Author's response to reviews

Title: The association of spatial T wave axis deviation with incident coronary events. The ARIC Study.

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Version: 3 Date: 30 October 2004

Author's response to reviews: see over
We thank the reviewers of our paper for their comments and suggestions. We implemented these suggestions in the re-submitted manuscript, mentioning the page where modifications have been made, as shown below. We also added two supplementary tables. The reviewers also raised several interesting questions, which we would like to address below, point by point.

**Reply to Dr. Marek Malik**

We thank Dr. Malik for his comments and suggestions. We implemented these suggestions in the re-submitted manuscript. In addition Dr. Malik raises several interesting questions, which we would like to address below.

1. **The vectorial deviation between QRS complex and T wave axis**

   **Author’s Response and Action:** We agree with the comment, but the vectorial deviation between QRS complex and T wave axis is not available in our database.

   **Our rationale follows.**

   We agree with Dr. Malik that the spatial QRS-T angle, defined as the angle between the directions of ventricular depolarization and repolarization is an informative parameter, akin to the concept of the ventricular gradient introduced by Wilson in 1934. We seem to be witnessing a renewed interest in the spatial QRS-T angle and several studies have attested to its usefulness.
in post-infarction [1] and hypertensive patients [2]. The spatial QRS-T angle was also the strongest predictor of fatal cardiac events, even after controlling for the frontal plane T axis, in the large population-based cohort of men and women aged 55 years or older of the Rotterdam study [3,4]. Unfortunately, this index is not currently available in our database.

2. Fatal events as a distinct outcome

Author’s Response and Action: We agree that the analysis of fatal events in comparison with combined events is informative and we are presenting this information in the re-submitted manuscript (page 14 last paragraph to page 15, in the text and Table 5). Our rationale follows.

We agree with Dr. Malik that combining fatal and non-fatal coronary events represents a rather broad category. While the follow-up procedures of the ARIC study are highly standardized in defining non-fatal events and differentiating them from a subclinical disease, it is the underlying electrophysiological mechanism that might raise concerns in our study. In both the Rotterdam and CHS studies the association between T wave axis and coronary events was stronger for fatal than non-fatal events. Similarly, the spatial QRS-T angle was recently reported to be associated with fatal but not with non-fatal cardiac events [4]. While experimental models are still sparse, it can be speculated that an abnormal spatial T wave axis may possibly reflect disturbances in the repolarization process caused by subclinical myocardial disease, with an increased propensity for arrhythmic events, and thus an increased risk for fatal cardiac events.

The rationale for using the combined outcome in our study was driven by concerns about statistical power, given the relatively small number of fatal events. While in the Rotterdam and CHS studies, the incidence rate for fatal events was 4.2 (95% CI 3.3-5.1) and 5.8 (95% CI 5.0-6.7) per 1000-person years respectively, this rate was much lower in our study. During an average follow-up time of 11.6 years, 143 fatal events were recorded in our study population, 62 among women and 81 among men. The overall cumulative incidence was 1.17% and the average annual incidence rate of 1.01 per 1000 person-years (95% CI, 0.84 –
1.17 per 1000 person-years). The relationship of fatal events with spatial T wave axis deviation followed the same pattern as the combined outcome, i.e a slight increase in the incidence rates in the fourth quartile of the T wave axis, for each gender.

As expected, the crude hazard rate ratios for fatal events were slightly larger in the multivariate models (Table 5 in the revised manuscript, and in the table presented below) than for the combined outcome. After adjustment for a limited number of risk factors (due to the small number of events), these modest associations were no longer statistically significant. Given the relatively small number of fatal events in our population, these patterns must be interpreted with caution.

Table. Hazard rate ratios and 95% CI for a 10 degrees increase in the spatial T wave axis deviation

<table>
<thead>
<tr>
<th>Model</th>
<th>Fatal +non-fatal events</th>
<th>Fatal events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>Crude</td>
<td>1.16 (1.04-1.29)</td>
<td>1.05 (0.96-1.15)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>1.06 (0.95-1.17)</td>
<td>0.96 (0.88-1.06)</td>
</tr>
</tbody>
</table>

*Adjusted for weight smoking HTN and DM

In sum, analysis of fatal events in comparison with combined events is informative and we are presenting this information in the re-submitted manuscript (page 14 last paragraph to page 15 in the text and Table 5).

3. **QRS duration**

Author’s Response and Action: We agree with that adding QRS duration as a covariate to our models is a valid alternative. We have added this information in page 14, 2nd paragraph in the resubmitted manuscript.

Our rationale follows
Dr. Malik suggests adding the QRS duration as a covariate to our models, as an alternative to the rather extensive exclusions performed in order to avoid secondary repolarization abnormalities. We welcome this suggestion and we report the findings in the revised manuscript as one more scenario in our post hoc analyses. Briefly, the relationship of incident CHD events with spatial T wave axis deviation followed the same pattern as in the restricted dataset, i.e. there was a slight increase in the incidence rates of CHD events in the fourth quartile of the T wave axis, for each gender. The crude hazard rate ratios (95%CI) for incident CHD events for a 10 degree increase in the spatial T wave axis were 1.18 (1.13-1.23) for women and 1.14 (1.09-1.19) for men. After adjustment for the same covariates as in the restricted data set and for QRS duration, the hazard rate ratios (95%CI) were 1.05 (0.99-1.16) and 1.04 (0.98-1.1). This alternative approach does not change the conclusion of our study, i.e. the spatial T wave axis deviation does not add predictive information above and beyond the traditional risk factors and usual ECG markers. We have inserted this information in page 14, 2nd paragraph in the resubmitted manuscript.

4. Heart rate

Author’s Response and Action: We explain why heart rate was not included in our models. We agree that the association between T wave axis and heart rate deserves more detail. We have added supplementary information and comments at page 9 (3rd paragraph) and page 17 (3rd paragraph) in the re-submitted manuscript.

Our rationale follows

Dr. Malik correctly points out that heart rate was not included in our multivariate models. The reason for this is that heart rate was not associated with both the exposure of interest and the outcome. While we found that spatial T wave axis is indeed slightly heart-rate dependent, heart rate was not associated with incident coronary events in our study population. Since our study does not support the usefulness of the spatial T wave axis in clinical and epidemiological studies, we did not expand on its association with heart rate in our manuscript as initially submitted. However, given the potential electrophysiological interest of this association, we added the following comments (pages 9 and 17) in the re-submitted manuscript:
“Our study found an inverse association between spatial T wave axis deviation and heart rate. From the first to the fourth T wave axis quartile the mean (SE) values for the heart rate were: 70.24 (0.30), 69.05 (0.23), 69.20 (0.23), 67.70 (0.23) bpm for women and 67.26 (0.28), 65.74 (0.28), 65.56 (0.28), 66.67 (0.28) bpm for men.

Heart rate influences have been reported on the frontal plane T wave angle [5] and on the spatial ST-T vector [6]. The physiologic explanation of the dependency of an angular measure on heart rate is not clear. It is plausible that this phenomenon is similar to some degree with that observed for another index of an altered repolarization, namely the T wave alternans, characterized by the change in amplitude, morphology and axis of the spatial T wave, and associated with an increased risk of sudden cardiac death. Even if the mechanism of the heart rate dependency of the spatial T wave axis remains elusive, it raises the questions about the need for “rate correction” of this measurement.”

5. **Bazett’s correction for heart rate**

**Author’s Response and Action:** We agree with the comment, we offer explanation and supplementary information on page 6, 2nd paragraph, last sentence in the re-submitted manuscript.

**Our rationale follows**

Dr. Malik observes that we used Bazett’s formula to “correct” for the heart-rate dependency of the QT interval. We are aware that Bazett’s formula is flawed and that its use allows a considerable residual correlation with the heart rate. The reason for using Bazett’s formula was to ensure comparability with other published studies on the T wave axis, especially the Rotterdam study. The QT interval was not associated with coronary events in our study population, regardless of the formula used for its heart rate “correction”, either Bazett, Fridericia, or the QT Index. As such, QT interval did not qualify as a confounder in our multivariate models and we did not further insist in refining its calculation. We have inserted a paragraph in our re-submitted manuscript, in order to clarify this issue (page 6, 2nd paragraph, last sentence).
References

Reply to Dr. Polychronis E Dilaveris.

We thank Dr. Dilaveris for appreciating our paper.

Reply to Dr. Lennart Bergfeldt.

We thank Dr. Bergfeldt for the detailed analysis of our paper and suggestions. We have implemented these suggestions in the re-submitted manuscript. In addition Dr. Bergfeldt raises several interesting issues regarding the design, methods and interpretation of our study, which we would like to address below.

I. Comments on issues regarded as requiring major revisions.

1) The ability of the spatial T wave axis to discriminate between cases and non-cases of CHD.

Author’s Response and Action: We accept the suggestion and have inserted supplementary information in the re-submitted manuscript at page 14, 1st paragraph.

Our rationale follows.

We agree with Dr. Bergfeldt that one of the criteria to judge the usefulness of the spatial T wave axis in clinical practice is its ability to discriminate between cases and non-cases of CHD. In comparing cases with non-cases in our initially submitted manuscript, we stated (page 9-10): “Spatial T wave axis deviation was only slightly increased among cases compared to non-cases (25.2 degrees versus 23.2 degrees among women, and 24.4 degrees versus 23.9 degrees among men). This statement pertains to incident CHD cases. In order to expand on Dr.’s Bergfeldt
suggestion we expanded our comparative analysis to prevalent CHD cases at baseline, as described below.

In our initial sample, before any exclusions were applied, the mean (SD) values for the spatial T wave axis deviation were 26.66 (16.81) and 44.88 (27.29) degrees for those without and those with CHD respectively (p value <.0001). The entire distribution of the spatial T wave axis deviation among those with CHD at baseline was shifted to the right of the distribution of participants without CHD at baseline. This statistically significant difference persisted even after adjustment for age and several standard cardiovascular risk factors (anthropometry, smoking, hypertension, diabetes, heart rate, QRS axis and QT interval) with adjusted mean values of 26.79 and 41.47 degrees respectively. Thus, it would seem that spatial T wave axis might have a discriminatory ability.

However, among those without CHD at baseline in our study, there were various conditions or markers of clinical interest, some of established predictive value, such as ST segment depression, negative T waves or atrial fibrillation. In the clinical setting, the need for improved prediction and discriminatory ability of a new potentially useful marker is particularly useful in the absence of such markers. Therefore, we repeated our analysis after excluding ECG markers based on the Minnesota codes (MC), such as ST depression or elevation (MC 4.1 to 4.4 and MC 9.2), negative T waves (MC 5.1 or 5.2), WPW pattern (MC 6.6), ventricular conduction defects (MC 7.1, 7.2, 7.4), and atrial fibrillation or flutter (MC 8.3). The difference between the mean T wave axis deviation was considerably attenuated after these exclusion: mean spatial T wave axis deviation of 23.84 (12.36) for those free of CHD and 24.08 (15.34) degrees for those with CHD (p value 0.006). While statistically significant (due to the large sample size), with such wide variations (large SDs), we doubt that a difference of 3-4 degrees would have a clinical significance.

The findings of approach are consistent with the results of our longitudinal analysis, indicating the lack of association between spatial T wave axis deviation and incident coronary events. The exclusion of the aforementioned Minnesota codes is consistent with the aim of restricting our analysis to primary repolarization abnormalities. The discrepant results between the analysis before and after these exclusions suggest that spatial T wave axis deviation has no ability to
capture relevant information about the process of ventricular repolarization above and beyond the secondary repolarization abnormalities. This may be one of possible explanations for discrepant results between different cohort studies exploring this issue, as different studies have used different exclusion criteria. This observation is presented in our discussion section.

In sum, we appreciate Dr.’s Bergfeldt observation, we agree that expanding on the discriminatory ability of the spatial T wave axis deserves a more extended discussion. Therefore, we incorporated such discussion into the re-submitted manuscript (page 14, 1st paragraph), with no change in the overall conclusion of our paper.

2) The repeatability of the spatial T wave axis deviation measurements.

Author’s Response and Action: We agree with the comment and we offer the relevant information as a revised citation 22 in the reference list.

Our rationale follows

As Dr. Bergfeldt points out, the repeatability/reproducibility of any measurement is very important. In the interest of maintaining the focus of the current paper on the association between the spatial T wave axis and incident coronary events, we only briefly mention the good repeatability properties of the spatial T wave axis measurements. We estimated the two-minute and one-week repeatability of the spatial T wave axis deviation under standardized conditions in a different study setting. This different study was indeed referenced in our initially submitted manuscript as an abstract. In the meantime, the paper on the repeatability study was accepted for publication and will appear in the December 2004 issue of the Journal of Electrocardiology. In the re-submitted manuscript, we accordingly provide the reader with the following citation (citation 22 in the reference list) for the full article:

3) Hypertension as a confounder and/or outcome of interest

**Author’s Response and Action:** We agree with the comment to offer supplementary information on hypertension. We added this information at page 9, 2nd paragraph, page 17 3rd paragraph and in a new Table 2 in the revised manuscript. Our rationale follows

Dr. Bergfeldt raises the issue of hypertension (HTN), suggesting that it should be treated as a confounder (which we did) and as a secondary outcome (which we did not). Indeed, several reports suggest that the T-loop features and the spatial QRS-T angle are significantly different between hypertensive and normotensive individuals [1,2]. Hypertension was also a confounder in our study population and as such we included it in our Cox proportional models. In the interest of parsimony in our initial manuscript we did not expand on this issue. However, given the potential relevance of this association, in the re-submitted manuscript we have added supplementary information, as described below.

The relationship between the spatial T wave axis in our study population and hypertension status according to the JNC-VII classification is presented in Table 2 in the re-submitted manuscript and below in this response. For each gender group the more pronounced the hypertension status the larger the mean values for the spatial T wave axis. Among the 3860 individuals defined as hypertensive, the mean (SD) values for the spatial T wave axis adjusted for age, height and weight were higher among those with uncontrolled HTN compared with those having blood pressure levels below the treatment goal: 26.73 (0.27) degrees vs. 25.90 (0.27) (p=0.03). The explanation for these associations is likely related to the presence of an increased left ventricular wall in the context of the left ventricular hypertrophy. It is also possible that increased spatial T wave axis deviation is related to other processes present in the hypertensive myocardium, such as microfocal areas of fibrous tissue and/or increased alteration of ionic channels. These findings suggest that spatial T wave axis deviation may serve as an auxiliary early marker of repolarization abnormalities in hypertensive individuals. A more in depth analysis of the value of the spatial T wave axis must take into account the presence of left ventricular hypertrophy (LVH). Because the prevalence of LVH in this study population was low, and in the interest of
maintaining focus on the association with incident CHD, we choose to limit the discussion of HTN.

In sum, we agree with Dr. Bergfeldt that HTN is associated with the spatial T wave axis deviation and that it may deserve a more detailed discussion. In the re-submitted manuscript we present the relationship with the JNC-VII classification at page 9, 2nd paragraph, page 17 3rd paragraph and in a new Table 2. Yet, in the interest of maintaining focus, we refrain from expanding extensively on this issue, which might be more appropriate in separate future papers.

4) A critical attitude towards the spatial T wave axis

Author’s Response and Action: We agree with the comment and we have incorporated a paragraph on the validity of the spatial T wave axis deviation in our re-submitted manuscript, at page 18, 3rd paragraph.

Our rationale follows

We agree with Dr. Bergfeldt that from an electrophysiological perspective, the spatial T wave axis has theoretical limitations and that a critical attitude toward this marker is warranted. Indeed T wave axis is only a global measure of direction during the repolarization process [3]. The pathophysiology of the ventricular repolarization is complex and we do not claim that spatial T wave axis captures these abnormalities entirely. Whether the level of criticism applied to T wave axis and QT interval dispersion should be equivalent, as Dr. Bergfeldt suggests, this might be the subject of a more elaborate discussion on electrophysiological grounds. Our study is based on the theoretical and experimental evidence suggesting that ECG indexes in the spatial-domain expressing the T-wave area or the T-wave vector are more accurately related to the “true” dispersion of ventricular repolarization than indexes in the temporal domain. In contrast, the assumed pathophysiological basis of QT interval dispersion appears to be false [4] and QT dispersion as currently measured from the surface ECG has been the subject of intense criticism [5,6]. As such, the premise of our study was that spatial T wave axis might be one of several
descriptors of T-wave morphology and spatial loop orientation, attempting to explore repolarization qualities from 12-lead surface ECGs, with the testable potential to be a marker of increased risk for cardiovascular disease. We also agree that the spatial loop contains more information, but our purpose was to explore the spatial T wave axis from the 12-lead standard ECGs, as an inexpensive and readily available marker, suitable for routine clinical and epidemiologic investigations.

In sum, we are grateful for the comments made by Dr. Bergfeldt and his appreciation for our data collection. We have incorporated a paragraph on the validity of the spatial T wave axis in our re-submitted manuscript, at page 18, 3rd paragraph.

5). Comment on the usefulness of the spatial T wave axis

**Author’s Response and Action:** We agree and we have modified the statements accordingly in our re-submitted paper at page 2, last paragraph and page 19 last paragraph

*Our rationale follows*

We agree with Dr. Bergfeldt that a more pertinent statement on the utility of the spatial T wave axis deviation is needed. Based on the findings of this “negative study”, the T wave axis deviation has no clear use in clinical and epidemiological practice. It is doubtful that T wave axis deviation would be of benefit in the prediction of CHD events above and beyond the current traditional risk factors. While this was implied by our findings, we now express it explicitly in our re-submitted paper at page 2, last paragraph and page 19, last paragraph.
II. Comments on issues regarded as requiring minor essential revisions

1) QT interval measurement

Author’s Response and Action: We agree and we provide the information in the re-submitted manuscript at page 6, second paragraph, last sentence.

Our rationale follows

Dr. Bergfeldt asks for clarification on the QT measurement in our study and how this measurement compares with that used in other published articles investigating this issue, mainly the Rotterdam study by Kors et al. We are glad to provide this information, both here and in the re-submitted manuscript at page 6, second paragraph, last sentence.

The QT interval from the digital 12-lead ECG was determined by the NOVACODE program [7]. An overall QT interval was calculated from the common QRS onset and T offset for all 12 leads together. This method is identical to that used in the Rotterdam study, except for the software used (MEANS software instead of NOVACODE). The Rotterdam study used Bazett’s formula for heart rate correction. For comparability purposes, we used the same Bazett’s formula.

2) T wave axis in the frontal plane

Author’s Response and Action: We disagree, and we offer the reason for using the frontal plane T axis at page 9, first paragraph.

Our rationale follows

The reason for analyzing the T wave axis in frontal plane in addition to the spatial T wave axis is to ensure comparability with Rotterdam study. As mentioned in our initially submitted manuscript, while ARIC, CHS and MRFIT study protocols all used the same definition of spatial T wave axis deviation, the Rotterdam study used the frontal plane T wave axis. We offer the reason for using the frontal plane T axis at page 9, first paragraph.
3) **Age and height**

**Author’s Response and Action:** We disagree and we offer explanation. No modification in the re-submitted paper.

*Our rationale follows*

Indeed, Dr. Bergfeldt correctly observes that in contrast to weight, age and height do not have an impact on the T wave axis. Two reasons persuaded us in preserving age and height in our models: to improve the precision of the estimates and epidemiologic tradition (age adjustment for cardiovascular outcomes, and height adjustment in the absence of a more accurate measure for ECG variables believed to be related to thoracic dimension and shape).

4) **Comment on the presence of subclinical disease.**

**Author’s Response and Action:** We agree and we have modified accordingly at page 16 first paragraph, in the re-submitted paragraph.

*Our rationale follows*

Dr. Bergfeldt takes issue with our discussion on the assumed presence of subclinical disease in the discussion section of the initially submitted manuscript, which contrasts discrepant results between different studies:

Our comment refers to the likelihood of a higher prevalence of subclinical disease in the older population of the Rotterdam study (which found an association between T wave axis and incident coronary events) than in the younger populations of the ARIC and MRFIT studies (both reporting a lack of association). We submit that subclinical disease may play a confounding role. Some indicators of subclinical disease such as the left ventricular hypertrophy (LVH) are clearly more prevalent in the Rotterdam than in the ARIC study. The presence of detected or undetected subclinical disease (LVH, patchy myocardial fibrosis) may lead to ventricular electrical instability and a higher proportion of cardiac death related to primary arrhythmic events in a
population. Given that none of these cohort studies ascertained arrhythmic events, it is plausible that the positive association found in the Rotterdam study was at least partially driven by a larger component of arrhythmic cardiac events, directly related to a higher prevalence of subclinical disease associated with large values for the T wave axis. This is further supported in the Rotterdam study by the finding that T wave axis is more strongly associated with fatal than non-fatal events.

In sum, we agree that various degrees of subclinical disease are possibly present in the ARIC study population and that our study population consists of individuals without clinical or ECG evidence of CHD. The presence (prevalence and severity) of subclinical disease, is invoked in our manuscript as a comparison of interest between studies investigating the association of the T wave axis with coronary events. We have modified our discussion section, and made these points more explicit at 16 in the re-submitted manuscript.

III. Comments on issues regarded as requiring discretionary revisions

1) Definition of T wave axis

Author’s Response and Action: we agree and we have provided supplementary information on page 6, first paragraph in the re-submitted manuscript

Our rationale follows

Dr. Bergfeldt suggests a more detailed definition of the spatial T wave axis. We have done this on page 6, first paragraph in the re-submitted manuscript, as stated here.

Spatial T-wave axis was calculated from integrated T-wave amplitudes of the XYZ leads. Briefly, the inverse transformation by Dower et al [8] was used to derive Frank's XYZ leads, with the polarity of the Z lead inverted in order to generate QRS and T wave patterns with a more familiar waveform in that lead. Thus, the positive direction of the Z axis is in the anterior direction. Spatial T-wave axis was calculated from the scalar product between the T vector and a
unit vector in a normal reference direction (x=1/√3, y=1/√3, and z=-1/√3, where x, y and z are the unit vector components in the X, Y and Z directions). T axis expresses spatial T vector deviation from the approximate normal direction of the T vector 45° anteriorly in the XZ plane and at 45° elevation from the Y axis.

2) Citation

**Author’s Response and Action: Accepted**

**Our rationale follows**

We thank Dr. Bergfeldt for the citation offered (Rubulis et al Heart Rhythm, 2004; 1: 317-325). We have incorporated it in our discussion section (page 18).

**References.**


Table. Mean spatial T wave axis deviation adjusted for age, height and weight, by JNC VII classification of blood pressure and gender.

<table>
<thead>
<tr>
<th>JNC VII BP stage</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Mean T axis (SE)</td>
</tr>
<tr>
<td>Normal</td>
<td>3765 (52.73)</td>
<td>9.86 (0.10)</td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>2286 (32.02)</td>
<td>18.29 (0.10)</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>841 (11.78)</td>
<td>25.81 (0.10)</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>248 (3.47)</td>
<td>39.04 (0.10)</td>
</tr>
</tbody>
</table>