Abnormal electrocardiographic QRS transition zone and risk of mortality in individuals free of cardiovascular disease

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Aims
We examined the prognostic significance of abnormal electrocardiographic QRS transition zone (clockwise and counterclockwise horizontal rotations) in individuals free of cardiovascular disease (CVD).

Methods and results
A total of 5541 adults (age 53 ± 10.4 years, 54% women, 24% non-Hispanic black, 25% Hispanic) without CVD or any major electrocardiogram (ECG) abnormalities from the US Third National Health and Nutrition Examination Survey were included in this analysis. Clockwise and counterclockwise horizontal rotations were defined from standard 12-lead ECG using Minnesota ECG Classification. Mortality and cause of death were assessed through 2006. At baseline, 282 participants had clockwise rotation and 3500 had counterclockwise rotation. During a median follow of 14.6 years, 1229 deaths occurred of which 415 were due to CVD. In multivariable-adjusted Cox proportional hazard analysis and compared with normal rotation, clockwise rotation was significantly associated with increased risk of all-cause mortality [hazard ratio (HR) [95% confidence interval (CI)]: 1.43 (1.15–1.78); P = 0.002] and CVD mortality [HR (95% CI): 1.61 (1.09, 2.37) P = 0.016]. In contrast, counterclockwise rotation was associated with significantly lower risk of all-cause mortality [HR (95% CI): 0.86 (0.76, 0.97); P = 0.017] and non-significant association with CVD mortality [HR (95% CI): 1.07 (0.86, 1.33); P = 0.549]. These results were consistent in subgroup analysis stratified by age, sex, and race.

Conclusion
In a diverse community-based population free of CVD and compared with normal rotation, clockwise rotation was associated with increased risk of all-cause and CVD mortality while counterclockwise rotation was associated with lower risk of all-cause mortality and non-significant association with CVD mortality. These findings call for attention to these often neglected ECG markers, and probably call for revising the current definition of normal rotation.

Keywords
Clockwise rotation • Counterclockwise rotation • Transition zone • Mortality • Electrocardiogram

Clinical perspective
Using data from the US Third National Health and Nutrition Examination Survey (NHANES III), we examined the association between clockwise and counterclockwise rotations with cardiovascular and all-cause mortality among a diverse, nationally representative community-based population free of cardiovascular disease (CVD). In multivariable-adjusted Cox proportional hazard analysis and compared with normal rotation, clockwise rotation was significantly associated with increased risk of all-cause mortality. In contrast, counterclockwise rotation was associated with significantly lower risk of all-cause mortality and non-significant association with CVD mortality. These findings call for attention to these often neglected electrocardiogram (ECG) markers, and probably call for revising the current definition of normal rotation.

Introduction
Current guidelines suggest the need to understand the utility of ECG in screening intermediate risk populations. Although the usefulness
What’s new?

- Although electrocardiographic rotation has been recognized since the addition of precordial leads and use of 12 ECG leads in clinical practice, its prognostic significance has not been thoroughly examined in ethnically diverse populations.
- Using data from the US Third National Health and Nutrition Examination Survey (NHANES III), we showed that clockwise rotation was associated with increased risk of all-cause and CVD mortality. On the other hand, counterclockwise rotation, which is very common, is associated with lower risk of all-cause mortality and non-significant association with CVD mortality.
- These findings call for attention to these often neglected ECG markers, and probably call for revising the current definition of normal rotation.

of several ECG markers as predictors of poor outcomes have been examined recently,2–21 there are still markers that yet to be explored. One of these markers is the electrocardiographic transitional zone, which identifies the direction of the QRS axis in the horizontal plane. Normal transition zone could be easily recognized from standard 12-lead ECG by observing V3 and V4 where a dominant of S-wave in V3 and a dominant of R-wave in V4 should be present. Transition outside of the normal zone is referred to as either clockwise or counterclockwise rotation.22

Although electrocardiographic rotation has been recognized since the addition of precordial leads and use of 12 ECG leads in clinical practice, its prognostic significance has not been thoroughly examined. In a Japanese sample, clockwise rotation was associated with increased risk of all-cause mortality. Nevertheless, there is no supporting literature for these findings in other populations. Furthermore, no standardized chest electrode positioning protocol was applied in that Japanese study which can introduce errors in ascertainment of QRS transitional rotation.

Using data from the US Third National Health and Nutrition Examination Survey (NHANES III), we examined the association between clockwise and counterclockwise rotations with cardiovascular and all-cause mortality among a diverse, nationally representative community-based population free of CVD. The high quality of digital ECG data that were collected in NHANES III using standardized protocol provides a unique opportunity to examine the prognostic significance of different patterns of rotation using appropriate methods.

Methods

NHANES III is a national survey conducted from 1988 to 1994 by the National Center for Health and Statistics of the Centers for Disease Control (CDC), which examined health and nutritional data from a sample of civilian non-institutionalized US population. The primary purpose of this survey was to identify health and nutrition trends in US populations that can be utilized to influence polices and improve national health. Baseline characteristics including demographics, past medical history, medication use, and history of traditional cardiovascular risk factors were obtained during home interviews and subsequent mobile examination centre visits. Blood pressure data were the averaged reading from three in-home measurements and three mobile centre measurements. Using the height and weight measured during the visit to mobile examination centre, the body mass index was calculated as the weight in kilograms divided by the height in metres squared. Diabetes was defined as fasting plasma glucose ≥126 mg/dL, a non-fasting plasma glucose ≥200 mg/dL, or concurrent use of anti-diabetics medications. Diagnosis of dyslipidaemia, history of cancer; and smoking were self-reported.

The documentation of ECG acquisition and analysis in NHANES III are available at ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/nhanes/nhanes3/2A/NH3ECG-acc.pdf. Briefly, standard 12-lead ECGs were acquired using the Marquette MAC system (Marquette Medical Systems) by trained technicians in mobile examination visits. To standardize the chest electrodes position, an electrode locator (Heartsquare) was used to position the V4 electrode at a 45° angle between the mid-sternal line and the left mid-axillary line (location of V6). Electrocardiogram tracings were transmitted electronically for reading at a central ECG core laboratory (EPICARE ECG Center, Wake Forest School of Medicine, Winston-Salem, NC, USA). Electrocardiogram abnormalities including transitional zone rotation were identified from automated computerized analysis using Minnesota ECG Classification.22 Normal transition zone was characterized by dominance of S-wave in V3 and dominance of R-wave in V4. Counterclockwise rotation was defined as transition zone at V3 or rightward, while clockwise rotation was defined as transition zone at V4 or leftward.22

Mortality data were obtained through 31 December 2006. The cause of death was determined based on death certificate records and the International Classification of Disease (ICD) codes.

Out of NHANES participants older than 40 years and younger than 75 years who underwent 12-lead ECG recording (n = 6931), this analysis included 5541 participants after excluding 542 participants with CVD, 844 participants with major ECG abnormality as defined by Minnesota ECG Classification,22 and 4 participants with poor quality/incomplete data. The list of excluded major abnormalities included major ventricular conduction defect, definite/possible myocardial infarction, major isolated ST/T abnormalities, left ventricular hypertrophy, major atrioventricular conduction abnormalities, atrial fibrillation/flutter, major QT prolongation, pacemaker, and other major rhythm disorders.

Statistical analysis

Baseline characteristics were tabulated and compared across study participants stratified by rotation status (normal, clockwise rotation, and counterclockwise rotation). ë-Test was used for dichotomous variables, and analysis of variance was used to test for any pair-wise difference among the three categories for continuous variables. Cox proportional hazards analysis was used to calculate the unadjusted and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for all-cause and CVD mortality, separately associated with clockwise and counterclockwise rotation, separately (normal rotation was the reference group). Multivariate analysis was performed with incremental models as follows: Model 1 adjusted for demographics (age, sex, and race); Model 2 adjusted for Model 1 variables plus smoking status, systolic blood pressure, body mass index, use of blood pressure lowering drugs, dyslipidaemia, and diabetes; and finally Model 3 adjusted for variables in Model 2 plus any other remaining ECG abnormalities by Minnesota ECG Classification, cancer, and pulmonary disease (bronchial asthma and chronic obstructive airway disease). Subgroup analysis by age (using the median age, 55 years, as the cut point), sex, and race (Whites vs. non-Whites) was conducted using models similar to Model 3 in the main analysis. Interactions between strata in each subgroup with rotation for each of the all-cause and CVD mortality events, separately, were examined.
The statistical analysis was conducted using SAS 9.3 (SAS Institute Inc.). Statistical significant was specified at \( P < 0.05 \).

The NHANES III protocol was approved by the institutional review board of the CDC and all participants provided written informed consent.

**Results**

Of the 5541 participants included in this analysis, 1759 had normal rotation, 282 had clockwise rotation, and 3500 had counterclockwise rotation. The mean age was 55.0 ± 10.4 years, with 54% women, 24% non-Hispanic black, and 25% Hispanic. Table 1 shows the baseline characteristics of the study participants stratified by rotation status. Participants with clockwise rotation were more likely to be older with a higher body mass index and a higher prevalence of diabetes, smoking, and pulmonary disease compared with participants with normal rotation. On the other hand, participants with counterclockwise rotation were more likely to be female and Hispanic compared with those with normal rotation (Table 1).

During a median follow-up of 14.6 years, a total of 1229 deaths occurred (incidence rate 16.1 per 1000 person-years) of which 415 deaths (5.4 per 1000 person-years) were due to CVD death. The incidence rates of all-cause and CVD mortality were higher in the clockwise rotation group compared with the rates in the normal rotation group (27.7 vs. 17.4 per 1000 person-years for all-cause mortality and 9.2 vs. 5.1 per 1000 person-years for CVD mortality). On the other hand, the incidence rate of all-cause mortality was lower in the counterclockwise rotation group compared with the rate in the normal rotation group (14.6 vs. 17.4 per 1000 person-years), but not difference in the incidence rates of CVD mortality (5.4 vs. 5.3 per 1000 person-years, respectively). Figures 1 and 2 show the Kaplan–Meier survival curves for all-cause mortality and CVD mortality, respectively, in the study participants stratified by rotation status.

Table 2 shows the association between clockwise rotation and counterclockwise rotation (compared with normal rotation) with all-cause and CVD mortality, separately. As shown, clockwise rotation was significantly associated with increased risk of both all-cause mortality and CVD mortality in all models. On the other hand, counterclockwise rotation was associated with significantly lower risk of all-cause mortality and no statistically significant association with CVD mortality in all models (Table 2). This pattern of associations was consistent across subgroups of the study participants stratified by age, sex, and race (Table 3).

**Discussion**

Although easily detectable, electrocardiographic rotation in the horizontal plane is an underutilized parameter which is often overlooked. This is probably because there are not much data on its mechanisms or prognostic significance. In this analysis from the NHANES III survey, we showed that deviation from what is considered as normal rotation is common in individuals free of CVD. The prevalence rates of clockwise and counterclockwise rotations in our study were 5.1 and 63.2%, respectively, while normal rotation was present in only 31.7% according to the current standards of definition.22,23 We also showed that clockwise rotation is associated with increased risk of all-cause and CVD mortality, while counterclockwise rotation is associated with less risk of all-cause mortality and no significant association with CVD mortality. These findings call for attention to these common yet neglected ECG markers. The facts that counterclockwise rotation in our study was more common than what is typically considered as a normal rotation, and is prognostically more benign, mandate reconsidering what should really be labelled as ‘normal’ rotation.

Tahara et al.24 evaluated the association of anatomic rotation of the heart as demonstrated by cardiac computed tomography with horizontal rotation on ECG. Two-thirds of rotated transition zones were related to anatomic rotations of the heart with a smaller measured septal angle in the majority of clockwise rotated hearts and a larger septal angle and thickened intraventricular septum in the majority.
Table 2 Rotation status and risk of all-cause mortality and cardiovascular mortality

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<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
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<tbody>
<tr>
<td></td>
<td>Clockwise rotation</td>
<td>Counterclockwise rotation</td>
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<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.51 (1.21–1.88)</td>
<td>0.80 (0.70–0.90)</td>
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<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.45 (1.16–1.81)</td>
<td>0.86 (0.76–0.97)</td>
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<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.43 (1.15–1.78)</td>
<td>0.87 (0.77–0.98)</td>
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</tbody>
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<sup>a</sup>Adjusted for age, sex, and race.

<sup>b</sup>Adjusted for variables in Model 1 variables plus smoking status, systolic blood pressure, body mass index, blood pressure medications, dyslipidaemia, and diabetes mellitus.

<sup>c</sup>Adjusted for variables in Model 2 plus any other ECG abnormalities, cancer, and pulmonary disease (bronchial asthma and chronic obstructive pulmonary disease).

Figure 1 Kaplan–Meier survival curves for all-cause mortality stratified by rotation status. Number of participants at risk (surviving) at Years 5, 10, and 15 is 5963, 5262, and 2431, respectively.

Figure 2 Kaplan–Meier survival curves for cardiovascular mortality stratified by rotation status. Number of participants at risk (surviving) at Years 5, 10, and 15 is 5963, 5262, and 2431, respectively.
Table 3: Rotation status and risk of all-cause mortality and cardiovascular mortality in sex, race, and age subgroups

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<thead>
<tr>
<th></th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
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<tbody>
<tr>
<td></td>
<td>Clockwise rotation</td>
<td>Counterclockwise rotation</td>
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<tr>
<td></td>
<td>HR (95% CI)*</td>
<td>Interaction P-value</td>
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<tr>
<td>Women</td>
<td>1.47 (1.05, 2.04)</td>
<td>0.982</td>
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<tr>
<td>Men</td>
<td>1.47 (1.09, 1.98)</td>
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<tr>
<td>Non-Whites</td>
<td>1.57 (1.14, 2.17)</td>
<td>0.401</td>
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<tr>
<td>Whites</td>
<td>1.30 (0.96, 1.77)</td>
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<tr>
<td>Age &lt;55 years</td>
<td>1.71 (1.07, 2.74)</td>
<td>0.408</td>
</tr>
<tr>
<td>Age &gt;55 years</td>
<td>1.35 (1.05, 1.74)</td>
<td>0.87 (0.76, 1.00)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and race, smoking status, systolic blood pressure, body mass index, blood pressure medications, dyslipidaemia, diabetes mellitus, any other ECG abnormalities, cancer, and pulmonary disease (bronchial asthma and chronic obstructive pulmonary disease).
cause mortality and no significant association with CVD mortality. These findings suggest that horizontal rotation carries important prognostic information, which may merit routine evaluation. Further investigation is needed to look into the mechanisms of developing rotation and its progression overtime as well as considering re-defining normal rotation.

Conflict of interest: none declared.

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References