Heritability of Tpeak-Tend interval and T-wave amplitude: A Twin Study

Running title: Haarmark et al.; Heritability of T-wave morphology

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Word count: 5941

Journal Subject Codes: [171] Electrocardiology; [89] Genetics of cardiovascular disease
Abstract:

**Background** - Tpeak-Tend interval (TpTe) and T-wave amplitude (Tamp) carry diagnostic and prognostic information regarding cardiac morbidity and mortality. Heart rate and QT interval are known to be heritable traits. The heritability of T-wave morphology parameters such as TpTe and Tamp is unknown. TpTe and Tamp were evaluated in a large sample of twins.

**Methods and Results** - Twins from the GEMINAKAR study (611 pairs, 246 monozygotic, 365 dizygotic, aged 38±11 years, 49 % men) who had an ECG performed during 1997-2000 were included. Tamp was measured in leads V1 and V5. Duration variables (RR interval, QTpeak and QTend interval) were measured and averaged over three consecutive beats in lead V5. TpTe was calculated as the QTend and QTpeak interval difference. Heritability was assessed using structural equation models adjusting for age, gender and BMI. All models were reducible to a model of additive genetics and unique environment. All variables had considerable genetic components. Adjusted heritability estimates were: TpTe 46%, Tamp lead V1 34%, Tamp lead V5 47%, RR interval 55%, QT interval 67% and QTcB 42%.

**Conclusions** - RR interval, QT-interval, T-wave amplitude and Tpeak-Tend interval are heritable ECG parameters.

**Key words:** ECG, Tpeak-Tend interval, T-wave amplitude, QT interval, Twins, Heritability
Introduction

T-wave morphology is increasingly being used to characterize repolarization in cardiac ventricles. T-wave amplitude (Tamp) and the interval from the peak to the end of the T-wave (Tpeak-Tend interval, TpTe) have been shown to carry prognostic information and has been associated with increased risk of arrhythmia syndromes1-5. In inherited arrhythmias (such as long and short QT syndromes, arrhythmogenic right ventricular cardiomyopathy) the T-wave shows characteristic morphological changes as well6-8. The twin study design has been used in cardiovascular research to demonstrate significant genetic contribution to a range of physiological measures such as heart rate, QT interval9,10, blood pressure11 and heart rate variability12. Multiple studies of the heritability of RR interval and QT interval have shown large genetic contribution to these variables9-11,13,14. The importance of repolarization and its heritability have been confirmed in monogenetic diseases such as long and short QT syndromes15 and the contribution of common genetic variants to the QT interval in the general population are increasingly well described16. Furthermore some of these variations increase the vulnerability to drug-induced arrhythmias17. However except for the QT interval, the genetic contribution of repolarization has not been assessed. Until now the heritability of Tamp and TpTe has not been characterized in large samples. The aim of this study was to investigate the heritability of Tamp and TpTe in a large population of monozygotic and dizygotic twins using a twin study design.

Method
Population

The GEMINAKAR study is a nationwide Danish twin study which evaluates the genetic and environmental influences on a variety of phenotypes, especially insulin resistance, obesity and cardiovascular risk factors. The twins in the GEMINAKAR study were recruited from the national, population-based Danish Twin Registry. Two birth cohorts (born between 1931-1952 and 1953-1982) were invited to participate in a full day clinical investigation conducted in the period 1997-2000. Exclusion criteria included diabetes, cardiovascular disease, pregnancy, breast feeding and conditions that would make a bicycle exercise test impossible. The twins in a pair were studied at the same time and day. The clinical investigation included an ECG, exercise test, measurement of weight, height and blood pressure. A total of 1512 twins underwent clinical examination. Zygosity was determined by DNA-based microsatellite markers 18, 19.

ECG acquisition and measurements.

Standard resting 12-lead ECGs was retrievable from 1290 twins. ECGs were recorded at either 25 mm/sec or 50 mm/sec paper speeds. Each twin pair was examined with the same device and paper speed. ECGs were manually scanned (24 bit color, resolution 300 dpi, HP Scanjet 8300, Hewlett-Packard, CA) and transferred to a PC. Using magnification and a digital caliper (Cardio Calipers, ver. 3.3, Iconico Software, NY) T-wave amplitude was measured in leads V1 and V5. The duration variables (RR interval, QTpeak- and QTend interval) were measured and averaged over three consecutive beats in lead V5. The end of the T-wave was defined as the tangent of the down slope crossing the isoelectric line. TpTe was calculated as the difference between QTend and QTpeak interval. Bazett corrected QT interval (QTcB) was calculated as QTcB = \frac{QTR}{\sqrt{RR}}.

Twin pairs were excluded from further analysis if one or both had one of the following 1) severe baseline wandering in leads V1 or V5 (6 pairs), 2) no visible T-wave in lead V5 (6 pairs), 3) noise in leads V1 or V5 that made identification of the T-wave impossible (7 pairs), 4) two or
more premature beats per tracing (5 pairs), 5) ECG bleached by light or torn affecting leads V1 or V5 (2 pairs), 6) only ECG from one twin (4 pairs), and 7) no available clinical information (4 pairs). In total 34 pairs was excluded (5.3 % of the cohort) leaving 611 pairs for further analysis (246 monozygotic, 365 dizygotic).

All measurements were done by CH and the investigators where blinded of all clinical information including zygosity until final statistical analysis after completion of ECG measurements.

Statistics:

Simple descriptive statistic was used to describe the population and electrocardiographic variables (mean, standard deviation (SD)). A two-sided Student’s T-test was used to test for differences between monozygotic and dizygotic twins. A p-value < 0.05 was considered significant. Pearson’s correlation coefficients for Tamp, TpTe, RR- and QT-intervals within monozygotic twins (rMZ) and dizygotic twins (rDZ) were calculated.

The strength of the classical twin study is that twins are either monozygotic or dizygotic and thus share either 100% or on average 50% of their segregating genes. With the assumption that co-twins experience the same environmental background these differences in genome make it possible to explore the genetic and environmental influence on a given phenotypic trait, e.g. blood pressure, heart rate or T-wave morphology. By determining the variance of a phenotype in large sets of both types of twins, it is possible to assess how much of the total variance is attributable to genetic factors (heritability) and how much is explained by shared environmental factors (as experienced by both twins) or unique (as only experienced by one twin).

Traditionally these three elements are called A (additive genetic variance), D (variance caused by dominance or epistatic effects, i.e. gene-gene interaction), C (common environmental variance), and E (unique environmental variance). Heritability is either the proportion of the total variance
explained by the additive genetic variance (narrow sense) or by both A and D (broad sense). The combination of A, C and E constitutes an ACE-model that explains the proportion of variance seen in a phenotype explained by additive genetic effects and environment. Usually the additive genetic effect (A) explains the majority of the genetic variation; multiple alleles may be involved all adding to the genetic variation. One example is seen in the variety of polymorphisms that influences the QT interval. Evidence of non-additive effects is tested via an ADE-model. Measurement errors are included in the estimate of environmental factors. Through the principle of parsimony, the ACE/ADE model is reduced, so that the data is explained with the fewest variables possible as long as the reduced model is not significantly worse than the full model (e.g. an ACE model may be reduced to an AE model or an E model). Finally the estimates of heritability and environmental influences are adjusted for covariates (age, gender and body mass index) by including them in the regression analysis. All statistical analyses were done using SAS statistical software (SAS v.9.1, SAS Institute Inc, NC).

To assess the intra-reader variability of the manual measured ECG variables sixty ECGs selected at random were re-measured by CH (5% of included population). Pearson correlation coefficients between the original and re-measured variables were calculated. There were overall high reproducibility for RR interval (r = 0.96), QT interval (r = 0.97) and Tamp in lead V5 (r = 0.98). The reproducibility of TpTe (r = 0.85) and Tamp in lead V1 (r = 0.85) were lower but still acceptable.

**Results:**

In table 1 the demographic data of the population is given together with the electrocardiographic data stratified by zygosity. There were no significant differences between the two groups of twins. As seen in table 2 the Pearson correlation coefficients for Tamp, TpTe, RR- and QT intervals within the two twin groups were higher in monozygotic twins compared to dizygotic
twins. In figure 1 the Tamp in lead V5 is plotted for a) monozygotic twin pairs, b) same sex dizygotic twins and c) unrelated individuals (amplitude plotted for monozygotic twins that were paired with unrelated other monozygotic twin). The association between pairs diminishes from monozygotic twins to dizygotic twins and from dizygotic twins to age matched unrelated pairs. The remaining correlation between the unrelated pairs is due to Tamp being age dependent (all pairs age matched)\textsuperscript{20}.

All estimation models could be reduced to an AE model without significant loss of information. Adding covariates to the initial ADE and ACE models lead to identical final models, thus allowing all models to be reduced to AE-models. All final heritability estimates reported are narrow sense heritability (also known as $h^2$), only addressing additive genetic effect.

The heritability estimates based on the structural modeling are given in table 3. Firstly the unadjusted values are given. Then results are given adjusting for one covariate at a time and finally adjusted for all covariates together. When adjusting for age, gender and BMI, the adjusted estimates of Tamp and QTcB heritability reduced more than the remaining variables, suggesting that Tamp and QTcB heritability is more dependent of the covariates than the other investigated variables.

To address the possible variance introduced by different ECG-paper speeds (25 vs 50 mm/sec), paper speed was added to the model as a covariate as well. There were very little to no effect of adjusting for ECG paper speed on heritability estimates for RR interval (0.55 vs. 0.53), QT interval (0.67 vs. 0.67), QTcB interval (0.42 vs. 0.41), TpTe (0.46 vs. 0.44) and Tamp lead V5 (0.47 vs. 0.47). However the heritability estimate for Tamp V1 decreased (0.34 vs. 0.25).

When adding the QT interval to the model, the heritability of Tamp remained unaltered (table 4), whereas the heritability estimate for TpTe was attenuated.
Discussion

The main finding of this study is that TpTe and Tamp are heritable with evidence for an additive genetic effect. There was no evidence of non-additive effects. Adjustment for age, gender and BMI did reduce the heritability estimates of Tamp whereas inclusion of QT interval reduced the heritability estimate of TpTe.

Heritability of TpTe

The TpTe interval is a measure of dispersion of repolarization in the ventricles of the heart\(^{21,22}\). TpTe reflects the gradients in the heart; the transmural, left vs. right ventricle, apical vs. basis and anterior vs. posterior. These gradients are caused by different expression of ion channels in various parts of the heart. The influence of the different gradients is heavily debated, but undoubtedly the TpTe interval is an expression of electrical dispersion, whether it is a measure of global dispersion or transmural dispersion\(^{21,22}\). Factors that inhibit this delicate balance between electric currents through ion channels may influence the electric heterogeneity and potentially trigger arrhythmias. It is believed that a prolonged TpTe is arrhythmogenic\(^{22}\), and a prolonged TpTe has been associated with adverse outcomes (death and arrhythmias)\(^{1,4}\) but TpTe is unrelated to syncope and arrhythmias in congenital long QT syndrome\(^ {23}\).

To our knowledge this is the first study to evaluate TpTe in a large sample of twins of both genders. The heritability of TpTe suggests that there is an additive genetic inheritance for the TpTe duration. A few polymorphisms have been reported to influence TpTe duration; these being located in either cardiac ion channels carrying potassium currents (KCNQ1 and KCNH2) or in nitric oxide synthase 1 adaptor protein (NOS1AP), which earlier has been associated with QT interval duration\(^ {24-26}\). Possibly these polymorphisms may increase the individual risk for arrhythmias in the same way polymorphisms associated with QT interval duration has proven
Important \cite{16,17}. Further quantitative trait loci studies will address this possibility. The addition of QT interval to the model results in a reduction of the heritability estimate of TpTe, suggesting that there is a genetic overlap between the QT interval and TpTe. This could be expected, as they both express the repolarization in the ventricles.

**Heritability of Tamp**

The prognostic significance of T-wave amplitude is well established \cite{2,5}. Tamp is influenced by a variety of factors, including heart rate \cite{27} and ionic concentrations \cite{28}. The explanatory model could be reduced to an AE model without loss of significance, suggesting additive genetic effects. This may reflect the genetic variance in both Tamp in itself (ion channels etc.) and the many factors influencing Tamp (potassium and calcium handling in the body, BMI, age etc.).

The heritability of amplitude in lead V5 was significantly higher than in lead V1. Biphasic T-waves are more common in lead V1 than in V5 and T-waves in lead V1 have lower amplitude, resulting in lower reproducibility and higher inaccuracy in measuring T-wave amplitude in V1. Statistically the measurement errors will be added to the environmental influence reducing the heritability. For most measures the influence of paper speed was limited, except in lead V1 where amplitudes were smaller and the influence of noise was greater. Since each twin pair was measured with the same ECG machine, the noise became a heritable element. This led to a larger reduction in heritability of T-wave amplitude in lead V1 compared to the other measures when including paper speed as a covariate. Recently polymorphisms in the beta subunit of the slow delayed rectifier ($I_{Ks}$) have been associated with decreased T-wave alternans \cite{29}. To our knowledge, no reports have suggested polymorphisms directly affecting T-wave amplitude, but it is known that patients with loss-of function mutations in the rapid delayed rectifier potassium channel ($Ikr$), long QT syndrome type 2, have lower T-wave amplitude \cite{6,8}. This underlines the
crucial role of cardiac ion channels in repolarization performance and makes the ion channels
genes and polymorphisms primary candidates for the source of TpTe and Tamp heritability.
A study in older female twins confirms our finding of polygenetic inheritance of T-wave
amplitude in lead V5 and II, with an unadjusted heritability estimate of 61-72%. However they
found evidence of a dominant genetic effect in lead V1 (DE-model, 53% heritability). To the
authors own surprise they found no evidence of genetic influence on QT interval (CE-model best
fit); however an AE-model was almost as explanatory. They conclude that they lacked statistical
power to discriminate between dominant and additive genetic influence, which would explain the
differences in results 30.

*Heritability of RR interval*

We found similar results for heritability estimates regardless of which method heart rate (HR)
was reported, as HR, RR interval or logHR (data not shown). In accordance with a range of other
studies of heart rate heritability we found that RR interval was highly heritable (heritability
ranging in these studies from 61% to 55%) 9-12, 31-34. This was due to additive genetic effect with
no sign of dominant or shared environmental effects, which is also in agreement with the
literature 10-12, 32-34. However some studies have found lower values ranging from less than 50%
to no heritability 35-38. The majority of these contradictive studies measured HR over longer time
frames 35, 37, 38, e.g. from half hour to 24 hour recordings. These studies cannot be directly
compared to our study as we only measured at one time point at rest and did not include diurnal
variations or activity. One study showed a limited heritability of 23%, but did not clarify how
HR was measured 36.

*Heritability of QT interval*
In the present study we found a high heritability of uncorrected QT interval (69%) with little effect in adjusting for BMI, age and gender. The high heritability with estimates ranging from 50% to 60% has been confirmed elsewhere \(^{10,32,39}\). Other studies show moderate to high heritability (25 to 36%) with one study using a classical approach without SEM \(^9\) and one using a parent/sibling design instead of twins \(^{40}\). An older study utilizing classical heritability estimates found no heritability of the QT interval \(^{31}\). Again the most prevailing model was the AE-model as in our study. The estimates for heritability of heart rate corrected QT (whether being Framingham or Bazett’s corrected) ranges from 25% to 52% \(^{10,13,14,39}\) which is in accordance with the present study except for a peculiar finding by Dalageorgou et al \(^{10}\). They found the same heritability for QT and Framingham corrected QT as the present study (data not shown), however they saw no genetic influence on Bazett corrected QT in contrast to our and others findings.

**Effect of BMI, gender, age and QT adjustment on T-wave heritability**

There was little effect of correction for BMI. High BMI has been associated with different ECG abnormalities, amongst them flattening of T-waves inferolaterally \(^{41}\). However this was not evident in our population. The reason why BMI adjustments did not lead to any significant change in heritability estimates may be due to the fact that less than 1% of our population had BMI > 35.

On the other hand there were larger effects on estimates when adjusting for age and gender, most evident for amplitude measures. T-wave amplitude’s age and gender dependency is well established\(^{20}\), with decreasing T-wave amplitude with age and in women. The age effect is also seen in figure 1, where the remaining correlation between unrelated individuals is due to the
individuals being age matched. TpTe estimates remained constant, and as we have shown earlier TpTe is neither age nor gender dependent \(^{20}\).

In our study adjustment for age and gender did reduce the heritability estimate for RR interval and heart rate corrected QT interval. It is well established that both age and gender has a significant effect on heart rate and QT interval, i.e. heart rate corrected QT intervals are prolonged in women \(^{20}\).

QT interval adjustment had a major effect on TpTe estimates, which would be expected as TpTe is a part of the QT interval. However, after adjustment there still remained evidence of QT-independent additive genetic effect, suggesting that there might be genetic variants specific for the TpTe duration not accounted for by the QT interval. There was no overlap between Tamp and QT interval. Dalageorgou and colleagues have earlier shown that roughly 40% of the variation in QT interval is caused by genes in common with heart rate, while 16% of the variation was due to genes specific to the QT interval \(^{10}\).

**Clinical perspective**

Variation in the genes coding for proteins involved in cardiac regulation may be a novel method of risk assessment. Polymorphisms in cardiac receptors, calcium handling and cardiac ion channels all have the potential to increase the vulnerability to arrhythmias, especially in populations already in risk of arrhythmias (e.g. heart failure) but also in otherwise healthy population (e.g. acquired long QT syndrome) \(^{42}\). Effort has been put into searching for genetic variants that influence the QT interval, as both prolonged and shortened QT interval is associated with increased cardiovascular mortality. Recently two large genome wide association studies were published identifying 14 common variants at ten loci associated with the QT interval. Most of the loci mapped near known ion channel genes, but variants was also shown in genes coding for or affecting nitric oxide synthase, Na/K ATPase, phospholamban, and also in loci with no
obvious candidate gene known to be involved in cardiac repolarization\textsuperscript{16,43}. Looking at the ten major QT associated variants, the QT interval increased 1.5 ms per allele on average. Individuals with more than sixteen alleles had 18 ms longer QT interval than individuals with six or less alleles\textsuperscript{16}. Presumably there are analogue genetic variants that increase TpTe and thus affects the repolarization reserve, in conjunction with other polymorphisms, medications, electrolyte disarrangements and cardiac diseases, leading to an increased susceptibility to arrhythmias\textsuperscript{44}.

Limitations

There are important limitations that apply to all twin studies. One assumption is that monozygotic twins are genetically identical, but there are examples of genetic discordance, e.g. somatic mutations. Another assumption is that the intrauterine milieu is identical; however differences in implantation sites, effect of intrauterine infections and mode of delivery do apply. Further it is assumed that the environment influences are identical among monozygotic and dizygotic twins. There is some evidence that monozygotic twins share more environmental influences after birth than dizygotic do, however this is most evident with subjective traits. Also difference in the chorionicity of the twins might affect outcome. In dichorionic twins there is a greater risk of one twin having a sub-optimal functioning placenta whereas mono-chorionic twins more often have complications from twin-twin vascular connections\textsuperscript{45}. However a study by Fagard et al showed no significant difference in heritability estimates for heart rate and blood pressure according to chorionicity\textsuperscript{34}. Twin-studies are not a random sample from the general population, but as far as the Danish Twin Registry is concerned there is plenty of evidence that the twins resemble to rest of the Danish population for example with regard to diabetes, thyroid disease and mortality\textsuperscript{46-48}. We have further assumed that the genetic and environmental factors are not correlated and there’s no genotype-environment interaction.
Measurement error will increase the proportion of variability explained by environmental factors and thus underestimate the genetic contribution. However the reproducibility of the electrocardiographic assessment was excellent, so underestimation of genetic influence seems less likely. Finally this study represents a very homogeneous population with the vast majority of participants being Caucasian, why we cannot address the possibility of ethnic diversity in heritability of TpTe and Tamp.

Conclusion
Tamp and TpTe, together with RR interval and QT intervals are highly inherited parameters with age, gender and BMI adjusted estimates of heritability ranging from 0.45 to 0.60. Future research might address the more precise genetic localization and assist in risk stratifying for cardiovascular morbidity and mortality.

Funding Sources: This study was funded by the Danish Heart Foundation, Danish Council for Strategic Research and Danish National Research Foundation

Conflict of Interest Disclosures: None.

References:


Table 1: Demographics and electrocardiographic variables by zygosity

<table>
<thead>
<tr>
<th>Zygosity</th>
<th>Monozygotic n=492</th>
<th>Dizygotic n=730</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>246 (50)</td>
<td>358 (49)</td>
<td>ns</td>
</tr>
<tr>
<td>Women</td>
<td>246 (50)</td>
<td>372 (51)</td>
<td>ns</td>
</tr>
<tr>
<td>Age – years</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>37.7(11)</td>
<td>37.5 (11)</td>
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</tr>
<tr>
<td>BMI – kg/m²</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.4 (3.5)</td>
<td>24.3 (3.5)</td>
<td>ns</td>
</tr>
<tr>
<td>RR interval - msec</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QT interval - msec</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTpeak interval - msec</td>
<td>Mean(SD)</td>
<td></td>
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<tr>
<td>QTcB interval - msec</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
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<tr>
<td>TpTe - msec</td>
<td>Mean(SD)</td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Tamp - µV</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead V1</td>
<td>-7 (171)</td>
<td>-8 (165)</td>
<td>ns</td>
</tr>
<tr>
<td>Lead V5</td>
<td>338 (159)</td>
<td>349 (162)</td>
<td></td>
</tr>
</tbody>
</table>

QTpeak: interval from Q-wave start to T-wave peak, QTcB: Bazzet corrected QT, TpTe: Tpeak-Tend interval, Tamp: T-wave amplitude, BMI: Body mass index

Table 2: Pearson correlation coefficients between individuals within twin pairs

<table>
<thead>
<tr>
<th></th>
<th>Monozygotic</th>
<th>Dizygotic</th>
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<tr>
<td></td>
<td>rMZ</td>
<td>rDZ</td>
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<tr>
<td>RR interval</td>
<td>0.60</td>
<td>0.29</td>
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<tr>
<td>QT interval</td>
<td>0.68</td>
<td>0.38</td>
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<tr>
<td>QTpeak interval</td>
<td>0.68</td>
<td>0.34</td>
</tr>
<tr>
<td>QTcB interval</td>
<td>0.55</td>
<td>0.34</td>
</tr>
<tr>
<td>TpTe</td>
<td>0.50</td>
<td>0.23</td>
</tr>
<tr>
<td>Tamp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead V1</td>
<td>0.46</td>
<td>0.27</td>
</tr>
<tr>
<td>Lead V5</td>
<td>0.64</td>
<td>0.26</td>
</tr>
</tbody>
</table>

For abbreviations see table 1.
Table 3: Heritability estimates for ECG variables, unadjusted and adjusted for BMI, Gender and Age

<table>
<thead>
<tr>
<th>Unadjusted</th>
<th>BMI Adjusted</th>
<th>Gender Adjusted</th>
<th>Age Adjusted</th>
<th>Adjusted All Covariates</th>
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</thead>
<tbody>
<tr>
<td>RR</td>
<td>0.61 0.39</td>
<td>0.60 0.38 0.01</td>
<td>0.57 0.38 0.05</td>
<td>0.60 0.39 0.01</td>
</tr>
<tr>
<td>QT</td>
<td>0.69 0.31</td>
<td>0.69 0.31 0.00</td>
<td>0.69 0.31 0.00</td>
<td>0.68 0.31 0.01</td>
</tr>
<tr>
<td>QTcB</td>
<td>0.59 0.41</td>
<td>0.59 0.40 0.01</td>
<td>0.52 0.40 0.08</td>
<td>0.50 0.42 0.08</td>
</tr>
<tr>
<td>TpTe</td>
<td>0.49 0.51</td>
<td>0.50 0.50 0.00</td>
<td>0.48 0.50 0.02</td>
<td>0.47 0.51 0.02</td>
</tr>
<tr>
<td>TampV1</td>
<td>0.47 0.53</td>
<td>0.46 0.53 0.01</td>
<td>0.41 0.52 0.07</td>
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<tr>
<td>TampV5</td>
<td>0.63 0.37</td>
<td>0.61 0.37 0.02</td>
<td>0.55 0.35 0.10</td>
<td>0.57 0.38 0.05</td>
</tr>
</tbody>
</table>

All AE models. A = heritability estimate, E = estimate of environmental influence, RR = RR interval in msec, QT = QT interval, QTcB = Bazett corrected QT interval, TpTe = Tpeak-Tend interval, TampV1 = T-wave amplitude lead V1, TampV5 = T-wave amplitude lead V5, BMI = Body mass index, Cov= covariates (BMI, Age and Gender)
**Table 4:** Effect of QT adjustment on heritability estimates

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>QT adjusted</th>
<th>Adjusted for QT and covariates</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>E</td>
<td>A</td>
</tr>
<tr>
<td>TpTe</td>
<td>0.49</td>
<td>0.51</td>
<td>0.37</td>
</tr>
<tr>
<td>TampV1</td>
<td>0.47</td>
<td>0.53</td>
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<tr>
<td>TampV5</td>
<td>0.63</td>
<td>0.37</td>
<td>0.63</td>
</tr>
</tbody>
</table>

For abbreviations see table 3.

**Figure Legend:**

Figure 1: Plots and linear regression of T-wave amplitude in lead V5 for pairs of A) Monozygotic twins, B) Same sex dizygotic twins and C) Unrelated individuals that are age and sex matched.
Monozygote

$r^2 = 0.42$

slope = 0.69

p < 0.0001

Dizygote

$r^2 = 0.18$

slope = 0.46

p < 0.0001

Unrelated

$r^2 = 0.03$

slope = 0.16

p = 0.0052
Heritability of Tpeak-Tend Interval and T-wave Amplitude: A Twin Study
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_Circ Cardiovasc Genet._ published online August 11, 2011;

_Circulation: Cardiovascular Genetics_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1942-325X. Online ISSN: 1942-3268

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http://circgenetics.ahajournals.org/content/early/2011/08/11/CIRCGENETICS.111.959551

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