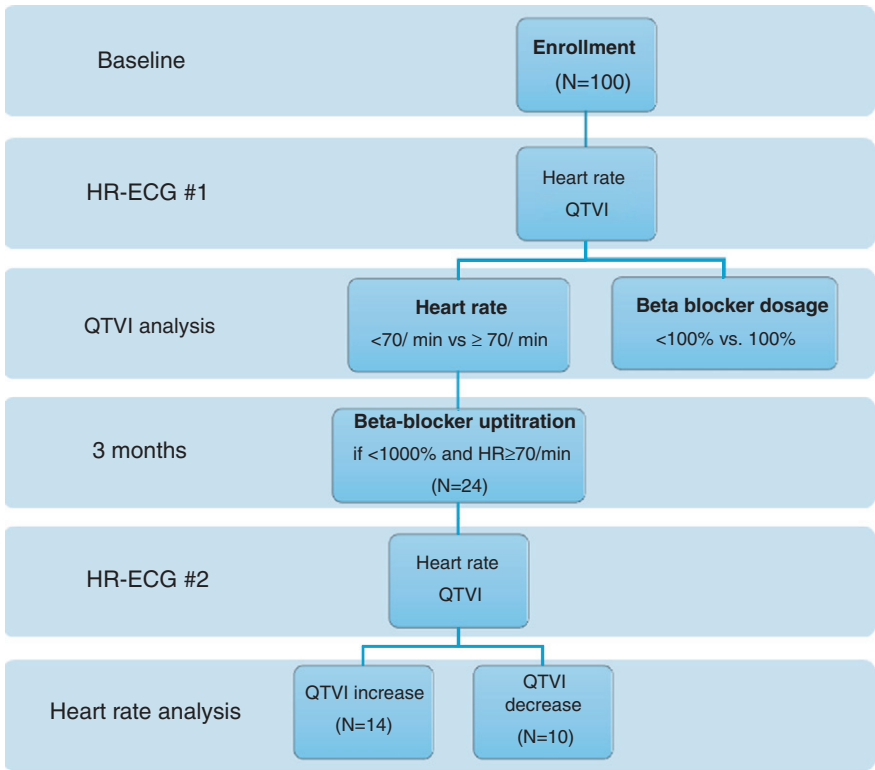

Fig. 1. Study protocol. In phase 1 of the study we recorded high resolution ECG (HR-ECG) in 100 patients with heart failure and compared QT variability (QTVI) in groups with- and without target heart rate (<70 bpm). In phase 2 we uptitrated beta blockers in patients without target heart rate and repeated HR-ECG after 3 months to analyze the relationship between heart rate a QTVI changes.