Screening Entire Health System ECG Databases to Identify Patients at Increased Risk of Death

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Background—Current methods to identify patients at higher risk for sudden cardiac death, primarily left ventricular ejection fraction \( \leq 35\% \), miss \( \approx 80\% \) of patients who die suddenly. We tested the hypothesis that patients with elevated QRS-scores (index of myocardial scar) and wide QRS-T angles (index abnormal depolarization–repolarization relationship) have high 1-year all-cause mortality and could be further risk stratified with clinical characteristics.

Methods and Results—We screened all 12-lead ECGs over 6 months at 2 large hospital systems and analyzed clinical characteristics and 1-year mortality. Patients with ECGs obtained in hospital areas with known high mortality rates were excluded. At the first hospital, QRS-score \( \geq 5 \) and QRS-T angle \( \geq 105^\circ \) identified 8.0% of patients and was associated with an odds ratio of 2.79 (95% confidence interval, 2.10–3.69) for 1-year mortality compared with patients below both ECG thresholds (13.9% versus 5.5% death rate). Left ventricular ejection fraction was \( \geq 35\% \) in 82% of the former group, and addition of ECG measures to left ventricular ejection fraction increased the discrimination of death risk (\( P<0.0001 \)). At the second hospital, the odds ratio was 2.42 (1.95–3.01) for 1-year mortality (8.8% versus 3.8%). Adjustment for patient characteristics eliminated interhospital differences. Multivariable adjusted odds ratio combining data from both hospitals was 1.53 (1.28–1.83). Increasing heart rate and chronic renal impairment further predicted mortality.

Conclusions—Screening hospital ECG databases with QRS-scoring and QRS-T angle analysis identifies patients with high 1-year all-cause mortality and predominantly preserved left ventricular ejection fraction. This approach may represent a widely available method to identify patients at increased risk of death. (Circ Arrhythm Electrophysiol. 2013;6:1156-1162.)

Key Words: arrhythmias, cardiac death, electrocardiography, fibrosis, mass screening

Prevention of sudden cardiac death in patients of indeterminate risk represents one of the most challenging issues in contemporary cardiology. Sudden cardiac death accounts for 200,000 to 450,000 deaths in the United States annually. However, the current method to identify patients at higher risk, primarily left ventricular ejection fraction (LVEF) \( \leq 35\% \), misses \( \approx 80\% \) of patients who die suddenly. To improve survival and reduce morbidity, it is critical to develop better strategies for accurate risk assessment in cases where traditional markers, such as clinical characteristics and LVEF, may be indeterminate. Ideally, initial screening for increased risk would involve simple and inexpensive tests that could be obtained at routine physician office visits and would be reproducible in different medical institutions.

Clinical Perspective on p 1162

Recent studies have revisited 12-lead ECG markers to stratify patients for risk of arrhythmic sudden cardiac death because, as demonstrated in previous work, large groups of patients at risk for sudden cardiac death have had contact with the medical system, which frequently entails the acquisition of routine 12-lead ECGs. Two ECG markers of interest are the QRS-score to detect myocardial scar and the spatial QRS-T angle to detect abnormal relationship between depolarization and repolarization.

QRS-scoring estimates fibrotic scar by measuring changes in Q-, R-, and S-wave durations, amplitudes, and morphologies. This approach has been shown to be a strong predictor of appropriate implantable cardioverter-defibrillator shocks and cardiovascular mortality. In the normal heart, the QRS- and T-spatial loops point in the same spatial direction. A wide QRS-T angle indicates that the mean ventricular depolarization and the repolarization vectors point in opposite spatial directions and have proved to be strong predictors of appropriate implantable cardioverter-defibrillator shocks,
sudden death, and cardiovascular mortality. Therefore, the combined use of the QRS-score and QRS-T angle could represent a powerful tool to screen large databases of individuals who had contact with the medical system that included the acquisition of a standard 12-lead ECG.

In the present study, we screened the clinical ECG databases of 2 large hospitals to test the hypothesis that 1-year total mortality is high among patients with elevated QRS-scores and wide QRS-T angles and that these patients can be further risk stratified with widely available clinical information.

Methods

The study protocol was approved by the Institutional Review Boards at Johns Hopkins Hospital (JHH) and Hospital of the University of Pennsylvania (HUP). A waiver of informed consent was given for retrospective screening.

ECG Screening

All ECGs acquired and stored at JHH (including outpatient clinics) between October 1, 2009, and March 31, 2010, from patients age 21 to 100 years (n=69088) were exported. Patients with ECGs from hospital areas with high risk of mortality (intensive care units, chemotherapy, radiation-oncology, transplant, catheterization laboratories, and inpatient dialysis) were excluded from the study (n=19829 ECGs from 5590 patients). After this review, 19750 eligible ECGs remained (only the most recent ECG from each patient), of which 1589 (8.0%) had QRS-score ≥5 and QRS-T angle ≥105°. A QRS-score threshold of ≥5 points was selected prospectively because this level had the highest accuracy for detecting cardiac magnetic resonance late gadolinium enhancement scar in ≥10% of the LV. A spatial QRS-T angle threshold of ≥105° was selected prospectively based on a study in a general population. Additional ECGs were excluded because they were duplicates or could not be linked to specific patients (n=191) or the patients had pacemakers (n=175), leaving 1223 patients with QRS-score ≥5 and QRS-T angle ≥105° for clinical outcomes analysis at JHH. In addition, a random sample of 1800 JHH patients not meeting both ECG thresholds was selected as a control group for clinical outcomes analysis, of which 89 ECGs were excluded because they were duplicates, paced, or could not be linked to specific patients.

A similar protocol was applied at HUP. After excluding duplicate ECGs from the same patient and patients who had ECGs in high-risk hospital areas, there were 15544 eligible ECGs at HUP, of which 1281 (8.2%) had QRS-score ≥5 and QRS-T angle ≥105°. As opposed to JHH where a random sample was used as a control group because manual review of medical records was required (described below), at HUP, automated medical record screening was performed, and thus the control group included all eligible patients.

ECGs were analyzed with 12SL software (GE Healthcare, Wauwatosa, WI) in the Magellan ECG Research Workstation software (GE Healthcare). Vectorcardiograms were reconstructed from 12-lead ECGs using a publicly available transformation matrix. The spatial QRS-T angle was calculated based on the difference between the mean QRS- and T-axes. Diagnostic statement codes, Q-, R-, and S-wave durations, and amplitudes were imported into Microsoft Excel (Redmond, WA). ECG confounder (conduction) types for QRS-scoring were classified based on diagnostic statement codes, QRS duration, and QRS-axis, and then QRS-scores were calculated (Figure I in the online-only Data Supplement).

Clinical and Mortality Screening

At JHH, the electronic medical records were screened manually to determine the clinical status of all patients with QRS-score ≥5 and QRS-T angle ≥105° and the random sample of patients not meeting both of these ECG thresholds. The following parameters were evaluated: age, sex, race, LVEF, history of coronary artery disease, history of myocardial infarction, history of coronary artery bypass graft surgery, history of percutaneous coronary intervention with or without stenting, history of atrial fibrillation, presence of an implantable cardioverter-defibrillator, and presence of a pacemaker. Patients with an estimated glomerular filtration rate <60 mL/min method (based on plasma creatinine level) were classified as having renal impairment. At HUP, automated medical record screening (Methods in the online-only Data Supplement) was performed to determine age, sex, race, and plasma creatinine levels. Deaths reported in the electronic medical record or identified by searching the Social Security Death Master File (Methods in the online-only Data Supplement) were considered if they occurred by December 31, 2010 (1-year median follow-up).

Statistical Analysis

QRS-score and QRS-T angle distributions were compared between the 2 hospitals by histograms. Univariate and multivariable logistic regression was used to compare 1-year mortality in each of the following 3 groups to patients with QRS-score <5 and QRS-T angle <105°: (1) QRS-score <5 and QRS-T angle ≥105°, (2) QRS-score ≥5 and QRS-T angle <105°, and (3) QRS-score ≥5 and QRS-T angle ≥105°; separate models were run for each group. Among patients with QRS-score ≥5 and QRS-T angle ≥105°, multivariable logistic regression was performed to determine whether the different absolute mortality rates between JHH and HUP were explained by baseline characteristics. Logistic regression incorporating random intercepts per hospital were used to calculate univariate and adjusted odds ratios (ORs) for the combined JHH–HUP population. With JHH patients (where LVEF data were available), receiver-operating characteristic area under the curve (AUC) analysis was used to compare risk stratification with LVEF alone to LVEF plus QRS-score and QRS-T angle. Logistic regression and receiver-operating characteristic-AUC analysis was also performed in the population meeting the ECG thresholds with LVEF≥35% to determine whether the population could be further risk stratified with the demographic and clinical variables contained in Table 1. All statistical analyses were performed using STATA (version 11.1; College Station, TX), with the exception that logistic regression combining the JHH and HUP populations was performed using the LME-4 package for R (version 3.0.0; Vienna, Austria). Two-sided P values <0.05 were considered significant.

Results

QRS-scores and QRS-T angles were similarly distributed at the 2 hospitals (Figure II in the online-only Data Supplement). At both JHH (Table 1) and HUP (Table 2), patients with QRS-score ≥5 and QRS-T angle ≥105° (compared with patients not meeting either threshold) were older, less commonly female, and more commonly whites. At JHH, the patients meeting the ECG thresholds had higher rates of coronary artery disease (39% versus 13%), history of myocardial infarction (24% versus 4.5%), atrial fibrillation (25% versus 7.5%), chronic renal impairment (29% versus 14%), and previous cardiac interventions. There was only a 5% difference in LVEF between the patient groups (median 55% versus 60%).

One-Year Mortality by QRS-Score and QRS-T Angle

At 1 year, 13.9% of JHH patients with both high QRS-score and wide QRS-T angle had died (Table 1) compared with only 5.5% in patients with both low QRS-score and narrow QRS-T angle (OR, 2.79 [95% confidence interval, 2.10–3.69]). At HUP, the OR (2.42 [1.95–3.01]) was similar to that at JHH, although the absolute mortality numbers of
those above versus below the ECG thresholds were reduced (8.8% versus 3.8%; Table 2). However, when age, sex, chronic renal impairment, and heart rate (clinical variables significantly associated with death that were available from both JHH and HUP) were controlled in a multivariable logistic regression model, JHH no longer had significantly higher mortality than HUP (*P*=0.24; Table I in the online-only Data Supplement).

### Table 1. Characteristics of Johns Hopkins Hospital Patients

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>QRS-Score &lt;5 and QRS-T Angle &lt;105° (n=1406)</th>
<th>QRS-Score &lt;5 and QRS-T Angle ≥105° (n=172)</th>
<th>QRS-Score ≥5 and QRS-T Angle &lt;105° (n=133)</th>
<th>QRS-Score ≥5 and QRS-T Angle ≥105° (n=1223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>700 (49.8%)</td>
<td>69 (40.1%)</td>
<td>64 (48.1%)</td>
<td>470 (38.4%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>714 (50.8%)</td>
<td>89 (51.7%)</td>
<td>74 (55.6%)</td>
<td>721 (58.9%)</td>
</tr>
<tr>
<td>Black</td>
<td>546 (38.8%)</td>
<td>72 (41.9%)</td>
<td>51 (38.3%)</td>
<td>411 (33.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>146 (10.4%)</td>
<td>11 (6.4%)</td>
<td>8 (6.0%)</td>
<td>91 (7.4%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>179 (12.7%)</td>
<td>55 (31.9%)</td>
<td>32 (24.1%)</td>
<td>480 (39.2%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>63 (4.5%)</td>
<td>23 (13.4%)</td>
<td>18 (13.5%)</td>
<td>289 (23.6%)</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>53 (3.8%)</td>
<td>27 (15.7%)</td>
<td>15 (11.3%)</td>
<td>197 (16.1%)</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>89 (6.3%)</td>
<td>20 (11.6%)</td>
<td>14 (10.5%)</td>
<td>191 (15.6%)</td>
</tr>
</tbody>
</table>

*ECG location data missing for 8 of 2934 (0.3%) patients.

### Table 2. Characteristics of Hospital of the University of Pennsylvania Patients

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>QRS-Score &lt;5 and QRS-T Angle &lt;105° (n=11595)</th>
<th>QRS-Score &lt;5 and QRS-T Angle ≥105° (n=1527)</th>
<th>QRS-Score ≥5 and QRS-T Angle &lt;105° (n=1151)</th>
<th>QRS-Score ≥5 and QRS-T Angle ≥105° (n=1281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>6127 (52.8%)</td>
<td>597 (39.1%)</td>
<td>591 (51.3%)</td>
<td>432 (33.7%)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>6492 (55.9%)</td>
<td>756 (49.5%)</td>
<td>717 (62.3%)</td>
<td>763 (59.6%)</td>
</tr>
<tr>
<td>Black</td>
<td>3878 (33.4%)</td>
<td>579 (37.9%)</td>
<td>321 (27.9%)</td>
<td>376 (29.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>1225 (10.6%)</td>
<td>192 (12.6%)</td>
<td>113 (8.9%)</td>
<td>142 (11.1%)</td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>1661 (14.3%)</td>
<td>205 (13.4%)</td>
<td>196 (17.0%)</td>
<td>142 (11.1%)</td>
</tr>
<tr>
<td>Heart rate, beats per minute</td>
<td>72 [63–84]</td>
<td>73 [63–86]</td>
<td>73 [63–85]</td>
<td>74 [64–86]</td>
</tr>
<tr>
<td>QRS-score, points</td>
<td>1 [0–2]</td>
<td>2 [0–3]</td>
<td>6 [5–7]</td>
<td>7 [6–9]</td>
</tr>
<tr>
<td>Deceased after 1 y</td>
<td>77 (5.5%)</td>
<td>11 (6.4%)</td>
<td>17 (12.8%)</td>
<td>170 (13.9%)</td>
</tr>
<tr>
<td>Outpatient* deceased</td>
<td>9/665 (1.4%)</td>
<td>2/81 (2.5%)</td>
<td>0/48 (0%)</td>
<td>27/608 (4.4%)</td>
</tr>
<tr>
<td>Emergency room deceased</td>
<td>11/343 (3.2%)</td>
<td>4/39 (10.3%)</td>
<td>3/36 (8.3%)</td>
<td>33/229 (14.4%)</td>
</tr>
<tr>
<td>Inpatient deceased</td>
<td>57/395 (14.4%)</td>
<td>5/51 (9.8%)</td>
<td>14/49 (28.6%)</td>
<td>110/382 (28.8%)</td>
</tr>
</tbody>
</table>

*ECG location data missing for 41 of 15554 (0.3%) patients.
Figure 1 shows Forest plots of univariate and multivariable adjusted ORs for each hospital individually, and with both hospitals combined. When considering the combined data, the 3 combinations of having (1) only a wide QRS-T angle, (2) only an elevated QRS score, or (3) both a wide QRS-T angle and elevated QRS score were all associated with an increase in mortality in both univariate (OR, 2.07, 2.33, and 2.59, respectively) and multivariable models (OR, 1.29, 1.72, and 1.53, respectively). Table 3 shows the adjusted ORs for age, sex, chronic renal impairment, and heart rate from the combined JHH and HUP population for the last multivariable model in Figure 1. Increasing age, male sex, chronic renal impairment, and increasing heart rate were all associated with a higher risk of death.

When grouped by ECG location (outpatient, emergency room, or inpatient), the absolute mortality numbers changed (Tables 1 and 2), but the combination of elevated QRS-score and wide QRS-T angle remained a predictor of mortality at both institutions.

**Added Predictive Value of New Markers**

LVEF $\leq 35\%$ is the current method used to identify patients at increased risk of arrhythmic death. At JHH, LVEF $\leq 35\%$ was associated with a 22% sensitivity and 93% specificity for identifying patients who died within 1 year (AUC, 0.57 [0.55–0.60]; Figure 2A). Addition of QRS-score/QRS-T angle to LVEF increased the AUC to 0.65 (0.62–0.69; $P<0.0001$ for comparison with LVEF only; Figure 2B). The main added value of the new ECG marker was to identify subjects with LVEF $>35\%$ who were at increased risk of death (70% sensitivity, 55% specificity; Figure 2B).

The increased sensitivity over LVEF with QRS-score and QRS-T angle to identify patients at increased risk of death came at the expense of decreased specificity. Thus, additional risk stratification may be warranted. At JHH, among patients with LVEF $>35\%$, QRS-score $\geq 5$, and QRS-T angle $\geq 105^\circ$, significant independent predictors of total mortality included chronic renal impairment, heart rate, further increases in QRS-score, and age. The model with these variables (Table II in the online-only Data Supplement) discriminated the 1-year risk for death with AUC=0.78 (0.74–0.82).

**Discussion**

This study demonstrates the feasibility of applying a novel strategy to screen entire ECG databases from large hospitals to identify patients at 1-year risk for mortality based on abnormal QRS-scores, reflecting the degree of myocardial scar, and on QRS-T angle measurements, indicating abnormal depolarization–repolarization relationship. We performed clinical screening and found that patients with both QRS-score $\geq 5$ and QRS-T angle $\geq 105^\circ$ had an increased 1-year risk of death. This ECG screening strategy may represent an inexpensive and widely available method to identify patients who are at increased risk of death.

**Pathophysiology Underlying the QRS-Score and QRS-T Angle**

In the current study, total mortality was used as the end point because of the inability to adjudicate cause of death, and thus potential applications for risk stratifying for arrhythmic death must be validated in future studies. However, there is a pathophysiological basis for the new electrophysiology makers to detect an increased risk of sudden arrhythmic death. Myocardial fibrosis likely represents the most common form of chronic myocardial substrate that predisposes to slowed conduction and re-entrant arrhythmic circuits. The presence of fibrosis demonstrated by cardiac magnetic resonance late gadolinium enhancement can predict ventricular tachyarrhythmias and prognosis. However, although cardiac magnetic resonance late gadolinium enhancement analysis of myocardial fibrosis is well established, it is costly and not available for use as a screening tool. In contrast, the 12-lead ECG is inexpensive and universally available and can readily be used to estimate infarct size and myocardial fibrosis caused by cardiomyopathy and to predict ventricular tachyarrhythmias.

Multiple methods of repolarization heterogeneity have also been studied; however, in general, these methods require prolonged ECG recordings with or without stress on the heart and thus cannot be applied to standard 10-second 12-lead ECGs.
In contrast, the spatial QRS-T angle can be measured on the standard 12-lead ECG. A wide spatial QRS-T angle represents discordance in the directions of global depolarization and repolarization vectors and thus reflects myocardial structural disease or electrophysiology alterations. Recent reports support the potential value of the QRS-T angle as a predictor of ventricular tachyarrhythmias and general cardiovascular morbidity and mortality in different populations.8–10 In this study, we demonstrate the ability to screen ECGs from standard 12-lead ECGs in an automated fashion.

In the current study, patients with both QRS-score ≥5 and QRS-T angle ≥105° had a 1-year mortality rate of 13.9% at JHH and 8.8% at HUP. The higher mortality at JHH is likely explained by differences in patient comorbidities because the ORs were similar at both hospitals. When age, sex, chronic renal impairment, and heart rate were controlled in a multivariable model, JHH no longer had significantly higher mortality than HUP.

**Heart Rate and Chronic Renal Impairment**

Among patients identified by both QRS-score and QRS-T angle analysis, the most significant predictors of all-cause mortality were increased heart rate and chronic renal impairment. Elevated heart rate is associated more closely with higher rates of sudden death than nonsudden death.17 Heart rate is primarily a marker of autonomic influence on the sinus node, and it is well documented that increased adrenergic activity is proarrhythmic, whereas increased vagal tone is cardioprotective.18 In addition, increased heart rate may be related to greater myocardial oxygen consumption and to coronary artery cyclic stretch, which heightens the likelihood of ischemia in patients with coronary artery disease.17

Chronic renal impairment was associated with a significantly increased risk of death within 1 year. This finding is in line with previous studies showing that mild renal insufficiency in the presence of cardiovascular disease was associated with a significant increase in the risk of sudden cardiac death and of cardiac death.19,20 The mechanism for increased risk of sudden cardiac death in patients with renal impairment is thought to be multifactorial and may be attributable to inflammation, development of endocardial and diffuse interstitial fibrosis, and dynamic metabolic changes.19,20

**Further Risk Stratification**

A recent Special Report from the American Heart Association on risk stratification for arrhythmic sudden cardiac death indicated that further efforts to stratify risk in patients with mild-to-moderately depressed LVEF may require the study of 10 to 20× as many patients as those studied in previous trials to identify the 5% to 10% of patients whose risk is sufficient to justify implantable cardioverter-defibrillator implantation.21 In the current study, we demonstrate the ability to screen ECGs from ~15,000 patients per hospital and identified ~8% of patients whose 1-year risk of all-cause mortality was increased and can additionally be discriminated through assessment of resting heart rate and chronic renal impairment. Ultimately, additional hierarchical strategies of risk stratification among patients identified by ECG screening might be beneficial, including blood biomarkers,22 dynamic markers of electric instability such as T-wave alternans,23 and myocardial fibrosis assessment by cardiac magnetic resonance14–16 or other methods.
Limitations
The novel approach used in this study has inherent limitations. The automated QRS-scoring algorithm used slightly modified criteria compared with those previously reported. Minor errors or differences in how patient identification numbers were entered at the time of clinical ECG acquisition resulted in duplication or poor identification of some patients. The patients in this study were a select group coming to a tertiary care hospital or its associated outpatient clinics, and thus the results cannot necessarily be extrapolated outside of this population. Mortality was determined by both electronic medical record and Social Security Death Master File for which cause of death is not reported. The high mortality rate found in patients with QRS-score ≥5 and QRS-T angle ≥105° may not only be related to cardiac causes, including sudden cardiac death, but also likely includes extracardiac causes. We tried to control for advanced neoplastic and acute pathological settings associated with higher risk of mortality by excluding patients from oncological and critical care units. Finally, the Social Security Death Master File does not capture all deaths,24 and thus some deaths were likely missed.

Conclusions
Screening of entire health system ECG databases is feasible and may represent an inexpensive and widely available method to identify patients whose 1-year risk of all-cause mortality is elevated. Patients enrolled in this study whose QRS-score suggested the presence of myocardial scar and whose wide QRS-T angle indicated an abnormal depolarization–repolarization relationship had a 1-year mortality of 8.8% to 13.9% (compared with 3.8%–5.5% in those not meeting the ECG thresholds) despite preserved or only moderately reduced LVEF. Future work should evaluate the ability of these ECG markers to predict the risk of arrhythmic sudden cardiac death in patients with LVEF>35% because it was not possible to determine cause of death in this study. The increase in sensitivity for detecting deaths with the ECG markers over LVEF came at a decrease in specificity, and thus further risk stratification is likely warranted before altering therapy. We demonstrate that elevated heart rate and renal impairment further stratified the identified population with high discriminatory power and may have a role in further risk stratification.

Acknowledgments
We thank Stephen Granite, MS, MBA, and Michael Shipway, Loriano Galeotti, PhD, and Robbert Zusterzeel, MD, for help with data management and analysis. We thank Jeannette Walker, RN, and Rosalie Cosgriff for contributions in screening medical records and Jim Clements for contributions to screening ECGs. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

Sources of Funding
This research was supported in part by grants P20HL101397 and R24HL085343 from the National Institutes of Health/National Heart, Lung, and Blood Institute, the Leducq Foundation, and the French Federation of Cardiology. Johns Hopkins University has a research agreement with GE Healthcare, Inc, which provided technical support only to this project.

Disclosures
None.

References

CLINICAL PERSPECTIVE

Current methods to identify patients at higher risk for sudden cardiac death, primarily left ventricular ejection fraction ≤35%, miss 80% of patients who die suddenly. In the current study, we demonstrate the ability to screen ECGs from 15,000 to 20,000 patients with predominantly preserved left ventricular ejection fraction at 2 large tertiary medical centers and identified 8% of patients whose 1-year risk of all-cause mortality was increased. Specifically, patients in this study whose QRS-score suggested the presence of myocardial scar and whose wide QRS-T angle indicated an abnormal depolarization-repolarization relationship had a 1-year mortality of 8.8% to 13.9% (compared with 3.8%–5.5% in those not meeting the ECG thresholds) despite having normal or only moderately reduced left ventricular ejection fraction. Furthermore, increasing heart rate on the ECG and the presence of chronic renal impairment based on serum creatinine further predicted mortality. Of note, total mortality was used as the end point because of the inability to adjudicate cause of death, and thus potential applications for risk stratification for sudden cardiac death must be validated in future studies. Ultimately, additional hierarchical strategies of risk stratification among patients identified by ECG screening might be beneficial, including blood biomarkers, dynamic markers of electric instability, and cardiac imaging. This 12-lead ECG screening strategy based on QRS-score and QRS-T angle analysis offers an inexpensive and widely available method to identify patients with preserved or moderately reduced left ventricular ejection fraction who are at increased risk of death from any cause during the coming year.
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Circ Arrhythm Electrophysiol. 2013;6:1156-1162; originally published online October 12, 2013; doi: 10.1161/CIRCEP.113.000411

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SUPPLEMENTAL MATERIAL

Methods

ECG Analysis

Vectorcardiograms were reconstructed from 12-lead ECGs using the reconstruction matrix developed by Kors et al. The spatial QRS-T angle was calculated based on the difference between the mean QRS- and T-axes. Subsequently, automated Q-, R- and S-amplitude and duration measurements along with diagnostic statement codes from the GE-Marquette 12SL (GE Healthcare, Wauwatosa, WI, USA) analysis program were imported into Microsoft Excel (Redmond, WA, USA). ECG confounder (conduction) types for QRS scoring were classified by automated analysis using slightly different criteria from those used in prior studies as outlined below.

1. Left bundle branch block (LBBB)
   a. Marquette 12SL ECG analysis program statement code for LBBB (# 460)
   b. AND QRS duration ≥140 ms (men) or ≥130 ms women

2. Right bundle branch block and left anterior fascicular block (RBBB+LAFB)
   a. Marquette 12SL ECG analysis program statement code for RBBB (# 440)
   b. AND QRS duration ≥120
   c. AND QRS axis -90º to -45º or QRS axis 181º to 270º

3. Right bundle branch block (RBBB) (without LAFB)
   a. Marquette 12SL ECG analysis program statement code for RBBB (# 440)
   b. AND QRS duration ≥120 ms
   c. AND QRS axis -44º to 180º

4. Left anterior fascicular block (LAFB)
   a. Not meeting prior criteria for LBBB, RBBB+LAFB or RBBB
   b. AND QRS duration ≥100 ms
   c. AND QRS axis -90º to -45º or QRS axis 181º to 270º

5. Left ventricular hypertrophy (LVH)
   a. Not meeting prior criteria for LBBB, RBBB+LAFB, RBBB or LAFB
   b. Meeting criteria for either Sokolow-Lyon or Cornell LVH criteria
      i. Sokolow Lyon criteria
         1. \( (S \text{ in V1}) + (R \text{ in V5 or V6}) \geq 2.60 \text{ mV} \)
         2. \( \text{or R in V5 or V6} \geq 2.60 \text{ mV} \)
      ii. Cornell Criteria
         1. \( \text{R in aVL + S in V3} \geq 2.80 \text{ mV} \text{ (men)} \)
         2. \( \text{or R in aVL + S in V3} \geq 2.00 \text{ mV} \text{ (women)} \)

6. No confounders – Not meeting any of the previous criteria

After classification of conduction/hypertrophy type, QRS scores were calculated using automated algorithms. Notch criteria along with R/R’ and S/S’ criteria in the QRS score in the presence of left bundle branch block (LBBB) were excluded because they are not captured by standard lead amplitude and duration measurements. Criteria shaded in gray are part of the manual/visual QRS score, but were not implemented in this automated analysis (Figure 1).
Searching the Social Security Death Master File

For this study, we searched the Social Security Death Master File (SSDMF), which contains over 86 million death records created from SSA payment records (www.ssdmf.com). We utilized the custom SSDMF interface created by the CardioVascular Research Grid (CVRG) Project, as outlined on the CVRG wiki (http://wiki.cvrgrid.org). We searched the death records for exact matches by first name, last name and date of birth that died during the study window (October 1, 2009 through December 31, 2010) and cross-matched the last four digits of the social security number for subjects identified to be deceased.

Automated Medical Record Screening at HUP

At HUP, the Penn Data Store was searched to extract age, sex, race and plasma creatinine levels for all subjects meeting ECG inclusion criteria. Data was extracted by querying the database with the medical record number for each ECG patient and matches were verified by confirming name and date of birth. The Penn Data Store is integrated into a central location via nightly Extract, Transform, and Load (ETL) processes built using IBM Data and Quality Stage (IBM Corp., Armonk, NY). The software utilized for mapping the structures of the database for which to load the records is SAP PowerDesigner (SAP America, Inc., Newtown Square, PA), in support with IBM FastTrack for the ETL mapping specifications. The combined effort of all of the software development solutions yields a database environment that cohesively combines the multiple information systems into a single, unified, data structure.
Table I. Comparison of Mortality Rates at Johns Hopkins Hospital vs. Hospital of the University of Pennsylvania in all Patients with QRS Score ≥5 and QRS-T angle ≥105°

<table>
<thead>
<tr>
<th></th>
<th>Univariate Odds Ratio (95% CI)*</th>
<th>P</th>
<th>Multivariable Model Adjusted Odds Ratio (95% CI) (n=2,504)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHH† (vs. HUP‡)</td>
<td>1.67 (1.30-2.15)</td>
<td>&lt;0.001</td>
<td>1.18 (0.90-1.55)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age (per 5-year ↑)</td>
<td>1.15 (1.10-1.20)</td>
<td>&lt;0.001</td>
<td>1.19 (1.13-1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10-bpm ↑)</td>
<td>1.32 (1.25-1.41)</td>
<td>&lt;0.001</td>
<td>1.38 (1.29-1.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal impairment</td>
<td>2.97 (2.28-3.86)</td>
<td>&lt;0.001</td>
<td>2.44 (1.83-3.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.98 (0.76-1.27)</td>
<td>0.90</td>
<td>0.72 (0.55-0.95)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

*CI = confidence interval; †HUP = Hospital of the University of Pennsylvania; ‡JHH = Johns Hopkins Hospital.
Table II. Significant Predictors of Mortality Among Johns Hopkins Hospital Patients with QRS Score ≥5, QRS-T Angle ≥105° and LVEF >35%

<table>
<thead>
<tr>
<th></th>
<th>Multivariable Model Adjusted Odds Ratio (95% CI* (n=1013))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic renal impairment</td>
<td>3.34 (2.20-5.06)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (per 10-bpm ↑)</td>
<td>1.43 (1.30-1.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS score (per 3-point ↑)</td>
<td>1.30 (1.07-1.59)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (per 5-year ↑)</td>
<td>1.13 (1.05-1.22)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*CI = confidence interval
### Table III. Odds Ratios for ECG Variables to Predict One-Year Mortality

<table>
<thead>
<tr>
<th>QRS Score Condition</th>
<th>JHH Univariate</th>
<th>HUP Univariate</th>
<th>Combined Univariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>QRS score &lt;5 and QRS-T angle ≥105º</td>
<td>1.18 (0.61-2.26)</td>
<td>0.58 (0.29-1.18)</td>
<td>0.58 (0.29-1.18)</td>
</tr>
<tr>
<td>JHH</td>
<td>2.21 (1.80-2.72)</td>
<td>1.41 (1.13-1.76)</td>
<td>1.41 (1.13-1.76)</td>
</tr>
<tr>
<td>HUP</td>
<td>2.07 (1.70-2.51)</td>
<td>1.29 (1.04-1.59)</td>
<td>1.29 (1.04-1.59)</td>
</tr>
<tr>
<td>Combined</td>
<td>2.07 (1.70-2.51)</td>
<td>1.29 (1.04-1.59)</td>
<td>1.29 (1.04-1.59)</td>
</tr>
<tr>
<td>QRS score ≥5 and QRS-T angle &lt;105º</td>
<td>2.53 (1.45-4.42)</td>
<td>1.61 (0.86-3.00)</td>
<td>1.61 (0.86-3.00)</td>
</tr>
<tr>
<td>JHH</td>
<td>2.31 (1.83-2.90)</td>
<td>1.73 (1.37-2.20)</td>
<td>1.73 (1.37-2.20)</td>
</tr>
<tr>
<td>HUP</td>
<td>2.33 (1.89-2.88)</td>
<td>1.72 (1.38-2.15)</td>
<td>1.72 (1.38-2.15)</td>
</tr>
<tr>
<td>Combined</td>
<td>2.33 (1.89-2.88)</td>
<td>1.72 (1.38-2.15)</td>
<td>1.72 (1.38-2.15)</td>
</tr>
<tr>
<td>QRS score &gt;5 and QRS-T angle ≥105º</td>
<td>2.79 (2.10-3.69)</td>
<td>1.37 (1.00-1.88)</td>
<td>1.37 (1.00-1.88)</td>
</tr>
<tr>
<td>JHH</td>
<td>2.42 (1.95-3.01)</td>
<td>1.47 (1.17-1.85)</td>
<td>1.47 (1.17-1.85)</td>
</tr>
<tr>
<td>HUP</td>
<td>2.59 (2.19-3.06)</td>
<td>1.53 (1.28-1.83)</td>
<td>1.53 (1.28-1.83)</td>
</tr>
</tbody>
</table>

* These odds ratios correspond to Figure 1 from the manuscript. The reference group is patients with QRS score <5 and QRS-T angle <105º. Multivariable model adjusted for age, sex, chronic renal impairment and heart rate.
**Figure I.** QRS Scoring Criteria. Abbreviations: LAFB = left anterior fascicular block; LBBB = left bundle branch block; LV = left ventricle; LVH = left ventricular hypertrophy; NchInIt40 = Notch in initial 40 ms; RAO = right atrial overload; RBBB = right bundle branch block. See prior publications (3-5) for detailed definitions.
Figure II. QRS score and QRS-T angle distributions – The median QRS score was 0 [interquartile range 0-3] at both institutions and the median QRS-T angle was 50° at both institutions with interquartile ranges of 30°-85° for Johns Hopkins Hospital and 30°-88° for Hospital of the University of Pennsylvania.