Modification of Atrioventricular Node Conduction Increases RR Variability but not RR Irregularity nor Atrial Fibrillation Rate in Atrial Fibrillation Patients

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Abstract

We aimed at studying whether variability and irregularity of RR are modified by the selective A1 adenosine receptor agonist tecadenoson, the beta-blocker esmolol and their combination in patients with atrial fibrillation (AF). Twenty-one patients with AF were randomly assigned to either 75, 150 or 300 μg i.v. tecadenoson, administered alone and in combination with esmolol. The ECG was recorded continuously in the following 10-min phases: i) baseline1, ii) post-tecadenoson-dose1, iii) baseline2, ending at the time of the esmolol injection, iv) esmolol maintenance, v) post-tecadenoson-dose2. For every segment, heart rate (HR) and atrial fibrillatory rate (AFR) were estimated as well as variability and irregularity of RR intervals. Variability and irregularity parameters include SDNN, rMSSD, pNN50 and the regularity index, approximate entropy, respectively. In all groups, HR decreased after tecadenoson and esmolol further decreased HR. The AFR was unaffected after tecadenoson. All the variability parameters were increased after tecadenoson. On the contrary, irregularity parameters did not change after tecadenoson. In conclusion, modification of AV node conduction using beta-blockade and A1-adenosine receptor agonist can increase RR variability but does not affect irregularity of RR intervals.

1. Introduction

The irregular and usually high rate ventricular activity during AF is largely determined by atrioventricular (AV) nodal blocking of the atrial electrical impulses reaching to the AV node at a high rate. However, the exact relationships between the atrial and ventricular rate during AF are not fully understood at this point. Electrophysiological factors such as intrinsic refractoriness of the AV node and concealed conduction are known to influence the ventricular response [1]. Due to the AV node intrinsic refractoriness, many of the impulses are blocked when reaching the AV node [2]. Although ventricular response during AF is highly irregular, it is not completely random on short [3] or long term analysis [4], thus assessment of variability and irregularity of the RR series could provide useful insights into the arrhythmia. The few studies analyzing variability and irregularity of the RR series showed that a reduced irregularity of RR intervals in permanent AF was associated with poor outcome [5–8]. Even though these factors play a prominent role in ventricular rate control, they are not routinely evaluated in clinical practice. Also, it is not fully understood whether and how modification on AV conduction using rate control drugs affects RR variability and irregularity measures. The aim of the present study was to assess whether the variability and irregularity of the ventricular rate as well as atrial fibrillation frequency (AFR) are modified by a selective A1 adenosine receptor agonist tecadenoson and its combination with beta-blocker esmolol.

2. Methods

2.1. Tecadenoson

Tecadenoson (CVT-510) is a selective A1-adenosine receptor agonist with an immediate onset of action (less than one minute) and a half-life of approximately 30 minutes [9] (but with no documented effect on ventricular conduction or refractory period) developed specifically to exploit the A1-adenosine receptor-mediated effect of slowing conduction through the AV node [9, 10] while avoiding effects mediated by the A2 and A3 receptors (eg, vasodilation and bronchospasm as seen with adenosine) [9, 11].

2.2. Protocol

The analysis is based on the data collected in a phase II, open-label, sequential-group, dose-escalation trial of tecadenoson administered i.v. alone and in combination with esmolol. Detailed study protocol is as accessible via http://www.clinicaltrials.gov/ct2/show/study/NCT00713401. The study was aimed at assessment of tolerability and safety of a range of i.v. bolus doses of tecadenoson ad-

ministered alone to patients with AF. By study protocol, twenty-one patients with AF in need of treatment for rate control but otherwise clinically stable were randomly assigned to receive either 75, 150 or 300 μg i.v. tecadenoson. Tecadenoson was administered alone and in combination with esmolol (100 μg/kg/min for 10 minutes then 50 μg/kg/min for 50 minutes), a short- acting beta-blocker with a distribution half-life of two minutes and an elimination half-life after i.v. infusion of approximately nine minutes. The ECG was recorded continuously and Figure 1 shows the five analyzed phases: i) a 10-minute segment, defined so that it ended at the time of the first tecadenoson bolus (first baseline, B1), ii) the first 10-minute post-tecadenoson segment (T), iii) a 10-minute segment defined so that it ended at the time of the esmolol injection (second baseline, B2), iv) the first 10-minute segment during esmolol maintenance (E), v) the first 10-minute post-dose2 segment after the second tecadenoson bolus (T+E).

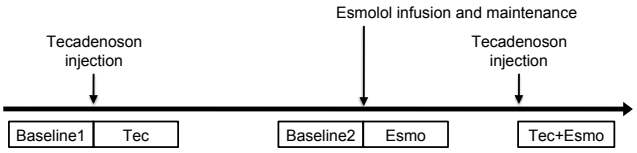

Figure 1. Protocol phases and drugs timing.

3. Methods

3.1. 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) [12].

Irregularity of RR intervals was assessed by non-linear measures such as regularity index (R) [13] and approximate entropy (ApEn) [14]. 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 [14].

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 [13].

3.2. Atrial fibrillatory rate

The AFR was computed in one-minute segment using spatiotemporal QRST cancellation and time frequency analysis as previously described [15]. Briefly, this procedure is based on a spectral profile, dynamically updated from previous spectra, which is matched to each new spectrum using weighted least squares estimation [16]. The frequency shift needed to achieve optimal matching then yields a measure of instantaneous fibrillatory rate of a 2.5-s ECG segment (overlapping with one segment each second) and was trended as a function of time. Frequencies were converted to fibrillatory rates with its unit fibrillations per minute (fpm, i.e., rate = frequency x 60). Mean fibrillatory rate (in fpm) was defined as the average of the instantaneous fibrillatory rates over the ten-minute ECG segment.

3.3. Statistical analysis

All the computed parameters were estimated for every 10-minute segment. A paired t-test or Wilcoxon-Mann-Whitney was applied for comparison between the different phases of the protocol for each dose regimen. A p-value <0.05 was considered statistically significant.

4. Results

Figure 2 shows the results divided according to the different doses for HR, AFR, rMSSD and R, exemplifying respectively the behavior of variability and irregularity parameters. In all groups, a marked decrease in HR can be observed after both tecadenoson injections, whereas almost no changes can be seen in AFR. Tecadenoson injection produced a decrease in HR of about 6% in all patients and esmolol further decreased HR in most patients. On the other hand, the AFR was unaffected immediately after the first tecadenoson injection, however, in patients taking either 150 or 300 μg of tecadenoson, esmolol significantly decreased the AFR.

In all patients, all the variability parameters were increased after tecadenoson bolus injection. On the contrary, irregularity parameters did not change after tecadenoson.

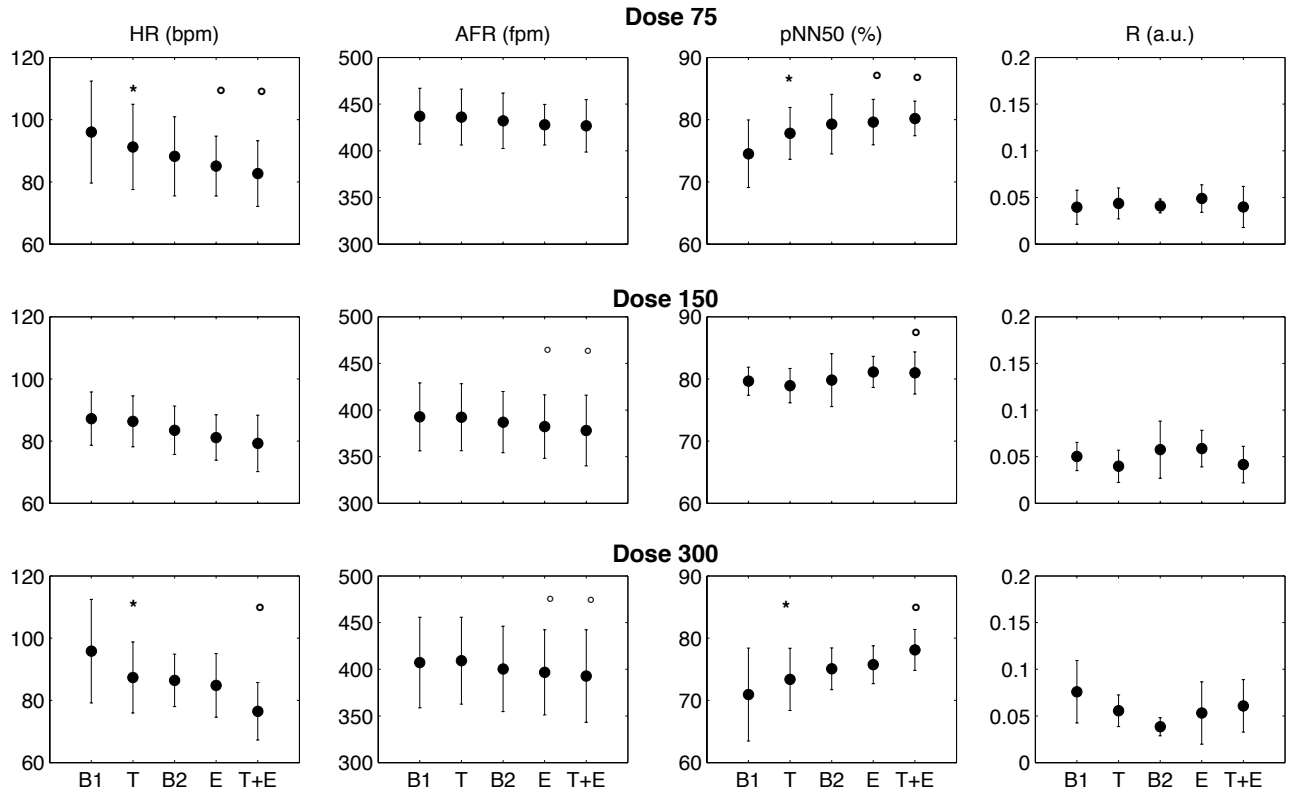

Figure 2. Mean and SD of heart rate (HR), atrial fibrillary frequency (AFR) rMSSD and R index for the five analyzed phases for patients taking tecadenoson dose 75 (top panels), 150 (middle panels) and 300 (bottom panels). * $p<0.05$ comparing tecadenoson (T) vs. baseline1 (B1); ° $p<0.05$ comparing esmolol (E) or tecadenoson plus esmolol (T+E) vs. baseline2 (B2).

5. Discussion and conclusion

The main findings of this study suggest that selective action of A1-adenosine receptor agonist tecadenosone results in reduction of HR, increase in time-domain measures of heart rate variability without effect on irregularity parameters and neutral effect on AFR. Beta-blockade with intravenous esmolol further increased all the variability parameters, decreased HR and AFR.

The current study, in which antiarrhythmics were administered in a controlled manner, demonstrate that RR-irregularity measures, which were significantly associated with the long-term outcome in earlier studies, seem to be unaffected by rate control using beta-blocker therapy and tecadenosone. Thus, the use of (at least) beta-blockers is not a concern that one should adjust the model for when assessing the hazard ratio of reduced regularity in AF population. Both RR irregularity and AFR seem to be stable parameters not affected by rate-control drug tecadenoson or beta-blocker.

In conclusion, modification of AV node conduction using beta-blockade and A1-adenosine receptor agonist can increase RR variability but does not affect irregularity of RR-intervals. Relative stability of RR-irregularity measures during AF supports the use of non-linear indices of RR behavior, such as ApEn, for prediction of clinical outcome in patients with AF in large-scale trials. Esmolol possesses modest effect on AFR slowing in patients with clinical AF while tecadenoson did not show AF provoking effect associated with non-selective adenosine receptor blockade.

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