Editorial: Determining Risk of Sudden Death-Is it all in the T wave?

PD Lambiase

Word Count : 1582

Addresses for Correspondence:

Professor Pier Lambiase
UCL Institute of Cardiovascular Science & Barts Heart Centre
Room 3.20, Rayne Institute
5 University Street
London, WC1E 6JF
United Kingdom
Email: *p.lambiase@ucl.ac.uk*
Word count: Text: 967 Refs: 370
Conflicts of Interest: None
PDL is supported by UCL/UCLH Biomedicine NIHR

The prediction of sudden cardiac death remains the "holy grail" of cardiology to enable optimal targeting of preventative therapies in at risk groups. This challenge is made greater by the fact that the numerical majority of patients at risk of sudden death due to ventricular tachycardia/fibrillation (VT/VF) have ejection fractions greater than the 35% cut-off employed in guidelines for internal cardiac defibrillators (ICDs) despite this being the crudest but most effective differentiator as highlighted by Myerberg (1). Although ICDs have proven to be highly efficacious, less than 1 in 10 of the implanted devices are actually needed. Hence, a large number of patients are unnecessarily exposed to their complications such as infection and inappropriate shocks, and needlessly contribute to the escalating cost, estimated as in excess of 2 billion euros per annum in Europe alone. Mechanistically, electrical instability of conduction and repolarisation underlies the development of VT and its degeneration into VF due to wavebreak of the activation wavefronts. Leaving aside the impact of plaque rupture causing acute coronary occlusion and major ischemic insult to trigger VF, we are left with the concept of a myocardial substrate susceptible to re-entry and subsequent VF.

Conceptually, the electrical behaviour of the heart can be viewed as an oscillator or pendulum which must be constrained within a tight dynamic envelope (Figure 1-*Phase portrait of the ECG*). Excessive changes in conduction and repolarisation disturb this equilibrium setting up the conditions for ventricular arrhythmias. Two schools of thought currently evaluate the substrate depending upon the perspective of the investigators' technology focusing on fibrosis with imaging using the latest CMR techniques or dissecting the fundamental electrical behaviour of the heart. The earliest insight into the role of electrical instability comes from Lewis' observation of T wave alternans degenerating into VF.

Initial studies of predicting risk from the ECG focused on simple parameters of conduction and repolarisation-QRS duration, QT duration but increasingly the dynamics of conduction and repolarisation are being recognised. With the advances in computer processing power, the capacity to analyse large multi-lead datasets mean that these dynamic changes can be processed at scale. Several dynamic tests have proven value as risk predictors of sudden cardiac death (Figure 1) such as baroreceptor sensitivity, heart rate turbulence, deceleration capacity, microvolt T-wave alternans, and tests of RR interval dynamicity (Figure 1)(2-4). The mechanistic link

between each of these risk predictors and arrhythmia is highly complex but a main focus centres in separating the balance between sympathetic and parasympathetic activityand their effects on cardiac ion channel currents and pumps plus their time constants that determine beat to beat cellular electrophysiological changes.

One novel parameter that has recently been shown to be predictive of sudden arrhythmic death is Periodic Repolarisation Dynamics (PRD) of the T wave: A fluctuating pattern of ventricular repolarization at a frequency <0.1 Hz, when enhanced, is highly predictive of ventricular arrhythmia and sudden cardiac death in cardiac patients (5). Previous work showed the ECG T-wave vector angle was first shown to exhibit oscillations in the low-frequency (LF) spectral range (<0.1 Hz, generally one cycle in a little over 10 s). These oscillations were independent of respiration and heart rate variability and were considered to represent oscillations of ventricular repolarisation.[2] Periodic repolarisation dynamics was shown to be strongly predictive of total mortality and cardiac mortality in post-MI patients[2] and of arrhythmia risk in a retrospective analysis of data from the MADIT-2 study (6). This parameter reflects the importance of dynamic repolarisation behaviour and provides a foundation to justify more detailed analysis of these dynamic changes.

In the journal, Hnatkova et al use a different parameter in the ECG to explore the role of dynamic changes in QRS and T wave vectors by assessing their departure from a 3 dimensional plane on a beat to beat basis with the assumption that these departures indicate instabilities in conduction and repolarisation to promote VT and VF. They studied 1948 primary prevention ICD patients (61.5% IHD) and assessed the predictive power of non-planarity twist of the 3-dimensional loops out of a single plane for cardiac mortality and ICD therapies taking into account age, heart rate, LV ejection fraction, QRS duration, spatial QRS-T angle, QTc interval, and T-peak to T-end interval to assess if these 2 parameters independently predicted all-cause mortality and appropriate ICD shocks. QRS non-planarity predicted all-cause mortality despite ICD prevention but not ICD shocks. However, T wave non-planarity independently predicted ICD shocks on multivariable analysis (HR 1.364 (1.180-1.576)) but it was not associated with all cause mortality indicating that this marker could be a useful biomarker to identify patients

most likely to benefit from ICD therapy (21.7% of patients who received a shock subsequently died during the first 5 years of follow-up).

The mechanisms driving changes in T wave amplitude and possibly planar angle are thought to be related to the effect of sympathetic tone on dynamic changes in action potential duration (APD). ECG T-wave vector oscillation is enhanced during increased sympathetic activity and reduced following beta-adrenergic blockade and measurable in ventricular monophasic APD in animal studies and humans. The underlying mechanisms are complex and have been reviewed recently (7). In summary, studies in myocytes and *in silico* modelling demonstrate a biphasic response of ventricular APD- in the immediate few beats following abrupt beta-adrenergic stimulation with isoprenaline transiently prolonging APD for a few beats and then subsequent progressive shortening occurring. This biphasic response was the result of a mismatch between the fast phosphorylation/dephosphorylation time constants of the L-type calcium current (I_{CaL}) and the slower time constants of slow component of the delayed rectifier current (I_{Ks}). The fast time constant of inward I_{CaL} current results in initial APD lengthening. After a few beats, outward I_{Ks} catches up, counterbalances I_{CaL}, and induces APD shortening. Modelling studies show that these effects modulate intracellular calcium cycling leading to early afterdepolarisations and triggered beats which can be coupled with similar oscillations seen in myocardial stretch activating ion channel opening to promote dispersion of repolarisation in turn initiating VT/VF.

There are a few limitations in Hnatkova et al's very informative study including those highlighted by the authors. One significant issue is that there are competing risks to promote mortality in these primary prevention patients including renal function, severity of heart failure, degree of LV impairment, systolic blood pressure, diabetes , BMI as highlighted in the MADIT-ICD benefit score aswell as myocardial viability and scar burden (8). These parameters need to be fully incorporated into any risk prediction model that can provide a clear picture of overall competing risks. Until these additional parameters are accounted for, utilising isolated ECG biomarkers is going to be limited in scope. Prospective studies need to be much more comprehensive in ICD cohorts. This will become more likely as electronic health record and digital data accumulate in more comprehensive prospective registries. Such approaches also need to be expanded beyond

traditional ICD recipient populations to include at risk groups with intermediate ejection fractions of 35-45% where there remains a significant challenge of much larger numbers of subjects at risk but dramatically lower actual percentage risks of cardiac arrest per individual.

The expansion of wearable technologies to detect dynamic ECG changes in this context aswell as ventricular ectopic and non-sustained VT burdens may mean that population level risk profiling will become more feasible. This will then be powered by machine learning and artificial intelligence approaches to create fully integrated multimodality risk models finally enabling truly personalised approaches.

References

1. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. Circulation 2012;125:1043–52.

2. Bauer A, Malik M, Schmidt G, Barthel P, Bonnemeier H, Cygankiewicz I et al. Heart rate turbulence: standards of measurement, physiological interpretation, and clinical use: international Society for Holter and Noninvasive Electrophysiology Consensus. J Am Coll Cardiol 2008;52:1353–65.

3. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Mäkikallio T, Ulm K et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet (London, England) 2006;367:1674–81.

4. Verrier RL, Klingenheben T, Malik M, El-Sherif N, Exner DV, Hohnloser SH et al. Microvolt T-wave alternans: physiological basis, methods of measurement, and clinical utilityconsensus guideline by international society for Holter and noninvasive Electrocardiology. J Am Coll Cardiol 2011;58:1309–24.

5. Bauer A, Klemm M, Rizas KD, Hamm W, Stülpnagel L V, Dommasch M et al. Prediction of mortality benefit based on periodic repolarisation dynamics in patients undergoing prophylactic implantation of a defibrillator: a prospective, controlled, multicentre cohort study. Lancet (London, England) 2019;394:1344–51.

6. Rizas KD, McNitt S, Hamm W, Massberg S, Kääb S, Zareba W et al. Prediction of sudden and non-sudden cardiac death in post-infarction patients with reduced left ventricular ejection fraction by periodic repolarization dynamics: MADIT-II substudy. Eur Heart J 2017;38:2110–8.

7. Taggart P, Pueyo E, Duijvenboden SV, Porter B, Bishop M, Sampedro-Puente DA, Orini M, Hanson B, Rinaldi CA, Gill JS, Lambiase P Emerging evidence for a mechanistic link between low-frequency oscillation of ventricular repolarization measured from the

electrocardiogram T-wave vector and arrhythmia. Europace. 2021 Sep 8;23(9):1350-1358.

8. Younis A, Goldberger JJ, Kutyifa V et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *Eur Heart J.* 2021;42:1676–84.

Figure Legend

Examples of dynamic markers of electrical instability.

Phase portrait plots the slope of QRS & T waves (dV/dtmax) of each heart beat against the corresponding voltage amplitude giving a dynamic picture of beat to beat changes in a 2 dimensional plot illustrating the oscillatory nature of the ECG signal (Annals of biomedical engineering 10.1114/1.1523030).

T wave alternans can be macro or microvolt in amplitude measuring beat-beat T wave amplitude changes (4).

V-CoS utilises multilead surface ECG recoding to measure beat to beat changes in QRS activation time as a measure of conduction stability-the greater the number percentage of leads with no significant (10ms) change, the higher the score and greater stability of conduction at high heart rates (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7868885).

Heart rate turbulence -Single sequences of RR intervals (thin lines) are aligned to the ventricular ectopic and averaged (bold line). Turbulence Onset (TO) quantifies the initial shortening of RR intervals, Turbulence Slope (TS) quantifies the subsequent prolongation of RR intervals (2).

Restitution Instability Index measures regional ECG changes in QT interval plotted against diastolic interval as a measure of dispersion in dynamic repolarisation changes across the heart. (https://heart.bmj.com/content/100/23/1878)

QRS and T wave loops measure the 3 dimensional change in QRS and T wave over time. Projections of QRS and T wave loops on frontal (F), horizontal (H) and right sagittal (S) plane and reconstruction of spatial vectorcardiogram. The spatial QRS-TA is an angular difference between the maximum QRS vector and maximum T vector.

Heart rate deceleration capacity measures the beat to beat rate of slowing in RR interval from prolonged Holter recording as part of Heart Rate Variability analyses. First, the heartbeat intervals longer than the preceding interval are defined as anchors. Segments of the same size around the anchors are selected and aligned at the anchors. Then, the

signals X within the aligned segments are averaged. DC is quantified using the equation $DC=1/4\ (X_0+X_1-X_{-1}-X_{-2})$. Where X_0 and X_1 are the averages of the anchor points and of the following R-R intervals, while X_{-1} and X_{-2} are the averages of the 2 R-R intervals preceding the anchor points (3).