Beta-blockade and A1-adenosine receptor agonist effects on atrial fibrillatory rate and atrioventricular conduction in patients with atrial fibrillation

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Introduction

The irregular and usually high-rate ventricular activity during atrial fibrillation (AF) is largely determined by atrioventricular (AV) node properties, being some atrial electrical impulses delayed, and others blocked by the AV node. 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] Owing to the AV node intrinsic refractoriness, many of the impulses are blocked when reaching the AV node.[2] Concealed conduction of a single atrial impulse, occurring when the impulse traverses part of the AV node but is not conducted to the ventricles, influences the conduction of subsequent beat or beats.[3,4]

Although ventricular response during AF is highly irregular, it is not completely random on short-[5] or long-term analysis;[6] thus assessment of the variability and irregularity of the RR series could provide useful insights into the arrhythmia. The few studies analysing variability and irregularity of the RR series showed that a reduced irregularity of RR intervals in permanent AF was associated with a poor outcome.[7–10] The very first study by Yamada *et al.*[7] showed that a reduced RR irregularity in a 24 h ambulatory electrocardiogram (ECG) had an independent prognostic value for cardiac mortality

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What's new?

- The selective A1-receptor agonist tecadenoson aiming at reduction of ventricular rate during atrial fibrillation does not affect the atrial fibrillatory rate. This suggests that the selective A1-receptor agonist action does not shorten atrial refractoriness and lacks the atrial fibrillation provoking effects associated with non-selective adenosine receptor agonist.
- Modification of atrioventricular node conduction using beta-blocker and A1-receptor agonist can increase RR variability, but does not affect the irregularity of RR intervals. The relative stability of the RR irregularity measures during atrial fibrillation supports the use of non-linear indexes of RR behaviour for outcome prediction in large-scale trials.

during long-term follow-up in patients with chronic AF. More recently, in a *post hoc* analysis, reduced variability of RR intervals during AF, probably caused by autonomic dysfunction, was found to be an independent predictor of all-cause mortality in patients with left ventricular dysfunction following myocardial infarction.[8] Reduced irregularity was an independent predictor of all-cause mortality, as well as sudden death and heart failure progression in patients with mild-to-moderate heart failure.[9] Nevertheless, the effect of rate-control drugs on irregularity of ventricular response has not been studied in controlled settings.

Higher atrial fibrillatory rate (AFR) has recently been associated with increased irregularity of the RR series[7] in a large population of patients with AF, taking various antiarrhythmic drugs. However, this study also indicated the variable effects of AV blocking agents on ventricular response, being the RR irregularity measures strongly associated with AFR in patients not taking antiarrhythmic drugs while this correlation is much weaker in the treated patients, which probably results from the unequal effects of antiarrhythmic drugs on atrial and AV nodal electrophysiology.[11] Whether the irregularity of the ventricular response depends exclusively on the AV node properties or it is also affected by the AFR is not fully elucidated at this point. It is not known to what extent the AFR and the irregularity of ventricular response are stable characteristics of the fibrillatory process that can be considered intrinsic features of the AF substrate or whether they are affected by drugs.

The aim of the present study was to assess whether the AFR and the variability and irregularity of the ventricular rate are modified by a selective A1-adenosine receptor agonist tecadenoson and beta-blocker esmolol.

Methods

Tecadenoson

Tecadenoson (CVT-510) is a selective A1-adenosine receptor agonist with an immediate onset of action ($<$1 min) and a half-life of $\sim$30 min[12] (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,[12,13] while avoiding the effects mediated by the A2 and A3 receptors (e.g. vasodilation and bronchospasm as seen with adenosine).[12,14]

Protocol

The analysis is based on the data collected in a phase II, open-label, sequential-group, dose-escalation trial of tecadenoson administered intravenous (i.v.) alone and in combination with esmolol. The detailed study protocol is accessible via http://www.clinicaltrials.gov/ct2/show/study/NCT00713401. The study was aimed at an assessment of tolerability and safety of a range of i.v. bolus doses of tecadenoson administered alone to patients with AF. As per the study protocol, 21 patients with AF in need of treatment for rate control, but otherwise clinically stable were randomly assigned to receive either 75 (Group A), 150 (Group B), or 300 (Group C) μg i.v. tecadenoson.

Tecadenoson was administered alone (Dose Period 1) and in combination (Dose Period 2) with esmolol (100 μg/kg/min for 10 min then 50 μg/kg/min for 50 min), a short-acting beta-blocker with a distribution half-life of 2 min and an elimination half-life after i.v. infusion of $\sim$9 min. The ECG recording started within 15 min prior to Dose Period 1. The start of esmolol infusion was to commence at least 75 min, but no more than 150 min after administration of the tecadenoson bolus injection in Dose Period 1. Following the tecadenoson bolus injection in Dose Period 2, ECG was recorded for 20 min. The protocol phases can be seen in *Figure 1*.

Any concomitant antiarrhythmic therapy (including AV nodal blocking agents) must have been temporarily discontinued from no later than 8:00 pm on the day prior to study drug dosing until completion of the last dose period assessment. Blood samples for plasma levels of antiarrhythmics and AV nodal blocking agents were collected prior to tecadenoson bolus in both Periods 1 and 2.

The study complied with the Declaration of Helsinki, the research protocol was approved by the ethics committee, and informed consent was obtained from all the subjects.

Phase definition

The Holter recording was divided into non-overlapping 10 min segments, thus the following segments were considered:

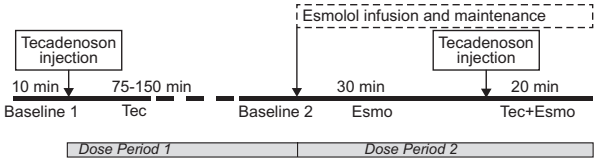

Figure 1 Protocol phases and drugs timing. Tecadenoson was administered alone (Dose Period 1) and in combination with esmolol (Dose Period 2). The ECG recording started within 15 min prior to Dose Period 1 and was continuously recorded throughout the whole protocol. The start of esmolol infusion was to commence at least 75 min but not more than 150 min after administration of the tecadenoson bolus injection in Dose Period 1. Electrocardiogram recording continued until 20 min after the tecadenoson bolus in Dose Period 2.

- Baseline1: the first 10 min segment, defined so that it ended at the time of the first tecadenoson bolus.
- Six post-dose1 segments, among whom the first one is named Tec (all the patients had at least 60 min after the first tecadenoson bolus).
- Baseline2: one 10 min segment defined so that it ended at the time of the esmolol injection.
- Three 10 min segments of esmolol maintenance, among whom the first one is named Esmo.
- Two post-dose2 segments after the second tecadenoson bolus, with esmolol still maintained, among whom the first one is named Tec + Esmo.

RR variability

Time-domain analysis includes the heart rate (HR), the standard deviation (SD) 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 20 ms (pNN20), 50 ms (pNN50), and 80 ms (pNN80).[15]

RR irregularity

Irregularity of RR intervals was assessed by non-linear measures such as regularity index (*R*) and approximate entropy (ApEn). For a visual explanation of the difference between variability and irregularity of RR series see *Figure 2*.

Approximate entropy

The ApEn is a regularity statistic quantifying the unpredictability of fluctuations in a time series such as an instantaneous HR 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. Approximate entropy 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 and a less predictable, i.e. more complex process has a higher ApEn.[16]

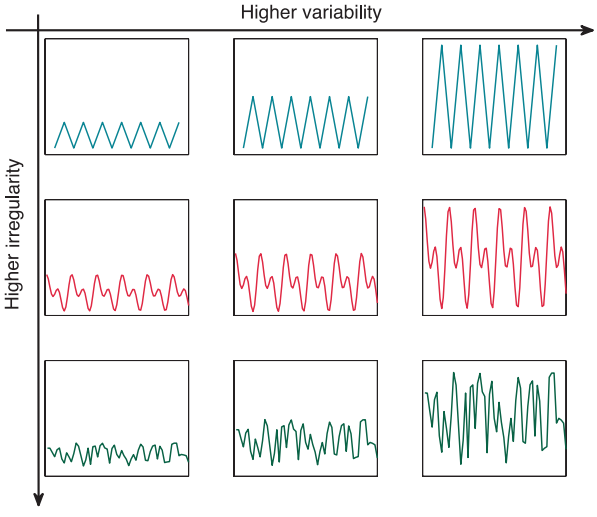

Figure 2 Figure explaining the difference between variability and irregularity in the time series. Each row shows series with the same irregularity but increasing variability going from the left to the right, whereas each column shows series with the same variability but different increasing irregularity moving from the top to the bottom.

Regularity

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. The regularity index, *R*, tends to 0 if the series is an unpredictable process and tends to 1 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.[17]

Atrial fibrillatory rate

The AFR was computed in a 1 min segment using spatiotemporal QRST cancellation and time–frequency analysis[18] and the resulting fibrillatory signal was downsampled to 50 Hz and subjected to spectral analysis. The time–frequency distribution of the atrial signal (obtained by short-term Fourier transform) was decomposed such that each spectrum can be modelled as a frequency-shifted and amplitude-scaled version of the spectral profile. This procedure is based on a spectral profile, dynamically updated from the previous spectra, which is matched to each new spectrum using weighted least-squares estimation.[19] 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. The frequencies were converted to fibrillatory rates with its unit fibrillations per minute (f.p.m., i.e. rate = frequency $\times$ 60). Mean fibrillatory rate (in f.p.m.) was defined as the average of the instantaneous fibrillatory rates over the 10 min ECG segment.

Statistical analysis

All the computed parameters were estimated for every 10 min segment. A paired *t*-test or Wilcoxon–Mann–Whitney was applied for comparison between different phases of the protocol for each dose regimen.

A *P* value <0.05 was considered statistically significant. All analyses and statistical tests were performed using MATLAB® R2008a (The MathWorks).

Results

Patient characteristics and data availability

In total, 21 patients (age 58 $\pm$ 7 years, 13 men) were included in the study, 7 in each dosing Groups A, B, and C. Twelve patients had long-standing persistent AF (defined as AF duration >12 months). The clinical characteristics are presented in *Table 1*. All the patients given tecadenoson were included in statistical summaries by dose regimen. One patient in Group B was excluded from the study because of a lengthy gap in the ECG recording, beginning just

before the second tecadenoson bolus dose administration and ending ~1 h later.

For rate control purposes, three patients were treated with verapamil and six with bisoprolol. Nine patients received amiodarone prior to inclusion in the study. Blood samples were collected for antiarrhythmic agent plasma concentration prior to tecadenoson infusion start and appeared below the therapeutic concentrations in all but one patient (Group A), who was treated with amiodarone (102% of the lower limit).

Table 1 Demographic characteristics and cardiovascular history in the study population

Variable	Group A (7)	Group B (6)	Group C (7)
Age (years)	57 ± 9	58 ± 7	58 ± 8
Gender (male/female)	6/1	3/3	4/3
AF duration (months)	14 (1–168)	20.5 (1–60)	60 (0.5–122)
BMI	27.4 ± 2.8	29.0 ± 2.5	26.9 ± 3.5
Heart failure	3	3	4
Diabetes	0	0	0
Hypertension	6	5	4
Dyslipidaemia	3	3	4
Previous MI	0	0	0

Group A (patients taking tecadenoson dose 75), Group B (patients taking tecadenoson dose 150), and Group C (patients taking tecadenoson dose 300). Atrial fibrillation duration is reported as median and range (minimum–maximum).

Non-antiarrhythmic medications included vitamin K antagonists (76% took warfarin), angiotensin-converting enzyme inhibitors (19% took captopril, 19% took enalapril, and 19% took perindopril), and platelet aggregation inhibitors (29% took acetylsalicylic acid). There was no difference in drug use between the groups.

Dosage effect

Figure 3 shows the trend of normalized HR and AFR at different dosages. In all groups, a marked decrease in HR can be observed after both tecadenoson injections, whereas almost no changes can be seen in the AFR.

The first tecadenoson injection produced a decrease in HR of about 6% and in all patients but three (one of Group A and two in Group B). In particular, a decrease of 5 ± 5 b.p.m. ($P < 0.05$), 1 ± 2 b.p.m. (ns), and 8 ± 6 b.p.m. ($P < 0.01$) was found in Groups A, B, and C, respectively, after the first bolus. Similar results were found after the second tecadenoson injection (2 ± 2 b.p.m. ($P < 0.05$), 3 ± 5 b.p.m. (ns), and 7 ± 3 b.p.m. ($P < 0.01$) in Groups A, B, and C, respectively). Esmolol further decreased HR in most patients.

On the other hand, the AFR was unaffected immediately after the first tecadenoson injection; however, in Groups B and C, esmolol decreased the AFR (*Table 2*). The second tecadenoson bolus on ttop of the ongoing esmolol infusion further decreased the AFR. In all dosage groups the combination of esmolol and tecadenoson resulted in lower AFR than tecadenoson alone (significant difference between Tec vs. Tec + Esmo).

Tables 2–4 present the variability and irregularity parameters values for the most relevant phases of the protocol.

In the patients of Group A, all the variability parameters were significantly increased after the first tecadenoson bolus injection: both

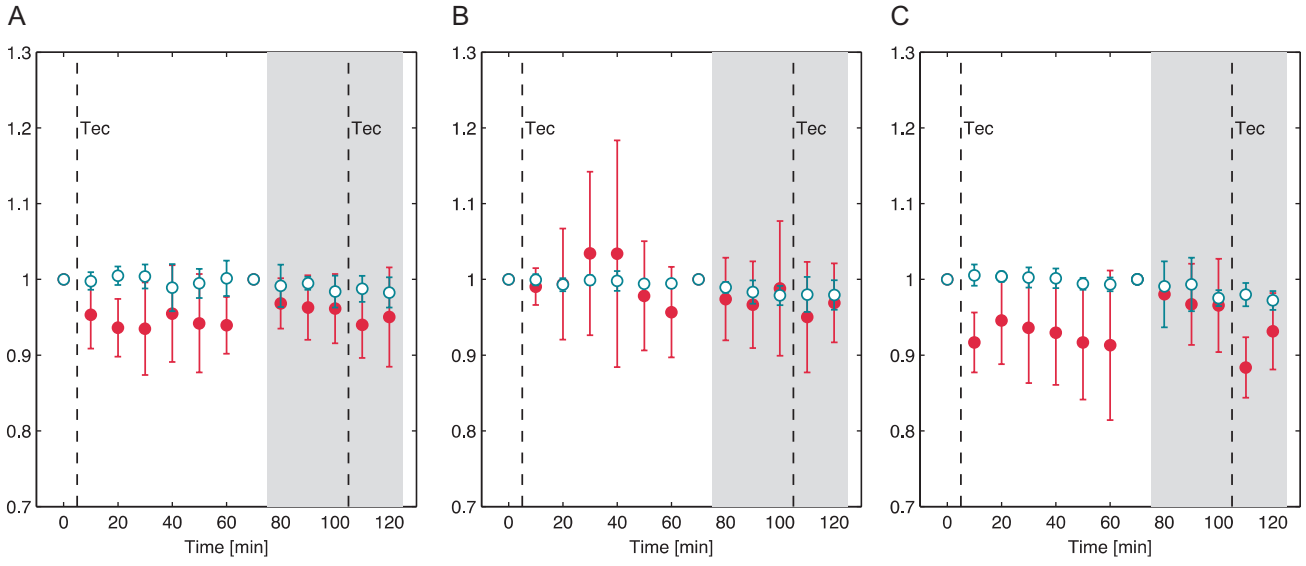

Figure 3 Trend of normalized HR (black circles) and normalized AFR (empty circles) plus SD, for the three groups of patients taking (*A*) 75, (*B*) 150, and (*C*) 300 mcg. Each dot represents the value of a 10 min segment, the timing of tecadenoson injections is shown by the dashed line, while the grey area represents esmolol maintenance. A significant decrease of HR can be noted after both tecadenoson injections, whereas the AFR remains un-changed. The first seven segments are normalized to Baseline1 (first point) whereas the others are normalized to Baseline2 (nineth point).

Table 2 Mean and SD of computed parameters for the most significant phases of the protocol for Group A (patients taking tecadenoson dose 75)

	Baseline1	Tec	Baseline2	Esmo	Tec + Esmo
HR (b.p.m.)	94 ± 16	91 ± 14*	88 ± 13	85 ± 10$^{\circ +}$	83 ± 11$^{\circ \# \S}$
AFR (f.p.m.)	437 ± 30	436 ± 30	432 ± 30	428 ± 22^{+}	427 ± 28§
SD (ms)	142 ± 31	154 ± 32*	161 ± 35	171 ± 32$^{\circ +}$	177 ± 40$^{\circ \S}$
pNN20 (%)	90 ± 3	92 ± 2*	92 ± 3	92 ± 2	92 ± 1
pNN50 (%)	74 ± 5	78 ± 4*	79 ± 5	80 ± 4^{+}	80 ± 3§
pNN80 (%)	64 ± 7	67 ± 5*	69 ± 6	71 ± 5$^{\circ +}$	70 ± 4§
rMSSD (ms)	196 ± 45	217 ± 44*	227 ± 49	241 ± 43$^{\circ +}$	250 ± 55$^{\circ \S}$
ApEn (a.u.)	1.63 ± 0.08	1.62 ± 0.06	1.61 ± 0.07	1.59 ± 0.06	1.61 ± 0.08
R (a.u.)	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.02

*$P < 0.05$ comparison with Baseline1.
$^{\circ}P < 0.05$ comparison with Baseline2.
$^{\#}P < 0.05$ Esmo vs. Tec + Esmo.
$^{\S}P < 0.05$ Tec vs. Tec + Esmo.

Table 3 Mean and SD of computed parameters for the most significant phases of the protocol for Group B (patients taking tecadenoson dose 150)

	Baseline1	Tec	Baseline2	Esmo	Tec + Esmo
HR (b.p.m.)	87 ± 9	86 ± 8	83 ± 8	81 ± 7^{+}	79 ± 9$^{\circ \S}$
AFR (f.p.m.)	426 ± 90	427 ± 90	422 ± 91	418 ± 93$^{\circ +}$	415 ± 97$^{\circ \S}$
SD (ms)	163 ± 20	166 ± 14	175 ± 13	181 ± 23^{+}	194 ± 28$^{\# \S}$
pNN20 (%)	92 ± 2	91 ± 1	93 ± 2	93 ± 1^{+}	93 ± 2
pNN50 (%)	80 ± 2	79 ± 3	80 ± 4	81 ± 2^{+}	81 ± 3§
pNN80 (%)	70 ± 4	69 ± 4	71 ± 4	72 ± 4^{+}	72 ± 5§
rMSSD (ms)	229 ± 26	233 ± 16	243 ± 29	252 ± 33	269 ± 37$^{\S \#}$
ApEn (a.u.)	1.61 ± 0.04	1.62 ± 0.05	1.60 ± 0.03	1.58 ± 0.02^{+}	1.55 ± 0.04$^{\S \#}$
R (a.u.)	0.05 ± 0.01	0.04 ± 0.02	0.06 ± 0.03	0.06 ± 0.02	0.04 ± 0.02

$^{\circ}P < 0.05$ comparison with Baseline2.
$^{+}P < 0.05$ Esmo vs. Tec.
$^{\#}P < 0.05$ Esmo vs. Tec + Esmo.
$^{\S}P < 0.05$ Tec vs. Tec + Esmo.

in the 10 min segment immediately after injection and after 30 min, i.e. half-life of tecadenoson (except for rMSSD). On the contrary, the irregularity parameters did not change after tecadenoson. When esmolol was infused, all the variability parameters further increased (both compared with tecadenoson only and to Baseline2). When assessing variability during the combination of tecadenoson and esmolol with tecadenoson alone they were all significantly higher.

In the patients of Group B, the variability parameters were not increased after the first tecadenoson bolus injection. During esmolol infusion and during its combination with tecadenoson, the parameters were significantly higher than during tecadenoson alone. In these patients, ApEn was significantly lower after esmolol and during its combination with tecadenoson when compared with tecadenoson alone.

In the patients of Group C, only the SD of the RR series and rMSSD were significantly increased after the first tecadenoson bolus injection: both in the 10 min segment immediately after injection and after 30 min. The irregularity parameters did not change after tecadenoson. When esmolol was infused, all the variability parameters further increased but not significantly. The combination of tecadenoson and esmolol significantly increased almost all the variability parameters in comparison with tecadenoson or esmolol alone.

Figure 4 shows the trend of variability (rMSSD) and an irregularity (R) measure in the three groups of patients. It can be noted that the variability measure is affected by tecadenoson whereas the irregularity measure is not.

Discussion

The main findings of this study suggest that the selective A1-receptor agonist tecadenoson reduces HR and increases time-domain measures of HR variability without effect on the irregularity parameters

Table 4 Mean and SD of computed parameters for the most significant phases of the protocol for Group C (patients taking tecadenoson dose 300)

	Baseline1	Tec	Baseline2	Esmo	Tec + Esmo
HR (b.p.m.)	96 ± 17	87 ± 11*	86 ± 8	85 ± 10	76 ± 9$^{\circ\S\#}$
AFR (f.p.m.)	407 ± 49	409 ± 47	422 ± 46	397 ± 46$^{\circ+}$	393 ± 50$^{\circ\S}$
SD (ms)	123 ± 21	136 ± 27*	139 ± 26	142 ± 19	174 ± 30$^{\circ\#\S}$
pNN20 (%)	88 ± 3	89 ± 2	91 ± 1	90 ± 2	92 ± 1§
pNN50 (%)	71 ± 7	73 ± 5	75 ± 2	76 ± 3	78 ± 3$^{\circ\S\#}$
pNN80 (%)	59 ± 10	61 ± 6	63 ± 5	65 ± 5^{+}	68 ± 4$^{\circ\S\#}$
rMSSD (ms)	161 ± 38	182 ± 39*	191 ± 37	196 ± 28	235 ± 37$^{\circ\S\#}$
ApEn (a.u.)	1.61 ± 0.06	1.59 ± 0.07	1.59 ± 0.05	1.60 ± 0.07	1.54 ± 0.07$^{\S\#}$
R (a.u.)	0.08 ± 0.03	0.06 ± 0.02	0.04 ± 0.01	0.05 ± 0.03	0.06 ± 0.03

*$P < 0.05$ comparison with Baseline1.
$^{\circ}P < 0.05$ comparison with Baseline2.
$^{+}P < 0.05$ Esmo vs. Tec.
$^{\#}P < 0.05$ Esmo vs. Tec + Esmo.
$^{\S}P < 0.05$ Tec vs. Tec + Esmo.

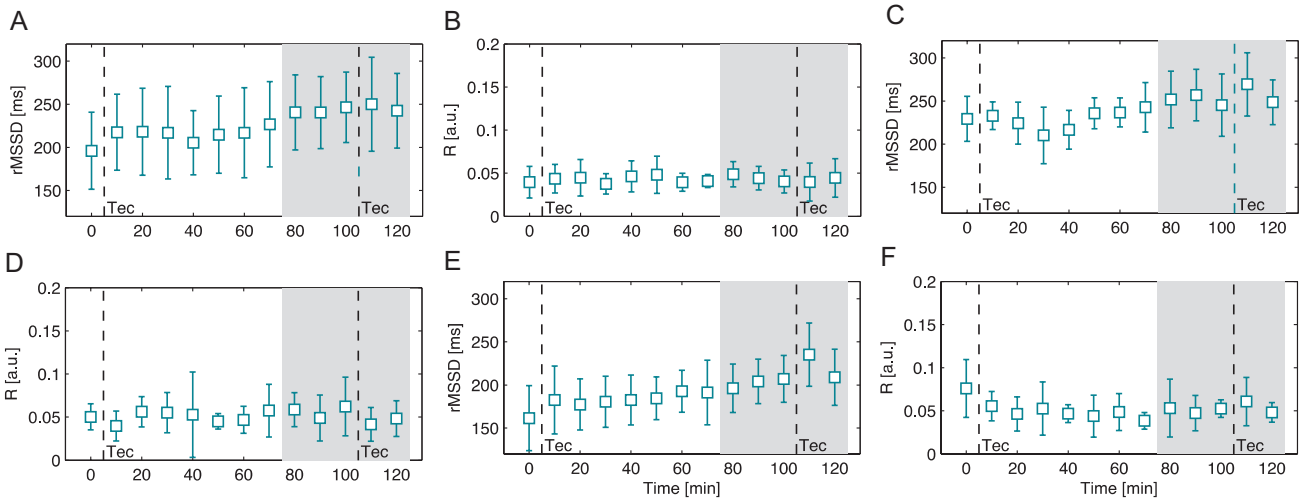

Figure 4 Trend of rMSSD (a variability parameter) and *R* (an irregularity parameter) plus SD for the three groups of patients taking (*A*) 75, (*B*) 150, and (*C*) 300 mcg. Each dot represents the value of a 10 min segment, the timing of the tecadenoson injections is shown by the dashed line, while the grey area represents esmolol maintenance. A significant increase of rMSSD can be noted after both tecadenoson injections, whereas *R* remains un-changed.

and has a neutral effect on AFR. Beta-blockade with intravenous esmolol further increased all the variability parameters and decreased HR and AFR.

To the best of our knowledge, any long-term clinical benefits of modulation of variability and regularity of AV conduction during AF, apart from the effect of ventricular rate reduction, has not been demonstrated. Therefore, our findings should be interpreted as an attempt to clarify, in a controlled manner, the effect rate-control drugs have on AV conduction characteristics to assess the reliability of RR variability and irregularity indices that appear to be linked to prognosis in patients with AF.[7–9] Reduced irregularity of the RR intervals in a 24 h ambulatory ECG appeared to be an independent predictor of cardiac mortality during long-term follow-up in patients with chronic AF.[7] More recently, a reduced variability of RR intervals during AF during long-term follow-up in patients with chronic AF, probably caused by autonomic dysfunction, was found to be an independent predictor of all-cause mortality in patients with left ventricular dysfunction following myocardial infarction[10] and in patients with mild-to-moderate heart failure.[9] Interpretation of the prognostic effect of the RR irregularity measures is, however, rather complex since a majority of patients with permanent AF take rate-control medication. In our earlier study,[20] we did not observe any difference in RR irregularity parameters during AF in patients with congestive heart failure regardless of the antiarrhythmic drug use. The current

study, in which antiarrhythmics were administered in a controlled manner, demonstrate that the 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 tecadenoson. Thus, the use of (at least) beta-blockers is not a concern that one should adjust the model when assessing the hazard ratio of reduced regularity in the AF population. Both the RR irregularity and the AFR seem to be stable parameters not affected by the rate-control drug tecadenoson or the beta-blocker.

With regard to the AFR response to antiarrhythmic drug use, earlier studies have shown antiarrhythmic class I and class III drugs propensity to prolong atrial fibrillatory cycle length and thus reduce AFR. Procainamide,[21–24] propafenone,[21] disopyramide,[25] cibenzoline,[26] sotalol,[27] and ibutilide[24,28] have all been shown to reduce the average frequency of fibrillatory activity. The magnitude of slowing appears to correlate with the drug effect. Boahene *et al.*[21] noted that procainamide- and propafenone-induced slowing of atrial cycle length was greater in patients who were successfully converted from AF to sinus rhythms.

In addition, some rate-control drugs such as verapamil have also been reported to reduce AFR but not to the extent sufficient for restoration of sinus rhythm.[29] With regard to the beta-blockade, their effect on AFR slowing has been uncertain even though beta-blockers possess moderate antiarrhythmic effect against AF recurrence,[30] and esmolol administration was associated with a higher rate of sinus rhythm restoration in patients with AF after coronary artery bypass surgery.[31] In one study by Sticherling *et al.*,[32] the effect of esmolol on atrial fibrillatory cycle length was assessed in patients with pacing-induced AF and appeared to be neutral. Our study included patients with permanent AF and showed that beta-blocker therapy alone, at least when given intravenously, can result in AFR reduction in a similar manner, even though at a lesser extent, as reported earlier for class I and class III antiarrhythmics.

Finally, the lack of tecadenoson effect on AFR suggests that despite the potent effect of the A1-adenosine receptor agonist on AV conduction resulting in significant slowing of the ventricular response, the electrophysiological properties of atrial myocytes are minimally affected. This is in contrast to the effect of non-selective A-receptor agonist adenosine that is used in acute treatment of supraventricular tachycardias, but its use can provoke AF and is associated with shortening of atrial refractoriness.[33] In the atrial-paced isolated guinea pig heart, tecadenoson has shown its potential to shorten the atrial, but not ventricular, monophasic action potential,[13] which could however not be translated in modification of the AFR in our clinical study. Apart from the difference between species that might explain the lack of tecadenoson effect on AFR, the patients who received tecadenoson in our study had significant cardiovascular comorbidities that may have had an effect on the atrial substrate and were associated with atrial structural remodelling that would affect the responsiveness of the atrial myocytes to the A1-receptor agonist.

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

Study limitations

Even though antiarrhythmic drugs were discontinued at least 24 h prior to start of the study drug infusion, as per the study protocol, this is certainly less than five half-lives commonly used in electrophysiological studies. We can therefore not completely rule out the residual effect of concomitant medications on AV conduction. However, plasma concentrations of antiarrhythmic drugs were checked prior to infusion start and were found to be below the therapeutic range in all but one subject who was treated with amiodarone.

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