T-wave alternans: predicting the unpredictable?

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This editorial refers to ‘T-wave alternans predicts mortality in a population undergoing a clinically indicated exercise test’ by T. Nieminen et al., on page 2332

Sudden cardiac death (SCD) due to ventricular arrhythmias has a high morbidity and mortality. It is no wonder that cardiologists, rather than patching up survivors, are dedicated to finding predictors of cardiac electrical instability to prevent SCD. The implantable cardiac defibrillator (ICD) has evolved as the ultimate strategy for sudden arrhythmic death. In secondary prevention, individuals are recognized by an aborted arrhythmic event. By stratifying according to left ventricular ejection fraction (LVEF) below 35%, SCD may also be prevented by an ICD in individuals without any prior arrhythmic event.¹ However, the relative SCD risk based on LVEF alone is lower, and additional stratifiers are needed that can more accurately identify who is at risk, and so save health care resources.

Microvolt T-wave alternans

Over the last 10 years, a new diagnostic strategy has emerged based on defining the electrical stability of the heart. Regional heterogeneity in refactoriness may provide a mechanism for re-entrant arrhythmias. Under specific conditions, beat-to-beat oscillations in repolarization setting the stage for ventricular arrhythmias can be observed in the ECG microvolt T-wave alternans (TWA).² This was translated into a diagnostic test where spectral TWA was determined during some minutes at a heart rate of up to 110 b.p.m. At higher heart rates, TWA is less specific and may also be observed in normal hearts. The test is either normal or abnormal, depending on a pre-specified amount of TWA. In patients with a history of myocardial infarction (MI), a positive test was associated with a high risk of cardiac events independent of LVEF, whereas a negative test had a very good prognosis.³⁻⁵ Similar results were obtained in patients with non-ischaemic cardiomyopathy.⁶ Also, TWA had a higher sensitivity and specificity than signal-averaged ECG or electrophysiological testing. Specifically, in patients with a MADIT-2 and SCHeFT profile with a primary prevention ICD indication, a negative TWA test was associated with only a 1% annual risk for non-fatal ventricular arrhythmias, and even lower mortality. This may provide a basis for more accurate allocation of ICD treatment.⁷

T-wave alternans in a random cardiac population

Nieminen et al.⁸ present the results of their study on the value of TWA in a large cohort of >1000 low risk patients referred for exercise testing. The authors found that the presence of TWA >65 μV at baseline, during a mean follow-up of 44 months was associated with a significant increase in relative risk of 7.4 for SCD, 6.0 for cardiovascular mortality, and 3.3 for total mortality. The authors suggest that the TWA test could therefore be an important diagnostic tool to identify patients that need more thorough cardiovascular screening and treatment. This is an appealing concept to cardiologists around the world, because it is easily applicable in daily routine. The specificity and negative predictive value of the test were very high (92 and >95%) and in line with those found in previous studies,³⁻⁵ providing additional security that a patient has a low absolute risk (<1.0%) and can be sent home.

There are several issues that may raise questions about the applicability of TWA testing in a general population. First of all, the phenomenon called TWA and its measurement from the ECG are rather complex. The microvolt changes can only be detected and quantified by a special machine. The presence or absence of TWA and its cut-off point are therefore a given fact, not open to interpretation by the cardiologist. In the present study, TWA was determined as an absolute value with a new time domain-modified moving average method. The authors tested multiple cut-off points and found that at 65 μV the best statistical values were obtained. However, since there is no gold standard, additional studies are needed in other specific populations to determine which amount of TWA provides the best diagnostic and prognostic information. The sensitivity and positive predictive value of TWA were fairly low (<35 and <15%), requiring additional diagnostic tests to establish cardiovascular risk. In the present study, the results and predictive value of exercise testing were not provided, thus the additional value of the TWA test remains unknown.

Another important issue concerns the mechanism of TWA in this low risk, general population. TWA may be observed...
in patients with a history of MI as a strong predictor for cardiac death, even if LV function is preserved.\textsuperscript{3,4} In the study by Nieminen et al., about 90% had a normal LVEF on echocardiography, although data were only obtained in half of the patients. Up to 30% had a history of coronary heart disease including MI, and 40–50% had important comorbidity such as hypertension and diabetes mellitus, but these did not surface as significant risk factors. One wonders what the basis for the positive TWA test might be then in a patient without any apparent cardiac abnormality. There is no information on how these patients were treated during follow-up on the basis of either exercise test or TWA test, and whether this affected the natural outcome. Moreover, how should one treat a person with a positive TWA test in the absence of an identifiable substrate? The mortality end-points of the study were taken from public records, in the absence of an identifiable substrate? The mortality end-points of the study were taken from public records, which may raise concern over definitions and reliability. How the TWA test related to specific causes of death in this population, such as acute coronary syndrome, acute heart failure, or ventricular arrhythmias, remains unclear.

Predicting cardiac events in a general population

In spite of the questions that may be raised by the study of Nieminen et al., their findings can become of great importance for cardiologists. We are in dire need of non-invasive tests that can better identify the potentially sick to allocate health care resources more efficiently. TWA seems to have proven its value for risk stratification in primary prevention ICD trials in patients with a low EF, primarily by identifying the patients at low risk for arrhythmias. However, it has not yet been embraced by the cardiological community and therefore has not been incorporated into clinical guidelines. Nieminen et al. now invite us to take the TWA test one step further to use it in a random population referred for exercise test. Their data support and match the results obtained by Ikeda et al.\textsuperscript{4} in patients after MI with preserved LV function. Promising as that may be, the test may not be quite ready for prime time yet. More research is needed to determine the underlying mechanism and optimal TWA measurement technique. The findings of Nieminen et al. will have to be validated and held against classic cardiological diagnostics in specific populations. The yield of TWA testing will largely depend on characteristics of the tested population. A large prospective community trial would be another alternative to determine the predictive value of TWA in a truly general population without a history of cardiovascular events. This may bring us closer to our goal of trying to prevent potentially fatal cardiac events. However, we have to accept that there will always be a limit in our ability to predict the unpredictable in the general population.

Conflict of interest: none declared.

References