



# Emerging evidence for a mechanistic link between low-frequency oscillation of ventricular repolarization measured from the electrocardiogram T-wave vector and arrhythmia

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**Abstract** Strong recent clinical evidence links the presence of prominent oscillations of ventricular repolarization in the low-frequency range (0.04–0.15 Hz) to the incidence of ventricular arrhythmia and sudden death in post-MI patients and patients with ischaemic and non-ischaemic cardiomyopathy. It has been proposed that these oscillations reflect oscillations of ventricular action potential duration at the sympathetic nerve frequency. Here we review emerging evidence to support that contention and provide insight into possible underlying mechanisms for this association.

**Keywords** Repolarization • T wave • Low-frequency oscillations • Electrophysiology • Beta-adrenergic stimulation • Action potential duration • Mechano-electric feedback • Arrhythmia

## Introduction

Oscillations of ventricular repolarization measured from the electrocardiogram (ECG) T-wave vector have recently been shown to be one of the strongest predictors of arrhythmia and sudden death in cardiac patients in a large prospective multicentre study. The results provide clear evidence that 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.<sup>1</sup> This trial builds on previous work in which 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 referred to as periodic repolarization dynamics (PRD) were independent of respiration and heart rate

variability and were considered to represent oscillations of ventricular repolarization.<sup>2</sup> Periodic repolarization dynamics was shown to be strongly predictive of total mortality and cardiac mortality in post-MI patients<sup>2</sup> and of arrhythmia risk in a retrospective analysis of data from the MADIT-2 study.<sup>3</sup> A subsequent large multicentre prospective trial involving 44 centres in 15 EU countries conducted between 2014 and 2019 showed that PRD strongly predicted shocks in implantable cardioverter-defibrillator (ICD) patients and predicted mortality in conservatively treated patients.<sup>4</sup>

Despite the obvious importance of these findings, the link between oscillation of the ECG T-wave vector and ventricular arrhythmia is at present unclear. Understanding the electrophysiological basis for this association is important in order to refine the PRD and facilitate its use as a potential clinical tool for risk stratification. Furthermore, the

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link between oscillatory behaviour of repolarization and ventricular arrhythmia may provide valuable insight into arrhythmia mechanisms. In this regard, several key questions arise. What does the ECG T-wave vector angle represent? It has been proposed that these oscillations of T-wave dynamics represent the effect of phasic changes in sympathetic activation on ventricular repolarization possibly associated with changes in action potential duration (APD) related to different layers of the myocardium. But does APD exhibit oscillations? If so what drives the oscillatory behaviour? What are the electrophysiological mechanisms linking APD oscillation and ventricular arrhythmia? Do LF oscillations of ventricular repolarization interact with proarrhythmic mechanisms such as beat-to-beat variability of repolarization and T-wave alternans? Here we review emerging evidence for a mechanistic basis to help answer these questions.

## The electrocardiogram T-wave vector

The ECG T-wave vector reflects the spatiotemporal orientation of the repolarization wavefront with respect to the body surface. Oscillations of the T-wave vector referred to as PRD occur in the LF range ( $<0.1$  Hz, Figure 1). In Figure 2, PRD recordings are shown from a post-MI patient who survived a 5-year period (left) and a patient who died 8 months after an MI (right). Typical PRD oscillations are seen which are of much greater amplitude in the patient who died compared to the survivor. It was proposed that these T-wave dynamics represent oscillations of repolarization which in turn reflect oscillations of ventricular APD.<sup>2,4</sup>

## Ventricular action potential duration may exhibit low-frequency oscillations

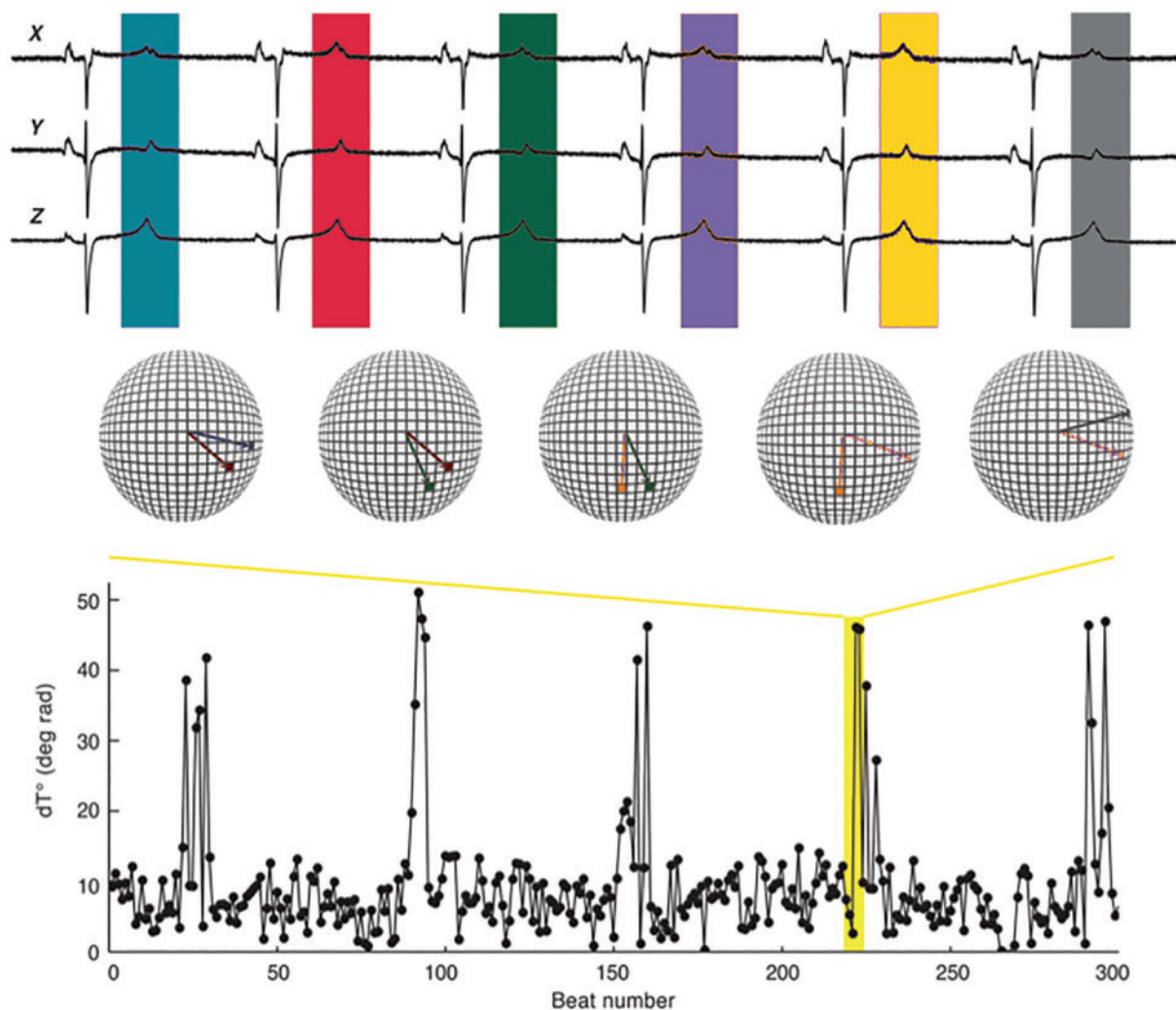
Oscillatory behaviour is a ubiquitous property throughout many biological systems. However, it is only relatively recently that ventricular APD has been shown to exhibit oscillatory behaviour.<sup>5,6</sup> This was first observed in patients undergoing routine electrophysiological procedures for supraventricular arrhythmias using left and right ventricular endocardial catheter electrodes. Activation recovery intervals (ARIs) derived from unipolar electrograms as a conventional surrogate for APD<sup>7–9</sup> showed oscillations at the LF spectral range in the region 0.04–0.15 Hz<sup>5,6</sup> (Figure 3). Oscillations typically occurred over a fairly narrow range within the LF spectrum (Figure 4). Low-frequency oscillations were subsequently observed in a number of other studies including recordings from the left and right ventricular endocardium,<sup>10</sup> studies recording ARIs from the left ventricular epicardium in ambulatory patients with an implanted cardioverter-defibrillator<sup>11,12</sup> and from monophasic action potential recordings in an established animal model.<sup>13</sup>

## Low-frequency oscillations of ventricular action potential duration enhanced by sympathetic provocation

The question arises as to what drives these rhythmic fluctuations of APD. It was suggested that LF oscillations of the ECG T-wave vector could be related to the characteristic oscillations of sympathetic nerve activity at this frequency.<sup>14</sup> This proposal was supported by clinical studies showing that the ECG T-wave vector oscillation was enhanced during increased sympathetic activity and reduced following beta-adrenergic blockade.<sup>2</sup> Recordings of ventricular APD (measured as ARIs) in patients showed that LF oscillations of APD were also increased following sympathetic provocation<sup>1</sup> and decreased following beta-adrenergic blockade.<sup>10</sup> In the study by Porter et al. sympathetic provocation was induced by the Valsalva manoeuvre during steady-state pacing in patients with an ICD. Recordings of left ventricular epicardial APD (ARI) showed an increase in LF power.<sup>1</sup> In another study in patients undergoing routine electrophysiological procedures for supraventricular arrhythmia, unipolar electrograms were obtained from 10 right and 10 left ventricular endocardial sites during steady-state pacing. Acute beta-adrenergic blockade reduced LF oscillation of ARIs.<sup>10</sup> Collectively, these studies support the contention that LF oscillations of the ECG T-wave vector reflect oscillations of ventricular APD and that the enhancement of the T-wave vector LF oscillations in response to enhanced sympathetic activity reflects the effect of phasic increases in sympathetic activity on ventricular APD.

## Electrophysiological mechanisms underlying low-frequency oscillations of ventricular action potential duration

What are the cellular mechanisms whereby phasic sympathetic activation generates an LF oscillatory pattern of APD? Beta-adrenergic stimulation initiates a signalling cascade in cardiac myocytes through G protein activation of adenylyl cyclase which enhances cyclic AMP production and activation of protein kinase A. Protein kinase A phosphorylates multiple targets including regulating the L-type calcium current ( $I_{CaL}$ ) and the slowly activating delayed rectifier current ( $I_{Ks}$ ).<sup>15</sup> Most studies examining the effect of beta-adrenergic stimulation on ventricular APD have reported a shortening.<sup>16</sup> However, these observations have traditionally been made under steady state or near steady-state conditions. Studies in myocytes and *in silico* modelling have recently demonstrated a biphasic response of ventricular APD in the immediate few beats following abrupt beta-adrenergic stimulation.<sup>17,18</sup> The application of Isoprenaline transiently prolonged APD for a few beats and then subsequently progressively shortened APD. 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

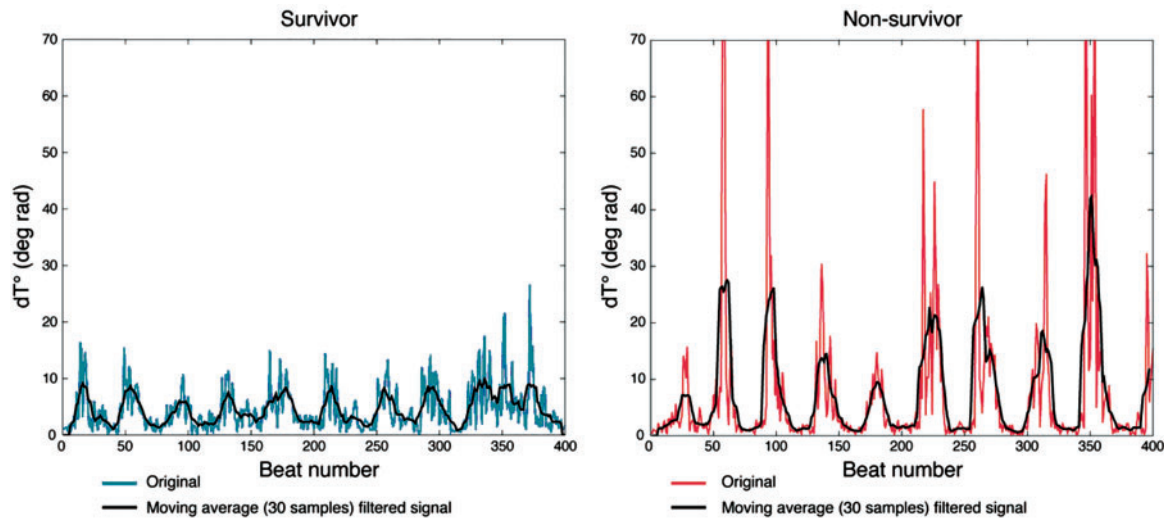


**Figure 1** Recording of ECG T-wave vector measures of ventricular repolarization (PRD). Upper panel: ECGs are recorded using the X, Y, Z configuration. (Middle) T waves are converted into polar vector angles. Two successive T-wave vectors are shown projected onto virtual spheres. The angle between successive vectors is taken as a measure of repolarization stability. Lower panel: Plot of vector angle over time showing pronounced regular peaks with a frequency of about 0.1 Hz, i.e. 1 per 10 s. From Rizas *et al.*<sup>2</sup> with permission.

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<sup>17,18</sup> (Figure 5). Pueyo *et al.*<sup>19</sup> used computational modelling to investigate the cellular mechanisms underlying LF oscillations of APD in response to phasic beta-adrenergic stimulation in the LF range. They found that  $I_{CaL}/I_{Ks}$  mismatch following beta-adrenergic stimulation as described above could play a major role. For their computations, they simulated an oscillatory pattern of beta-adrenergic stimulation by consecutive 10 s on/off sequences of isoprenaline. A biphasic APD response was observed for each isoprenaline application, with initial transient APD prolongation accompanied by dominant  $I_{CaL}$  followed by APD shortening accompanied by dominant  $I_{Ks}$ .<sup>19</sup> Similarly, isoprenaline washout led to transient APD shortening followed by APD prolongation (Figure 6A–C).

## A contributory role of mechano-electric feedback to the generation of low-frequency oscillations of ventricular action potential duration

Beta-adrenergic stimulation increases cardiac contractile function by excitation contraction coupling<sup>15</sup> with an increase in the force of contraction and muscle fibre excursion. These alterations in stress/strain patterns exert a feedback effect on the cardiac electrophysiology by a process known as mechano-electric feedback (MEF).<sup>20–22</sup> Mechano-electric feedback is a complex process involving stretch-activated channels and calcium cycling mechanisms. Experimental work has shown that sympathetic provocation amplifies the effect of



**Figure 2** Low-frequency oscillations of the ECG T-wave vector and ventricular APD. Low-frequency ECG T-wave oscillations in a post-MI survivor (left) and a non-survivor (right) showing higher amplitude oscillations in the non-survivor. From Rizas et al.<sup>2</sup> with permission.

alterations in ventricular loading on the electrophysiology.<sup>23</sup> Studies in patients during sympathetic provocation showed an increase in left ventricular contractility, measured as  $dp/dt_{max}$ , the first derivative of systolic pressure,<sup>24</sup> and showed a correlation between the increase in LF power of APD and the LF power of  $dp/dt_{max}$ . Pueyo and colleagues incorporated MEF in their modelling of mechanisms underlying LF APD oscillations, simulated as phasic LF changes in sarcomere length. Mechano-electric feedback exerted a synergistic effect with the beta-adrenergic-induced  $I_{CaL}/I_{Ks}$  mismatch mechanism described above in the generation of LF oscillations of APD following enhanced sympathetic activity<sup>19</sup> (Figure 6D).

Thus the foregoing provides a possible framework whereby phasic LF sympathetic stimulation may induce an oscillatory pattern of ventricular APD at the same frequency through cellular mechanisms which include a mismatch between the time constants of the L-type calcium current ( $I_{CaL}$ ) and the slow component of the delayed rectifier potassium current ( $I_{Ks}$ ) together with MEF.

## Oscillations of ventricular action potential duration and arrhythmogenesis: importance of disease conditions

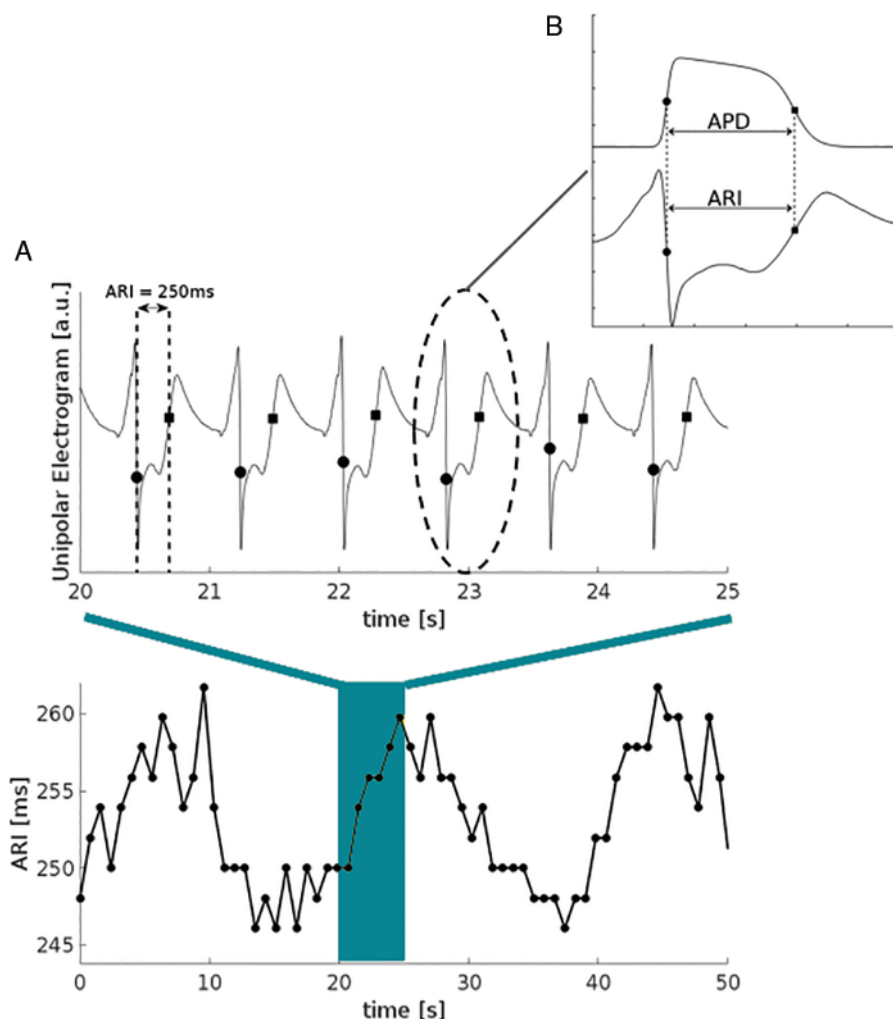
The autonomic nervous system, particularly enhanced sympathetic activity, has long been known to play an important role in arrhythmogenesis.<sup>25,26</sup> The majority of studies investigating mechanisms have mainly Focused on steady-state conditions and until recently relatively little attention had been given to transient or oscillatory dynamics. As described above Liu et al.<sup>17</sup> showed in genetically engineered rabbit cardiac myocytes that the mismatch between the faster phosphorylation/dephosphorylation kinetics of  $I_{CaL}$  and the slower  $I_{Ks}$  kinetics following isoprenaline could result in a window after about 5–

10 beats when  $I_{CaL}$  could be reactivated and generate EADs and triggered activity. Pueyo et al simulated consecutive 10 or 20 s cycles of beta-adrenergic stimulation in the presence of disease conditions by incorporating calcium overload and reduced repolarization reserve, modelled as reduced rapid delayed rectifier potassium current ( $I_{Kr}$ ) and reduced slow component of the delayed rectifier potassium current ( $I_{Ks}$ ). They found that the LF power of APD oscillations was substantially increased and early afterdepolarizations and runs of triggered activity were observed<sup>19</sup> (Figure 7). In an established A-V block dog model, ventricular APD was measured using monophasic action potentials.<sup>13</sup> Low-frequency oscillations were present under control conditions in sinus rhythm and the LF power increased following acute A-V block, and increased further in chronic A-V block conditions (2 weeks later) attributed to the effect of ventricular remodelling. Inducibility of Torsades de Pointes with dofetilide ( $I_{Kr}$  blocker) showed that LF power of APD was larger in inducible chronic A-V block dogs.<sup>13</sup> Thus both modelling and experimental work provide a possible mechanistic basis for a role of oscillatory repolarization dynamics in generating afterdepolarization and highlight the importance of the presence of disease/remodelling in facilitating arrhythmogenesis.

## Interaction between low-frequency oscillation of ventricular action potential duration and proarrhythmic beat-to-beat variability of repolarization

Beat-to-beat variability of ventricular repolarization (BVR) has been shown to be proarrhythmic in a wide range of experimental models and humans particularly when enhanced in response to beta-



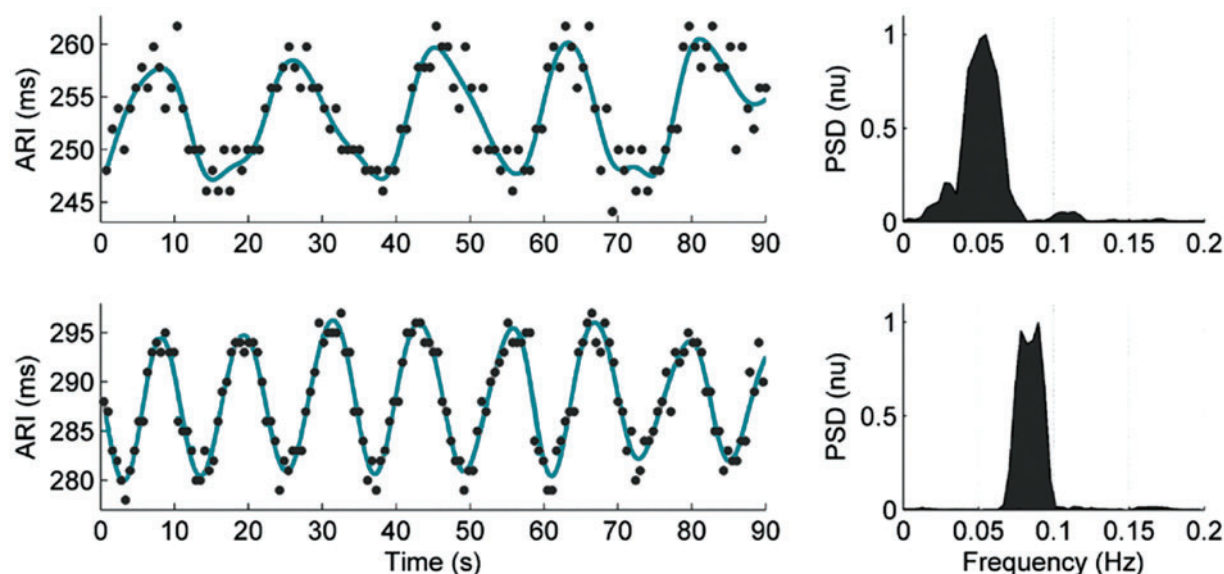


**Figure 3** Recording of activation-recovery intervals (APD). (A) Upper panel: Unipolar electrogram recorded from the LV lead of an ICD device in a patient. Dots represent  $dv/dt$  min of the QRS and  $dv/dt$  max of the T wave. The interval between them defines the ARI widely used as a surrogate for APD. Lower panel: Beat-by-beat plot of ARI showing oscillatory pattern at a frequency of about 15–20 s, 0.05 Hz within the LF range. (B) Activation recovery interval provides an established measure of APD.

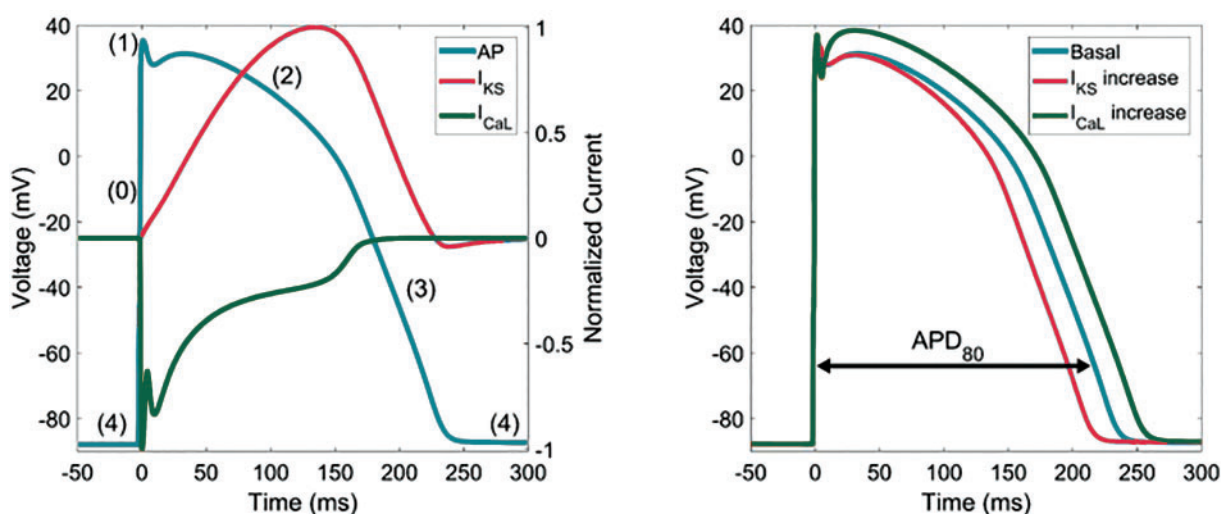
adrenergic stimulation.<sup>12,27–30</sup> In a recent study in patients with an ICD,<sup>11</sup> beat-to-beat variability of left ventricular epicardial APD (measured as ARI during RV pacing) was shown to increase following sympathetic provocation (Valsalva). This effect was almost entirely eliminated by a beta-adrenergic blocking agent. An interactive effect has been demonstrated between LF oscillation of APD and BVR.<sup>11</sup> The mechanism for this interaction at the cellular level was investigated using computer simulation. The major ionic contributors to concomitant variations in LF oscillation of APD and BVR were the magnitudes of  $I_{K_r}$ ,  $I_{CaL}$ , and the inward rectifier potassium current ( $I_{K1}$ ).<sup>31</sup> The same three ionic currents were found to explain the development of proarrhythmic events in the form of afterdepolarizations and runs of spontaneous beats in response to enhanced sympathetic activity.<sup>31</sup>

## Theoretical considerations

In the foregoing, we have reviewed evidence supporting the contention that LF oscillations of ventricular repolarization are related to the effect of rhythmic sympathetic nerve activity on APD. However, the PRD is an electrocardiographic phenomenon and could also be influenced by structural changes and functional properties of the myocardium. For example, it has been suggested that the different intrinsic properties of myocardial cells across the ventricular wall observed in single cells may play a role.<sup>2</sup> However, in the whole heart where cells are electrically and mechanically coupled differences in APD between cells may be markedly attenuated by electrotonic interaction.<sup>32,33</sup> In diseased hearts, the presence of structural changes such as scar and fibrosis can impact on repolarization. Therefore, in



**Figure 4** Beat-to-beat plot of left ventricular ARI as a surrogate for APD showing oscillations in the low-frequency range at  $\sim 0.05$  Hz (upper trace) and 0.1 Hz (lower trace). Corresponding power spectral densities (PSD) are shown to the right of each trace.



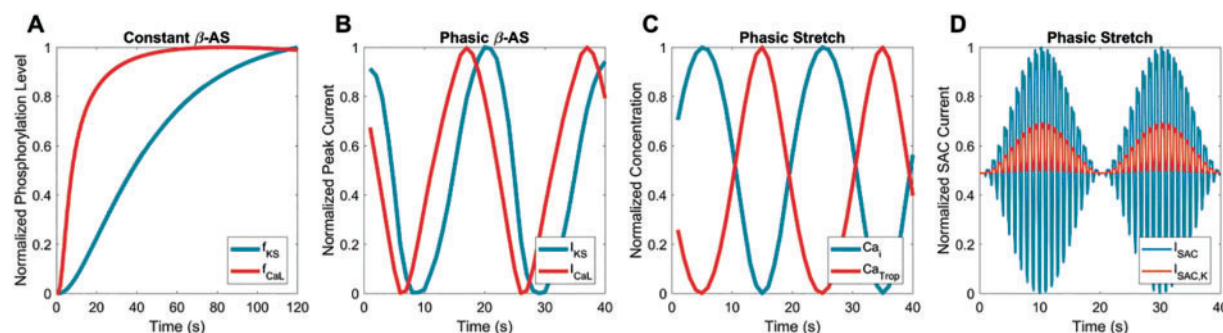
**Figure 5** Left panel: Illustration of the timing of two currents thought to play a key role in generation oscillations of the ventricular action potential in humans. The inward L-type calcium current ( $I_{CaL}$ ) occurs early during phases 0, 1, and 2 and the outward potassium current ( $I_{Ks}$ ) occurs later during phases 2 and 3. Right panel: The overall effect of  $I_{CaL}$  is APD prolongation and the effect of  $I_{Ks}$  is APD shortening.

these hearts, phasic sympathetically mediated changes in APD might be expected to induce phasic increases in dispersion of repolarization and contribute to the PRD.

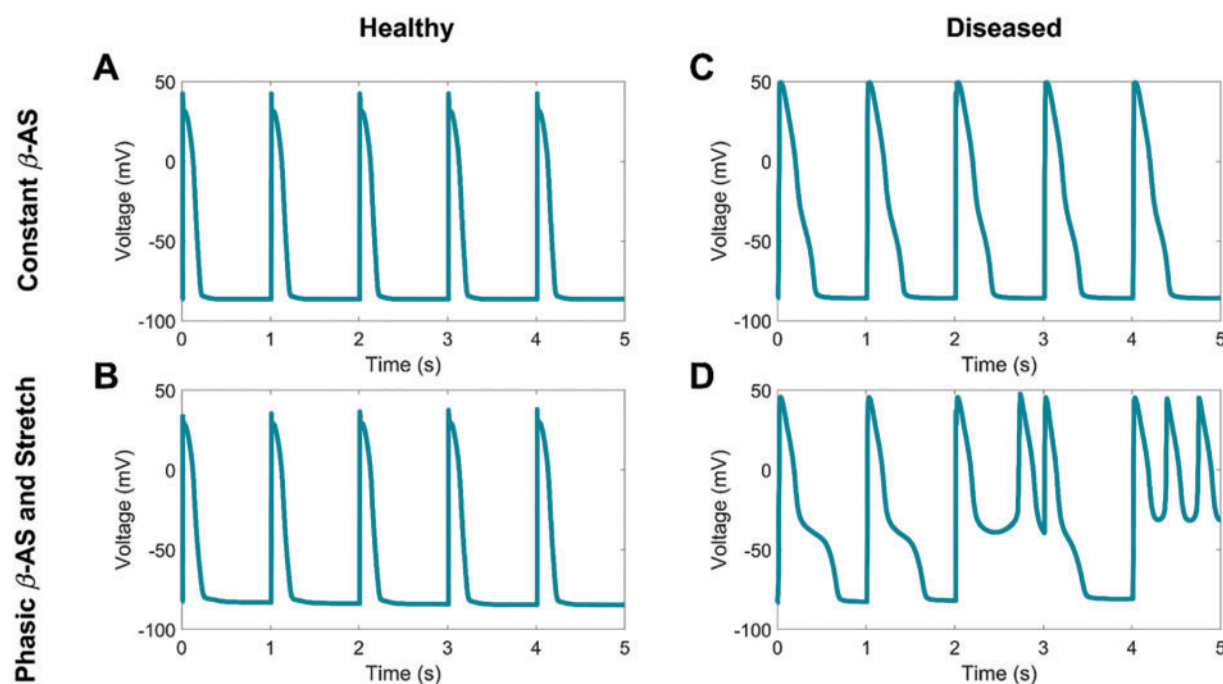
## Clinical implications

Low-frequency oscillatory behaviour of ventricular repolarization may provide a novel approach to both risk stratification and

mechanisms of arrhythmogenesis. There is urgent need to improve risk stratification for the use of ICD devices for the prevention of ventricular arrhythmia and sudden cardiac death. Current guidelines from the American Heart Association, American College of Cardiology, and the European Cardiac Society recommend prophylactic ICD implantation in patients with ischaemic and non-ischaemic cardiomyopathy with ejection fraction below 35%.<sup>34,35</sup> Although ICD implantation has proved to be highly effective, less than 1 in 10 of the implanted devices are actually needed. Hence a large number of



**Figure 6** (A) Time course of normalized phosphorylation levels for the slow delayed rectifier potassium  $I_{Ks}$  current (blue) and L-type  $I_{CaL}$  current following constant beta-adrenergic stimulation. (B) Normalized peak current values for  $I_{Ks}$  (blue) and  $I_{CaL}$  current (red) following prolonged beta-adrenergic stimulation. (C) Systolic levels of free cytosolic calcium ( $Ca_i$ , blue) and calcium bound to troponin ( $Ca_{Trop}$ , red) following prolonged phasic and mechanical stretch. (D) Current through all stretch-activated channels ( $I_{SAC}$ , blue) and through  $K^+$ -selective stretch-activated channels ( $I_{SAC,K}$ , red) following prolonged mechanical stretch.



**Figure 7** Simulated ventricular action potentials during beta-adrenergic stimulation (BAS). (A) Healthy myocardium during constant BAS, (B) Healthy myocardium during phasic BAS and stretch, (C) Myocardium with diseased conditions (simulated by addition of reduced repolarization reserve and calcium overload) during constant BAS, (D) Diseased conditions during phasic BAS and stretch. In C early afterdepolarizations are seen but no arrhythmia occurred. In D early afterdepolarizations and triggered activity are evident (see text).

patients are unnecessarily exposed to side effects such as infection and inappropriate shocks, and needlessly contribute to the escalating cost estimated at in excess of 2 billion euros per annum in Europe alone. In ICD patients, PRD  $<7.5$  deg was associated with only a 31% reduction in mortality by the device compared to a 75% reduction in patients with PRD  $>7.5$  deg. Numbers need to treat to prevent one death were reduced from 18.3 in patients with PRD  $<7.5$  deg

compared to 3.1 in patients with PRD  $>7.5$  deg. Periodic repolarization dynamics is a dynamic measure operating over a time frame of seconds in contrast to a number of other risk markers which measure static or near static properties.<sup>36</sup> Several dynamic tests have proven value as risk predictors of sudden cardiac death such as baroreceptor sensitivity,<sup>37</sup> heart rate turbulence,<sup>38</sup> deceleration capacity,<sup>39</sup> microvolt T-wave alternans,<sup>40</sup> and tests of RR interval

dynamicity.<sup>41</sup> The mechanistic link between each of these risk predictors and arrhythmia is highly complex but a main focus centres round separating the balance between sympathetic and parasympathetic activity, whereas PRD may relate more to the electrophysiological time constants that govern the repolarization process. The potential value of incorporating the dimension of time into risk stratification protocols has been suggested particularly in regard to tests incorporating autonomic function.<sup>36,42</sup> Future work might focus of elucidating the physiology and electrophysiology of these dynamic markers in combination. This approach may be beneficial not only for risk stratification strategies but also for the development of anti-arrhythmic drug therapy and device therapy.

## Conclusions

The powerful role of LF oscillatory dynamics of ventricular repolarization in the prediction of ventricular arrhythmia and sudden cardiac death is now firmly established.<sup>2–4</sup> It was proposed that these oscillations reflect oscillations of ventricular APD at the sympathetic nerve frequency. There is now a substantial body of evidence to support this contention and to provide a framework for underlying mechanisms. Specifically, the demonstration of the existence of oscillatory behaviour of ventricular APD in humans; its amplification by sympathetic activity and reduction by beta-adrenergic blockade similar to LF T-wave vector oscillations; the demonstration of possible cellular mechanisms including mismatch of the phosphorylation kinetics of ICa and I<sub>Ks</sub> in response to beta-adrenergic stimulation together with MEF; the generation of afterdepolarizations and triggered activity in the presences of disease conditions and interaction between LF oscillations of ventricular APD with other proarrhythmic mechanisms.

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**Conflict of interest:** none declared.

## References

1. 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.
2. Rizas KD, Nieminen T, Barthel P, Zürn CS, Kähönen M, Viik J et al. Sympathetic activity-associated periodic repolarization dynamics predict mortality following myocardial infarction. *J Clin Invest* 2014;**124**:1770–80.
3. Rizas KD, McNitt S, Hamm W, Massberg S, Kääh 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.
4. Hanson B, Gill J, Western D, Gilbey MP, Bostock J, Boyett MR et al. Cyclical modulation of human ventricular repolarization by respiration. *Front Physiol* 2012; **3**:379.
5. Hanson B, Child N, Duijvenboden SV, Orini M, Chen Z, Coronel R et al. Oscillatory behavior of ventricular action potential duration in heart failure patients at respiratory rate and low frequency. *Front Physiol* 2014;**5**:414.
6. Haws CW, Lux RL. Correlation between in vivo transmembrane action potential durations and activation-recovery intervals from electrograms. Effects of interventions that alter repolarization time. *Circulation* 1990;**81**:281–8.
7. Coronel R, Bakker J. D, Wilms-Schopman FJG, Opthof T, Linnenbank AC, Belterman CN et al. Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: experimental evidence to resolve some controversies. *Heart Rhythm* 2006;**3**:1043–50.
8. Potse M, Vinet A, Opthof T, Coronel R. Validation of a simple model for the morphology of the T wave in unipolar electrograms. *Am J Physiol Heart Circ Physiol* 2009;**297**:H792–801.
9. Duijvenboden SV, Porter B, Pueyo E, Sampedro-Puente DA, Fernandez-Bes J, Sidhu B et al. Complex interaction between low-frequency APD oscillations and beat-to-beat APD variability in humans is governed by the sympathetic nervous system. *Front Physiol* 2020;
10. Porter B, Bishop MJM, Claridge S, Behar J, Sieniewicz BJ, Webb J et al. Autonomic modulation in patients with heart failure increases beat-to-beat variability of ventricular action potential duration. *Front Physiol* 2017;**8**:
11. Porter B, Duijvenboden SV, Bishop MJ, Orini M, Claridge S, Gould J et al. Beat-to-beat variability of ventricular action potential duration oscillates at low frequency during sympathetic provocation in humans. *Front Physiol* 2018;**9**: 12–77.
12. Porter B, Bishop MJ, Claridge S, Child N, Duijvenboden SV, Bostock J et al. Left ventricular activation-recovery interval variability predicts spontaneous ventricular tachyarrhythmia in patients with heart failure. *Heart Rhythm* 2019;**16**:702–9.
13. Sprenkeler DJ, Beekman JDM, Bossu A, Dunnink A, Vos MA. Pro-arrhythmic ventricular remodeling is associated with increased respiratory and low-frequency oscillations of monophasic action potential duration in the chronic atrioventricular block dog model. *Front Physiol* 2019;
14. Furlan R, Diedrich A, Rimoldi A, Palazzolo L, Porta C, Diedrich L et al. Effects of unilateral and bilateral carotid baroreflex stimulation on cardiac and neural sympathetic discharge oscillatory patterns. *Circulation* 2003;**108**:717–23.
15. Bers DM. Cardiac excitation-contraction coupling. *Nature* 2002;**415**:198–205.
16. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J Clin Invest* 2005;**115**: 2305–15.
17. Liu GX, Choi BR, Ziv O, Li W, Lange E D, Qu Z et al. Differential conditions for early after-depolarizations and triggered activity in cardiomyocytes derived from transgenic LQT1 and LQT2 rabbits. *J Physiol* 2012;
18. Xie Y, Grandi E, Puglisi JL, Sato D, Bers DM.  $\beta$ -adrenergic stimulation activates early afterdepolarizations transiently via kinetic mismatch of PKA targets. *J Mol Cell Cardiol* 2013;
19. Pueyo E, Orini M, Rodríguez JF, Taggart P. Interactive effect of beta-adrenergic stimulation and mechanical stretch on low-frequency oscillations of ventricular action potential duration in humans. *J Mol Cell Cardiol Elsevier Ltd* 2016;**97**: 93–105.
20. Lab MJ. Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance. *Circ Res* 1982;
21. Taggart P, Sutton PMI. Cardiac mechano-electric feedback in man: clinical relevance. *Prog Biophys Mol Biol* 1999;
22. Peyronnet R, Nerbonne JM, Kohl P. Cardiac mechano-gated ion channels and arrhythmias. *Circ Res* 2016;
23. Horner SM, Murphy CF, Coen B, Dick DJ, Lab MJ. Sympathomimetic modulation of load-dependent changes in the action potential duration in the in situ porcine heart. *Cardiovasc Res* 1996;
24. Monge Garcia MI, Jian Z, Settels JJ, Hunley C, Cecconi M, Hatib F et al. Performance comparison of ventricular and arterial dP/dtmax for assessing left ventricular systolic function during different experimental loading and contractile conditions. *Crit Care* 2018;**22**:325.
25. Zipes DP, Rubart M. Neural modulation of cardiac arrhythmias and sudden cardiac death. *Heart Rhythm* 2006;**3**:108–13.
26. Marmar V, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. *Prog Cardiovasc Dis* 2008;**50**:404–19.
27. Thomsen MB, Volders PGA, Beekman JDM, Matz J, Vos MA. Beat-to-beat variability of repolarization determines proarrhythmic outcome in dogs susceptible to drug-induced Torsades de Pointes. *J Am Coll Cardiol* 2006;
28. Baumert M, Porta A, Vos MA, Malik M, Couderc JP, Laguna P et al. QT interval variability in body surface ECG: Measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electroph. *Europace* 2016;**18**:925–44.
29. Johnson DM, Heijman J, Bode EF, Greensmith DJ, Linde HVD, Abi-Gerges N et al. Diastolic spontaneous calcium release from the sarcoplasmic reticulum increases beat-to-beat variability of repolarization in canine ventricular myocytes after  $\beta$ -adrenergic stimulation. *Circ Res* 2013;**112**:246–56.
30. Szentandrassy N, Kistamás K, Hegyi B, Horváth B, Ruzsnavszky F, Váczi K et al. Contribution of ion currents to beat-to-beat variability of action potential duration in canine ventricular myocytes. *Pflügers Arch Eur J Physiol* 2015;



31. Sampedro-Puente DA, Fernandez-Bes J, Porter B, Duijvenboden S. V, Taggart P, Pueyo E. Mechanisms underlying interactions between low-frequency oscillations and beat-to-beat variability of cellular ventricular repolarization in response to sympathetic stimulation: implications for arrhythmogenesis. *Front Physiol* 2019;
32. Opthof T, Meijborg VMF, Belterman CNW, Coronel R. Synchronization of repolarization by mechano-electrical coupling in the porcine heart. *Cardiovasc Res* 2015;**108**:181–7.
33. Boukens BJ, Meijborg VMF, Belterman CN, Opthof T, Janse MJ, Schuessler RB et al. Local transmural action potential gradients are absent in the isolated, intact dog heart but present in the corresponding coronary-perfused wedge. *Physiol Rep* 2017;**5**:e13251.
34. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Heart Rhythm* 2018;**15**:e190–252.
35. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Russ J Cardiol* 2016;
36. Wellens HJJ, Schwartz PJ, Lindemans FW, Buxton AE, Goldberger JJ, Hohnloser SH et al. Risk stratification for sudden cardiac death: current status and challenges for the future. *Eur Heart J* 2014;
37. Schwartz PJ, Vanoli E, Stramba-Badiale M, Ferrari GD, Billman GE, Foreman RD. Autonomic mechanisms and sudden death. New insights from analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. *Circulation* 1988;**78**:969–79.
38. 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.
39. Bauer A, Kantelhardt JW, Barthel P, Schneider R, Mäkilä 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.
40. Verrier RL, Klingenhöfen T, Malik M, El-Sherif N, Exner DV, Hohnloser SH et al. Microvolt T-wave alternans: physiological basis, methods of measurement, and clinical utility: consensus guideline by international society for Holter and noninvasive Electrocardiology. *J Am Coll Cardiol* 2011;**58**:1309–24.
41. Rovere ML, Pinna GD, Maestri R, Mortara A, Capomolla S, Febo O et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003;
42. Myerburg RJ, Junttila MJ. Sudden cardiac death caused by coronary heart disease. *Circulation* 2012;**125**:1043–52.