

Modification of Atrioventricular Node Conduction Increases RR Variability but not RR Irregularity in Atrial Fibrillation Patients

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Abstract

The aim of the present study was to evaluate the effect of rate-control drugs on variability and irregularity of RR series in patients with AF. We analyzed data of 30 patients (age 72 ± 8 years, 23 men) with permanent AF, from the RATAF (RATE control in Atrial Fibrillation) study. Three 20-min segments were selected at baseline, during beta-blocker (carvedilol) and calcium channel blocker (diltiazem) administration. For every 20-min segment, heart rate (HR) was estimated as well as variability (SDNN, rMSSD, pNN50) and irregularity (regularity index, approximate (ApEn) and sample (SampEn) entropy) of RR intervals. A significant lower HR is obtained with both drugs. Both drugs also increased the variability of ventricular response compared to baseline. On the contrary, only carvedilol increased the irregularity of the RR series. Modification of AV node conduction using beta-blockers or calcium-channel-blockers seems different: both classes of rate-control reduce HR and increase time-domain measures of heart rate variability, but only beta-blockers increase the irregularity measures.

1. Introduction

It has been suggested that irregularity measures are risk indicators in patients with atrial fibrillation (AF). A reduced irregularity of RR intervals in permanent AF was associated with poor outcome [1–4], having an independent prognostic value for cardiac mortality during long-term follow-up in patients with chronic AF [1]. More recently, reduced irregularity was found to be an independent predictor of all cause mortality, as well as sudden death in patients with AF and mild to moderate heart failure [3]. Even if these recent studies suggest potential use of irregularity measures as risk indicators in patients with AF, the effect of rate-control drugs on them has not been deeply

studied. Thus it is not known to what extent commonly used rate-control drugs can affect irregularity of RR series.

The aim of the present study was to evaluate the effect of rate-control drugs on variability and irregularity of RR series in patients with permanent AF. In particular, data from patients of the RATE control in Atrial Fibrillation (RATAF) study, designed to compare drug regimens used to reduce the ventricular heart rate in patients with permanent AF [5], were analyzed. The effect of carvedilol and diltiazem was assessed.

2. Methods

2.1. Patients

The present study is based on patient data collected in the RATE control in Atrial Fibrillation (RATAF) study. The RATAF study was a prospective, randomized, investigator-blind, crossover study designed to compare four drug regimens (metoprolol, diltiazem, verapamil, and carvedilol) used to reduce the ventricular heart rate (HR) in patients with permanent AF. Each drug was given for at least three weeks to ensure an adequate period of washout of the previous treatment and steady-state plasma concentrations. Before starting the first treatment and at the last day of each of the 4 treatment periods, 24-h Holter recordings were made. A detailed protocol of the study is described elsewhere [5].

In this study, we analyzed data from 30 patients, their characteristics are shown in Table 1. For each patient three 20-min segments were analyzed: during baseline, and after carvedilol and diltiazem administration, both starting at 2pm (when the drug effect was found to be maximal [5]).

Table 1. Clinical characteristics of the study population. Data are expressed as mean \pm SD or median (range).

Variable	Value
Age (years)	72 \pm 8
Gender (male/female)	23/7
AF duration (months)	15 (2-88)
Left Atrium Diameter (mm)	51 \pm 7
LAA	30 \pm 5
Ejection Fraction (%)	64 \pm 8

2.2. RR variability and irregularity

Variability parameters, computed in the time domain, include the mean (M), the standard deviation (SDNN) of all normal RR intervals, the root of the mean squared differences of successive RR intervals (rMSSD) and the percentage of interval differences of successive RR intervals greater than 50ms (pNN50) [6].

Irregularity of RR intervals was assessed by non-linear measures such as regularity index (R) [7] and approximate entropy (ApEn) [8]. The approximate entropy (ApEn) is a regularity statistic quantifying the unpredictability of fluctuations in a time series such as an instantaneous heart rate time series. Intuitively, the presence of repetitive patterns of fluctuation in a time series makes it more predictable than a time series in which such patterns are absent. ApEn reflects the likelihood that similar patterns of observations will not be followed by additional similar observations. A time series containing many repetitive patterns, i.e., a regular and predictable series, has a relatively small ApEn; a less predictable, i.e., more complex, process has a higher ApEn [8].

Conditional entropy may be used to estimate a regularity index, R, defined as the degree of recurrence of a pattern in a signal. The conditional entropy represents the amount of information carried by the most recent sample of a normalized realization of the series when its past L-1 samples are known. R tends to zero if the series is an unpredictable process and tends to one if the series is a periodic signal and it assumes intermediate values for those processes that can be partially predicted by the knowledge of the past samples [7].

2.3. Statistical analysis

A paired t-test or Wilcoxon test was applied. A p-value $<$ 0.05 was considered statistically significant.

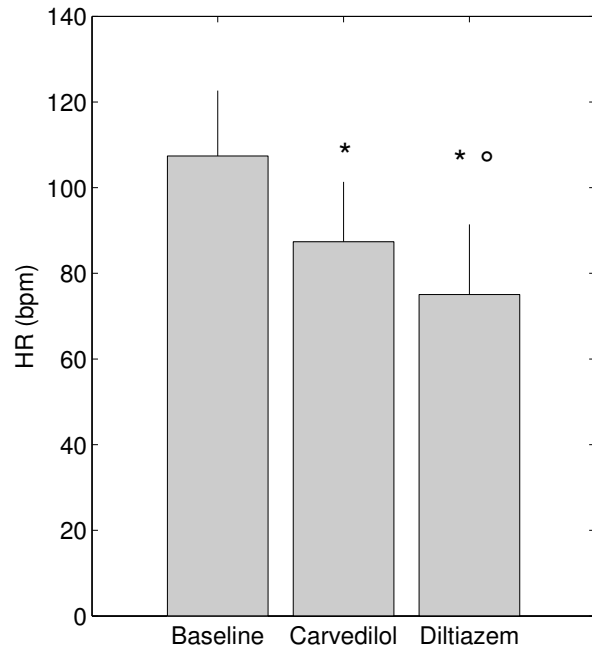


Figure 1. Mean and standard deviation of heart rate at baseline and after carvedilol and diltiazem administration. * p $<$ 0.001 vs. baseline, ° p $<$ 0.001 carvedilol vs. diltiazem

3. Results

Figure 1 shows the mean HR at baseline and after carvedilol and diltiazem administration. A significant reduction in HR can be observed with both drugs. In addition, the calcium channel blocker diltiazem reduced the HR more than the beta-blocker carvedilol.

The variability and irregularity parameters at baseline and after carvedilol and diltiazem administration are shown in Figure 2. Both drugs increased the variability of ventricular response compared to baseline. Moreover, diltiazem induced the highest increase in variability, resulting in a value of rMSSD significantly higher than carvedilol. On the contrary, it can be noted that only the beta-blocker carvedilol increased the irregularity of the RR series, making the series more irregular than at baseline, whereas the calcium channel blocker diltiazem did not affect it.

4. Discussion

In this study, we assessed for the first time the effect of rate-control drugs on heart rate variability and irregularity in the setting of randomized prospective cross-over designed study. We found a significant difference between

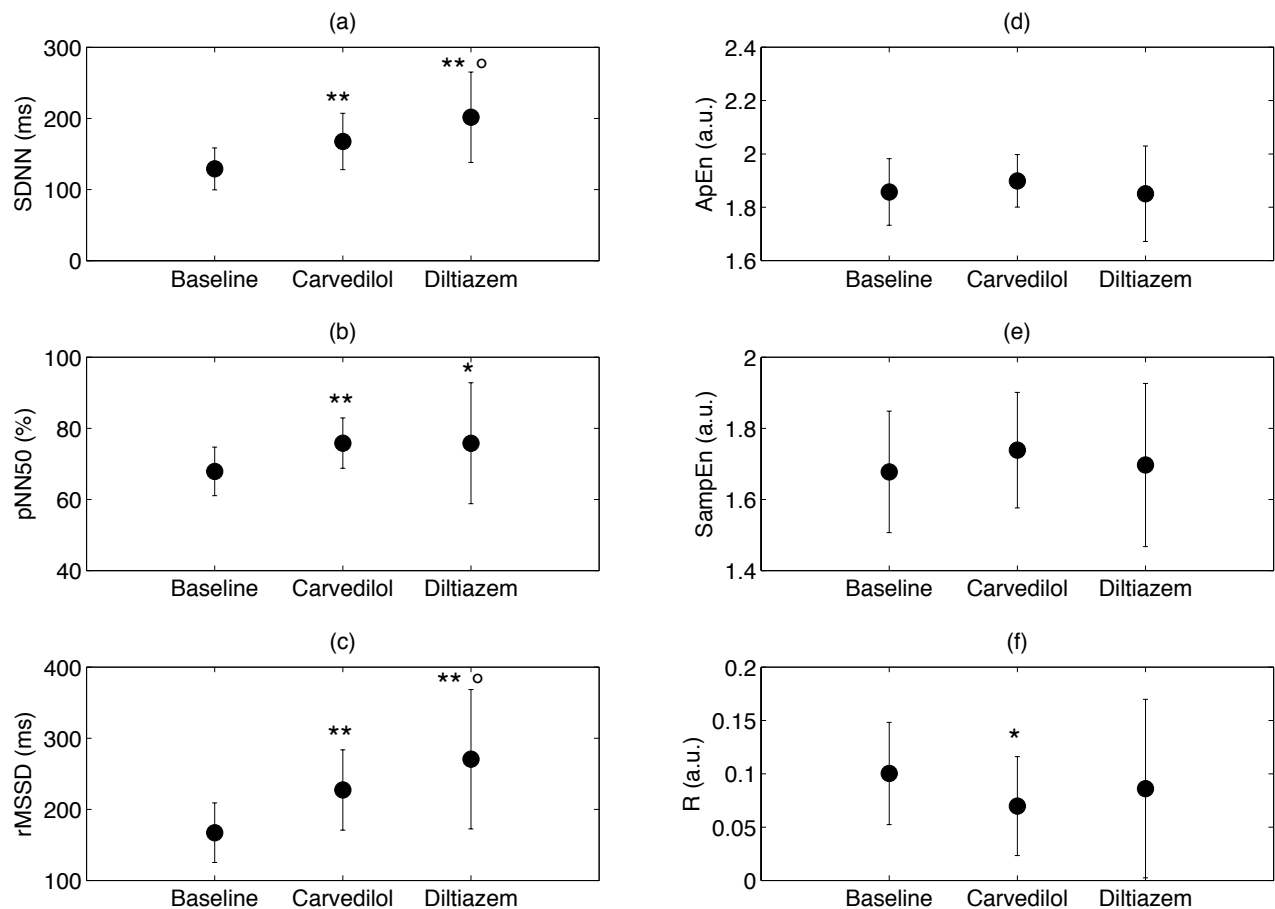


Figure 2. Mean and standard deviation of a variability (rMSSD) and an irregularity (ApEn) parameter at baseline and after carvedilol and diltiazem administration. * $p < 0.001$ vs. baseline, ° $p < 0.05$ carvedilol vs. diltiazem

the calcium channel blocker diltiazem and the beta-blocker carvedilol in regard to their effect on variability and irregularity of ventricular response in patients with permanent AF. The calcium channel blocker diltiazem reduced HR, increased time-domain measures of heart rate variability without effect on irregularity parameters. The beta-blocker carvedilol did not only reduce HR and increased time-domain measures of heart rate variability but also increased the irregularity parameters.

As irregularity measures were significantly associated with the long-term outcome in earlier studies [1–4], the different effect of rate-control drugs may need to be taken into account when assessing irregularity in AF patients as risk indicators.

However, to interpret the prognostic impact of RR-irregularity measures is very complex as most patients with permanent AF take rate-control medications. Previously, we studied patients with AF, and we did not observe any difference in RR-irregularity parameters between patients with congestive heart failure in regard to the use of either rate-control, rhythm-control or no antiarrhythmic

mic drugs at baseline [9]. In this study, rate-control drugs were administered in a controlled manner, and we showed that RR-irregularity measures seem to be unaffected by calcium channel blockers, whereas beta-blockers significantly, even though rather modestly, increased them.

In conclusion, we found that carvedilol and diltiazem influenced AV node conduction in patients with AF differently. They both reduced HR and increased time-domain measures of heart rate variability, but only carvedilol increased the irregularity measures. Therefore, use of beta-blocker carvedilol should be adjusted for when assessing irregularity in AF patients, that has been suggested as risk indicators in patients with AF.

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