SYMPOSIUM REVIEW

Predicting the risk of sudden cardiac death

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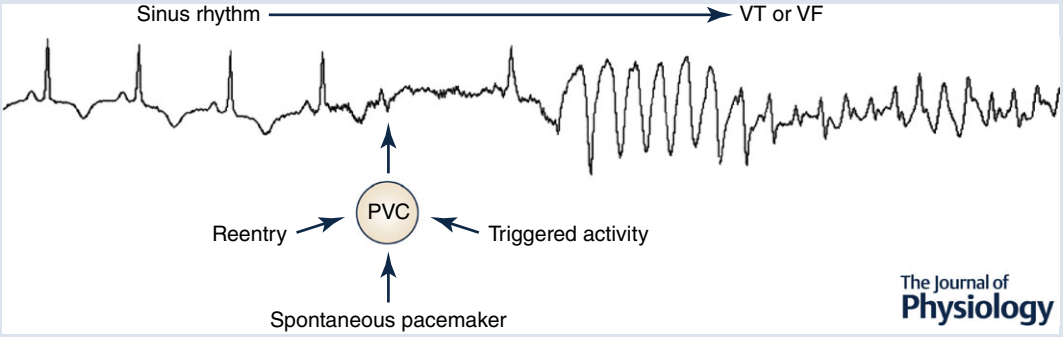

Abstract Sudden cardiac death (SCD) is the result of a change of cardiac activity from normal (typically sinus) rhythm to a rhythm that does not pump adequate blood to the brain. The most common rhythms leading to SCD are ventricular tachycardia (VT) or ventricular fibrillation (VF). These result from an accelerated ventricular pacemaker or ventricular reentrant waves. Despite significant efforts to develop accurate predictors for the risk of SCD, current methods for risk stratification still need to be improved. In this article we briefly review current approaches to risk stratification. Then we discuss the mathematical basis for dynamical transitions (called bifurcations) that may lead to VT and VF. One mechanism for transition to VT or VF involves a perturbation by a premature ventricular complex (PVC) during sinus rhythm. We describe the main mechanisms of PVCs (reentry, independent pacemakers and abnormal depolarizations). An emerging approach to risk stratification for SCD involves the development of individualized dynamical models of a patient based on measured anatomy and physiology. Careful analysis and modelling of dynamics of ventricular arrhythmia on an individual basis will be essential in order to improve risk stratification for SCD and to lay a foundation for personalized (precision) medicine in cardiology.

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Abstract figure legend Schematic diagram showing sudden cardiac death as a transition from sinus rhythm to ventricular tachycardia (VT) or ventricular fibrillation (VF). The onset of VT or VF is preceded by premature ventricular complex (PVC), which could originate by any of these mechanisms: reentry, spontaneous pacemaker or triggered activity. The ECG trace was taken from the Sudden Cardiac Death Database (record number 32) from www.physionet.org.

Abbreviations CI, coupling interval; DAD, delayed afterdepolarization; EAD, early afterdepolarization; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; NIB, number of intervening beats (between two consecutive PVCs); NN interval, time between two sinus beats; MRI, magnetic resonance imaging; PVC, premature ventricular complex; SCD, sudden cardiac death; SDCI, standard deviation of the coupling interval; SNIB, score of NIB; VF, ventricular fibrillation; VT, ventricular tachycardia; VV interval, time between two consecutive PVCs.

Introduction

Sudden cardiac death (SCD) refers to death within 2 h of onset of symptoms or during sleep due to a cardiac cause (Zipes & Wellens, 1998). Although SCD can occur due to a slow heart rhythm (bradycardia) caused by a stopping or blocking of the normal sinus pacemaker, more commonly it is due to a rapid heart rhythm (tachycardia), usually originating in the ventricles – ventricular tachycardia (VT) or ventricular fibrillation (VF). One major route to SCD is secondary to a heart attack (coronary infarct) in which a coronary artery is blocked. Although bradyarrhythmias and coronary infarcts are also causes of SCD, developing risk stratification for these occurrences lies outside the scope of this review. Rather, we consider SCD associated with a transition from a normal sinus rhythm to VT or VF. Since an implantable cardioverter defibrillator (ICD) may be an effective therapy for this class of arrhythmias (Moss *et al.* 2002; Bardy *et al.* 2005; Tung *et al.* 2008), a major clinical question involves risk stratification for SCD (Goldberger *et al.* 2008, 2011; Bastiaenen *et al.* 2012; Bilchick *et al.* 2012; Huikuri, 2015).

Recent reviews summarize studies on risk stratification for SCD (Wellens *et al.* 2014; Deyell *et al.* 2015). The paradigms for these studies are similar. First measure some set of parameters and dynamical features based on cardiac anatomy and physiology in some large subset of patients meeting a predefined clinical profile. Then assess the incidence of SCD over several years to see which factors show a strong correlation with the future incidence of SCD. These reviews underscore the conclusions that: (i) many different factors are associated with an increased risk for SCD; and (ii) current methods for risk stratification still need significant improvement in order to better define the roles for various existent and emerging medical and device therapies. One strategy to improve risk stratification for SCD is to carry out large observational studies, similar to those carried out previously (Huikuri, 2015). Although large observational studies play an important role in clinical decision making, we believe that alternative strategies will also be useful to improve risk stratification for SCD.

In this review, we address SCD from a basic science perspective. In SCD, the spatio-temporal organization of cardiac activity changes typically from a pattern in which the normal sinus pacemaker is setting the rhythm of the entire heart, to a rhythm in which an accelerated ventricular pacemaker or ventricular reentrant waves set a rapid ventricular rhythm leading to VT or VF. Dynamical transitions such as these are called bifurcations and can be studied mathematically using techniques developed in the field of nonlinear dynamics (Glass *et al.* 1987; Krogh-Madsen & Christini, 2012; Weiss *et al.* 2015).

In the next section, we briefly summarize the various physiological and electrocardiographic factors that have been the main focus of clinical investigations for risk stratification. After that we discuss generic mathematical properties of cardiac tissue and summarize conditions leading to blocking of excitation, alternans, and initiation of extra beats and pacemakers. These basic processes are implicated in the transition from sinus rhythm to the onset of arrhythmias. In the following section, we focus on mechanisms of premature ventricular complexes (PVCs) and discuss evidence that shows that not all PVCs are equal – some mechanisms confer a higher risk of SCD than others. The section after that discusses a new method for identifying mechanisms of PVCs based on their dynamic properties measured over 24 h. Such an analysis could provide a basis for better identifying mechanisms of PVCs and improving risk stratification for SCD. Then we discuss realistic and patient-specific modelling of cardiac arrhythmias with a view towards improving the diagnosis and therapy for SCD. Finally, we identify directions for future research.

Prediction of sudden cardiac death

Clinical studies of risk stratification for SCD have investigated and identified a large number of physiological and anatomical characteristics that have been

associated with an elevated risk of SCD (Wellens *et al.* 2014; Deyell *et al.* 2015). These different characteristics include anatomical substrate, autonomic function, genetic mutations, electrophysiological function and provocative testing.

Anatomical substrate. According to current guidelines, the main criterion for implantation of an ICD for primary prevention of SCD is a low left ventricular ejection fraction (Moss *et al.* 2002; Bardy *et al.* 2005; Epstein *et al.* 2008). Although this criterion has been verified in numerous clinical studies, a large fraction of patients who meet the criterion do not receive an ICD, a large fraction of patients who meet the criterion and do receive an ICD do not have triggering events, and a large number of people who do not meet the criterion do experience SCD (Goldberger *et al.* 2011; Albert & Stevenson, 2013). Indication of scarring in the ventricles is provided by fragmented QRS complexes on the electrocardiogram and this has also been used for risk stratification (Jain *et al.* 2014). Alternative approaches to assessing the anatomical substrate for arrhythmia involve imaging the heart using a variety of methods including echocardiography, magnetic resonance imaging and photon emission tomography (Vadakkumpadan *et al.* 2014). Prospective assessments of these modalities have not yet been carried out.

Autonomic function. The period of the cardiac cycle is continuously modulated by activity from the sympathetic and parasympathetic systems where greater sympathetic activity increases the heart rate and greater parasympathetic activity reduces the heart rate. Reduced heart rate variability is associated with an increased risk of SCD (Kleiger *et al.* 1987; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). The observation that blocking sympathetic activity using beta blockers reduces the incidence of SCD provides additional strong evidence of the importance of autonomic function in the pathophysiology of SCD (Shen & Zipes, 2014).

Patients with diseased hearts typically have increased heart rate and reduced fluctuations in the heart rate associated with increased sympathetic hyperactivity, decreased vagal activity, or both (La Rovere *et al.* 1998; Shusterman *et al.* 1998). Reduced heart rate variability (HRV) as measured by assessment of standard deviation of interbeat intervals (Goldberger *et al.* 2008), power spectral density of HRV (Huikuri *et al.* 2009), analysis of the complexity of HRV using entropy-related measures (Wessel *et al.* 2000; Costa *et al.* 2002; Norris *et al.* 2008), and reduced values of scaling coefficients associated with fluctuations of heart rate (Au-Yeung *et al.* 2015) show correlations with impaired health and increased risk for serious disease and/or SCD. Decreased entropy of rapid cardiac rhythm may also be useful to distinguish VT and VF from atrial fibrillation, thereby reducing the occurrence of inappropriate ICD shocks (DeMazumder *et al.* 2013).

Another measure associated with autonomic function is heart turbulence, measured by determining the transient heart rates following a PVC. Heart rate turbulence describes the short-term fluctuations in sinus cycle length that follow a PVC (Barthel *et al.* 2003). After a PVC, the next sinus beat is typically blocked leading to a pause before the next sinus beat. This leads to an increase in blood pressure due to prolonged filling time and consequent slowing of the heart rate through operation of the baroreceptor reflex mediated by decreased sympathetic activity and increased parasympathetic activity. In patients who survived an acute myocardial infarction, indices reflecting increased sympathetic activity and reduced parasympathetic activity following a PVC were predictors of mortality (Barthel *et al.* 2003) and life-threatening arrhythmias (Huikuri *et al.* 2010). In patients with congestive heart failure these indices were associated with a higher risk of SCD (Au-Yeung *et al.* 2015). Although the measures of autonomic function are correlated with the risk for SCD, the correlations are not sufficiently strong to provide a basis for risk stratification.

Genetic mutations. Advances in genetics and cardiac electrophysiology have led to the identification of a large number of different genetic mutations affecting ion channels that have been associated with increased incidence of cardiac arrhythmias and SCD. The best understood are mutations of potassium and sodium channels that lead to longer action potentials manifested by an increased duration of QT interval on the electrocardiogram (long QT syndrome) (Priori *et al.* 2003; Amin *et al.* 2013). The longer durations of action potentials may lead to PVCs as a consequence of early afterdepolarizations, and these may in turn induce a potentially lethal VT, torsade de pointes. However, since other factors including sympathetic activity and drugs also affect repolarization, it is not simple to assess the risk for SCD based solely on the presence of a mutation (Priori *et al.* 2003). Another group of mutations was discovered from genetic analysis of individuals that were identified initially by electrocardiographic abnormalities in a family that had several instances of cardiac arrest (Chen *et al.* 1998; Brugada *et al.* 2013). These mutations of the sodium channel, associated with the Brugada syndrome, lead to slow conduction predisposing to reentrant tachycardias (Brugada *et al.* 2013). Another class of mutations in receptors associated with calcium handling lead to calcium overload and VT induced by sympathetic stimulation

(catecholaminergic polymorphic ventricular tachycardia) (Mohamed *et al.* 2007). Because there can be multiple sites of mutation in a single gene and there are other modulating factors of cardiac activity that are poorly understood, observation of mutations must be combined with electrophysiological data to assess risk.

Electrophysiological function. One of the earliest recognized risk factors for SCD is an increased numbers of PVCs (Kotler *et al.* 1973; Berkowitsch *et al.* 2004; Carrim & Khan, 2005). As is well known, the cardiac arrhythmia suppression trial demonstrated that reducing the incidence of PVCs with drugs led to an increased incidence of SCD (Echt *et al.* 1991). This study is partially responsible for a reduced emphasis on the role of PVCs in the assessment of risk and the genesis of SCD. However, a recent study, that reexamined ventricular ectopy in heart failure patients, showed increased risk with increased ectopy (Dukes *et al.* 2015) and concluded that there is a need for better understanding mechanisms of PVCs.

Another electrophysiological marker for increased risk for SCD is alternans of the T-wave (Weiss *et al.* 2006; Verrier *et al.* 2011; Nieminen *et al.* 2014). From a dynamics perspective, T-wave alternans is of particular interest since analysis of mathematical models of action potential duration have demonstrated the possibility for instabilities (bifurcations) leading to alternating action potential durations (Qu *et al.* 2010). T-wave alternans on the electrocardiogram (ECG) could arise from this instability. However, it could also arise in other ways such as from 2:1 conduction in some parts of the heart and 1:1 conduction in other regions of the heart.

The stability of ventricular repolarization, as evaluated by the maximum slope of the relationship between the action potential duration and the diastolic interval (restitution curve), is a known factor for the onset of ventricular arrhythmias (Garfinkel *et al.* 2000). From the ECG, an estimated restitution curve is obtained from the relationship between the QT interval and the preceding TQ interval, to estimate the QT interval dynamics stability. In patients with myocardial infarction, the instability of QT interval dynamics is increased before VT (Chen *et al.* 2011), and a QT instability has predictive value for ventricular arrhythmia in patients with an implanted ICD (Chen *et al.* 2013). However, direct measurement of action potential restitution curves in patients failed to show a direct correlation between steep restitution curves and T-wave alternans (Narayan *et al.* 2007). Since alternation of the action potential voltage can occur in the absence of alternans of the action potential duration (Bayer *et al.* 2010), an important question in basic science is to clarify the mechanisms of alternans in normal and heart failure patients and to clarify the role of calcium handling (Narayan *et al.* 2008; Wilson *et al.* 2009).

Electrophysiological testing. The development of clinical cardiac electrophysiology has been greatly advanced by the development of intracardiac catheters that can be used to record local activity, deliver electrical stimuli, and ablate cardiac tissue using radio-frequency stimulation (Josephson, 2008). Provocative testing involves pacing the heart at a fixed rate and delivering a sequence of up to three premature stimuli from one or more sites in the ventricles in an effort to induce VT that would be substantially the same as a VT that would arise spontaneously (Roy *et al.* 1983; Buxton *et al.* 2000). Such procedures have provided a basis for testing antiarrhythmic drugs as well as for risk stratification for SCD. However, such procedures are invasive and impossible to implement on a routine basis. Although electrophysiological testing has the ability to predict patients at increased risk for SCD in patients with ischaemic heart disease and reduced ejection fraction, it has poor negative predictive power, and its predictive power for individuals in other populations at elevated risk for SCD is largely unknown (Thomas & Josephson, 2008). As discussed below, work is underway to develop patient-specific models that can be used to assess the anatomical substrate for arrhythmias to help guide risk stratification and to assess targets for ablation in individuals (Trayanova, 2014).

Dynamics of wave propagation

Given the difficulties in developing risk stratification for SCD using standard clinical approaches, we think it is useful to discuss this question from a more basic theoretical perspective. Excitable media, such as the heart, can support propagation of waves of electrical activity. Simple and complex mathematical models reproduce and in some cases can be used to predict dynamic features associated with the onset of arrhythmias in cardiac tissues (Moe *et al.* 1977; Keener, 1981; Guevara *et al.* 1984; Glass *et al.* 1986; Courtemanche *et al.* 1989; Fenton & Karma, 1998; Chialvo *et al.* 1990; Lewis & Guevara, 1990; Vinet *et al.* 1990; Ito & Glass, 1992; Courtemanche *et al.* 1993; Starmer *et al.* 1993; Karma, 1994; Schulte-Frohlinde *et al.* 2002). We discuss conduction block, alternans, and initiation of extra beats.

Conduction block. Following an excitation wave, cardiac tissue has a refractory period and a stimulus or excitation will not conduct if it is delivered too close to a previous stimulus. In addition, the velocity of propagation of cardiac excitation typically slows as the latency from a previous conducted beat decreases. As a consequence, as the pacing frequency of cardiac tissue increases, either from an external pacemaker or from an intrinsic source (the sinus pacemaker, an ectopic atrial or ventricular pacemaker, or a reentrant circuit) conduction may be blocked locally (Keener, 1981; Shrier *et al.* 1987; Courtemanche &

Winfree, 1991; Karma, 1994). Such blocking of conduction plays a crucial role in atrio-ventricular heart block, unidirectional block leading to reentry and termination of reentry as a consequence of anti-tachycardia pacing, and transitions from monomorphic to polymorphic tachycardias. If there is blocking of cardiac excitation locally due to refractory tissue, there may be initiation of rotors or three-dimensional reentrant waves (Krinsky, 1966; Courtemanche & Winfree, 1991; Karma, 1994; Fenton & Karma, 1998; Bub *et al.* 2002).

Alternans. During rapid pacing of cardiac tissue, in addtion to blocked beats, an instability may lead to alternation of electrophysiological properties (Chialvo *et al.* 1990; Lewis & Guevara, 1990; Vinet *et al.* 1990; Echebarria & Karma, 2002). The action potential duration decreases as the time from a preceding action potential decreases. If this decrease is steep enough, there will be an alternation of action potential duration (the technical term for this instability is a period-doubling bifurcation). Since local alternation of action potential duration in ventricular tissue would lead to T-wave alternans, this may provide insight into the reason why T-wave alternans is associated with an increased risk of SCD (Rosenbaum *et al.* 1994; ten Tusscher & Panfilov, 2006; Weiss *et al.* 2006; Qu *et al.* 2010).

Initiation of extra beats. Cardiac tissue can also generate extra beats. Early afterdepolarizations and delayed afterdepolarizations may arise due to genetic abnormalities (Amin *et al.* 2013) or drug effects (Farkas & Nattel, 2010; Gonano *et al.* 2011). Theoretical models rely on detailed analyses of the underlying ionic mechanisms (Qu *et al.* 2013). It is also possible to have localized regions of cardiac tissue make a transition from an excitable cell to a pacemaker leading to an ectopic focus (Antzelevitch *et al.* 1983). If the localized pacemaker has a lower frequency than the sinus rhythm, then the pacemaker may be entrained in a one-to-one fashion to the sinus rhythm, and the localized pacemaker properties would not be evident. If, however, the pacemaker was in an anatomical region that had entrance block, the pacemaker might act as an ectopic focus generating a parasystolic rhythm (Antzelevitch *et al.* 1983), such as sometimes occurs in the right ventricular outflow tract. Although mathematical models for transtions from oscillatory to non-oscillatory states are well developed (the transition can take place via a Hopf bifurcation) (Qu *et al.* 2013), theoretical models of physiological mechanisms that lead to such transtions, such as variation of catecholamine levels (Shen & Zipes, 2014), need to be developed better. Independent of specific mechanisms for ectopic pacemaker initiation, the consequence of ectopic pacemakers can be analysed theoretically (see the next section).

Dynamics of PVCs

The preceding section summarized several dynamic features of cardiac models. Transitions from sinus rhythm to VT often occur as a consequence of a PVC. Consequently, it is of interest to consider possible mechanisms of PVCs. In this section we briefly review this work from a perspective of improving methods for risk stratification. Although PVCs are commonly found in normal individuals and may be considered benign, there is also significant clinical data that show that frequent PVCs confer a risk for SCD (Kotler *et al.* 1973; Berkowitsch *et al.* 2004; Carrim & Khan, 2005; Dukes *et al.* 2015). The onset of ventricular tachyarrhythmia preceded by PVCs has been documented in different clinical contexts. In idiopathic VF patients, spontaneous VF episodes are initiated by PVCs with very short coupling intervals (Viskin *et al.* 1997; Haïssaguerre *et al.* 2008). Spontaneous VF initiated by PVCs with short–long–short sequences have been documented in 72% of VF episodes in patients with early repolarization and in 15% of VF episodes in Brugada syndrome patients (Nam *et al.* 2010). In long QT syndrome patients, the onset of polymorphic VT (torsade de pointes) is typically pause dependent: most episodes of polymorphic VT are preceded by either a single PVC or short–long–short sequences that arise due to PVCs in complex rhythms, such as ventricular bigeminy (Viskin *et al.* 1996). In other clinical contexts such as myocardial infarction, there is a less clear relationship between PVCs and the onset of VT or VF. An early study with 77 patients describes 492 episodes of VT that occurred during the first 48 h following the onset of myocardial infarction. PVCs were observed in 76% of cases during the 10 min preceding VT, but the incidence dropped to 40% during the minute prior to VT (Bluzhas & Lukshiene, 1985). The frequency of PVCs per minute had a large range (1 to 20) and the complexity of PVCs also varied, with groups of PVCs (24%), early PVCs (12%) and multifocal PVCs (30%). Since transition from VT to VF was observed in only 1% of cases, the frequency and complexity of PVCs were concluded to be of little predictive value for VF in patients with myocardial infarction. Regardless of the lack of a clear link between PVCs and the onset of VT or VF in myocardial infarction patients, the assessment of PVCs as precursor of VT or VF is still important for certain groups of myocardial infarction patients (Makikallio *et al.* 2005; Lerma *et al.* 2013). We now consider different mechanisms for the generation of PVCs.

Reentry. Reentry of ventricular beats can lead to PVCs. One scenario for this involves entrance of ventricular activity from a sinus beat into a ventricular scar resulting from an infarct via an isthmus of viable tissue (Josephson, 2008). If the conduction velocity is sufficiently slow, the exit from the scar tissue would occur after the refractory

time of the sinus beat and lead to a PVC. The conduction time through the scar would be expected to be affected by a variety of factors including the sinus rate, prior conduction through the scar, drugs, and levels of catecholamines. Depending on these factors, it is possible that the PVC would lead to VT using the same pathway (Bogun *et al.* 2008). In that case one would expect that the morphology of the VT would be close to the morphology of the PVC (Pogwizd & Corr, 1987; Bogun *et al.* 2008; Chinushi *et al.* 2011). Conduction through the isthmus would be expected to show similar properties to conduction in excitable media including decremented conduction and various patterns of block (Callans *et al.* 1993). Theoretical models have addressed the dynamics of PVCs arising from reentry (Kinoshita *et al.* 1990; Schulte-Frohlinde *et al.* 2002).

Parasystole. Ventricular parasystole results from the interaction between an ectopic ventricular pacemaker and the normal sinus rhythm. In the classic manifestation both rhythms are independent. Given different mechanisms for PVCs, this is the mechanism best understood. A PVC will be observed if the timing of the parasystolic beats falls outside the refractory period of the sinus beat; the ectopic beat will be blocked if it falls during the refractory period of the sinus beat; and there will be a fusion beat with different morphology if the ectopic beat falls simultaneously with the onset of the QRS complex of the ECG. Classically, parasystole is identified on the ECG from a triad of characteristics: intervals between PVCs are multiples of a common divisor, the coupling interval from the sinus beat to a PVC varies, and there are fusion beats. Mathematical analysis of parasystole revealed surprising properties for the sequence of integers that gives the number of sinus beats between two consecutive PVCs. In this sequence assuming that sinus frequency and the ectopic frequencies are fixed, there will in general be three integers that can be predicted based on the periods of the sinus and ectopic beats and the refractory time following the sinus beat (Glass *et al.* 1986). An important early paper by Moe and Jalife demonstrated that it is also possible for the parasystolic focus to be re-set (or modulated) by the sinus beat (Moe *et al.* 1977). If only one sinus beat falls between two consecutive PVCs, plotting the interval between two consecutive PVCs as a function of the timing of the sinus beat in the PVC cycle generates a resetting curve. Modulated parasystole can lead to repetitive sequences such as bigeminy, in which there is one sinus beat between two consecutive PVCs, or trigeminy, in which there are two sinus beats between two consecutive PVCs (Antzelevitch *et al.* 1983; Courtemanche *et al.* 1989). An early paper that assessed malignancy of arrhythmias in individual patients concluded that although parasystole could lead to frequent ectopy, it did not confer an elevated risk of SCD (Kotler *et al.* 1973). Thus, identification of a parasystolic mechanism for PVCs based on dynamic features could play an important role in risk stratification. Because of the independent timing of sinus and parasystolic beats, in parasystole there will be occurrences of PVCs at different times in the sinus cycle and in particular on the T-wave of the ECG. If one assumes that PVCs occurring during the T-wave are proarrhythmogenic (Smirk, 1949), one would expect that parasystole would be a malignant rather than a benign arrhythmia. This apparent inconsistency indicates the possible importance of mechanism of PVCs, and bears further investigation.

Early afterdepolarizations and delayed afterdepolarizations. Early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) are depolarizations following a cardiac action potential that occur earlier than would otherwise be expected. EADs occur during the action potential and DADs occur shortly after the action potential. In contrast to parasystolic PVCs, PVCs that arise as a consequence of EADs and DADs give rise to malignant arrhythmias. Although EADs and DADs are typically identified based on intracellular recordings, optical recordings from tissue culture provide a powerful new method to assess repolarization abnormalities on a tissue level. Several different mechanisms can lead to abnormal depolarizations; for a review see Roberts *et al.* (2012). They include genetic mutations of sodium channels leading to enhanced automaticity (Brugada syndrome; Brugada *et al.* 2013), genetic mutations of potassium channels leading to prolonged action potentials (long QT syndrome; Amin *et al.* 2013), drug effects leading to prolonged action potentials (acquired long QT syndrome; Farkas & Nattel, 2010), defects in calcium handling that may be exacerbated in conditions of catecholaminergic stimulation (catecholaminergic polymorphic ventricular tachycardia; Mohamed *et al.* 2007), drug effects from digitalis and other drugs leading to calcium overload and DADs (Gonano *et al.* 2011). Recent papers have developed mathematical models of the cardiac action potential and demonstrated bifurcations that can lead to the onset of arrhythmias induced by EADs (Chang *et al.* 2012; Karagueuzian *et al.* 2013; Qu *et al.* 2013).

Detailed ionic models have been useful in understanding the circumstances that can lead to PVCs. EADs that occur during phase 2 of the action potential (phase-2 EADs) can markedly prolong the action potential duration but cannot generate propagating PVCs (Sato *et al.* 2009). An animal model of isolated ventricular rabbit myocytes exposed to H_2O_2 produced phase-2 EADs due to slowed IKs activation (Qu *et al.* 2013). Phase-3 EADs, produced for example with IKr blockade using dofetilide in isolated rabbit ventricular myocites (Guo *et al.* 2007), can

prolong the action potential duration and also generate propagating PVCs (Qu *et al.* 2013). Phase-3 EADs can also result from electrotonic coupling between regions with and without phase-2 EADs in heterogeneous tissue (Maruyama *et al.* 2011). Finally, late phase-3 EADs, which are similar to DADs, can arise from intact tissue (not from isolated myocytes) when the Ca^{2+} transient outlasts the action potential duration and Ca^{2+} inward currents depolarize the membrane voltage until it reaches the I_{Na} threshold (Qu *et al.* 2013).

Heartprint

Since some mechanisms for PVCs are associated with lethal arrhythmias, distinguishing mechanisms of PVCs in individual patients may provide useful clinical information. Based on theoretical analysis of models of PVC generation, we have developed a visual method, called the heartprint, to characterize long-term dynamics of the mechanism of PVCs. It was created as a visual and qualitative method to display statistical properties of intervals related to the PVCs: (i) the coupling interval (CI) between each PVC and the preceding sinus beat, (ii) the time interval between PVCs (VV interval), and (iii) the number of intervening sinus beats (NIBs) between two consecutive PVCs (Schulte-Frohlinde *et al.* 2002). To explore the dependencies between these indexes and the underlying cardiac rhythm (represented by NN intervals, usually sinus rhythm), bivariate histograms are represented as grey scale plots where the ordinate is the NN interval, the abscissa axis is one of the heartprint indexes, and the incidence of VV intervals, NIB values and CI are indicated in the greyscale plots respectively, where the relative frequency of occurrence is indicated by the shading (darker shading representing more events) (Fig. 1). The example in Fig. 1 is derived from a Holter recording in the Sudden Cardiac Death Database in a patient who experienced an episode of sustained VT of unknown cause (Goldberger *et al.* 2000). The CI, observed in the ECG (Fig. 1*A*), remained fixed throughout the 24 h recording (Fig. 1*B*).

Based on the hearprint, new quantitative indices have been found which are associated with a higher risk of SCD, including the standard deviation of the CI (SDCI) and the NIB score (SNIB), which is the number of incidences (i.e. the height of the histogram in the heartprint) of the most prevalent values in the range 1–8 (Lerma *et al.* 2013). In survivors of acute myocardial infarction with depressed left ventricular function, repeating forms of PVCs (SNIB $\geq$ 83) was associated with a higher risk of fatal or near-fatal sudden arrhythmias (primary endpoint of the study) with a hazard ratio of 3.5 (1.3–9.5). Although this is better than some other non-invasive markers of risk for SCD based on the signal averaged ECG or heart rate turbulence

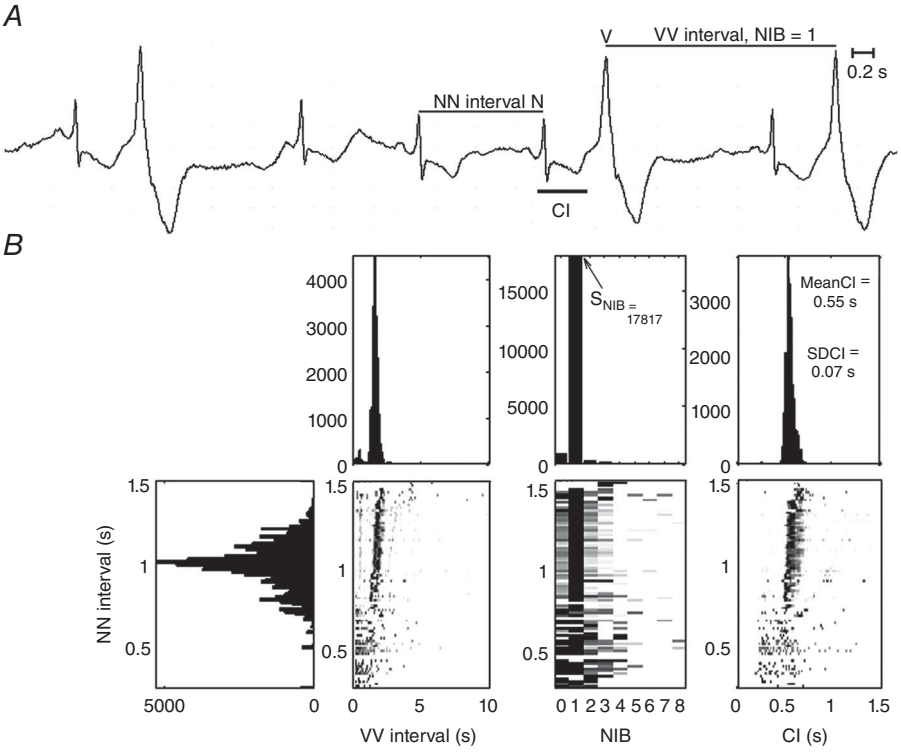

Figure 1. Example of ECG trace (*A*) and heartprint (*B*) from a Holter recording of the Sudden Cardiac Death database (no. 47) with repetitive arrhythmia with fixed coupling interval (CI)
NIB, number of intervening sinus beats between two PVCs; SNIB, NIB index.

(Huikuri *et al.* 2009), it requires further development and confirmation before it can be incorporated in new methods for risk stratification. A fixed CI (SDCI ≤ 80 ms) was associated with a higher risk of all-cause mortality with a hazard ratio of 2.89 (1.13–7.38) and with cardiac death with a hazard ratio of 3.36 (1.00–11.22) (Lerma *et al.* 2013).

The heartprint was created as a visual tool to identify patterns in the interaction between the arrhythmia characteristics and the sinus interval, which could be associated to specific arrhythmogenic mechanisms (Schulte-Frohlinde *et al.* 2002). Patterns with fixed CI may reflect either reentry or triggered activity, while patterns with broad CI are expected in parasystole. Using data from the Holter cardiac death database (Goldberger *et al.* 2000), a pattern of fixed CI and persistent ventricular bigeminy (as is shown in the example of Fig. 1) was found in 6 out of 15 recordings (Lerma *et al.* 2007). Since the recordings with such a pattern had also long QT interval and polymorphic VT (torsade de pointes), it is possible that EADs are the mechanism underlying the PVCs.

We conclude that it is important to understand the mechanisms of PVCs (Glass *et al.* 2011). Others have a similar perspective. A recent study found an increased risk associated with frequent PVCs (Dukes *et al.* 2015). A commentary on this paper concludes, 'A patient-specific physiological characterization is crucial to better understand the mechanistic links between [PVCs] and increased risk of adverse cardiovascular events' (Santangeli & Marchlinski, 2015).

Realistic and patient-specific diagnosis and modelling

In contrast to the simplified models discussed above (Dynamics of wave propagation), realistic models attempt to incorporate detailed features of cardiac tissue including multiple types of ion channels, anisotropy, extracellular medium, and three-dimensional geometries including measured geometries in the individual. Of course, depending on the particular objectives, only a subset of these factors may be included in any particular model. The realistic models are playing an important role in understanding the effects of genetic mutations on ion channels, and the analysis of anti- and pro-arrhythmic drugs on cardiac function (Fenton & Cherry, 2008).

Noble and colleagues pioneered the development of ionic models for cardiac cells. Detailed models now exist for a broad range of cell types and a broad range of species. Since the development of ionic models is based on voltage clamp experiments, development of these models is difficult due to many technical issues, including effects of tissue preparation on ionic properties, differences between homologous ion channels in different species, and variability between different cells of the same tissue type in the same species (Carusi *et al.* 2012; Britton *et al.* 2013; Sanchez *et al.* 2014).

The main observable of the models is the membrane voltage, and after fitting individual currents to available data, the model parameters are adjusted to fit the membrane voltage under some set of physiological conditions. One limitation of the approach is that the resulting models do not necessarily agree with other sorts of experimental data including dependence of cell and tissue properties on stimulation frequency (restitution properties) and the resetting properties of pacemaker cells. Indeed, different models of the same tissue often have important differences when exercised under various stimulation routines (Cherry & Fenton, 2007). A discussion of the problems involved in parameter estimation and possible approaches can be found in an article in this issue (Krogh-Madsen *et al.* 2016).

In parallel with development of realistic ionic models, work is also underway on the development of whole-heart models that incorporate three-dimensional geometry of the heart based on magnetic resonance imaging (MRI). Although the potential for this has been recognized for a long time (Vigmond *et al.* 2001; Virag *et al.* 2002), there are many challenges given the complexity of the anatomy and physiology. However, significant progress has been made in simulation of both atrial and ventricular arrhythmias. Computational models can provide insight into determining potential loci for ablations (Hwang *et al.* 2014; Trayanova, 2014; McDowell *et al.* 2015). Whole-heart modelling of the ventricles based on MRI imaging may also provide a novel approach to risk stratification. Trayanova and colleagues have pioneered this analysis with the study of the induction of VT in 13 patient-specific models (Ashikaga *et al.* 2013; Trayanova *et al.* 2014). Inducibility of VT in the computer model correlates well with the risk of VT or VF in patients with implanted ICDs (Dickfeld *et al.* 2011; Ringenberg *et al.* 2014, 2015) and may play a potential role in risk stratification.

Challenges for risk stratification for SCD

Risk stratification for SCD poses a major problem for clinical medicine. Although ICDs offer the prospect of a life-saving therapy for a subset of patients, they are highly invasive and expensive, and have associated risks due to infection and various types of malfunction including mis-sensing and lead fracture. Since ICDs are not triggered in a large fraction of the patients who receive them, and many patients who experience SCD do not meet current criteria for implantation, there is a need for new approaches (Goldberger *et al.* 2008, 2011; Bastiaenen *et al.* 2012; Bilchick *et al.* 2012; Huikuri, 2015).

Our review of current approaches to risk stratification, theoretical modelling of cardiac dynamics, and dynamics of PVCs makes clear that the range of normal and pathological dynamics is large. Although simple

algorithms and criteria for medical diagnoses and treatments have traditionally provided a basis for decision making in clinical medicine, recent work emphasizes that individual differences must be evaluated in decision making. Personalized or precision medicine, in which individual variability is taken into account for prevention, diagnosis and therapy of disease, has the potential to improve medical care (Collins & Varmus, 2015). Although precision medicine is most often discussed in the context of the influence of genetic differences on cancer biology, we believe that individualized analysis of cardiac dynamics will be an essential component of the application of personalized medicine to cardiology.

Some aspects of cardiac electrophysiology already adopt a personalized approach. Medical procedures involving cardiac ablation to treat arrhythmias involve mapping the intracardiac substrate using a variety of protocols to determine the arrhythmic loci and pathways in each individual. Such procedures are invasive, expensive and require specialized personnel. As mentioned earlier, significant progress is being made to assess the cardiac arrhythmia substrate using MRI combined with whole-heart modelling to identify ablation targets and to do risk stratification for SCD (Trayanova, 2014). Since whole heart models simulate complex anatomy and physiology, these methods now require powerful computational facilities and high levels of technical expertise.

In a recent review, Goldberger *et al.* write, 'Given the desirability of accurate risk stratification [for sudden cardiac death] and the long history of research in this area, it is important to understand why the field is not further advanced.' (Goldberger *et al.* 2011).

We believe that it is possible to do a better job for risk stratification for SCD. However, there is a need for new strategies employing richer data subjected to mathematical analysis and modelling. Until recently, most research has been carried out by clinicians based on data collected over a limited time frame. Since cardiac arrhythmias often have significant fluctuations during the day and tachycardias have paroxysmal onsets, determining the physiological changes that lead to the arrhythmia onset and mechanism presents a problem in data collection as well as a problem in analysis. However, the increasing development of wearable devices, cloud computing, and big data offers the prospect of carrying out analysis of electrocardiographic data with a perspective of developing a better understanding of the mechanisms of arrhythmias and the factors that lead to their onset. We believe that it will be useful to examine fluctuating dynamics of arrhythmias over many hours or days, develop quantitative methods to identify distinguishing features, and carry out simulations of dynamics to compare with the data. Since the changing physiological conditions during the day may lead to bifurcations in the dynamics, it will be necessary for people with mathematical expertise to collaborate with cardiac electrophysiologists to develop appropriate theoretical models. Although this is still at a research stage, it provides the potential for understanding mechanisms of arrhythmias in individuals. We believe that this is a crucial step for the development of better methods for risk stratification for SCD.

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Additional information

Competing interests

The authors hold a patent in the subject matter.

Author contributions

Both authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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