Inverse Correlation between the Atrial Fibrillatory Rate and the Ventricular Repolarization Time: Observations at Baseline and after an Intravenous Infusion of a Combined Potassium and Sodium Current Blocker

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Background: The atrial fibrillatory rate (AFR) and the ventricular rate and repolarization (QTcF) were studied at baseline and under the influence of the combined potassium and sodium current blocker AZD7009.

Methods: Ninety-two patients with atrial fibrillation (AF) were randomized to an intravenous infusion of AZD7009 or placebo. The atrial fibrillatory activity in lead V₁ was extracted using spatiotemporal QRST cancellation. The exponential decay (ED) characterized the degree of atrial signal organization.

Results: The mean (SD) AFR at baseline was 396 ± 57 (range 253–584) and 410 ± 33 (range 363–469) bpm in patients randomized to AZD7009 and placebo, respectively. The AFR decreased within the first minutes of the AZD7009 infusion and reached its minimum of 235 ± 34 bpm after 18 minutes. On placebo, the AFR was unchanged. On AZD7009, the ED decreased from 1.2 ± 0.3 to reach its lowest level at 0.7 ± 0.2 after 14 minutes. The ventricular rate did not change significantly over time. The AFR was statistically significantly related to the ventricular repolarization at baseline, the QTcF being longer at lower AFR values, and this relationship remained during and after AZD7009. In the full multivariate linear regression model, including age, sex, left ventricular ejection fraction, QRS duration, heart rate, QTcF, AF episode duration, AF history duration, and right atrial or left atrial size, only QTcF and age were statistically significantly correlated with the AFR. The correlation remained when the uncorrected QT interval was used.

Conclusions: The QTcF was inversely correlated with AFR, both at baseline and during administration of AZD7009. The AFR was not correlated with the ventricular rate.

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The atrial fibrillatory rate (AFR) is high, typically reported as being between 350 and 600 fibrillations per minute (fpm). The ventricular heart rate (HR) also varies greatly but at a much lower level. The role of the atrioventricular (AV) node as a

modulator of the HR is well known, but there is as yet limited information about any relationship between the AFR and the HR, including the relative effects of medications on the AFR and HR. The AFR has not been shown to be an independent

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predictor of the HR, but circadian patterns in AFR concurring with HR changes suggested a modulating influence of the autonomic nervous system on atrial electrophysiology in persistent human AF.¹ However, an early study in the isolated rabbit heart found an inverse relationship between the AFR and HR during electrically induced AF, thus concluding that the HR during AF is not only determined by the properties of the AV node but also by the rate and irregularity of the fibrillatory process.² This is in keeping with the observation of a relation between populations of predominant RR intervals and multiples of the dominant atrial cycle length, suggesting that RR intervals are caused by different conduction ratios of the AFR.³

In a study on conversion of AF to sinus rhythm (SR) by the investigational compound AZD7009, there was a consistent and rapid slowing of the AFR, and the rate of the decrease was significantly higher in converters to SR. The standard deviation of the AFR (AFR-SD) and the exponential decay (ED) decreased as well. The AFR at baseline was not predictive of conversion by AZD7009. An estimated short duration of the AF episode correlated significantly with an AZD-7009-induced decrease of the AFR, but a small atrial area was the only baseline variable that predicted AZD-7009-induced conversion to SR.⁴

The aim of the present analysis was to study the AFR and its relationship to the ventricular rate and repolarization at baseline and under the influence of AZD7009.

METHODS

Patients

This substudy of a double-blind, randomized, placebo-controlled, parallel group study included 92 patients, aged between 18 and 80 years and with a clinical indication for conversion of AF and a current AF episode of 2–90 days' duration. The main study was designed to investigate the efficacy of intravenous cardioversion by AZD7009, a combined sodium and potassium channel blocker, the main results of which have been reported previously.⁴ Patients who met the inclusion and exclusion criteria and provided their written informed consent were randomized to receive one of three dose regimens of the active

drug, 3.25 mg/mL for 15 minutes (n = 14), 3.25 mg/mL for 30 minutes (n = 42), and 4.4 mg/mL for 15 minutes (n = 14), or placebo (n = 22). If patients achieved pharmacological conversion during infusion, the infusion was stopped after SR had been maintained for 2 minutes. If patients did not achieve pharmacological cardioversion within 90 minutes of the start of infusion, they underwent biphasic direct current (DC) cardioversion. The study was carried out in accordance with the Declaration of Helsinki and was approved by appropriate local and national ethical review boards. The present analysis included all 35 patients who received AZD7009 and converted to SR and 35 nonconverters, who were matched so that the current AF episode differed <1 week in conjunction with a difference in an atrial size of <10 cm². The placebo group of 22 patients was also included.

Continuous recording of the 12-lead ECG was started 5 minutes before and lasted until 3 hours after the end of infusion in converters and up to 5 hours in patients who did not convert pharmacologically. The digital signal (1 kHz sampling) was transferred to a computer for subsequent off-line processing, and the surface ECG was processed using analysis techniques described previously.⁴ Briefly, the atrial fibrillatory activity in lead V₁ was extracted using spatiotemporal QRST cancellation in which the average beats of adjacent leads were mathematically combined with the average beat of the analyzed lead in order to produce an optimal cancellation for each individual beat.⁵ Since the AFR is well below 25 Hz, the resulting fibrillatory signal was downsampled to 50 Hz and subjected to spectral analysis. A sequential approach to time-frequency analysis was employed for robust frequency estimation. One frequency estimate of the atrial signal was obtained every second from overlapping 2.56-second windows (128 samples) by short-term Fourier transform (segment-wise Fast Fourier transform). Before frequency estimation, each analyzed window was evaluated in terms of its total power and maximum absolute amplitude for identification of large QRST-related residuals and other disturbances. As a result, the peaks of the spectral profile become more distinct, such that determination of the harmonic structure of the atrial signal, that is the f-wave organization, was facilitated. The ED of the harmonic magnitudes in the spectral profile characterizes the degree of atrial signal organization, as more organized

rhythms have stronger harmonics and thus a lower ED (resulting from a more distinct wave form) whereas more disorganized heterogeneous rhythms have a broader frequency content and hence do not exhibit strong harmonics (caused by the less distinct waveform), that is have a higher ED.

The mean AFR, the AFR standard deviation (AFR-SD), the ED, the RR interval, the HR, and the HR-SD were determined in 1-minute segments, except for the baseline AFR which was determined as the mean of the 5 minutes preceding the start of infusion. Each consecutive minute in AF was compared to the baseline value. The AFR-SD values at baseline and during each minute in AF were taken as a measure of the regularity of the atrial rhythm.

Statistical Methods

The statistical analysis was performed by Biostatistics at AstraZeneca R&D, Mölndal, Sweden. Descriptive statistics were summarized with means, standard deviations, and ranges for continuous variables, and with number of patients and percentages for categorical variables. Correlation coefficients (Pearson product-moment), with associated P values, were calculated between continuous variables of interest. Stepwise multivariate regression modeling was conducted to assess potential prognostic variables for levels of AFR. Statistical tests associated with P values <5% (two-sided) were judged to be statistically significant.

RESULTS

Patient demographics are reported in Table 1. The mean age of patients was 63 ± 11 (range 20–78) and 57 ± 9 (range 45–72) years in patients randomized to AZD7009 and placebo, respectively. Seventy percent of the patients randomized to AZD7009 were males versus 86% of those randomized to placebo. The estimated duration of the ongoing AF episode was 38 (range 1–85) versus 47 (range 8–90) days. Patients randomized to AZD7009 more often had beta blockers (91% vs. 64%) and ACE inhibitors (56% vs. 36%).

Lack of Relationship between the Atrial and Ventricular Rate and Rhythm

The baseline AFR was 396 ± 57 (range 253–584) fpm in patients randomized to AZD7009 and 410 ± 33 (range 363–469) fpm in those randomized to placebo. The AFR decreased within the first 2–3 minutes of AZD7009 infusion and reached its minimum at around 235 ± 34 fpm after 18 minutes; this level was maintained throughout the infusion. The AFR in placebo patients was unchanged at around 410 ± 31 fpm.

The mean HR at baseline was 80 ± 18 (range 47–158) bpm. The mean HR in patients randomized to AZD7009 was 81 (range 54–130) bpm in converters and 84 (range 48–158) bpm in nonconverters, as compared to 74 (range 47–97) bpm in patients randomized to placebo. The median HR was not different, 78 bpm versus 76 bpm, in patients randomized to AZD7009 or placebo. The HR did not change significantly over time in patients exposed to AZD7009 or to patients on placebo. There was neither a relationship between the AFR and the HR at baseline (Fig. 1) nor a relationship over time in patients exposed to AZD709 or in patients on placebo ($r = 0.08$, $P = 0.52$). There was no relationship between the variability of the atrial (AFR-SD) and ventricular rate (HR-SD), neither at baseline, $r = 0.16$, $P = 0.13$, nor at 10 minutes into the infusion, $r = 0.21$, $P = 0.09$.

The AFR was highly significantly correlated with the ED, which was higher at lower AFR, also independent of exposure or no exposure to AZD7009 (Fig. 2). The AFR was furthermore highly statistically correlated to age and gender, being lower at increasing age and in women. The baseline ED was similar in patients randomized to AZD7009 and in those randomized to placebo, 1.2 ± 0.3 versus 1.4 ± 0.3 . During AZD7009, the ED decreased and reached its lowest level at 0.7 ± 0.2 after 14 minutes. The ED remained unchanged at 1.4 ± 0.3 in the placebo group. There was no relationship between the ED and the HR, neither at baseline, $r = 0.09$, $P = 0.38$, nor at 10 minutes into the infusion, $r = 0.12$, $P = 0.32$.

Inverse Correlation between the Atrial Rhythm and the Duration of Ventricular Repolarization

The AFR was highly significantly related to the QT_{cF} at baseline (Fig. 3), where the QT_{cF} was

Table 1. Demographic Characteristics (n, mean $\pm$ SD or %) at Baseline in AZD7009 Converters and Nonconverters and Patients Receiving Placebo

Variable	AZD7009, All Patients		Placebo
	Converters	Nonconverters	
n	35	35	22
Age (years)	63 $\pm$ 12	64 $\pm$ 9	58 $\pm$ 9
Gender, male (%)	63	77	86
AF episode duration (days)	33 $\pm$ 24	44 $\pm$ 23	47 $\pm$ 23
AF rate (fpm)	393 $\pm$ 59	400 $\pm$ 56	410 $\pm$ 33
AF rate SD	27 $\pm$ 7	26 $\pm$ 10	23 $\pm$ 6
Exponential decay	1.2 $\pm$ 0.3	1.2 $\pm$ 0.3	1.4 $\pm$ 0.3
Left ventricular ejection fraction (%)	57 $\pm$ 11	56 $\pm$ 8	57 $\pm$ 8
LA area (cm ²)	22 $\pm$ 6	27 $\pm$ 6	26 $\pm$ 5
β -Blocker (%)	94	89	64
ACE inhibitor (%)	60	51	36
Angiotensin ATI receptor antagonist (%)	0	17	18
Statin (%)	26	23	14
Angina pectoris (%)	6	9	5
Myocardial infarction (%)	9	3	0
Heart failure (%)	17	26	14
Diabetes mellitus (%)	14	20	5
Hypertension (%)	74	71	68
CHADS ₂ , score	1.4 $\pm$ 1.2	1.5 $\pm$ 1.0	0.9 $\pm$ 0.6
CHA ₂ DS ₂ -VASc, score	2.4 $\pm$ 1.8	2.3 $\pm$ 1.5	1.3 $\pm$ 1.0

Abbreviations as in text.

longer at lower AFR values, and this correlation did not change over time and remained after exposure to AZD7009 (Fig. 4). This relationship did not differ between converters and nonconverters. The effects on AFR and QT_{cF} developed rapidly during administration of AZD7009 (Fig. 5). The correlation persisted with uncorrected QT_{tang} and with correction of the QT interval according to Bazett (QT_{cB}). There was no correlation between the AFR and the QRS duration or the appearance of morphological T wave changes, the duration of the AF episode, the duration of the AF history, the right atrial (RA) or left atrial (LA) size, or conversion to SR.

At the ventricular level, there was a significant relationship between the HR-SD and the QT_{cF}-SD, $r = 0.50$, $P \leq 0.0001$, 10 minutes into the infusion, but not between the HR-SD and QT_{cF}, $r = 0.19$, $P = 0.43$ (Fig. 6). There were no such relationships at baseline.

Role of Ongoing Medication

Warfarin (n = 76), β -blockers (n = 65), angiotensin-converting enzyme inhibitors (n = 37), and potassium (n = 22) were medications taken by 20 or more of the patients. Potassium had a

negative correlation with AFR ($P = 0.02$), which disappeared after correction for age, and a positive correlation with QT_{cF} ($P = 0.03$). The negative correlation between AFR and QT_{cF} remained after correction for potassium ($P < 0.0001$). No other statistically significant correlation was detected between AFR or QT_{cF} and any type of concomitant medication, for example class IC (n = 18) or class III agents (n = 13).

Multivariate Analysis

Multivariate regression modeling was conducted with AFR at baseline as the dependent variable, investigating the potential prognostic value of age, sex, left ventricular ejection fraction, QRS duration, HR, QT_{cF}, AF episode duration, AF history duration, LA and RA size, common classes of concomitant medications (e.g., statins, β -blockers and potassium), and medical history (hypertension, cardiac failure, myocardial infarction, angina pectoris and diabetes mellitus). QT_{cF} and age were the only variables that were found to be statistically significantly correlated at the 5% level, with the AFR following a step-wise selection algorithm (Table 2). In the final model, QT_{cF} remained as the most important variable in terms

Figure 1. There was a linear correlation between the exponential decay and the AFR both at baseline and at 10 minutes into the infusion. The correlation in the figures relates to all patients. The correlation for placebo was r 0.79, $P < 0.0001$, and for AZD7009 r 0.84, $P < 0.0001$.

of correlation with AFR. A history of heart failure was correlated with QT_{cF} ($P = 0.03$) but not to AFR.

DISCUSSION

The main finding in this analysis of the AFR and its relation to ventricular electrophysiology was the strong inverse correlation between the AFR and the QT_{cF} in the absence of correlation between AFR and HR. The correlation was stronger at lower AFR levels. AFR was also more positively correlated with QT_{cF} at higher age, and more so in men compared to women.

The QT interval is dependent on the HR, which in turn can be modulated in various ways, e.g. via

the autonomic nervous system and the AV node. The role of the AV node is well known, while the lack of correlation between the AFR on the HR has not been previously described. Correction formulas have been created in order to minimize the influence of changes in the HR. The Fridericia formula has advantages over other rate correction formulas in that it can be used over a wider range of HRs with less risk of overestimation or underestimation of the QT interval. In the present analysis the inverse correlation between the AFR and the QT interval duration was present both with the uncorrected QT_{tang} interval and with the rate corrected QT_{cF}, which in turn most probably depended on the lack of change in HR during administration of AZD7009.

Figure 2. There was no correlation between the heart rate and the AFR at baseline.

Figure 3. There was an inverse linear correlation between the QTcF and the AFR at baseline in patients, both in subsequent converters and nonconverters. The correlation in the figure relates to all patients.

The inverse correlation was not caused by AZD7009, since it was present already at baseline. Nevertheless, AZD7009 had a pronounced effect on the AFR and the correlation was stronger at lower AFR levels. This may lead us to speculate that the wide range of the mean AFR values among patients seen already at baseline made it possible to establish the previously undetected correlation. In fact, some patients had at baseline AFR values below 260 bpm, that is very close to the minimal mean value 235 ± 34 bpm that was seen after administration of AZD7009. We know that AZD7009 simultaneously affected both conduction, refractoriness and repolarization on

the atrial and ventricular levels, which means that effects might be caused at both levels without being the result of a link between the atria and the ventricles. Therefore, this does not fully explain the connection between the AFR and the QT interval duration at baseline and during placebo.

The suggestion that the irregularity of the HR during AF is primarily a consequence of the irregularity inherent in the atrial activity, whereas the role of the AV node would predominantly be confined to that of scaling the atrial activity,⁶ was not confirmed in this study, since there was no correlation between the HR-SD and the

Figure 4. At 10 minutes into the infusion, there was strong inverse correlation between the AFR and the QT_{cF} in patients receiving AZD7009, and conversion to sinus rhythm was common among these patients.

AFR-SD, neither at baseline nor at 10 minutes into the infusion. Incremental regular atrial pacing of the isolated rabbit heart produced stable second degree AV block, during which a monophasic inverse relationship between atrial and ventricular rates appeared as a result of an increased occurrence of concealed conduction in the AV junction. During irregular pacing stable AV block disappeared, and during induced AF an inverse relationship was found between the atrial and ventricular rate.² However, these results may not necessary translate to findings in humans with more or less long-lasting AF. In a study of Holter recordings of patients with persistent AF populations of predominant RR intervals were identified, and in half of the patients with one such population and in all with more than one, the RR interval populations were statistically related with multiples of the dominant atrial cycle length during AF. A decrease of the ventricular rate at night was associated with a variation of the percentages of occurrence of each predominant RR interval, but there was no difference in the mean dominant atrial cycle length. The results suggested that more probable RR intervals were caused by different conduction ratios of the atrial rate.³ Looking at the AFR rate, its variability and organization over a wide range of rates, we found no associations between the AFR and what actually happened in the ventricles.

A significant positive correlation was found, in patients with heart failure, between AFR and

indices of RR irregularities, showing that a higher AFR was related to a less organized RR series. In the same report, a significant correlation was found between AFR and variability parameters of HR variability during AF, but only in patients not treated with rate or rhythm control drugs.⁷ In this study there was no correlation between the AFR and HR irregularities, measured as HR-SD. A prolongation of the functional AV nodal refractory period was observed after metoprolol, an expected effect of β -blockade.⁸ The class IC agent flecainide decreased AFR and increased the QRS interval without changing the RR interval or the QT_c interval.⁹ In an experimental study in goats, AF-induced atrial electrical remodeling did not modulate the effects of flecainide on atrial conduction and refractoriness, while the class III effects of ibutilide and d-sotalol were strongly reduced after 2 days. The prolongation of the QT duration was not affected, however.¹⁰ Ibutilide-induced slowing of the AFR was more intense and rapid in patients who converted to SR,¹¹ whereas ECG-derived indices of AF organization did not predict the effects of vernakalant.¹² None of these studies commented on effects at the ventricular level.

The mode of action of AZD7009 includes effects on the atrial, AV nodal and ventricular refractoriness and conduction, AV node and intra-ventricular conduction, in addition to prolongation of the myocardial repolarization. The AFR is also commonly believed to start at a lower rate that increases as electromechanical remodeling

Figure 5. The effects on AFR and QT_{cF} developed rapidly after start of the infusions of AZD7009.

develops. In new and/or short-lasting episodes, fewer wavelets would give rise to a lower atrial rate, whereas longer-lasting AF would allow the development of atrial remodeling, which in turn would increase the number of wavelets and thereby also the AFR. Even if the wavelet theory may be correct, it is as yet unknown how stable the AFR may be or whether the ever changing directions of the wavelets would create changes in the rate or in the regularity of the rhythm. One could hypothesize that fewer wavelets would be operative when the AFR is low and/or when the rhythm is more regular, but we could not confirm that the regularity was correlated with the atrial rate, not even at the highest AFR of about 580 bpm.

Our patient population was chosen such as to be suitable for pharmacological cardioversion and thus consisted of patients whose ongoing AF episode was not to have lasted longer than 90 days. The mean AF duration of the 167 randomized patients was 47 days. There were no further limitations to their previous AF history than that they could have had a maximum of two previous successful but no unsuccessful DC cardioversions. Some patients had their first documented AF experience up to 18 years before randomization, while as many as 54% were experiencing their first AF episode. This means that there was a mix of properties that can have influenced the atrial rate as well as the ventricular electrophysiology.

Figure 6. At 10 minutes, there was strong correlation between the HR-SD and the QTcF-SD but not between the HR-SD and the QTcF.

Rhythm control agents such as flecainide,¹³ ibutilide,¹¹ dofetilide,¹⁴ amiodarone,^{14,15} dronedarone,¹⁵ metoprolol,⁸ and verapamil³ decreased the AFR, as did other pharmacological agents such as candesartan,¹⁶ although only in patients with high AFR. Almost no change in AFR was seen after the A1-adenosine receptor agonist tecadenoson,¹⁷ whereas an increase of variability parameters was observed together with a marked decrease in HR, meaning that modification of AV node conduction can increase RR variability but not the regularity of RR intervals

or AFR. Vernakalant did not decrease the AFR but increased the organization of the atrial rhythm,¹² whereas AZD7009, a combined potassium and sodium current blocker, did both.⁴ The agents causing this effect have a variety of modes of action, and there are potential confounding factors that could, per se, have an impact on the AFR, such as the duration of the on-going AF episode, the time since the first AF episode and underlying comorbidities, and many of them seem to be related to the vicious circuit of atrial remodeling.

Table 2. Univariate and Multivariate Linear Regression Analyses of Potential Prognostic Variables^{1a} for AFR at Baseline

Variable	Unit	Univariate Analyses		Multivariate Analyses ^b	
		Estimated Slope ^c (95% CI)	P value	Estimated Slope ^c (95% CI)	P value
QTcF at baseline	ms	−1.10 (−1.51 to −0.69)	<0.0001	−0.78 (−1.14 to −0.42)	<0.0001
Age	Years	−2.84 (−3.70 to −1.97)	<0.0001	−2.48 (−3.32 to −1.64)	<0.0001
Gender	Male/female	−37.4 (−61.6 to −13.1)	0.003		
Potassium medication	No/yes	−25.5 (−49.5 to −1.5)	0.037		
Previous myocardial infarction	No/yes	−53.3 (−106.0 to −0.6)	0.047		

^aOnly variables associated with $P < 0.05$ in univariate analyses are displayed.

^bOnly factors associated with $P < 0.05$ in the presence of other selected variables were retained in the final multivariate model.

^cFor example, for QTcF, it is estimated that the AFR will be 1.1 bpm lower for each increase in QTcF by 1 ms.

LIMITATIONS

The AFR was measured after QRS cancellations and applying certain filters. It cannot be excluded that other measurement techniques could give different results.

CONCLUSIONS

The QTcF was inversely correlated with AFR, both at baseline and during administration of AZD7009. The rapid effects on AFR and QTcF during treatment most likely contributed to the high efficacy of AZD7009 in converting AF episodes of short duration. The AFR was not correlated with the HR.

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