Heritability of Tpeak-Tend Interval and T-Wave Amplitude
A Twin Study

Christian Haarmark, MD, PhD; Kirsten O. Kyvik, MD, PhD; Esben Vedel-Larsen, MSc; Esben Budtz-Jørgensen, PhD; Jørgen K. Kanters, MD

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; mean age, 38±11 years; 49% men) who had an ECG performed during 1997 to 2000 were included. Tamp was measured in leads V1 and V5. Duration variables (RR interval, QTpeak and QTend interval) were measured and averaged over 3 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, sex, and body mass index. All models were reducible to a model of additive genetics and unique environment. All variables had considerable genetic components. Adjusted heritability estimates were as follows: TpTe, 46%; Tamp lead V1, 34%; Tamp lead V5, 47%; RR interval, 55%; QT interval, 67%; and Bazett-corrected QT interval, 42%.

Conclusions—RR interval, QT interval, Tamp, and TpTe interval are heritable ECG parameters. (Circ Cardiovasc Genet. 2011;4:516-522.)

Key Words: electrocardiography ♦ twins ♦ heredity ♦ cardiac electrophysiology

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 have been associated with increased risk of arrhythmia syndromes.1–5 In inherited arrhythmias (eg, long- and short-QT syndromes, arrhythmogenic right ventricular cardiomyopathy), the T-wave shows characteristic morphological changes as well.6–8 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 interval,9,10 blood pressure,11 and heart rate variability.12 Multiple studies of the heritability of RR interval and QT interval have shown a large genetic contribution to these variables.9–11,13,14 The importance of repolarization and its heritability have been confirmed in monogenic diseases such as long- and short-QT syndromes,15 and the contribution of common genetic variants to the QT interval in the general population are increasingly well described.16 Furthermore, some of these variations increase the vulnerability to drug-induced arrhythmias.17 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 the present study was to investigate the heritability of Tamp and TpTe in a large population of monozygotic and dizygotic twins using a twin study design.

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Methods

Population
The GEMINAKAR study is a nationwide Danish twin study that evaluates 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 and 1952 and between 1953 and 1982) were invited to participate in a full-day clinical investigation conducted in the period from 1997 to 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; an exercise test; and a measurement of weight, height, and blood pressure. A total of 1512 twins underwent clinical examination. Zygosity was determined by DNA-based microsatellite markers.\textsuperscript{18,19}

**ECG Acquisition and Measurements**

Standard resting 12-lead ECGs were retrievable from 1290 twins. ECGs were recorded at either 25-mm/s or 50-mm/s 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; Palo Alto, CA) and transferred to a personal computer. Using magnification and a digital caliper (Cardio Calipers version 3.3; Iconico Software, New York, NY), Tamp was measured in leads V1 and V5. The duration variables (RR interval, QTpeak and QTend interval) were measured and averaged over 3 consecutive beats in lead V5. The end of the T-wave was defined as the tangent of the downslope crossing the isoelectric line. TpTe was calculated as the difference between QTend and QTpeak interval. Bazett-corrected QT interval (QTcB) was calculated as follows:

\[ \text{QTcB} = \frac{\text{QT}}{\text{RR}^{0.5}} \]

Twin pairs were excluded from further analysis if 1 or both had 1 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) 2 or more premature beats per tracing (5 pairs); (5) ECG bleached by light or torn, affecting leads V1 or V5 (2 pairs); (6) only an ECG from 1 twin (4 pairs); and (7) no available clinical information (4 pairs). In total, 34 pairs were excluded (5.3% of the cohort), leaving 611 pairs for further analysis (246 monozygotic, 365 dizygotic). All measurements were done by C.H., and the investigators where blinded to all clinical information, including zygosity, until final statistical analysis after completion of the ECG measurements.

**Statistical Analysis**

Simple descriptive statistics were used to describe the population and ECG variables (mean±SD). A 2-sided Student \( t \) test was used to test for differences between monozygotic and dizygotic twins. A \( P<0.05 \) was considered significant. Pearson correlation coefficients for Tamp, TpTe, RR interval, and QT interval within monozygotic twins and dizygotic twins 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 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 (eg, blood pressure, heart rate, 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), how much is explained by shared environmental factors (as experienced by both twins), and how much is unique (as only experienced by 1 twin). Traditionally, these 3 elements are called A (additive genetic variance), D (variance caused by dominance or epistatic effects [ie, gene-gene interaction]), C (common environmental variance), and E (unique environmental variance). Heritability is either the proportion of the total variance explained by A (narrow sense) or by both A and D (broad sense). The combination of A, C, and E constitutes a model (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 nonadditive effects is tested through 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 are explained with the fewest variables possible as long as the reduced model is not significantly worse than the full model (eg, 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, sex, body mass index [BMI]) by including them in the regression analysis. All statistical analyses were done using SAS version 9.1 (SAS Institute Inc; Cary, NC) statistical software.

To assess the intrarreader variability of the manually measured ECG variables, 60 ECGs selected at random were remeasured by C.H. (5% of included population). Pearson correlation coefficients between the original and remeasured variables were calculated. There was overall high reproducibility for RR interval (\( r=0.97 \)), 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 (\( r=0.85 \)) was lower but still acceptable.

**Results**

Table 1 shows the demographic data of the population together with the ECG data stratified by zygosity. There were no significant differences between the 2 groups of twins. As seen in Table 2, the Pearson correlation coefficients for Tamp, TpTe, RR interval, and QT intervals were higher in the monozygotic twin group than in the dizygotic twin group. The Figure shows Tamp in lead V5 plotted against monozygotic twins (Figure A), same-sex dizygotic twins (Figure B), and unrelated individuals (amplitude plotted for monozygotic twins that were paired with unrelated other monozygotic twins) (Figure C). 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 led 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 $h^2$) that only address an additive genetic effect.

The heritability estimates based on the structural modeling are shown in Table 3. First, the unadjusted values are given, then the results adjusting for 1 covariate at a time, and finally the results adjusted for all covariates together. When adjusting for age, sex, and BMI, the adjusted estimates of Tamp and QTcB heritability reduced more than the remaining variables, suggesting that Tamp and QTcB heritability are more dependent on the covariates than the other investigated variables.

To address the possible variance introduced by different ECG paper speeds (25 versus 50 mm/s), paper speed was added to the model as a covariate. There was very little to no effect of adjusting for ECG paper speed on heritability estimates for RR interval (0.55 versus 0.53), QT interval (0.67 versus 0.67), QTcB interval (0.42 versus 0.41), TpTe (0.46 versus 0.44), and Tamp in lead V5 (0.47 versus 0.47). However, the heritability estimate for Tamp in lead V1 decreased (0.34 versus 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 the present study is that TpTe and Tamp are heritable, with evidence for an additive genetic effect. There was no evidence of nonadditive effects. Adjustment for age, sex, and BMI reduced 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 (ie, transmural, left versus right ventricle, apical versus basis, anterior versus posterior). These gradients are caused by different expressions 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 electric 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).\(^{1,4}\)

However, TpTe is unrelated to syncope and arrhythmias in congenital long-QT syndrome.\(^{23}\)

To our knowledge, this study is the first to evaluate TpTe in a large sample of twins of both sexes. 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
Table 3. Heritability Estimates for ECG Variables Unadjusted and Adjusted for BMI, Sex, and Age

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>BMI Adjusted</th>
<th>Sex Adjusted</th>
<th>Age Adjusted</th>
<th>Adjusted All Covariates</th>
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<td>0.39</td>
<td>0.60</td>
<td>0.38</td>
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<tr>
<td>QT</td>
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<td>0.31</td>
<td>0.69</td>
<td>0.31</td>
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<tr>
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<td>0.41</td>
<td>0.59</td>
<td>0.40</td>
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<tr>
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<td>0.51</td>
<td>0.50</td>
<td>0.50</td>
<td>0.48</td>
</tr>
<tr>
<td>Tamp</td>
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</tr>
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<td>0.53</td>
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<td>0.41</td>
</tr>
<tr>
<td>V5</td>
<td>0.63</td>
<td>0.37</td>
<td>0.61</td>
<td>0.37</td>
<td>0.55</td>
</tr>
</tbody>
</table>

All AE models. A indicates heritability estimate; E, estimate of environmental influence; Cov, covariates (BMI, age, and sex). Other abbreviations as in Table 1.

Heritability of Tamp

The prognostic significance of Tamp is well established. Heritability of Tamp is influenced by a variety of factors, including heart rate and ionic concentrations. The explanatory model could be reduced to an AE model without loss of significance, suggesting additive genetic effects, and may reflect the genetic variance in both Tamp in and of 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 lead V5, and T-waves in lead V1 have lower amplitude, resulting in lower reproducibility and higher inaccuracy in measuring Tamp 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 greater. Because each twin pair was measured with the same ECG machine, the noise became a heritable element, leading to a larger reduction in heritability of Tamp in lead V1 compared with the other measures when including paper speed as a covariate. Recently, polymorphisms in the β-subunit of the slow delayed rectifier (I\textsubscript{s}) have been associated with decreased T-wave alternans. To our knowledge, no reports have suggested polymorphisms directly affecting Tamp, but it is known that patients with loss-of-function mutations in the rapid delayed rectifier potassium channel (I\textsubscript{k}) long-QT syndrome type 2 have lower Tamp, underlining the crucial role of cardiac ion channels in repolarization performance and making the ion channel 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 Tamp in leads V5 and II, with an unadjusted heritability estimate of 61% to 72%. However, the study found evidence of a dominant genetic effect in lead V1 (DE model, 53% heritability). To the authors’ surprise, they found no evidence of genetic influence on QT interval (CE model best fit); however, an AE model was almost as explanatory. The authors concluded that they lacked statistical power to discriminate between dominant and additive genetic influence, which would explain the differences in results.

Heritability of RR Interval

The present study found similar results for heritability estimates regardless of which method was reported for heart rate (as heart rate, RR interval, or log heart rate [data not shown]). In accordance with a range of other studies of heart rate heritability, we found that RR interval was highly heritable (heritability range in these studies, 61%–55%). This was due to an additive genetic effect with no sign of dominant or shared environmental effects, which also agrees with the literature. However, some studies have found lower values, ranging from <50% to no heritability. The majority of these contradictive studies measured heart rate over longer time frames, (eg, half-hour to 24-hour recordings). These studies cannot be directly compared to the present study because we only measured at 1 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 heart rate was measured.

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 sex. The high heritability, with estimates ranging from 50% to 60%, has been confirmed elsewhere. Other studies showed moderate to high heritability (25%–36%), with 1 study using a classical approach without SEM and 1 using a parent/sibling design instead of twins. An older study using classical heritability estimates found no heritability of the QT interval. Again, the most prevailing model was the AE model, as in the present study. The estimates for heritability of heart rate-corrected QT (whether being Framingham or Bazett corrected) range from 25% to 52%, which is in accordance with the present study, except for a peculiar finding by Dalageorgou et al. They found the same heritability for QT and Framingham-corrected QT as the present study (data not shown) but no genetic influence on QTcB in contrast to the present and others’ findings.

Effect of BMI, Sex, 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, among them flattening of T-waves inferolaterally, but this was not evident in our population. The reason why BMI adjustments did not lead to any significant change in heritability estimates may be because <1% of our population had a BMI of >35 kg/m².

On the other hand, there were larger effects on estimates when adjusting for age and sex, most evident for amplitude measures. Tamp age and sex dependency is well established, with decreasing Tamp with age and in women. The age effect is also seen in the Figure, where the remaining correlation between unrelated individuals is due to their being age matched. TpTe estimates remained constant, and as we have shown earlier, TpTe is neither age nor sex dependent.

In the present study, adjustment for age and sex reduced the heritability estimate for RR interval and heart rate-corrected QT interval. It is well established that both age and sex has a significant effect on heart rate and QT interval (ie, heart rate-corrected QT-intervals are prolonged in women).

QT-interval adjustment had a major effect on TpTe estimates, which would be expected because TpTe is a part of the QT interval. However, after adjustment, there still remained evidence of a 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 shown that roughly 40% of the variation in QT interval is caused by genes in common with heart rate, whereas 16% of the variation was due to genes specific to the QT interval.

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 at risk for arrhythmias (eg, heart failure) and in otherwise healthy populations (eg, acquired long-QT syndrome). Effort has been put into searching for genetic variants that influence the QT interval because both prolonged and shortened QT intervals are associated with increased cardiovascular mortality. Recently, 2 large genome-wide association studies were published that identified 14 common variants at 10 loci associated with the QT interval. Most of the loci mapped near known ion channel genes, but variants also were shown in genes coding for or affecting nitric oxide synthase, Na/K ATPase, and phospholamban and in loci with no obvious candidate gene known to be involved in cardiac repolarization. Looking at the 10 major QT-associated variants, the QT interval increased 1.5 ms per allele on average. Individuals with >16 alleles had an 18-ms longer QT interval than those with ≤6 alleles. Presumably, there are analog genetic variants that increase TpTe and, thus, affect the repolarization reserve in conjunction with other polymorphisms, medications, electrolyte disarrangements, and cardiac diseases, leading to an increased susceptibility to arrhythmias.

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 (eg, somatic mutations). Another assumption is that the intrauterine milieu is identical, but differences in implantation sites, effect of intrauterine infections, and mode of delivery 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 twins do, but this is most evident with subjective traits. Additionally, difference in the chorionicity of the twins might affect outcome. In dichorionic twins, there is a greater risk of 1 twin having a suboptimal functioning placenta, whereas monochorionic twins more often have complications from twin-twin vascular connections. However, a study by Fagard et al showed no significant difference in heritability estimates for heart rate and blood pressure according to chorionicity. 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 the rest of the Danish population with regard to diabetes, thyroid disease, and mortality, for example. We have further assumed that the genetic and environmental factors are not correlated and that there is 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 ECG assessment was excellent, so underestimation of genetic influence seems less likely. Finally, the present study represents a very homogeneous population, with a large majority of participants being white; thus, we cannot address the possibility of ethnic diversity in heritability of TpTe and Tamp.

Conclusions

Tamp and TpTe together with RR interval and QT interval are highly inherited parameters, with age-, sex-, 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.

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References


T-wave morphology is emerging as a novel way of characterizing the repolarization process in the cardiac ventricles. T-wave amplitude and the interval from the peak to the end of the T wave (TpTe) have shown promise as a marker of risk for cardiac arrhythmias and cardiovascular mortality. This study addresses the genetic background with regard to these new arrhythmia markers. Using a traditional twin study design, the study shows that T-wave amplitude and TpTe both are heritable factors, with approximately one half of the variation explained by genes. Even though TpTe is a subinterval of the QT interval, the genetic factors underlying TpTe are independent of the genes causing QT-interval variation. Thus, this study provides evidence that there are TpTe-specific genes to be found that ultimately could be linked to arrhythmia susceptibility.
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