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Is the T_{peak}-T_{end} interval as a measure of repolarization heterogeneity dead or just seriously wounded?

By

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This commentary relates to the article by Srinivasan et al [1], who studied relationships between intracardiac ventricular repolarization in normal human hearts in situ and the T-wave in the body surface ECG. They report not only that the slope of the T-wave upstroke in frontal precordial leads relates to repolarization differences between left and right ventricles but also that they found no meaningful relationship between myocardial repolarization heterogeneity, measured as differences in apicobasal, right-left ventricular, and transmural repolarization times, and duration of the T_{peak}-T_{end} (Tpe) interval. While limitations of the latter observation are well listed by Srinivasan et al [1], the data seem to undermine seriously the concept that Tpe interval measured in the surface ECG is a valid measure of ventricular repolarization heterogeneity. The results might be quite different in diseased hearts, where larger repolarization heterogeneity is expected. Still, if this concept is not valid in normal hearts, when neither surface nor intracardiac measurements are influenced by pathological processes, it is dubious whether the concept has any general validity.

As is well known, the proposal of concordance between Tpe intervals and repolarization heterogeneity was derived from myocardial wedge experiments [2]. While these experiments provided useful models of some aspects of myocardial tissue electrophysiology, their relationship to processes in the complete organ *in situ* is complex and, as far as the Tpe interval is concerned, likely led to unfounded extrapolations. Indeed, the ECG-like signals recorded from myocardial wedges were largely influenced by observations of the middle layer of the so-called M-cells [3], which have not been confirmed in hearts in situ and might have been artefacts of the wedge preparations. By design, the myocardial wedges, *i.e.*, localized slices of myocardium, cannot cover many site-specific repolarization differences, including the apex-to-base gradient, left-to-right distribution, free wall versus septum difference, etc. On the contrary, all such intra-myocardial distributions and heterogeneity of action-potential durations and profiles contribute to the duration and morphology of the T waves recorded on the thorax surface, including the Tpe intervals. In this sense, the observations by Srinivasan et al [1] are not surprising despite only partially fitting with other direct experiments, which still did not agree with the results of the wedge-based observations [4].

A literature review including superficial meta-analyses [5] might suggest that repolarization heterogeneity represented by Tpe interval has been proven by studies showing the association of prolonged Tpe with proarrhythmia and other risks. However, as already discussed [6], detailed comparisons of such studies report important differences in several crucial aspects including patient characteristics, methods of ECG measurement, heart rate correction, and outcome events. Simply stated, what one groups calls a prolonged Tpe is frequently rather different from the understanding and publications on Tpe prolongation by another group. In addition, other systematic and well-conducted studies directly contradict the notion that prolonged Tpe interval is proarrhythmic [7,8].

Of all these problems, the lack of systematic ECG measurement seems to be the most important shortcoming. Srinivasan et al [1] measured Tpe interval separately in different ECG leads and found no meaningful correlations in any of these leads with repolarization heterogeneity and gradients measured in different directions, including transmural differences that might anatomically be closest to the wedge preparations. However, other previous publications reported the interval measured in only one lead, in a composite of all 12 leads, or even the maximum Tpe interval found in a sub-selection of leads. In addition, other measurement aspects also contribute to the differences in previous reports. While identification of the end of the T wave is frequently problematic in pathological ECGs, it is believed that localization of the T-wave peak can be made with much greater certainty. However, this belief is unjustified [6]. When these measurement problems are combined with the variety of reported heart rate corrections (often used without sufficient justification) and when such data are subjected to the standard bias of publishing only positive results, a misleading picture of the importance of the Tpe interval might emerge.

Similar to other clinical characteristics, ECG-based indices require consensus on measurement, heart rate relationship and correction, definition of normal values (potentially sex-specific), and on the sensitivity and specificity of proposed clinical applications. We do not believe that Tpe interval assessment meets these criteria, despite wide interest spanning several years. Systematic prospective studies using the very same methodology are needed to ascertain whether any meaningful progress can be made. Useful suggestions of measurement standards are available and there is little reason for not adopting these standards universally [9].

Assessment of repolarization heterogeneity based on electrocardiographic indices has been the holy grail of noninvasive electrophysiology for many decades [10]. It remains to be seen whether the T-wave upslope indices reported by Srinivasan et al [1] contribute to this unmet need. Experience with other seemingly simple indices such as QT dispersion or areas under the T wave is not particularly encouraging. Indeed, it is easy to see the similarity between the present interest in the Tpe interval and the interest given to QT dispersion some twenty years ago, before it was recognized to be highly problematic. The lack of merit of QT dispersion was probably the reason that it was not considered by Srinivasan et al, [1] albeit showing that QT dispersion also did not correlate with intracardiac measurements might have been beneficial for those who still try to rekindle it.

Electrocardiography is certainly a very valuable tool and we believe that important information in ECG signals remains to be deciphered including assessment of repolarization heterogeneity in terms of both spatial and temporal dispersion. Nevertheless, it seems rather unlikely that obtaining such information could be based only on simple measurements made with the naked eye and ruler. Albeit

surely of crucial importance, repolarization heterogeneity and its clinically important abnormalities are too subtle to be visible and quantifiable in standard ECG printouts or clinical displays that have changed little since the inception of electrocardiography. Although standard ECG printouts might be attractive from a routine clinical standpoint, it is much more likely that the route towards the important goal of assessing repolarization heterogeneity is in high-precision digital ECGs and advanced analyses of their multi-lead representations. Obtaining such recordings during controlled provocative conditions might also allow examination of responses of myocardial repolarization to autonomic and other cardiac regulatory processes. In addition to static heart rate dependency, the dynamic dependency, *i.e.,* how quickly an equilibrium is reached after different changes, needs also to be understood in detail. Only when comprehending all these subtle details of electrocardiography shall we be ready to propose physiologically valid and meaningfully focused quantification of localized repolarization abnormalities.

Thus, Tpe interval as a measure of repolarization heterogeneity appears at the least seriously wounded. Not only its appropriate repair but also evaluation of other seemingly simple techniques including the observation by Srinivasan et al [1] will require careful thought.

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