Prevalence and Prognostic Significance of T-Wave Inversions in Right Precordial Leads of a 12-Lead Electrocardiogram in the Middle-Aged Subjects

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Background—T-wave inversion in right precordial leads V1 to V3 is a relatively common finding in a 12-lead ECG of children and adolescents and is infrequently found also in healthy adults. However, this ECG pattern can also be the first presentation of arrhythmogenic right ventricular cardiomyopathy (ARVC). The prevalence and prognostic significance of T-wave inversions in the middle-aged general population are not well known.

Methods and Results—We evaluated 12-lead ECGs of 10 899 Finnish middle-aged subjects (52% men, mean age 44±8.5 years) recorded between 1966 and 1972 for the presence of inverted T waves and followed the subjects for 30±11 years. Primary end points were all-cause mortality, cardiac mortality, and arrhythmic death. T-wave inversions in right precordial leads V1 to V3 were present in 54 (0.5%) of the subjects. In addition, 76 (0.7%) of the subjects had inverted T waves present only in leads other than V1 to V3. Right precordial T-wave inversions did not predict increased mortality (not significant for all end points). However, inverted T waves in leads other than V1 to V3 were associated with an increased risk of cardiac and arrhythmic death (P<0.001 for both).

Conclusions—T-wave inversions in right precordial leads are relatively rare in the general population, and are not associated with adverse outcome. Increased mortality risk associated with inverted T waves in other leads may reflect the presence of an underlying structural heart disease. (Circulation. 2012;125:2572-2577.)

Key Words: cardiomyopathy ■ electrocardiography ■ epidemiology ■ mortality ■ T-wave inversion

T-wave inversion in right precordial leads V1 to V3 of a 12-lead ECG is a common finding in children and adolescents,1 but this electrocardiographic pattern is also present in 0.1% to 3% of apparently healthy adults.2–4 However, inverted T waves may mimic abnormalities in ventricular repolarization observed in patients with structural heart disease such as arrhythmogenic right ventricular cardiomyopathy (ARVC), which can be responsible of ventricular arrhythmias and even sudden cardiac death.5 In ARVC, right precordial T-wave inversions are present in 48% to 85% of patients.5–10 The use of electrocardiographic depolarization and repolarization criteria plays a large role in establishing the diagnosis of ARVC, and, in the recent guidelines for the clinical diagnosis of the disease, T-wave inversion in the right precordial leads (V1, V2, and V3) or beyond was upgraded to a major criterion.11

Clinical Perspective on p 2577

There have been several studies on the prevalence and clinical significance of T-wave inversions in young athletes,2,12,13 but the frequency and long-term clinical significance of inverted T waves in the general population is unknown. Therefore, in the present study, we evaluated the prevalence and characteristics of right precordial T-wave inversions and other repolarization abnormalities in a large middle-aged general population and assessed the clinical outcome associated with these changes.

Methods

Study Population

The study population comprises of a total of 10 957 men and women aged 30 to 59 years, who participated in the Finnish Social Insurance Institution’s Coronary Heart Disease Study (CHD Study) between 1966 and 1972. We excluded 58 subjects with unreadable or missing ECGs, thus our final study group consisted of 10 899 subjects (52% of whom were men, mean age 44.0±8.5 years) from the original cohort. The CHD Study was a part of the larger prospective Mobile Clinic Health Survey that was conducted in 35 populations from different geographical areas in Finland with varying mortality rates representing the middle-aged Finnish population. The population groups consisted of either the whole population or a random sample of the population of a geographical area, and the overall participation rate of the invited population was 89.6%. A detailed account of the study rationale and procedures performed at the baseline examination has been described previously.14 In brief, a standard 12-lead

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ECG was recorded and blood pressure, body mass index, and serum cholesterol were measured. Before the examination, the subjects completed a questionnaire regarding their history of previous diseases, drug therapy, and smoking habits, which was then checked and completed, if necessary, by a specially trained nurse at the examination. All symptoms of cardiovascular disease were documented during the examination.

Follow-Up
From the baseline examination between 1966 and 1972, the subjects were followed for a mean of 30±11 years until the end of 2007. After a median follow-up time of 6 years, a reexamination of most of the subjects was performed between 1973 and 1976. Less than 2% of the subjects were lost to follow-up as a result of moving abroad, but, for the vast majority of even this group, the survival status could be determined. The mortality data were obtained from the Causes of Death Register maintained by Statistics Finland, and the death certificates were obtained for each deceased. Death from cardiac causes was determined based on the relevant International Classification of Diseases codes. To identify cases of sudden death from arrhythmia, all deaths from cardiac causes were reviewed by the use of hospital records and necropsy reports, if available, based on the definitions presented in the Cardiac Arrhythmic Pilot Study, as described by our group previously. All episodes of congestive heart failure, ventricular arrhythmias, and coronary artery disease serious enough to require hospitalization were obtained from the Finnish Hospital Discharge Register, which includes nationwide data on all inpatient episodes in Finland at an individual level.

ECC Measurement
A standard 12-lead ECG was recorded with the subject at rest in a supine position at paper speed of 50 mm/s and calibration of 1 mV/10 mm. The presence or absence of bundle branch block and left ventricular hypertrophy according to the Sokolow-Lyon criteria was assessed, and QT-interval (corrected for heart rate according to Bazett formula) was measured at the time of baseline examinations. Later, all baseline ECGs were independently reevaluated by 5 physicians for the presence of inverted T waves (T wave negative by definition), left bundle branch block (QRS duration >110 ms, and terminal activation duration (longest value in leads V1 through V3 from the nadir of the S wave to the end of all depolarization) were measured. All ECGs with inverted T waves in leads V1 through V3 were double checked, and the presence of T-wave inversions and epsilon waves was established by consensus. Epsilon wave was defined as a distinct deflection after the end of the QRS complex. For the majority of subjects, an additional ECG was taken after a median of 6 years from the baseline examination, and the persistence of precordial T-wave inversions was assessed.

Statistical Analysis
All continuous data are presented as means±SD. The general linear model was used to compare the age- and sex-adjusted mean values for continuous variables and the prevalence of categorical variables between the groups. Primary end points were all-cause mortality, cardiac mortality, and arrhythmic death, and secondary end points were hospitalization because of congestive heart failure, ventricular arrhythmias, or coronary artery disease. The hazard ratios and 95% confidence intervals for death and hospitalization were calculated by uses of Cox proportional hazards model, with adjustments for age and sex, subjects without T-wave inversions serving as the reference group. Kaplan-Meier survival curves were plotted for T-wave inversions in leads V1 to V3 and other leads and were compared by means of the log-rank test. The statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute) and with the Statistical Package for Social Studies, version 14.0 (SPSS). A probability value of <0.05 was considered to indicate statistical significance.

Results
ECG Characteristics
Inverted T waves in right precordial leads V1 to V3 were observed in 54 (0.5%) of the subjects. In 14 (26%) of these individuals, only minor (<0.2 mV) right precordial T-wave inversions were present, and in 36 (67%) individuals T-wave amplitude was between −0.2 mV and −0.4 mV. Only 2 subjects had deep negative T waves between −0.5 mV and −0.9 mV, and giant negative T waves with amplitude of −1.0 mV or less were present in 2 subjects. ST-segment was elevated at least 1 mm at QRS-ST junction (J point) in right precordial leads in 9 (17%) of the subjects with T-wave inversion in these leads. In 32 (59%) individuals with right precordial T-wave inversion, inverted T waves were present also in lead V4 or beyond. Examples of ECGs with inverted T waves in V1 to V3 only, and with T-wave inversions in leads other than V1 to V3 are presented in Figures 1 and 2, respectively. More examples of T-wave inversions are presented as online-only Data Supplement Figures I through IV.

Only 1 subject with T-wave inversions in leads V1 to V3 had prolonged terminal activation duration ≥55 ms, and he was the only one having a duration of QRS complex >110
ms in the right precordial leads. The same subject was also the only one with an epsilon wave (online-only Data Supplement Figure V), and thus fulfilled 2 major criteria of ARVC according to the new modification of the Task Force Criteria (repolarization abnormality demonstrated by inverted precordial T waves and depolarization abnormality exhibited by epsilon wave and prolonged terminal activation duration), which is sufficient for the diagnosis of the disease.11

The baseline characteristics of the subjects with inverted T waves in leads V₁ to V₃ are shown in the Table. Inverted right precordial T waves were present in 47 women (0.9% of all women) and 7 men (0.1% of all men) in the study population. These subjects had lower heart rate, but no difference in age, smoking, blood pressure, medication, left ventricular hypertrophy, or cardiovascular disease was observed between the 2 groups. A second ECG measurement a median of 6 years after the baseline visit was available for 52 (96%) of the 54 subjects with right precordial T-wave inversions in the initial ECG. Inverted T waves were still present in 41 (79%) of the subjects with right precordial T-wave inversions in the initial ECG. Four of these subjects had T-wave inversions only in V₃, and 23 had inverted T waves also in V₄ or beyond.

Overall, 130 subjects (12.2%) had inverted T waves present in either frontal or precordial ECG leads. Seventy-six of these individuals had T-wave inversions only in leads other than V₁ to V₃. These subjects were older, had a higher blood pressure, and were more likely to have a suspected cardiovascular disease such as hypertension, valve disease, or heart insufficiency, or to be on medication than the rest of the population. They also had a longer duration of QRS complex, but no differences in cholesterol levels, body mass index, smoking, or history of coronary artery disease were present (Table).

Complete right bundle branch block (RBBB) was present in 33 (0.3%) of the subjects, and, in 3 subjects with RBBB, T-wave inversions continued also beyond V₃. Although this represents a minor criterion for the diagnosis of ARVC, all the subjects with bundle branch block or preexcitation were excluded from further analysis.

Table. Baseline Characteristics of Subjects

<table>
<thead>
<tr>
<th></th>
<th>No TWI</th>
<th>TWI V₁–₃</th>
<th>TWI Other</th>
<th>TWI V₁–₃</th>
<th>TWI Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, %*</td>
<td>52.4</td>
<td>12.9</td>
<td>60.4</td>
<td>&lt;0.001</td>
<td>0.17</td>
</tr>
<tr>
<td>Age, y†</td>
<td>44.0±8.5</td>
<td>43.6±8.4</td>
<td>49.3±7.6</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker, %‡</td>
<td>34.0</td>
<td>34.1</td>
<td>39.2</td>
<td>0.98</td>
<td>0.30</td>
</tr>
<tr>
<td>Cholesterol, mmol/L‡</td>
<td>6.50±1.31</td>
<td>6.56±1.78</td>
<td>6.64±1.77</td>
<td>0.72</td>
<td>0.36</td>
</tr>
<tr>
<td>BMI, kg/m²‡</td>
<td>25.9±3.8</td>
<td>26.0±4.4</td>
<td>26.7±4.7</td>
<td>0.94</td>
<td>0.08</td>
</tr>
<tr>
<td>Heart rate, bmp‡</td>
<td>76±15</td>
<td>69±13</td>
<td>76±17</td>
<td>&lt;0.001</td>
<td>0.95</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hgt</td>
<td>138±21</td>
<td>135±22</td>
<td>148±26</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hgt</td>
<td>82±12</td>
<td>80±9</td>
<td>87±16</td>
<td>0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronotropic medication, %‡</td>
<td>4.2</td>
<td>2.3</td>
<td>19.3</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease, %‡</td>
<td>7.9</td>
<td>14.1</td>
<td>30.0</td>
<td>0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Electrocardiographic LVH, %‡</td>
<td>31.4</td>
<td>23.7</td>
<td>39.2</td>
<td>0.22</td>
<td>0.13</td>
</tr>
<tr>
<td>QTc duration, ms‡</td>
<td>408±27</td>
<td>408±31</td>
<td>408±35</td>
<td>0.93</td>
<td>0.98</td>
</tr>
<tr>
<td>QRS duration, ms‡</td>
<td>87±8</td>
<td>87±6</td>
<td>90±11</td>
<td>0.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of prior myocardial infarction, %‡</td>
<td>1.1</td>
<td>0.4</td>
<td>0.0</td>
<td>0.63</td>
<td>0.19</td>
</tr>
<tr>
<td>History of angina pectoris, %‡</td>
<td>2.3</td>
<td>0.0</td>
<td>0.6</td>
<td>0.17</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. Subjects with no TWI serve as the comparison group for P values. To convert the values of cholesterol to milligrams per deciliter, divide by 0.02586. TWI indicates T-wave inversion; LVH, electrocardiographic left ventricular hypertrophy according to the Sokolow-Lyon criteria; QTc, QT corrected for heart rate.

*Adjusted for age.†Adjusted for sex.‡Adjusted for age and sex.

Risk of Death and Hospitalization

During the follow-up (mean follow-up 30±11 years) 6133 subjects (56.5%) died. Death from cardiac causes occurred in 1969 individuals (32.1% of all deaths), and 795 (40.4%) of these were classified as sudden arrhythmic deaths. No additional mortality was associated with right precordial T-wave inversions in V₁ to V₃. In this group, 25 subjects (46%) died during the follow-up. Nine of these deaths were due to cardiac causes, and 2 were classified as sudden arrhythmic deaths. The age and sex adjusted relative risk (RR) of death was 0.95 (95% CI, 0.64–1.41; P=0.81), RR for cardiac mortality 1.18 (95% CI, 0.61–2.27; P=0.63), and RR for sudden arrhythmic death 0.76 (95% CI, 0.19–3.06; P=0.69) in these subjects in comparison with the subjects without T-wave inversions. When the subjects with inverted T waves also in V₄ or beyond (n=32) were considered separately, in the subjects with inverted T waves also in V₁ to V₃, 33 (0.3%) of the subjects, and, in 3 subjects with RBBB, T-wave inversions continued also beyond V₃. Although this represents a minor criterion for the diagnosis of ARVC, all the subjects with bundle branch block or preexcitation were excluded from further analysis.
T waves in V1 to V3. However, the subjects with inverted T waves in leads other than V1 to V3 predicted adverse outcome. In previous studies, the prevalence of inverted T waves in right precordial leads V1 to V3 was present in 0.5% of the middle-aged population, but additional features suggestive of ARVC, such as epsilon wave or prolonged duration of terminal QRS activation in the right precordial leads, were extremely rare. The prognosis associated with right precordial T-wave inversion was good and did not differ from the rest of the population. However, inverted T waves in leads other than V1 to V3 predicted adverse outcome. In another study that assessed the prevalence of T-wave inversions in adolescent athletes, T-wave inversions beyond V2 were present in only 0.1% of the subjects >16 years of age. In trained athletes, a broad range of abnormal patterns may be present in the 12-lead ECG and mimic ECG changes seen in structural heart diseases. However, in a recent study, distinctly abnormal repolarization patterns were found only in 1% of a large population of young athletes, and more than one-third of these subjects had evidence of structural heart disease or developed a cardiomyopathy during follow-up. In another study of asymptomatic children with T-wave inversion at preparticipation screening, diagnosis of cardiomyopathy was made in only 2.5% of the subjects with abnormal ECG.

In the present study, the overall prevalence of inverted right precordial T waves was 0.5% in this 30- to 59-year-old population. This is somewhat lower than what is reported in some previous studies, probably because of exclusion of the youngest age groups, in which juvenile inverted T waves are more prevalent. In most of the cases, T waves were only mildly inverted (1–3 mm), and deeply inverted T waves (5 mm or more) were present in only 0.1% of the subjects. Only in ≈20% of the subjects having T-wave inversions on the initial ECG, inverted T waves were normalized in the control ECG taken a median of 6 years later. Therefore, it seems that this repolarization abnormality is in most cases a constant finding, and not due to, eg, hyperventilation, or transient emotional or other stimuli causing increased sympathetic activity. Especially in trained athletes, inverted T waves in right precordial leads are often associated with early repolarization, which is traditionally regarded as a benign ECG phenomenon. However, only <20% of the subjects in our study population with T-wave inversions in V1 to V3 had early repolarization pattern in these leads. An interesting novel finding was also the sex difference in the prevalence of inverted T waves (0.9% in women and 0.1% in men). The reason for this phenomenon is unclear, but it may be related to different levels of sympathetic activation or female hormones.

Although T-wave inversions in right precordial leads are occasionally found in asymptomatic individuals, they may also imply the presence of a heart disease such as hypertrophic cardiomyopathy, myocardial ischemia, or ARVC. The esti-
mated prevalence of right precordial T-wave inversions in patients with ARVC has been reported to be up to 85% in advanced forms of the disease, the extent of inverted T waves reflecting the degree of right ventricular involvement. However, in a recent study of newly diagnosed patients with suspected ARVC, inverted T waves limited to V1 to V3 were present in only 16% of the subjects, and 32% of the subjects had right precordial T-wave inversions extending beyond V3. Abnormalities in repolarization and depolarization observed in a standard 12-lead ECG play a pivotal role in the diagnosis of ARVC. The repolarization abnormalities are early and sensitive markers of the disease, and inverted right precordial T waves seem to demonstrate the most optimal sensitivity and specificity for identifying these patients.

Therefore, in the recently proposed modification of the Task Force Criteria for the clinical diagnosis of ARVC, T-wave inversion in leads V1 to V3 was upgraded as major criteria, and T-wave inversion in V1 to V2 or V4 to V6 was upgraded as minor criteria in the repolarization category. Furthermore, in the presence of complete RBBB, according to these new guidelines, inverted T waves beyond V3 represent a minor criterion in the repolarization category. In the present population, these extensive T-wave inversions were rare and were observed only in <10% of the subjects with RBBB.

In the category of depolarization abnormalities for diagnosing ARVC, epsilon wave in the right precordial leads is considered a major and prolonged terminal activation duration ≥55 ms a minor criterion. The prevalence of an epsilon wave ranges between 8% and 33% in ARVC patients. In contrast, an epsilon wave is a rare finding in the general population. In young Korean men, epsilon wave was present in 0.05%. In our study, only 1 subject had an epsilon wave, and the same subject had also T waves inverted in right precordial leads, thus fulfilling the ECG criteria for the diagnosis of ARVC. The estimated prevalence of ARVC in the general population has been ranging from 1 in 1000 to 1 in 5000. Nevertheless, mutations that may predispose to ARVC are more prevalent in the population, and it has been estimated that up to 1 of 200 Finns carries such a mutation, suggesting a low penetrance of this mutation. Based on the results of the present study, however, no exact estimations of the prevalence of ARVC phenotype in the Finnish population can be made, because no further diagnostic procedures besides the 12-lead ECG were performed to diagnose the disease. In addition to lack of increased mortality of subjects with T-wave inversions in V1 to V3, the hospitalization due to congestive heart failure or ventricular arrhythmias was not more common among these subjects, suggesting that this ECG pattern observed here in middle-aged subjects is probably not an early sign of ARVC.

Although T-wave inversions in V1 to V3 was a benign finding in the present middle-aged population, inverted T waves in other leads carried >2-fold risk of cardiac and sudden arrhythmic death, and predicted hospitalization due to congestive heart failure or coronary artery disease. It is well recognized that T-wave changes can be present in a variety of different circumstances affecting the heart and homeostasis of the body. These conditions include ischemia, ventricular hypertrophy, cardiomyopathies, myocarditis, certain drugs, electrolyte abnormalities, hyperventilation, and sympathetic stimulation. Presence of coronary artery disease was rare in the present population, but the diagnosis was based only on past medical history and clinical examination. Besides, echocardiography was not generally available at the time of baseline examination, and therefore some of the subjects with inverted T waves might have had a structural cardiac disease not evident during the clinical examination, but yet caused repolarization abnormalities in their 12-lead ECGs. Another limitation of the present study is the relatively small number of subjects with right precordial T-wave inversions, which precludes definitive conclusions on the prognostic significance of this ECG pattern.

In summary, right precordial T-wave inversion in leads V1 to V3 is a relatively rare finding in the middle-aged general population, especially in men. Although this electrocardiographic pattern can raise a suspicion of a cardiomyopathy, in the absence of deeply inverted T waves or other features suggestive of heart disease, right precordial T-wave inversions appear to carry normal prognosis in the general population. In contrast, inverted T waves in other than right precordial leads may imply an underlying cardiac pathology and are associated with increased cardiac mortality.

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Disclosures
None.

References
Aro et al. T-Wave Inversions in General Population


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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2012/04/23/CIRCULATIONAHA.112.098681.DC1
Figure 1 (Supplement Data).

Electrocardiogram of a 46-year-old female with mild right precordial T-wave inversions in V1-3 extending into leads V4 to V6. She died of non-cardiac causes at the age of 77.
Electrocardiogram of a 51-year-old male with inverted T-waves in right precordial leads V1 to V3 associated with ST-segment elevation and electrocardiographic left ventricular hypertrophy. He died of non-cardiac causes at the age of 75.
Electrocardiogram of a 44-year-old female with giant inverted T-waves in all precordial leads, electrocardiographic LVH and deep q-waves in inferior leads. She died of myocardial infarction 17 years later.
Electrocardiogram of a 45-year-old male with T-wave inversions in other than right precordial leads V1-3 associated with electrocardiographic LVH and strain. He died of myocardial infarction nine years later.
**Figure 5 (Supplement Data).**

12-lead ECG of a male subject with inverted T-waves and epsilon wave (arrow) in leads V₁-V₃ thus fulfilling two major criteria of ARVC diagnosis. He also had prolonged TAD ≥ 55ms, and duration of QRS complex over 110ms in the right precordial leads. The subject died of cardiac causes at the age of 67 years.