



Comparison of QT dispersion during atrial fibrillation and sinus rhythm in the same patients, at normal and prolonged ventricular repolarization

B. Houltz, B. Darpö¹, K. Swedberg, P. Blomström², H. J. G. M. Crijns³,
S. M. Jensen⁴, E. Svernhage⁵ and N. Edvardsson⁶

Department of Medicine, Sahlgrenska University Hospital, Östra, Göteborg, Sweden; ¹Department of Cardiology, Karolinska Hospital, Stockholm, Sweden; ²Department of Cardiology, Uppsala University Hospital, Uppsala, Sweden; ³Department of Cardiology, University Hospital, Groningen, The Netherlands; ⁴Department of Cardiology, Umeå University Hospital, Umeå, Sweden; ⁵Astra-Hässle AB, Mölndal, Sweden; ⁶Division of Cardiology, Sahlgrenska University Hospital, Sahlgrenska, Göteborg, Sweden

Aims Drug-induced increase in QT dispersion has been associated with increased risk of ventricular proarrhythmia. The aim of the present study was to compare QT dispersion during atrial fibrillation and sinus rhythm in the same patients at normal and prolonged ventricular repolarization.

Methods and Results Sixty-one patients who had had chronic atrial fibrillation for 8 ± 14 months received a 6 h infusion of the I_{kr} -blocker almokalant, the first 90 min of which are used for this analysis. The following day, after conversion to sinus rhythm, by almokalant ($n=19$) or direct current cardioversion ($n=42$), an identical 90 min infusion was administered. Prior to infusion, there was no difference in precordial QT dispersion between atrial fibrillation and sinus rhythm (29 ± 12 vs 36 ± 17 ms, $P=ns$). During infusion, at prolonged repolarization, the increase in QT

dispersion was greater during sinus rhythm than during atrial fibrillation (58 ± 49 vs 30 ± 15 ms, $P=0.0011$, after 30 min infusion). No correlation was found between QT dispersion and the QT or RR interval.

Conclusion QT dispersion during atrial fibrillation does not differ from QT dispersion during sinus rhythm during normal repolarization, while measurement of QT dispersion during prolonged repolarization, induced by an I_{kr} -blocker, yielded larger values during sinus rhythm than during atrial fibrillation.

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Key Words: QT dispersion, ventricular repolarization, class III antiarrhythmic agent, atrial fibrillation, sinus rhythm, almokalant.

Introduction

QT dispersion, defined as the interlead variability of the QT interval, is an electrocardiographic marker of differences in ventricular repolarization^[1,2]. QT dispersion is increased in patients with the inherited long QT syndrome and torsades de pointes^[3]. Furthermore, increased QT dispersion has been associated with increased risk of ventricular arrhythmias and sudden death^[4], and recently it has also been shown to predict cardiac mortality in the elderly^[5]. Class IA and III

antiarrhythmic drugs prolong ventricular repolarization, and a correlation between an increase in QT dispersion caused by these drugs and a proarrhythmic response in susceptible individuals has been proposed^[6–8]. Almokalant is a class III antiarrhythmic agent, which blocks the rapid component of the delayed, rectifying, potassium current, I_{kr} ^[9]. In vitro, selective potassium channel blockers cause action potential prolongation, which is more pronounced in Purkinje fibres than in ventricular muscle^[9]. This inhomogeneity of repolarization may result in the development of reentry phenomena and contribute to the development of proarrhythmias^[10]. In a previous analysis of the present material, patients with atrial fibrillation who developed torsades de pointes after an intravenous infusion of almokalant exhibited a greater increase in QT dispersion

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Correspondence: Dr Birgitta Houltz, Department of Clinical Physiology, Sahlgrenska University Hospital, 413 45 Göteborg, Sweden.

Table 1 Baseline Demographics

n	61
Age (years)	67 ± 8
Male	42 (69%)
Atrial flutter	4 (7%)
Time since first arrhythmia episode (months)	31 ± 79 (range 1–588)
Duration of current arrhythmia episode (months)	8 ± 14 (range 1–99)
Hypertension >5 years	12 (20%)
History of heart failure	16 (26%)
Functional class	
NYHA I-II	59 (97%)
NYHA III	2 (3%)
Coronary artery disease	10 (16%)
Valvular heart disease	32 (53%)
Lone atrial fibrillation	14 (23%)
Medication	
Digoxin	43 (71%)
Beta-blockers	16 (26%)
Diuretics	22 (36%)
Calcium antagonists	15 (25%)
Antiarrhythmic drug prestudy	11 (18%)
Fractional shortening (%)	30 ± 1
Interventricular septum (cm)	1.1 ± 0.2
Left ventricular posterior wall (cm)	1.0 ± 0.2

Values are the number of patients unless otherwise stated.
NYHA=New York Heart Association.

than control patients^[6]. In five of six patients, proarrhythmia developed during sinus rhythm, and in three of these patients it appeared shortly after conversion to sinus rhythm. This observation raised the question whether the effect on QT dispersion caused by a class III antiarrhythmic agent is different after conversion to sinus rhythm compared with administration during atrial fibrillation. Since, as far as we know no previous study investigating QT dispersion during atrial fibrillation has been published, the present analysis was undertaken to explore further the impact of the underlying rhythm on QT dispersion during normal and prolonged repolarization.

Methods

Patients and study design

The efficacy and safety of intravenous infusions of almokalant were evaluated during atrial fibrillation and after conversion to sinus rhythm in 100 consecutive patients, enrolled in eight centres and scheduled for direct current cardioversion of chronic atrial fibrillation (n=95) or atrial flutter (n=5), with a duration of the present episode of more than 4 weeks. Sixty-one of the patients (42 male, 19 female, mean age 67 ± 8 years), who received an almokalant infusion during atrial fibrillation (n=57), or flutter (n=4), also received an almokalant infusion during sinus rhythm the following day and constitute the patient group included in the present study. Nineteen of these patients converted to sinus rhythm during or 3 h after the first almokalant infusion, and in 42 patients sinus rhythm was restored with direct current cardioversion 2 ± 1 h prior to the

start of the second almokalant infusion. Exclusion criteria were: high degree atrioventricular block, sick sinus syndrome, previous proarrhythmic reaction to antiarrhythmic drugs, New York Heart Association class IV heart failure, acute myocardial infarction, coronary angioplasty or coronary artery bypass surgery within the last 4 weeks, untreated thyroid dysfunction or clinically significant hepatic or renal disease.

The patients were kept fasting for at least 2 h prior to the start and until the end of the almokalant infusions. On the first study day, almokalant was administered intravenously in three dose levels: 2.12 µg . kg⁻¹ . min⁻¹ for 30 min followed by 1.06 µg . kg⁻¹ . min⁻¹ for 60 min, and thereafter 0.71 µg . kg⁻¹ . min⁻¹ for 270 min. The first two dose levels were used for the present analysis. On the following day, a 90 min infusion of almokalant was given during sinus rhythm in the same doses as the first 90 min of infusion on the first study day. Blood samples for almokalant plasma assay were drawn at scheduled times during the infusions and analysed with reversed phase liquid chromatography. The infusions were discontinued when any ventricular tachycardia exceeded five beats, or in cases with significant side effects, such as symptomatic hypotension, bradycardia, or sustained complete bundle branch block. Since two cases of torsades de pointes proarrhythmia occurred among the first 17 patients, new criteria for discontinuation of the infusion were added: a QT interval >650 ms, or any new wide QRS complex tachycardia of at least three beats.

The baseline demographics of the 61 patients evaluated during both atrial fibrillation and sinus rhythm are shown in Table 1. In 14 patients (23%), the medical history and the pre-investigational examinations did not

reveal any signs of cardiac disease, including coronary artery disease, congestive heart failure, valvular heart disease, and hypertension. Any concomitant anti-arrhythmic drug therapy was withdrawn for five half-lives of the drug, whereas treatment with digitalis (provided serum digoxin was $<2.6 \text{ nmol} \cdot \text{l}^{-1}$), beta-blockers, and calcium antagonists was allowed to continue. Serum potassium had to be $\geq 3.8 \text{ mmol} \cdot \text{l}^{-1}$, serum magnesium $\geq 0.8 \text{ mmol} \cdot \text{l}^{-1}$, and the heart rate-corrected QT interval (QT_c interval), according to Bazett's formula^[11], less than 500 ms (calculated as a mean of five consecutive beats at a heart rate of 50 to 120 $\text{beats} \cdot \text{min}^{-1}$). All patients were treated with anticoagulants at a therapeutic level for at least 3 weeks prior to the study. Each patient underwent two-dimensional echocardiography.

The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committees of all participating hospitals. Written informed consent was obtained from all patients.

ECG measurements

A 12-lead ECG was recorded at a paper speed of $50 \text{ mm} \cdot \text{s}^{-1}$, using an amplification of $1 \text{ mV} \cdot 10 \text{ mm}^{-1}$, prior to, and after 10, 30, and 90 min of the almokalant infusions. In 51 patients, the precordial leads V_1 to V_6 and the extremity leads aVL, I, aVR, II, aVF, and III were recorded separately in immediate succession, while in 10 patients all 12 leads were recorded simultaneously. The ECG measurements were performed manually on the paper recordings by one investigator (B.H.), who was blinded to the identity of the patients. The ECG variables were measured and calculated as a mean of five (during atrial fibrillation) or three (during sinus rhythm) consecutive beats. The baseline level of the ECG was defined by the line intersecting two points immediately preceding the QRS complex or, in patients with sinus rhythm, immediately preceding the P wave. When almokalant-induced morphological T wave changes, or the presence of atrial fibrillation or flutter waves made the end of the T wave impossible to delineate, these QT complexes were excluded. QT dispersion was calculated if at least two leads were measurable. The RR intervals were measured in leads V_2 and II. The measured ECG variables were defined as follows:

QT interval (ms): the interval from the beginning of the QRS complex to the point at which the T wave returned to baseline. When a U wave could not be discriminated from the T wave by the presence of a nadir less than 2 mm above the baseline, the interval was measured to the end of the U wave.

QT_c interval (ms): the corrected QT interval according to Bazett's formula^[11].

QT dispersion (ms): the difference between the maximal and the minimal QT intervals was measured for each beat, and the dispersion was calculated as the mean of these differences.

QT_c dispersion (ms): each QT interval was heart rate-corrected^[11] before the calculation of the QT dispersion.

Transoesophageal atrial stimulation

Previous studies have shown transoesophageal atrial stimulation to be a useful method for studying drug effects on repolarization^[12,13]. At one of the study centres, transoesophageal atrial stimulation was performed during sinus rhythm prior to and after 30 min of the second 90 min almokalant infusion ($n=13$). A bipolar silicon catheter (Medtronic Bipolar Pacing Lead 6992A, Medtronic Inc., Minneapolis, MN, U.S.A.) was positioned through one of the nares into the distal oesophagus and adjusted to obtain the atrial electrogram with the largest amplitude. The electrode was then left in position until the last measurement was completed. A programmable stimulator (Medtronic 5328, Medtronic Inc., Minneapolis, MN, U.S.A.) was connected to an Arzco Stimulator 7A (Arzco Medical Electronics Inc., Chicago, IL, U.S.A.), capable of delivering square wave pulses of 9.9 ms duration. Pacing was performed at the lowest current that allowed stable atrial stimulation, which was achieved at 3–18 mA. Atrial pacing for 30 s was repeated three times at a cycle length within 10 $\text{beats} \cdot \text{min}^{-1}$ above the sinus rate, and at 800, 700, 600, 500, and 450 ms. The precordial ECG leads V_1 to V_6 were recorded during the transoesophageal atrial stimulation procedure, at a paper speed of $50 \text{ mm} \cdot \text{s}^{-1}$. These recordings were later evaluated by one investigator (B.H.), blinded to the identity of the patients. The QT interval was measured at each cycle length in each lead on the last paced beat and was calculated as a mean of the values obtained during the three pacing periods. The precordial QT dispersion was calculated as described above.

Statistics

Comparison of continuous electrocardiographic variables prior to, and 10, 30, and 90 min after the start of the almokalant infusions was performed using a two-way repeated measures ANOVA followed by mean comparison contrast analyses (single-degree of freedom comparisons). All values are presented as mean \pm standard deviation (SD). A difference was regarded as significant when the *P* value was <0.05 . No correction was made for multiple comparisons. Correlation between data obtained during atrial fibrillation and sinus rhythm was analysed according to the procedure described by Bland and Altman^[14,15]. The intra-individual difference between QT dispersion assessed during sinus rhythm and atrial fibrillation was plotted against the mean of the two measurements. Limits of agreement were calculated as ± 2 SD of all intra-individual differences.

Table 2 QT intervals during atrial fibrillation and sinus rhythm prior to and during almokalant infusion

Lead	0 min		10 min		30 min		90 min	
	AF	SR	AF	SR	AF	SR	AF	SR
V ₁	367 ± 48 (12)	395 ± 39 (37)	398 ± 54 (14)	430 ± 40 (38)	442 ± 61 (15)	480 ± 68 (40)	450 ± 75 (12)	483 ± 68 (37)
V ₂	383 ± 38 (56)	412 ± 32 (60)	412 ± 47 (54)	447 ± 48 (58)	442 ± 54 (54)	495 ± 77 (55)	451 ± 69 (53)	509 ± 79 (55)
V ₃	385 ± 38 (59)	416 ± 35 (60)	414 ± 49 (59)	456 ± 62 (60)	444 ± 54 (59)	499 ± 84 (59)	454 ± 72 (59)	522 ± 87 (57)
V ₄	384 ± 41 (61)	413 ± 37 (60)	414 ± 47 (59)	458 ± 59 (61)	443 ± 56 (58)	503 ± 79 (59)	450 ± 69 (59)	515 ± 81 (58)
V ₅	380 ± 40 (60)	411 ± 40 (59)	412 ± 46 (60)	451 ± 50 (59)	441 ± 56 (58)	501 ± 77 (56)	445 ± 66 (59)	509 ± 77 (58)
V ₆	377 ± 41 (59)	405 ± 38 (57)	407 ± 45 (57)	443 ± 50 (58)	436 ± 57 (57)	488 ± 68 (55)	441 ± 61 (59)	498 ± 70 (52)
aVL	373 ± 39 (39)	402 ± 36 (39)	415 ± 48 (36)	440 ± 46 (37)	438 ± 51 (39)	485 ± 57 (34)	444 ± 51 (31)	494 ± 59 (36)
I	371 ± 37 (54)	404 ± 37 (53)	407 ± 51 (49)	439 ± 42 (47)	433 ± 54 (46)	481 ± 55 (43)	435 ± 55 (38)	484 ± 61 (41)
-aVR	370 ± 43 (53)	404 ± 37 (51)	408 ± 50 (47)	433 ± 40 (45)	432 ± 52 (46)	481 ± 53 (42)	434 ± 51 (37)	488 ± 65 (42)
II	374 ± 41 (55)	406 ± 35 (52)	410 ± 51 (48)	441 ± 49 (45)	430 ± 55 (43)	484 ± 56 (40)	434 ± 50 (39)	495 ± 71 (38)
aVF	367 ± 42 (50)	400 ± 38 (48)	403 ± 51 (44)	436 ± 51 (38)	433 ± 58 (41)	484 ± 65 (36)	429 ± 53 (35)	486 ± 65 (38)
III	366 ± 46 (40)	398 ± 44 (40)	407 ± 54 (42)	437 ± 52 (40)	428 ± 56 (36)	485 ± 65 (29)	433 ± 50 (31)	487 ± 59 (32)

All values in ms. (n)=the number of observations. **Bold (italic)** values are the **maximal (minimal)** QT intervals at each measuring point and with values within the range of - (+) 5 ms. Abbreviations: 0, 10, 30, and 90 min=prior to, and after 10, 30 and 90 min of almokalant infusion; AF=atrial fibrillation; SR=sinus rhythm.

Table 3 Number of measurable leads, mean ± SD (median), in the calculation of QT dispersion

	Precordial leads	Extremity leads	12 leads
During atrial fibrillation:			
0 min:	4.9 ± 0.7 (5)	4.8 ± 1.0 (5)	9.0 ± 2.1 (10)
10 min:	4.9 ± 0.8 (5)	4.9 ± 0.9 (5)	8.5 ± 2.4 (9)
30 min:	4.9 ± 0.6 (5)	4.7 ± 1.1 (5)	8.3 ± 2.4 (9)
90 min:	4.9 ± 0.7 (5)	4.7 ± 1.1 (5)	7.9 ± 2.4 (9)
0-90 min:	4.9 ± 0.7(5)	4.8 ± 1.0(5)	8.5 ± 2.4 (9)
During sinus rhythm:			
0 min:	5.4 ± 0.7 (6)	5.1 ± 0.8 (5)	9.9 ± 2.3 (11)
10 min:	5.4 ± 0.6 (5)	5.1 ± 0.8 (5)	9.1 ± 2.7 (10)
30 min:	5.5 ± 0.7 (6)	5.0 ± 0.9 (5)	9.1 ± 2.5 (10)
90 min:	5.5 ± 0.8 (6)	4.9 ± 1.0 (5)	9.1 ± 2.7 (10)
0-90 min:	5.5 ± 0.7(6)	5.0 ± 0.9(5)	9.3 ± 2.5(10)
P (0-90 min AF vs SR):	<0.0001	<0.0001	<0.0001

SD=standard deviation. Other abbreviations as in Table 2.

Results

In one of the 61 patients, the second almokalant infusion was prematurely terminated due to the development of a QT interval exceeding 650 ms. In two patients, in whom atrial fibrillation relapsed during the second infusion, the measurements were only included while these patients were still in sinus rhythm. During the second infusion, two patients developed short episodes of torsades de pointes after 31 and 85 min, respectively. These proarrhythmias were not recognized during the infusion, which was therefore continued; hence, all measurements from these two patients are included.

The QT and RR interval (Tables 2 and 3)

The QT interval in all leads, and the RR interval was longer during sinus rhythm than during atrial fibrillation prior to, and during, the almokalant infusion

($P < 0.0001$). The heart rate was not changed by almokalant. In lead V₂, almokalant caused a prolongation of the QT interval during sinus rhythm of 83 ms (20%) after 30 min of infusion, which was further increased to 97 ms (22%) after 90 min of infusion ($P < 0.0001$ vs prior to infusion). This QT prolongation was greater ($P = 0.01$ sinus rhythm vs atrial fibrillation) than the corresponding prolongation during atrial fibrillation (59 ms [15%], and 68 ms [18%], respectively; $P < 0.0001$ vs prior to infusion). Overall, the QT intervals during both sinus rhythm and atrial fibrillation were longest in leads V₂ through V₅ and shortest in leads V₁, II, aVF, and III.

During atrial fibrillation, measurements of the QT interval in lead V₁ were possible in only 12 (17%) and 15 (25%) patients prior to and during almokalant infusion, respectively, compared to 37 (61%) and 40 (66%) patients during sinus rhythm. This difference was mainly explained by the superimposed fibrillatory waves. During sinus rhythm, the main reason for

exclusion of lead V_1 was changes in the T wave morphology, which made the delineation of the end of the T wave impossible.

In the extremity leads, the QT interval was generally more difficult to measure both during atrial fibrillation and sinus rhythm, mostly due to the T wave morphology and, to a small extent, superimposed fibrillatory waves (2–8%).

On all occasions the number of leads with measurable QT intervals were greater during sinus rhythm than during atrial fibrillation (Table 4).

The QT_c interval (Table 3)

The QT_c interval did not differ between sinus rhythm and atrial fibrillation prior to infusion, and almokalant caused a prolongation of the QT_c interval that was equally pronounced during both rhythms ($P < 0.0001$ vs prior to infusion for QT_c measured in leads V_2 and II).

QT dispersion (Table 3)

No difference in precordial QT dispersion between atrial fibrillation and sinus rhythm was present prior to the almokalant infusions. The increase in precordial QT dispersion caused by almokalant was more pronounced during sinus rhythm (from 36 ± 17 to 58 ± 49 ms [56%] after 30 min of infusion) than during atrial fibrillation (from 29 ± 12 to 30 ± 15 ms [4%], $P = 0.001$ for sinus rhythm vs atrial fibrillation). The increase in QT dispersion during sinus rhythm could be observed after 10 min of infusion, while the increase during atrial fibrillation was not detected until after 90 min of infusion (37 ± 26 ms [28%], $P = 0.02$). The QT dispersion measured in the extremity leads increased to a lesser extent than when the precordial leads were used, and no differences between sinus rhythm and atrial fibrillation were observed. The QT dispersion calculated from the 12-lead ECG was greater than the dispersion calculated in separately recorded precordial and extremity leads. As in the case of the precordial QT dispersion, no difference was found in the 12-lead dispersion between sinus rhythm and atrial fibrillation prior to infusion, and the increase caused by almokalant was greater during sinus rhythm (from 49 ± 17 to 75 ± 52 ms [53%]) than during atrial fibrillation (from 48 ± 16 to 53 ± 22 ms [10%], $P = 0.003$ for sinus rhythm vs atrial fibrillation). Numerically similar increases were found in the 10 patients in whom QT dispersion was measured from 12 simultaneously recorded leads, although in this case the observed differences in dispersion between the two rhythms did not reach statistical significance.

Precordial QT dispersion during atrial stimulation at a rate similar to the heart rate during atrial fibrillation was not significantly different from the dispersion found during atrial fibrillation prior to almokalant infusion (32 ± 13 ms during pacing vs 29 ± 13 ms during atrial

fibrillation). During infusion, the dispersion during pacing increased more than the dispersion during atrial fibrillation in the same patient (69 ± 46 vs 33 ± 14 ms after 30 min of infusion, $P = 0.0089$), confirming the observation without transoesophageal atrial stimulation during sinus rhythm.

The intra-individual differences in precordial QT dispersion between sinus rhythm and atrial fibrillation are shown in (Figs 1(a) and (b)). Prior to infusion, the dispersion was 7 ± 17 ms greater during sinus rhythm than during atrial fibrillation, and after 30 min of infusion the dispersion was 26 ± 46 ms greater during sinus rhythm. A positive correlation was found between the magnitude of the QT dispersion and the intra-individual differences in QT dispersion between atrial fibrillation and sinus rhythm. The limits of agreement were wide (± 34 ms) and increased during prolonged repolarization (± 92 ms).

QT_c dispersion (Table 3)

Heart rate correction did not substantially alter the QT dispersion prior to or during the almokalant infusions. The precordial QT_c dispersion did not differ between the two rhythms prior to infusion, and almokalant caused a greater increase in precordial QT_c dispersion during sinus rhythm (from 36 ± 16 to 57 ± 45 ms [58%]) than during atrial fibrillation (from 32 ± 13 to 34 ± 16 ms [6%], $P = 0.0041$ for sinus rhythm vs atrial fibrillation). The extremity lead QT_c dispersion was, as for the uncorrected values, smaller than the precordial QT_c dispersion, and almokalant caused a small, non-significant, increase during both rhythms.

The relationship between QT dispersion, QT_c interval, and RR interval

No relationship was found between QT dispersion and the QT interval (Figs 2 and 3) or the QT_c interval. Neither was there any relationship between QT dispersion and the RR interval, calculated as the mean of the difference in dispersion of the beats measured (i.e. five beats during atrial fibrillation, three during sinus rhythm) and the mean of the preceding RR intervals, nor between the QT dispersion calculated from each beat and the preceding RR interval (Figs 2 and 3).

No relationship was found between the almokalant plasma concentration and the QT dispersion.

Discussion

Class III antiarrhythmic drugs exert their antiarrhythmic effect by prolongation of myocardial repolarization. Homogeneous prolongation of repolarization is considered antiarrhythmic, while any inhomogeneity in this process may be proarrhythmic since it would facilitate reentry phenomena^[10,16]. Several studies in which QT

Table 4 QT Dispersion, QT_c and RR interval during atrial fibrillation and sinus rhythm prior to and during almokalant infusion

	0 min		10 min		30 min		90 min	
	AF	SR	AF	SR	AF	SR	AF	SR
RR V	818 ± 155 (61)	976 ± 168 (61)***	832 ± 135 (61)	992 ± 169 (61)	812 ± 149 (60)	1011 ± 168 (59)**	826 ± 166 (58)	1025 ± 153 (57)*
RR E	830 ± 167 (54)	975 ± 165 (54)***	836 ± 192 (50)	989 ± 169 (47)	818 ± 141 (46)	1022 ± 160 (43)*	815 ± 143 (39)	1036 ± 153 (42)*
QT _c V ₂	424 ± 29 (61)	420 ± 35 (61)	450 ± 39 (60)	453 ± 48 (61)	490 ± 43 (60)	492 ± 64 (58)	495 ± 49 (58)	504 ± 69 (57)
QT _c II	416 ± 38 (50)	413 ± 35 (47)	449 ± 50 (44)	445 ± 45 (41)	476 ± 42 (40)	479 ± 47 (36)	479 ± 40 (35)	490 ± 55 (33)
QT dispersion								
Disp V	29 ± 12 (61)	36 ± 17 (61)	28 ± 13 (60)	44 ± 32 (61)	30 ± 15 (57)	58 ± 49 (59)**	37 ± 26 (58)	60 ± 50 (57)*
Disp E	28 ± 11 (56)	30 ± 14 (54)	32 ± 12 (51)	36 ± 18 (48)	35 ± 16 (45)	44 ± 33 (44)	33 ± 15 (40)	39 ± 23 (43)
Disp V+E	48 ± 16 (61)	49 ± 17 (61)	48 ± 19 (61)	59 ± 34 (61)	53 ± 22 (58)	75 ± 52 (59)**	54 ± 30 (59)	78 ± 54 (57)**
Disp 12 leads	49 ± 14 (10)	51 ± 16 (10)	45 ± 14 (10)	68 ± 19 (10)	51 ± 21 (8)	72 ± 36 (10)	54 ± 14 (10)	79 ± 41 (10)
QT _c dispersion								
Disp _c V	32 ± 13 (61)	36 ± 16 (61)	31 ± 14 (60)	44 ± 28 (61)	34 ± 16 (57)	57 ± 45 (59)**	40 ± 25 (58)	59 ± 47 (57)
Disp _c E	31 ± 12 (54)	31 ± 14 (54)	35 ± 13 (50)	36 ± 18 (47)	40 ± 18 (46)	44 ± 31 (43)	38 ± 17 (39)	39 ± 22 (42)

All values in ms. (n)=the number of observations. QT_c V₂ (II)=heart rate corrected QT interval measured in V₂ (II); Disp V (E)=QT dispersion in precordial (extremity) leads; Disp V+E=12-lead dispersion calculated from precordial and extremity leads recorded in immediate sequence; Disp 12-lead=12-lead QT dispersion in 10 patients with simultaneous 12-lead ECG registrations; Disp_c V (E)=QT_c dispersion in precordial (extremity) leads; RR V (E)=RR interval calculated in precordial (extremity) leads. Other abbreviations as in Table 2. *=*P*<0.05; **=*P*<0.01; ***=*P*<0.001 AF vs SR prior to, and after 30 and 90 min of almokalant infusion. Note that no statistical tests were performed at 10 min.

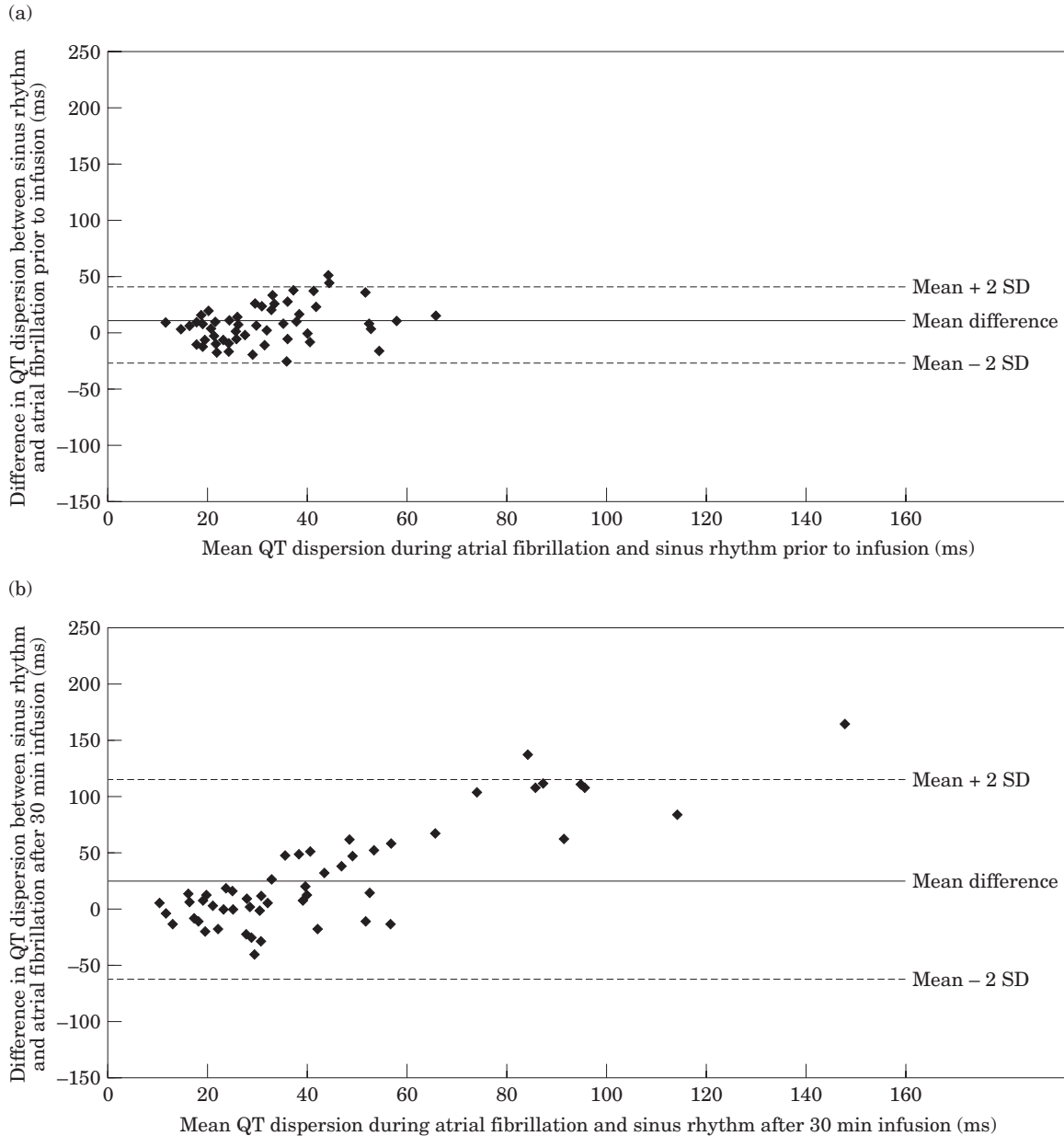


Figure 1(a and b) The relationship between the intra-individual differences in precordial QT dispersion during sinus rhythm and atrial fibrillation (y axis) and the mean of the precordial QT dispersions during both rhythms (x axis) prior to (a) and after 30 min of almokalant infusion (b).

dispersion has been assessed during sinus rhythm have shown the dispersion to be largely unaffected, or to decrease, following class IA or III drug therapy^[1,8,17-23], while increased QT dispersion has been demonstrated in patients with proarrhythmia^[7,8,24-26]. We have previously demonstrated that almokalant-induced proarrhythmia in patients with atrial fibrillation occurs shortly after conversion to sinus rhythm, and that this proarrhythmia is associated with an increase in QT dispersion observed early while the patients are still in atrial fibrillation^[6]. To explore the effect of the heart rhythm on QT dispersion, we have compared QT dis-

person values obtained in the same patient during sinus rhythm and atrial fibrillation during normal and prolonged repolarization.

Prior to the almokalant infusions, there was no difference in precordial QT dispersion between the two rhythms. Almokalant caused an increase in QT dispersion, which was greater during sinus rhythm than during atrial fibrillation. As expected, the QT dispersion calculated from the 12-lead ECG was greater than the precordial dispersion on all occasions. The same pattern was present whether the 12-lead dispersion was calculated from the precordial and extremity leads recorded

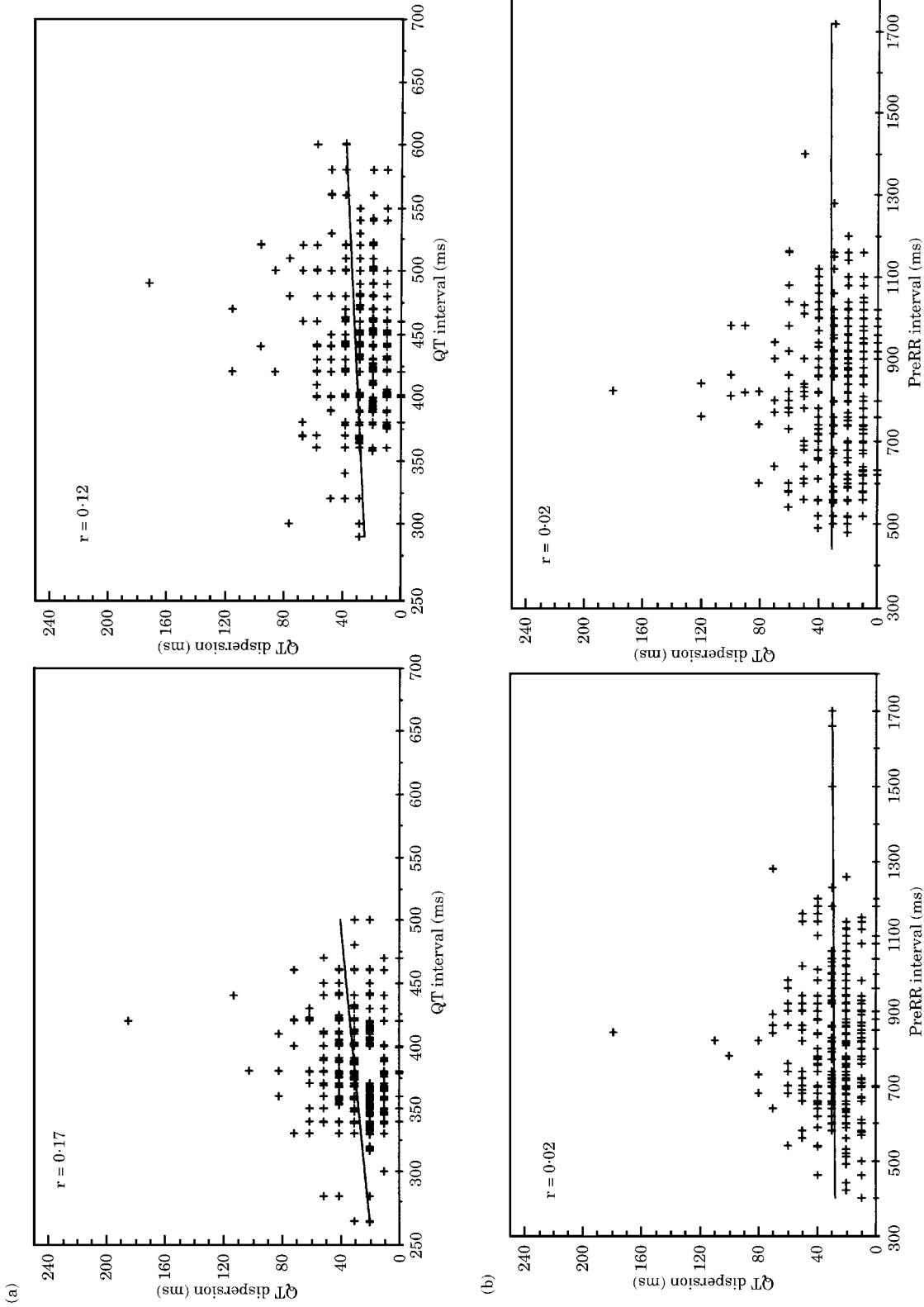


Figure 2 (a and b) The relationship between precordial QT dispersion for each beat (y axis) and the QT interval measured in lead V₂ (x axis) (a) and the preceding RR interval (x axis) (b), prior to and after 30 min of almokalant infusion. r = coefficient of correlation.

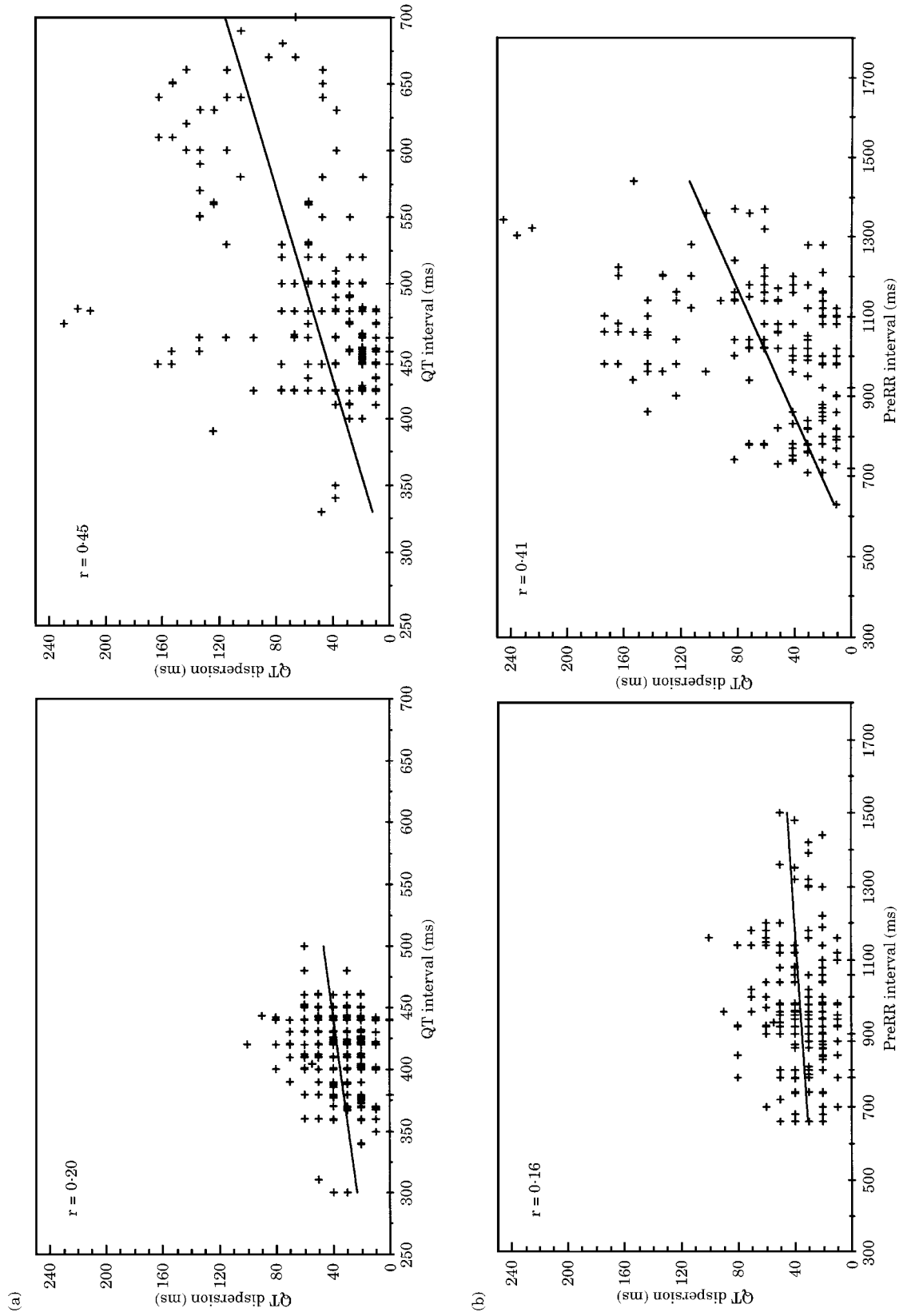


Figure 3(a and b) The relationship during sinus rhythm between precordial QT dispersion for each beat (y axis) and the QT interval measured in lead V₂ (x axis) (a) and the preceding RR interval (x axis) (b), prior to and after 30 min of atropine infusion. r = coefficient of correlation.

in immediate succession or from a simultaneous recording of all 12 leads.

Due to a lower heart rate, the QT interval was longer during sinus rhythm than during atrial fibrillation both prior to and during infusion. The QT dispersion was, however, not altered by heart rate-correction of the QT intervals. Accordingly, no correlation was found between the QT dispersion and the RR interval or the QT interval (Figs 2 and 3), a finding which is in accordance with previous data on QT dispersion assessed during sinus rhythm^[27]. Thus, the difference in QT dispersion between atrial fibrillation and sinus rhythm observed in the present study was not explained by differences in the RR interval, neither by a difference in the mean RR interval, nor by a greater variation in the RR intervals during atrial fibrillation than during sinus rhythm. This excludes the possibility of important beat-to-beat variations in QT dispersion during atrial fibrillation corresponding to variations in RR interval. Thus, it seems that atrial fibrillation per se obscures the development of QT dispersion, since the differences between atrial fibrillation and sinus rhythm cannot be explained by the methods used.

Methodological aspects of analysis of QT dispersion

Several methodological aspects of comparison of QT dispersion at normal and prolonged repolarization during atrial fibrillation and sinus rhythm have to be considered. QT dispersion is calculated as the difference between the longest and the shortest QT interval measured in different leads for the same heart beat. An intrinsic limitation of this technique is the dependence on the number of measurable leads. Ideally, calculations should include all leads at all times. This is often impossible because of difficulties in the delineation of T waves, due to their being flat or to fibrillatory waves superimposed on the end of them. Hypokalaemia and drugs that prolong ventricular repolarization, such as almokalant, may cause quite pronounced morphological changes in the T wave and also development of prominent U waves. In order to reduce difficulties with discrimination between large U waves and biphasic T waves, we included all of the T wave, whether biphasic or not, in the QT interval^[28]. Despite this, the number of measurable leads was lower during atrial fibrillation than during sinus rhythm (Table 4). We did not adjust the QT dispersion for the number of measurable leads, as the difference in number was small (Table 4), and questions have been raised whether such an adjustment is justified^[28-30].

In general, fewer leads will result in less QT dispersion, and vice versa. The QT dispersion was calculated if at least two leads were measurable. In the precordial leads, less than 2% of the beats were measurable in only two leads during atrial fibrillation, and during sinus rhythm all beats were measurable in at least three leads.

In the extremity leads, less than 5% of the beats were measurable in two leads only. Thus, this small number of beats that were only measurable in two leads has a minor impact on the calculated QT dispersion.

It is important, however, to emphasize that QT dispersion is influenced not only by the number of leads measured, but also by which leads are excluded, as discussed by Hnatkova *et al.* and Cowan *et al.*^[29,31]. These authors found significant differences in QT dispersion depending on which leads were used for the calculation, and especially if V₁ and aVL were omitted. If the lead with the shortest, or the longest, QT interval is consistently excluded, this will obviously result in less QT dispersion. In our study, aVL was excluded to a similar extent during both rhythms (39 patients, 64%). During sinus rhythm, the shortest precordial QT interval was observed most often in leads V₁ and V₆. During atrial fibrillation, lead V₁ was measurable in only 12 to 15 patients (20% to 25%), and the shortest QT interval was usually measured in this lead. When the precordial QT dispersion was recalculated after exclusion of lead V₁, the results were essentially unaltered, however (27 ± 10 ms during atrial fibrillation vs 27 ± 13 ms during sinus rhythm prior to infusion, and 29 ± 14 vs 45 ± 43 ms during infusion, respectively, *P*=0.01 for atrial fibrillation vs sinus rhythm during infusion). This supports the hypothesis that differences in assessability of lead V₁ did not cause the observed difference in QT dispersion.

Assessment of the longest QT interval caused fewer problems. The maximal precordial QT interval was most often seen in lead V₃ during both rhythms, and this lead was measurable in a high proportion of the patients (97%).

Effects of heart rate on QT dispersion

In 11 of the 13 patients in whom transoesophageal atrial stimulation was performed, an atrial paced rate could be obtained that was close to the heart rate at corresponding times during atrial fibrillation. The precordial QT dispersion was not different prior to the almokalant infusions (29 ± 13 ms during pacing vs 32 ± 13 ms during atrial fibrillation) and showed a larger almokalant-induced increase during pacing than during atrial fibrillation (69 ± 46 vs 33 ± 14 ms, *P*=0.0073). This observation argues against differences in heart rate as the cause of the greater QT dispersion during sinus rhythm.

Effects of QT interval on QT dispersion

In the present study, no correlation was found between QT dispersion and the QT interval, either during normal or prolonged repolarization. Thus, the increase in QT dispersion observed during infusion was not explained by the almokalant-induced prolongation of the QT

interval. This indicates that almokalant caused a homogeneous prolongation of ventricular repolarization in the majority of the patients, but in a subset of patients, inhomogeneous prolongation of repolarization caused an increase in QT dispersion. Furthermore, the greater increase in QT dispersion during sinus rhythm could not be explained by the difference in the increase in the QT interval between the two rhythms alone, as this increase was proportionally not as great as the difference in the increases in QT dispersion (Table 2 and 3). Furthermore, the increase in the QT intervals was observed at corresponding times during both infusions, while the increase in QT dispersion was detected earlier during sinus rhythm. Thus, atrial fibrillation did not have the same influence on the QT interval during prolonged repolarization as was observed for QT dispersion.

QT dispersion and arrhythmogenicity

Torsades de pointes tachycardia is associated with agents that prolong myocardial repolarization^[32–34] and has been observed with all class III antiarrhythmic drugs in clinical trials^[35–39]. Both in vivo experiments and several clinical studies support the concept that increased QT dispersion is linked to the development of torsades de pointes in both the congenital and the acquired form^[3,7–9,25,40]. The case for the relationship has recently been argued by Coumel and colleagues^[41]. The findings in the present study indicate that sinus rhythm may enhance the risk of proarrhythmia by increasing the dispersion during prolonged repolarization. An increased susceptibility to proarrhythmia immediately following conversion to sinus rhythm has been suggested in other studies^[8,42–45], and a different neuroendocrine activation during atrial fibrillation compared with sinus rhythm has been suggested as a cause of this difference^[46]. It should also be noted that dispersion assessed during atrial fibrillation correlated poorly with dispersion during sinus rhythm in the same patient (Figs 1(a) and (b)). On an individual basis, it may therefore not be sufficient to monitor QT dispersion during atrial fibrillation to predict the proarrhythmia risk after conversion to sinus rhythm.

Conclusions

QT dispersion is increased during both sinus rhythm and atrial fibrillation during prolonged ventricular repolarization induced by almokalant. This increase in QT dispersion is more pronounced during sinus rhythm and is less evident during atrial fibrillation. This difference is not explained by differences in heart rate, the degree of QT interval prolongation, or by the methods used for analysis. The findings of the present study indicate that QT dispersion is more easily detected during sinus rhythm, and that other reference values for the measurement of QT dispersion during atrial fibrillation have to

be adopted than those presently employed during sinus rhythm.

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