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Association between T_{peak}-T_{end} interval and QT prolongation: A study of sertindole and sotalol

Saeed Shakibfar^{*1}, Johannes J. Struijk¹, Jørgen K. Kanter^{2,3}, Jimmi Nielsen⁴, Samuel Schmidt¹ and Claus Graff¹

¹Department of Health Science and Technology, Aalborg University, Aalborg, Denmark

²Department of Cardiology, Herlev&Gentofte University Hospitals, Copenhagen, Denmark

³Laboratory of Experimental Cardiology, Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark

⁴Centre for Schizophrenia, Aalborg Psychiatric Hospital, Aalborg University Hospital, Aalborg, Denmark

Abstract

The electrocardiographic interval between the peak and the end of the T-wave (T_{pe}) is believed to be an arrhythmic risk marker. However, there are also a number of reports that are inconsistent with the usefulness of T_{pe} for identifying abnormal repolarization. This study was designed to investigate how the T_{pe} prolongation is correlated to a prolonged QT interval, induced by I_{Kr}-blockers. The study included two data sets. A first group of 21 healthy subjects received 160 mg and 320 mg doses of d,l-sotalol. The second group, of 40 patients with schizophrenia, was switched to 16 mg sertindole treatment. The Fridericia corrected QT prolongations (QT_{cF}) and the mean T_{pe} changes (Δ T_{pe}) were: d,l-sotalol 160 mg: Δ QT_{cF}=29 ms & Δ T_{pe}=4.7 ms, 320 mg: Δ QT_{cF}=51 ms & Δ T_{pe}=6.2 ms, sertindole 16 mg: Δ QT_{cF}=17 ms & Δ T_{pe}=8.5 ms. There were low correlations (r) between Δ QT_{cF} and Δ T_{pe} in both d,l-sotalol groups and sertindole group.

Given the lack of linear relationship between T_{pe} and QT in response to potential torsadogenic drugs, this study raises doubt about the usefulness of T_{pe} as a biomarker for repolarization changes and torsadogenic potential in drug safety studies.

Introduction

Features of the morphology of the T-wave of the body surface electrocardiogram (ECG) can reflect abnormalities of ventricular repolarization. For example, the T-wave peak-to-end (T_{pe}), which is defined as the interval from the peak of the T-wave to the end of the T-wave, may be a relatively simple marker for observing repolarization changes and identifying drugs with torsadogenic potential.

There is some evidence suggesting that a prolonged T_{pe} interval represents repolarization heterogeneity and that the interval may be a marker of arrhythmogenesis [1-4]. The prolonged T_{pe} interval might be associated with a high risk for developing torsades de pointes (TdP) in patients with acquired and congenital long QT syndromes (LQTS). The T_{pe} interval can also be prolonged in patients with a history of drug-related TdP [5-11].

However, there are also a number of reports about inconsistencies of the T_{pe} interval as a sensitive biomarker for identifying abnormal repolarization [8,12-18]. Importantly, these reports show that the clinical usefulness of the T_{pe} interval for identifying patients at risk of ventricular arrhythmias is still far from being established.

The T_{pe} interval was proposed to quantify transmural dispersion of repolarization (TDR), based on results from the wedge preparation obtained from the free wall of the canine left ventricle [19]. The measure of dispersion was based on differences in the action potential durations (APD) of the principal layers that comprise the ventricular myocardium. It was demonstrated in this setting that the peak of the T-wave coincided with the end of epicardial repolarization, whereas the end of the T-wave coincided with the end of repolarization of the mid-mural M cells. Therefore, by testing, e.g., d-sotalol, a known QT prolonging drug, Antzelevitch *et al.*, showed that longer APDs in the M

cells with relatively shorter APDs in endocardial and epicardial layers lead to T_{pe} prolongation [20,21].

In the case of more complex T-waves, including negative, biphasic and triphasic ones, it was suggested that the estimation of TDR could be based on the interval from the nadir of the T-wave to the end of the T-wave instead of the interval from the peak of the T-wave to the end of the T-wave [22]. However, the representation of TDR in the ECG is a controversial subject [23,24].

The T_{pe} to QT interval ratio (T_{pe}/QT) has also been proposed to provide an estimate of dispersion of repolarization. This measurement estimates the T_{pe} interval relative to the total duration of activation and repolarization and since the QT interval varies with heart rate, the T_{pe}/QT ratio could also be less heart rate dependent than T_{pe} itself [25]. The T_{pe}/QT ratio has thus been suggested as a more sensitive index of repolarization changes and risk of arrhythmia compared to the T_{pe} interval alone. However, in one study of the T_{pe} interval we showed that T_{pe} was heart rate dependent but the effect of rate was only minor at near resting heart rates [16]. We have also shown that, despite QT_c prolonging effects of sertindole, no increase in the duration of the T_{pe} interval was found [18]. In addition, we have shown that in patients with the long QT syndrome and elevated risk of TdP, it was not possible to use T_{pe} to distinguish symptomatic from asymptomatic patients

Correspondence to: Saeed Shakibfar, University of Copenhagen, Department of Computer Science, Sigurdsgade 41, Copenhagen, DK 2200, Tel: +45 35331269, E-mail: saeed@di.ku.dk

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[16]. In comparisons of ECG data from survivors and non-survivors of cardiovascular disease, Smetana *et al.*, showed that the Tpe interval was significantly shorter in non-survivors, both uncorrected and corrected for heart rate [15]. Therefore, there are serious problems with a direct extrapolation of the findings in vitro about the Tpe interval to clinical populations. Particularly, Opthof *et al.*, argued that there are influential biological differences between in vitro preparations and the in vivo heart, such as autonomic, humoral, and hemodynamic factors [26].

In addition, there is a small body of data dealing with the functional role of M cells in the human heart. Some data has failed to show the role of M cells in effecting Tpe changes [27,28]. According to the studies by Opthof *et al.*, the Tpe interval is unlikely to be correlated with TDR in vivo [26,29]. These studies conclude that, in general, epicardial repolarization occurs later than endocardial repolarization in the free wall of the left ventricle. Hence, the functional and clinical importance of M cells for Tpe changes in vivo is not clear.

It thus remains controversial what the Tpe interval actually represents. However, it is important to quantify the extent to which the Tpe interval is correlated with the whole heart repolarization time, represented by the QT interval.

Aim of the study

The present study was designed to examine the association between the Tpe interval and QT prolongation induced by two torsadogenic drugs: sertindole and d,l-sotalol, both I_{Kr} -blockers, capable of inducing QT prolongation and TdP [30,31].

Methods

Study population and design

The present study included data from two different I_{Kr} -blockers. The first group of 39 healthy subjects received 0, 160 mg and 320 mg doses of d,l-sotalol on three consecutive days. All subjects were males, between 18 and 45 years of age. Their healthy status was confirmed by history, physical examination, normal blood pressure and no use of concomitant medication. The second group of 37 patients carried a WHO ICD-10 diagnosis of schizophrenia. This group was switched to 16 mg sertindole treatment. The study was approved by the Scientific Ethical Committee of Northern Jutland. None of the subjects had a history of cardiac diseases and all had normal baseline ECG. In some cases the V5 on ECG data could not be analysed based on signal noise. Further demographic information on subjects receiving d,l-sotalol and sertindole can be found in Sarapa *et al.*, Graff *et al.* and Nielsen *et al.* [32-34].

All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board. All subjects gave written informed consent to the study protocol approved by an independent Institutional Review Board.

Written informed consent was obtained from all subjects in the first group for the study protocol. However, in the second group obtaining informed consent was not required because the study was non-interventional and ECG was indicated for therapeutic monitoring.

ECG acquisition

For d,l-sotalol, ECG segments of 10 s duration were obtained from 12-lead digital Holter recordings (H12Recorder, Mortara Instrument, Milwaukee, WI). ECG recordings at the time of maximum plasma concentrations, 3.5 h post-dose were used, both for 160 mg and 320 mg d,l-sotalol. The corresponding study time was used on the baseline day. Each ECG extracted from Holter was resampled from 180 Hz to 500 Hz as previously described [33].

For sertindole, digital ECGs were recorded with GE MAC5000 and GE CardioSoft (GE Healthcare, Milwaukee, WI). At baseline five consecutive 12-lead digital ECGs of 10 sec duration were recorded from each schizophrenia patient at a sample rate of 500 Hz and transferred to a MUSE database (GE Healthcare, Milwaukee, WI). ECGs were recorded again when patients reached steady-state concentration of sertindole 16 mg, after a minimum of 3 weeks as recommended in the Summary of Product Characteristics of Serdolect [34].

ECG analysis

From each 10 s ECG recording a median beat was formed in the recorded leads using MUSE/Interval Editor software (GE Healthcare, Milwaukee, WI). Lead V5 was used to measure the Tpe interval because V5 is the lateral precordial lead which is considered to best reflect the electrical phenomena in the left ventricle during I_{Kr} -blocker-induced repolarization disorders. Based on the early studies, lead V5 was targeted to measure the Tpeak-Tend interval to predict TdP [5]. Since analyses were performed on a median beat, ECGs were not filtered to measure Tpeak location.

QT intervals were measured automatically (12SL, GE Healthcare, Milwaukee, WI). QT intervals were corrected for heart rate with Fridericia's equation: $QTcF = QT/RR^{1/3}$.

The peak of the T-wave was defined as the point of highest amplitude of the T-wave. In cases of notched or bifid T-waves the interval from the nadir, between the peaks of the T-wave, to the end of the T-wave was used [20-22].

Statistical analysis

Data were analyzed using Matlab R2012b (Mathworks Inc, Natick, MA). Results are presented as means and standard deviations. Pearson's correlation coefficients were used for investigating linear relationships. All findings were compared by Student's t-test for paired data. A p-value <0.05 was considered statistically significant.

Results

ECG characteristics for the sertindole and d,l-sotalol groups are outlined in Table 1. The mean Tpe did change significantly from baseline with sertindole and for d,l-sotalol 320 mg, but not significantly for 160 mg. Also, the QT and QTcF intervals increased significantly following both d,l-sotalol and sertindole administration (Figure 1).

A scatter plot for Tpe versus QTcF, for all data, is shown in Figure 2. Correlation coefficients for the linear relationships are given in table 2. The largest correlation coefficient (r) was $r=0.45$, $p=0.005$ for sertindole, whereas the correlation coefficients for Tpe on QTcF for sotalol were small and not significant (160 mg: $r=0.15$, $p=0.54$ and 320

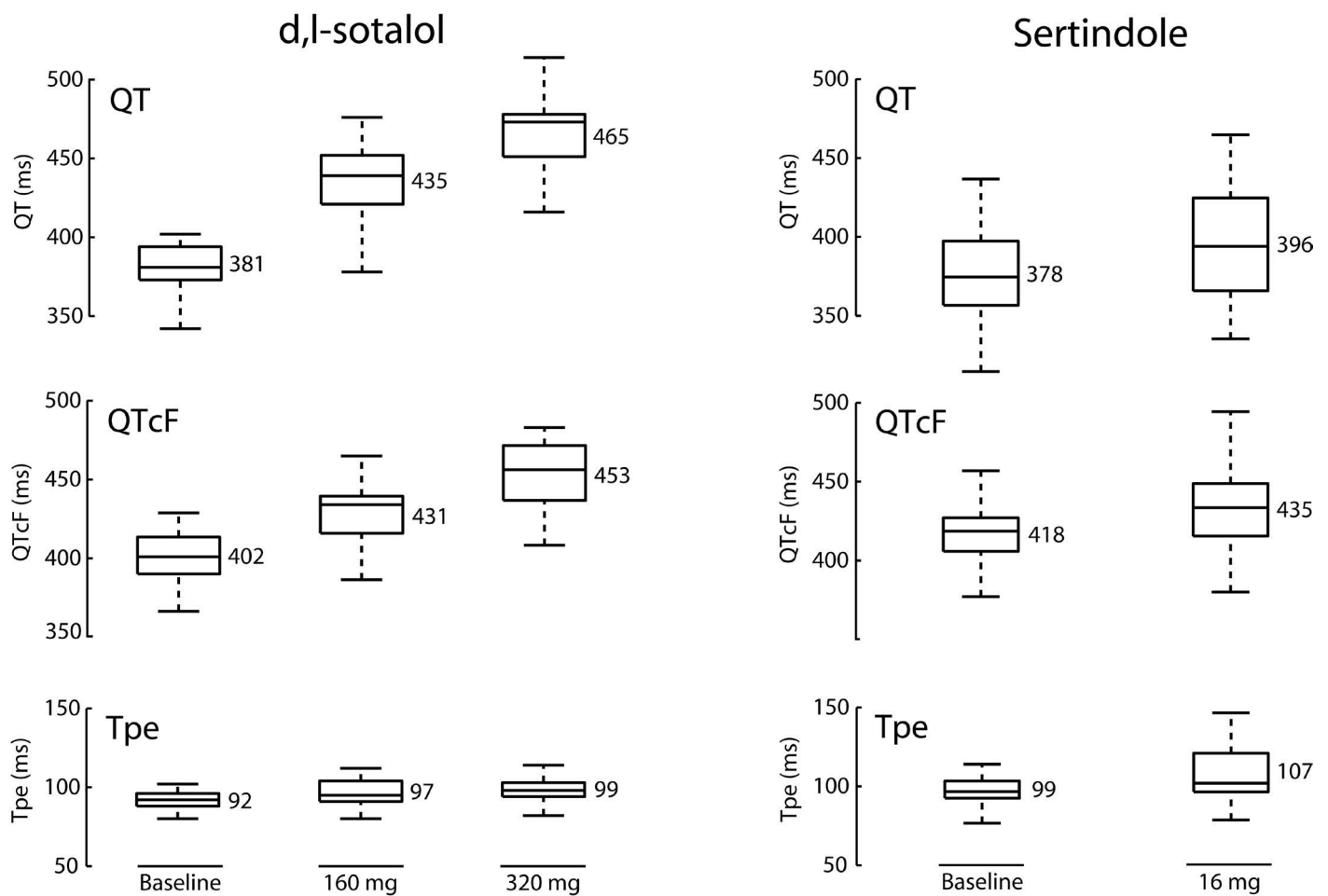


Figure 1. QT, QTcF and Tpe for d,l-sotalol (left column) and sertindole (right column) Boxplots: median, interquartile range and full range. Mean values are given for each measurement.

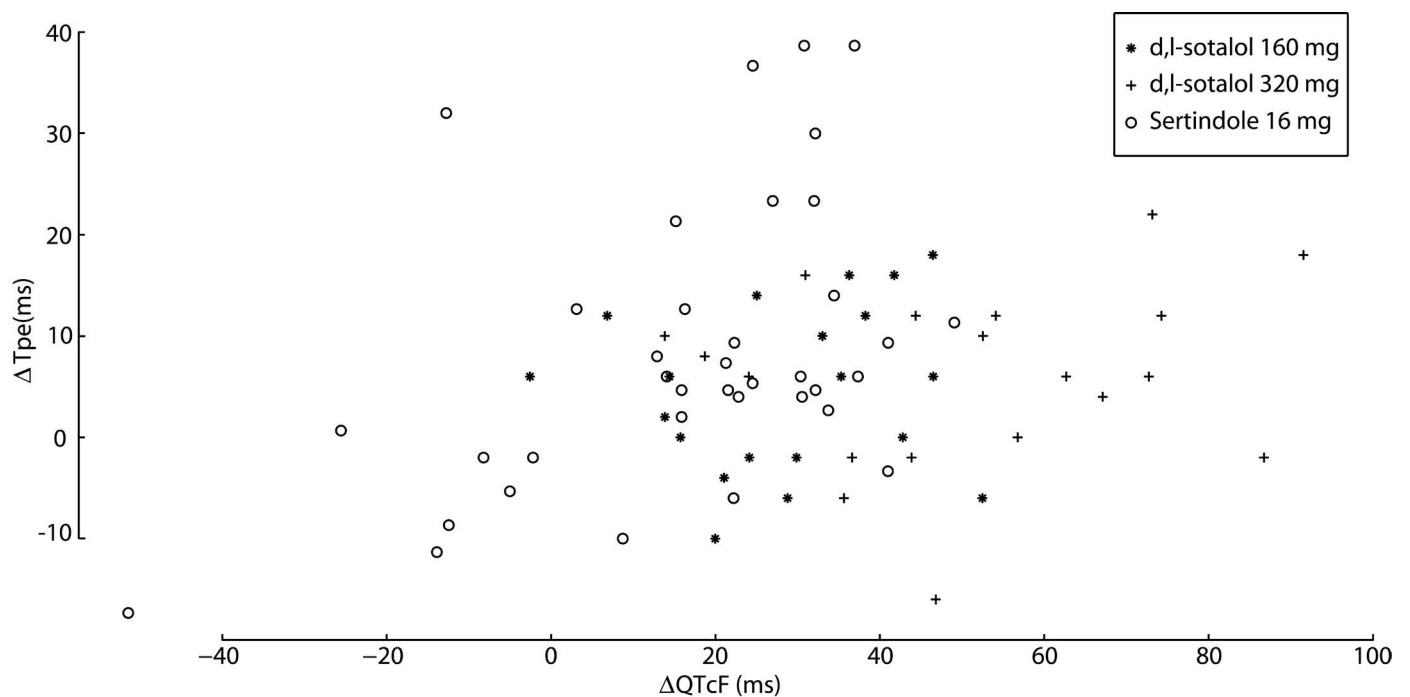


Figure 2. Scatter plot for changes in QTcF and Tpe from baseline for sotalol 160 mg (*), sotalol 320 mg (+) and sertindole (o)

Table 1. ECG characteristics for sertindole and sotalol.

	Sertindole			Sotalol				
	Baseline	treatment	p-value*	baseline	160mg	p-value	320mg	p-value
QT (ms)	378 ± 56	396 ± 71	<0.05	381 ± 35	435 ± 51	<0.001	465 ± 50	<0.001
T _{pe} (ms)	99 ± 24	107 ± 34	<0.05	92 ± 16	97 ± 19	0.09	98.5 ± 18	<0.05
QTcF (ms)	418 ± 42	435 ± 48	<0.05	402 ± 31	431 ± 39	<0.001	453 ± 43	<0.001

Table 2. Pearson's correlation coefficients between prolongation of QTcF and T_{pe} intervals.

$\Delta\text{QTcF} \ \& \ \Delta\text{T}_{\text{pe}}$	Pearson Correlation Coefficient (r)	p-value
d,l-sotalol (320mg)	0.15	0.52
d,l-sotalol (160mg)	0.15	0.54
Sertindole (16 mg)	0.45	0.005

mg; $r=0.15$, $p=0.54$). Despite the statistically significant correlation for sertindole between QTcF and Tpe, the relationship explains only a small percentage (20%) of the variation of Tpe with QTcF.

Discussion

We found that, despite marked QT and QTcF prolongation, induced by potential torsadogenic I_{Kr}-blockers d,l-sotalol and sertindole, little linear association was observed between the Tpe interval and the QTcF interval. Tpe changes with a lower significant value (see P-value in Table 1). Figure 2 shows a high variance of Tpe relative to the drug-induced changes and, compared with QTcF, Tpe therefore is not a robust predictor of potential torsadogenicity prolonging repolarization.

Our results are not in accordance with a number of previous studies [1-11]. On the basis of prolonged Tpe intervals, those studies concluded that the Tpe interval can be an important marker of arrhythmia susceptibility. However, there is also a number of studies that support our findings whether prolongation of the Tpe interval can be used to predict the risk of arrhythmia [12-18]. In one case, Tpe was even found to be statistically significantly shorter in non-surviving cardiovascular patients compared to survivors [15].

Our studies on T-wave morphology have shown that, compared to the QT interval, T-wave morphology is a more sensitive marker for assessing repolarization changes and arrhythmic potential with I_{Kr}-blockers [33-36]. This is not surprising since the electrophysiological effects that occur with torsadogenic drugs are expected to have a larger effect on T-wave changes and a stronger association with TdP compared to the QT interval [37]. In addition, T-wave shape changes are not captured by the Tpe interval which measures only the duration of the poorly defined final part of repolarization. Interestingly, our recent work has proposed the minimal T-wave representation by making T-wave independent of QT duration and thus much less dependent on heart rate. The results of analyzing the minimal T-wave shape showed that it could identify normal from abnormal repolarization significantly better compared to heart rate corrected QT interval (QTc) and most of the prolongation occurred in the ascending segment of the T-wave whereas T-peak to T-end was less sensitive relatively after d,l-sotalol [38]. Also, studies of the effects of some IKr blockers on multiple sub-intervals of the QT interval showed that hERG potassium channel block equally affects the whole T-wave duration, early and late repolarization (Tj to Tend and Tpe intervals) whereas additional inward current block (calcium or late sodium) preferentially shortens early repolarization [39,40]. In addition, Johannesen *et al.*, showed that QTc (QTc prolongation in 20 of 26 drugs, $P=0.014$) is a more sensitive biomarker of hERG potassium channel block compared with Tpe (Tpe prolongation in 18 of 26 drugs, $P=0.051$) [40]. The measurement of Tpe alone can therefore, not be expected to provide adequate information

about the complex repolarization changes that occur with torsadogenic drugs.

There are two important sources of error in the Tpe interval. First, the end of the T-wave can be difficult to determine, since it may not reach the baseline and may be followed by a superimposed U-wave or P-wave. This is the same problem as occurs when determining the QT interval. Secondly, I_{Kr}-blockers may produce considerable T-wave changes particularly flatness, notches and asymmetry. The drug-induced shape changes add to the difficulty of measuring the time of occurrence of the peak of the T-wave, which thus has a great influence on the assessment of changes of the Tpe interval. Due to the short duration of the Tpe interval, those measurement errors will have a relatively larger impact on absolute values of the Tpe interval compared to the QT interval. This is an undesirable property of the Tpe interval as a biomarker for repolarization changes. Finally, the absolute values for the Tpe interval is heavily influenced by the method used to measure the duration. For example, the tangent method will tend to measure QT and Tpe intervals which are shorter compared to the method used in this study which estimate the end of the T-wave from superimposition of recorded leads. The discrepancy between measuring methods explains why studies that do not use the same method for estimating the end of the T-wave, can report very different QT and Tpe intervals, even on the same data. The discrepancy in measuring technique does not explain however, the lack of effect on the Tpe interval in this study, despite marked QT interval changes.

Based on Xia *et al.*, it is not useful to average Tpe as index of TDR, among several leads because TDR might vary in different regions of the ventricular myocardium under different pathophysiologic conditions [41]. Therefore, it is advisable to measure Tpe independently in each of the precordial leads. Also, early studies used the V5 lead reflecting electrical phenomena in left ventricle to show that the Tpe interval of the T-wave loop might be a useful predictor of TdP in long QT syndrome (LQTS) patients whose I_{Kr} current is (partially) blocked. Consequently, in this study lead V5 was targeted to measure the Tpe interval, because it could be considered to best reflect the electrical phenomena in the left ventricle during I_{Kr}-blocker-induced repolarization disorders.

One limitation of the study is that different devices were used in the two groups for ECG recording. Also, this study is based on a retrospective analysis and that the conclusion should be interpreted with appropriate levels of caution.

In conclusion, we have shown much lower effect sizes for drug-induced changes of Tpe than for QTcF, which implies that QTcF is a more robust biomarker for repolarization changes in drug safety studies.

Compliance with ethical standards

Funding

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Conflict of interest

Regarding this work the authors do not report any conflict of interest.

Ethical approval

Written informed consent was obtained from all subjects in the first group for the study protocol and was approved by the Scientific

Ethical Committee of Northern Jutland. However, in the second group obtaining informed consent was not required because the study was non-interventional and ECG was indicated for therapeutic monitoring. Further demographic information on subjects receiving d,l-sotalol and sertindole can be found in Sarapa *et al.*, Graff *et al.*, and Nielsen *et al.*, [32-34].

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