Association between Tpeak-Tend interval and QT prolongation
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The Tpe 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 Tpe 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 Tpe to QT interval ratio (Tpe/QT) has also been proposed to provide an estimate of dispersion of repolarization. This measurement estimates the Tpe interval relative to the total duration of activation and repolarization and since the QT interval varies with heart rate, the Tpe/QT ratio could also be less heart rate dependent than Tpe itself [25]. The Tpe/QT ratio has thus been suggested as a more sensitive index of repolarization changes and risk of arrhythmia compared to the Tpe interval alone. However, in one study of the Tpe interval we showed that Tpe was heart rate dependent but the effect of rate was only minor at near resting heart rates [16]. We have also shown that, despite QTc prolonging effects of sertindole, no increase in the duration of the Tpe 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 Tpe to distinguish symptomatic from asymptomatic patients.

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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 the whole heart repolarization time, represented by the QT interval. 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 sertindole 16 mg, after a minimum of 3 weeks as recommended in the institutional review board. None of the subjects had a 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 sertindole 16 mg, after a minimum of 3 weeks as recommended in the institutional review board. None of the subjects had a history, physical examination, normal blood pressure and no use of concomitant medication.

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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). QT 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 Seroquel [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 mg: r=0.13, p=0.53).

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**Table 1.** ECG characteristics for sertindole and d,l-sotalol groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>QT (ms)</th>
<th>QTcF (ms)</th>
<th>Tpe (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertindole</td>
<td>398</td>
<td>369</td>
<td>32.4</td>
</tr>
<tr>
<td>D,L-Sotalol</td>
<td>385</td>
<td>357</td>
<td>27.3</td>
</tr>
</tbody>
</table>

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**Table 2.** Correlation coefficients for the linear relationships.

<table>
<thead>
<tr>
<th></th>
<th>QT vs Tpe</th>
<th>QTcF vs Tpe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertindole</td>
<td>r=0.45</td>
<td>p=0.005</td>
</tr>
<tr>
<td>D,L-Sotalol</td>
<td>r=0.15</td>
<td>p=0.54</td>
</tr>
</tbody>
</table>

**Figure 1.** Scatter plot for Tpe versus QTcF, for all data.
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)
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 than for QTcF, which implies that QTcF is 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 left ventricle during I_{Kr} -blocker-induced repolarization disorders. 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

This study was partially supported by the Region Nordjylland Sundhedsvidenskabelige Forskningsfond (Health Research Fund of Central Denmark Region).

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

Table 1. ECG characteristics for sertindole and sotalol.

|                | Sertindole          | Sotalol            | p-value*  
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>QT (ms)</td>
<td>378 ± 56</td>
<td>396 ± 71</td>
</tr>
<tr>
<td>Tₚₑ (ms)</td>
<td>99 ± 24</td>
<td>107 ± 34</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>418 ± 42</td>
<td>435 ± 48</td>
</tr>
<tr>
<td>QT (ms) baseline</td>
<td>381 ± 35</td>
<td>415 ± 51</td>
</tr>
<tr>
<td>QTc (ms) baseline</td>
<td>92 ± 16</td>
<td>97 ± 19</td>
</tr>
<tr>
<td>QTcF (ms) baseline</td>
<td>402 ± 31</td>
<td>431 ± 39</td>
</tr>
<tr>
<td>QTcF (ms) 160mg</td>
<td>453 ± 43</td>
<td>453 ± 43</td>
</tr>
<tr>
<td>QTcF (ms) 320mg</td>
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Table 2. Pearson’s correlation coefficients between prolongation of QTcF and Tₚₑ intervals.

<table>
<thead>
<tr>
<th>ΔQTcF &amp; ΔTₚₑ</th>
<th>Pearson Correlation Coefficient (r)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>d,L-sotalol (320mg)</td>
<td>0.15</td>
<td>0.52</td>
</tr>
<tr>
<td>d,L-sotalol (160mg)</td>
<td>0.15</td>
<td>0.54</td>
</tr>
<tr>
<td>Sertindole (16 mg)</td>
<td>0.45</td>
<td>0.005</td>
</tr>
</tbody>
</table>

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.
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