T-wave window ever be moved the opposite way, and 3) could the T-wave window be shortened progressively, in order to "unravel the contributions of different portions of the entire J–T interval, in rendering microvolt level T-wave alternans (MTWA) positive, in various patient populations"?

To address the first question, it should be noted that far fewer patients with structural heart disease have significant QT prolongation than do patients in the long-QT population that constituted the basis of our study.[1] Thus, it is likely that only a small subset of patients referred for MTWA analysis will require adjustment of the T-wave window. However, in these individuals, appropriate T-wave window adjustment could mean the difference between a negative and a nonnegative test result. Modification of the software to provide a picture of where the T-wave window was positioned, as we have suggested, would allow the interpreter to assess the adequacy of the study.

Should the T-wave window ever be moved the opposite way (to encompass more of the ST segment and/or QRS complex)? Probably not, if MTWA analysis is being used to assess the risk of sudden cardiac death in patients with stable structural heart disease. In this population, it is alternans within the T wave (and especially involving the apex of the T wave) that appears to predict life-threatening ventricular arrhythmia.[2–5] Although it is theoretically possible that patients with pathologically short QT intervals might require backward adjustment of the T-wave window in order to encompass the T wave, the likelihood of this seems remote.

Dr. Madias suggests that we manipulate the T-wave window in order to dissect out the contributions of the different portions of the J–T interval to alternans in various populations. Indeed, there is increasing interest in understanding the different mechanisms by which various disease processes create alternans in the electrocardiogram. A recent simulation study[6] showed that action potential duration alternans produced maximum alternans at the peak of the T wave, whereas both action potential amplitude alternans and conduction block alternans produced alternans in the ST segment, and conduction delay alternans caused alternans at the QRS complex. Through dissection of the J–T interval to determine where alternans in occurring in a given disease process, together with further modeling studies, we may, in the future, be able to determine the mechanism of a patient's alternans and tailor treatments to reduce the risk of arrhythmia. We have only begun to explore the mechanisms and clinical utility of alternans.

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Clinical correlates of early repolarization and J wave patterns…are they proarrhythmic on their own?

We have read the manuscript by Lanza et al.[1] entitled "Prevalence and clinical correlates of early repolarization and J wave in a large cohort of subjects without overt heart disease," in which the authors detail their prospective study involving 4176 electrocardiograms of subjects without presumed structural heart disease. A differentiation between typical early repolarization (ER) and slurred or notched J wave is emphasized, yet the authors conclude that neither the former nor the latter is associated with symptoms potentially related to arrhythmias, such as syncope or palpitations.

Their research adds new data to our current understanding of the clinical relevance of ER or J waves. To our knowledge, this study is among the very few that clearly differentiates typical ER from J wave patterns and their conclusions are considerably robust, considering the very high number of patients included. The lack of association between those ECG patterns and the occurrence of arrhythmia-related symptomatology may contradict the findings of other studies that have shown an increased risk of arrhythmic death during very long-term follow-up in asymptomatic adults with J waves >2 mm in amplitude,[2] especially if combined with horizontal/descending ST segment.[3] Increased transmural dispersion of repolarization potentiating the risk for phase 2 reentry and polymorphic ventricular tachycardia/ventricular fibrillation, or delayed depolarization of those segments with heterogeneous remote scar tissue, irrespective of its etiology, creating an anatomic/functional substrate for reentrant ventricular arrhythmias, are some of the mechanisms potentially associated to the malignant role of J wave patterns with horizontal/descending ST-segment.

The findings of Lanza et al. deserve some additional comments:

- It is possible that the occurrence of isolated J waves or ER patterns does not increase arrhythmic mortality on its own, but only in the presence of additional proarrhythmic factors or triggers, such as acute myocardial ischaemia,[4] neurohormonal and sympathetic activation in ischemic or non-ischemic

chronic heart failure[5] and severe hypokalemia.[6] Patients included in this study were presumably low-risk patients, as they did not have any evidence of structural heart disease according to clinical history, ECG results and noninvasive cardiac investigation, when required. Therefore, occurrence of proarrhythmic triggers was probably rare, which could explain the lack of clinical correlation of slurred or notched J wave pattern with ST segment elevation. If the cohort had included patients with a known cardiac condition, or older patients (even without known cardiac disease), we might have obtained contrasting results. However, this possibility is unproven at present and should be clarified by appropriately designed studies.

- A diagnosis of ER has usually been based on the presence of a typical concave, upsloping, ST-segment elevation, often associated with low heart rate, suggestive of a vagal etiology. Independent predictors of the occurrence of an ER/J wave pattern were younger age, male sex and lower heart rate, reinforcing its potential vagally mediated origin. Nevertheless, the mechanism behind ER or J wave pattern in older patients may be of different electrogenic etiology. This should be further clarified in the future. It would be interesting if the authors could test the potential association between ER/J wave and arrhythmia-related symptoms in elderly patients or in those with arterial hypertension and/or diabetes mellitus (more likely to have endothelial dysfunction, subclinical or manifest cardiovascular disease and, probably, a lower vagal tone).
- A potential similarity between the Brugada and early repolarization syndromes in terms of response to heart rate, pharmacologic agents and neuromodulation has been proposed. There might be a linkage in their genetic[7] or pathophysiological mechanisms.[8] In fact, it has been suggested that the Brugada syndrome (BS) may represent a more localized (right ventricular outflow tract) and pronounced form of early repolarization/delayed depolarization. Sudden cardiac death is often the first clinical manifestation of BS and the same phenomenon might happen in the *malignant* variant of ER, provided additional proarrhythmic factors or triggers are present. Symptoms such as sustained palpitations or syncope may as well occur only in the presence of additional arrhythmic triggers.
- An association between ER and occurrence of ventricular arrhythmias has been shown in longitudinal studies. A potential relationship between ER or J wave patterns and the occurrence of syncope and/or palpitations is less likely to be detected in a cross-sectional study, such as the one by Lanza et al.

In conclusion, ER or slurred/notched J wave patterns are not necessarily associated with higher arrhythmic risk in patients without structural heart disease or any potential arrhythmic trigger such as myocardial ischemia, sympathetic activation or electrolyte disturbance. In fact, ER and all of its variants are relatively common in healthy young males with slower heart rates.[9] However, given the conflictual and controversial currently available data on this subject, we look forward to seeing the future analysis of Lanza and colleagues on the potential association of ER/J wave and long-term clinical outcome. Currently, we reinforce their suggestions concerning the need for detailed and standardized definitions and methods for measurement of ST elevation and J wave.

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Author's Response

To the Editor:

We very much appreciate the interest of Barra et al. in our study on the prevalence and clinical correlates of early repolarization (ER) in apparently healthy subjects.[1]