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The search for non-invasive markers of cardiac diseases comes back to the 12-lead electrocardiogram

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Identification of patients at high risk of acute myocardial ischemia and/or malignant ventricular arrhythmias is a major but still unsolved research issue and an important unmet clinical need. During the past 30 years, several groups have researched different clinically-defined populations and developed and tested methodologies to identify patients at risk, often with contrasting and unsatisfactory results [1]. Generally, whereas negative tests were consistently associated with a low disease incidence and/or favorable outcomes, positive tests often failed to identify the majority of patients at risk. Consequently, despite the variety of available techniques, clinical risk stratification remains mainly based on individual judgement and guideline recommendations. Risk prediction methodologies, including the most validated technique of heart rate variability [2], remain mainly confined to research settings.

As supported theoretically and by a large body of experimental evidence, ventricular repolarization abnormalities are a disease marker and a sign of greater susceptibility to ventricular arrhythmias [3]. ST segment and/or T wave morphology changes on surface electrocardiogram reflect repolarization abnormalities secondary to either myocardial ischemia or abnormal ion channel traffic. They generate electrophysiologic substrate potentially related to the development of malignant ventricular arrhythmias. This explains why during the past 30 years, several indexes of repolarization duration and duration variability have been proposed as markers of cardiac risk [4]. However, repolarization duration is not only affected by ischemia, inflammation, myocardial fibrosis, or altered ion channels. It also varies in normal hearts between left and right ventricles, base and apex and epicardial and endocardial layers. This makes interval-based clinical electrocardiographic (ECG) measurements complex and often inaccurate besides being poorly supported by tissue experiments, e.g. those with myocardial wedge preparations. The limits and shortcoming of a number of ECG interval-based risk markers, such as the so-called QT dispersion or T apex variability are now well understood [5,6].

To overcome these limitations, Nearing and Verrier [7] developed a methodology called the T wave heterogeneity that analyses the entire T wave waveform of adjoining leads and, using second central moment analysis, provides quantification of the interlead morphology spread.

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Since T wave heterogeneity is measured over the entire JT waveform with a low amplitude in the T wave tail, it does not depend on any specific T-wave offset as do interval-based indices of repolarization dispersion. The spatial dissimilarities across precordial leads can be computed in relation to R, J and T wave of a digital 12-lead ECG, providing ventricular heterogeneity indices.

In a large Finnish population [8], T wave heterogeneity was an independent predictor of sudden cardiac death and the methodology was considered suitable for the screening of sudden cardiac death risk in the general population.

In the present issue of the journal, the group of technology inventors report an interesting albeit rather small study in which they investigated whether interlead T-wave heterogeneity during exercise tolerance testing or pharmacologic stress testing could improve the detection of significant coronary artery stenoses in patients with chronic coronary artery disease (CAD) [9]. The authors observed that T wave heterogeneity levels at rest were similar for cases and controls. However, during exercise and dipyridamole stress testing, T wave heterogeneity significantly increased in CAD cases but not in controls, with a significant association with the angiographic findings of critical coronary artery stenosis. The authors propose that the ability of this methodology to detect repolarization inhomogeneity secondary to opening of ATP-sensitive K+ channels is a possible mechanism for their findings.

These results are of pathophysiologic and clinical interest but also generate new questions on the significance and specificity of this parameter in predicting arrhythmic mortality and/or myocardial ischemia. In the previous studies, T wave heterogeneity was significantly associated with sudden cardiac death in different clinical settings including a large epidemiological health survey [8]. Unfortunately, in the Finish study [8], the incidence of myocardial infarction during 7-year follow-up was not reported. This prevents addressing the question of whether myocardial ischemia was the most likely mechanism responsible for arrhythmic deaths in this population. In the present study [9], that investigated a limited number of patients with chronic CAD, no follow-up outcomes are reported thus excluding the possibility of combining T wave heterogeneity with clinical arrhythmia incidence. The finding that an increased ventricular repolarization heterogeneity was superior to either exercise or pharmacological stress test in predicting significant coronary stenosis is surely of interest but deserves further confirmation in larger populations. Nevertheless, the technique is relatively simple and well suited to be applied to digital ECG recordings with adequate sampling rates. Since such recordings are presently widely used, the technique overcomes most of conceptual and technical limitations known from studies of methodologies based on ECG interval measurements.

It also remains to be determined in which way this technique might be made available for general use so that confirmatory studies might be conducted by different teams without the problems of software implementation nuances.

Finally, on a general note independent of the discussed studies [8,9], we also believe that every new proposal of T wave morphology characterization would benefit from a comparison with previously reported technologies that have been found to predict cardiac risk in multiple independent studies. The indices of spatial 3-dimensional QRS-T angle and of the so-called T wave spatial residua come to mind [5,10]. Such comparisons are well known from studies of other risk indicators, e.g. valid studies of new heart rate variability indices are expected to make comparisons to SDNN, spectral indices, or to deceleration capacity. Gradual improvements of the predictive power of ECG processing technologies are difficult to understand or even note if the question is left open of whether a newly proposed index brings any advances to indices and characteristics that have been successfully researched previously. For instance, it would be interesting to compare the T wave heterogeneity results with those obtained by the technology of T wave morphology dispersion [10] that was proposed some two decades ago (Fig. 1). The principles of T wave morphology dispersion are similar those of T wave heterogeneity since it also measures the full morphological differences between different ECG leads.

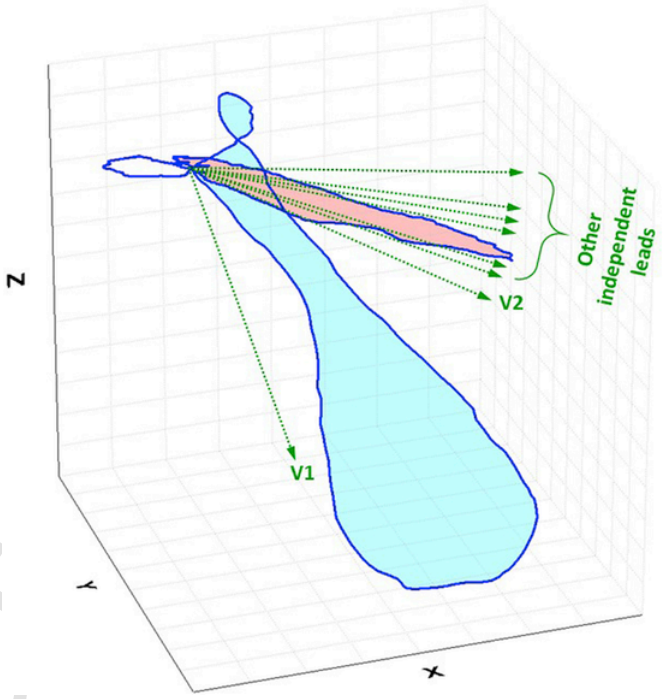

Fig. 1. Schematic representation of the technique of T wave morphology dispersion. Based on singular value decomposition applied to 8 algebraically independent leads of the 12-lead ECG, optimized vectorcardiographic loop is created in which the loops of the P wave (open loop), QRS complex (cyan loop) and T wave (pink loop) can be distinguished. For each of the independent ECG lead, a 3-dimensional projection vector is found along which the T wave loop is seen in the given lead. The T wave morphology dispersion subsequently measures the spread of the angles between the projection vectors while omitting lead V1 which is positioned remotely from the ventricles. The technology was shown to offer clinical value, e.g. providing very strong separation between hypertrophic cardiomyopathy ECGs and normal controls [10]. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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