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MECHANISM OF SUDDEN CARDIAC DEATH IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Context: heart failure is a major cause of morbidity and mortality in Europe and in the United States. The aim of this review article was to assess the mechanism of sudden death in patients with heart failure and Identification of the arrhythmogenic substrate in cardiomyopathy.

Evidence Acquisition: Reports published with the following search terms were searched: ischemic cardiomyopathies, idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, arrhythmia, ventricular tachycardia, sudden cardiac death, myocardial scar, Ejection fraction. The investigation was restricted to reports published in English.

Evidence Synthesis: The outcome of this analysis suggests the mechanism underlying SCD is frequently ventricular arrhythmias and these are more common in patients with structural heart disease.

Conclusions: The mechanism underlying SCD is frequently ventricular arrhythmias and these are more common in patients with structural heart disease. NICM is an important and perhaps globally under-recognized form of structural heart disease that may be a significant contributor to SCD

INTRODUCTION

Sudden cardiac death (SCD) is an important cause of mortality worldwide. Sudden cardiac death (SCD) is a term used to signify an abrupt and unexpected cessation of cardiac activity leading to complete hemodynamic collapse and resulting in the death of the victim. (Buxton *et al*., 2006) Autopsy and clinical studies have shown that the presence of structural heart disease increases the risk of SCD, with coronary heart disease accounting for the majority of cases. In up to 20% of cases, coronary artery disease is absent and either non-ischemic cardiomyopathies or primary electrical disorders (channelopathies) are implicated as the causative factor. (Betensky and Dixit, 2014) However, in at least 5% of patients presenting with SCD, a cardiac abnormality remains undetected. (Chugh *et al*., 2000) Although SCD is most often associated with coronary heart disease, the risk of SCD in patients without ischemic heart disease is well-established. Nonischemic cardiomyopathies, including idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy represent three unique disease entities that have been shown to be highly associated with SCD and ventricular arrhythmias.

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A variety of risk stratification tools have been investigated, although the optimal strategy remains unknown. Identification of the arrhythmogenic substrate and treatment of ventricular arrhythmias in these subgroups can be challenging. (Betensky and Dixit, 2014) Although it is difficult to consistently determine the inciting rhythm for many out-of-hospital arrests, some studies have reported ventricular tachyarrhythmias in up to 80% of these patients. (Bayés de Luna *et al*., 1989; Gang *et al*., 2010) Despite these data, the true prevalence of SCD remains unknown. The estimates range from 180,000 to 450,000 cases annually, accounting for approximately 5-20% of the total annual mortality in the United States and other industrialized nations. (Zheng *et al*., 2001)

There have been long-standing efforts to treat those who have previously experienced lethal ventricular arrhythmias and to identify patients at risk of unexpected arrhythmic death. Early attempts involved the use of anti-arrhythmic drugs to reduce arrhythmic death post-myocardial infarction but this was abandoned due to higher mortality associated with these agents. (Echt *et al*., 1991) The advent of implantable cardioverter defibrillators (ICDs) enabled prompt recognition and termination of ventricular tachyarrhythmias, including sustained monomorphic ventricular tachycardia and ventricular fibrillation (VT/VF), leading to a demonstrable survival benefit in both ischemic and non-ischemic

cardiomyopathy (NICM) for primary and secondary prevention of SCD. (NCBI, 2015; Kuck *et al*., 2000; AVID, 1997; Connolly *et al*., 2000) Although ICD therapy has been reproducibly shown to improve mortality in eligible patients, the costs associated with this therapy warrant that it is used appropriately. To that end, a wide variety of noninvasive techniques for risk stratification are available, including LV ejection fraction assessment by echocardiography, QRS duration estimates by surface 12-lead ECG, QT interval/dispersion and heart rate variability, among others. (Goldberger *et al*., 2008) More recently, cardiac magnetic resonance imaging (CMRI) has been put forth as a highly sensitive and specific noninvasive diagnostic modality for delineating myocardial scar in the setting of NICM. (Gulati *et al*., 2013) Invasive electrophysiologic study and/or intracardiac catheter mapping also offer an alternate means of identifying and characterizing arrhythmogenic substrate, although the prognostic value of programmed stimulation remains unclear. Despite the plethora of available options, there is a paucity of randomized clinical trials and a lack of consensus in support of any one diagnostic algorithm that can consistently stratify the risk for sudden cardiac death. The present review addresses the implications for non invasive imaging in identifying high risk of SCD in patients with dilated cardiomyopathy causing heart failure

Mechanism of sudden death

Heart failure is associated with life threatening ventricular arrhythmias. Although about 50% of deaths in patients with heart failure is caused by pump failure, the remainder is associated with cardiac arrhythmias (Tomaselli and Zipes, 2004). The mechanisms of these arrhythmias differ and depend on the underlying electrophysiological changes caused not only by heart failure itself but also by the processes that have led to heart failure in the first place. (Coronel *et al*., 2013)

The primary electrophysiological changes and the mechanism of arrhythmogenesis associated with heart failure therefore depend on the cause of heart failure. This is equally true for the mechanism of the trigger of the arrhythmia as for the electrophysiological substrate. This is one of the explanations why cardiac arrhythmias in heart failure are so difficult to treat and why the choice of the therapeutic approach is not straightforward (Nakahara *et al*., 2010). The electrophysiological changes during heart failure are, therefore, multiple, and dependent on the underlying disease. They involve ion channel remodeling, alterations in calcium handling, remodeling of the extracellular matrix, the presence of scars, activation of the sympathetic nervous system and the renin– angiotensin– aldosterone-system, and dilatation and stretch. In addition, insufficient blood supply associated with heart failure may also affect the heart and may lead to acute myocardial ischemia, with its own arrhythmogenic mechanisms (Janse *et al*., 1980). Thus, heart failure is not characterized by a single set of electrophysiological changes.

Ejection fraction (EF)

Reduced EF is the most widely used marker for increased risk of SCD in patients with ischemic as well as non-ischemic cardiomyopathy and recommendations for implantable cardioverter defibrillator treatment for primary prevention of SCD, now considered standard of care, are heavily dependent on levels of EF (Epstein *et al*., 2008), namely left ventricular ejection fraction of 35% in symptomatic patients (II_III) and < 30% in post MI patients with lesser symptoms. It is immediately obvious that our major guidelines are based on a very crude parameter - EF measurement is highly unreliable with great inter-observer variation (Marwick, 2013) and this is even worse in patients with AF or multiple PVCs, both of which are common and portend SCD. Moreover, SCD is more common in patients with lesser degrees of LV dysfunction and those with the lowest EF die more often with pump failure. Finally, many variables influence arrhythmic death and EF alone is not as predictive in some studies when considered alone. In a study by Buxton *et al*, (Buxton *et al*., 2007) patients with EF $\leq$ 30% without other risk factors had a low mortality risk (2% a year risk of arrhythmic death, suggesting no ICD benefit in the majority) while those with EF > 30% but with other risk factors had higher risk of sudden death than some patients with EF $\leq$ 30%. Not surprisingly, reduced ejection fraction per se, has a low sensitivity and specificity as a risk stratification tool in identifying patients at risk of SCD. (Buxton *et al*., 2007).

Furthermore, most SCD events (in terms of absolute number of cases) occur in patients with preserved left ventricular ejection fraction (Epstein, *et al*., 2008). Thus using EF to stratify for SCD will miss a major portion of subjects prone to SCD. Currently, CMR remains the best option to measure EF. It is highly accurate and reproducible. Radionuclear techniques are also available for EF measurements but suffer from many of the same limitations in patients with abnormal rhythms (e.g. AF). Major working groups have concluded that while current methods of clinical risk prediction are inadequate and LV ejection fraction is effective in only a small subgroup. (Fishman *et al*., 2010) It is however important to remember that most of the trials showing benefit in identification and treatment of patients prone to SCD have used Echo as their main instrument for measuring EF. (Tamene *et al*., 2014)

Mechanisms of Ventricular Arrhythmia

The pathophysiology of ventricular arrhythmias is complex and involves the anatomic and functional substrate, transient factors altering the electrophysiological stability of the sub-strate and proximate mechanisms of arrhythmia. (Bertini *et al*., 2012) In patients with structural heart disease (ischemic heart disease, dilated, and hypertrophic cardiomyopathy), reentry is the most frequent mechanism of ventricular tachycardia/fibrillation (VT/VF). A central area of conduction block (functional or fixed), an unidirectional conduction block and a zone of slow conduction, allowing the impulse to re-excite the tissue proximal to the line of unidirectional block, are prerequisites for reentry to occur and all require certain spatial heterogeneity of the tissue (Schalij *et al*., 2000). In infarcted areas (and their border zones) inexcitable scar tissue is the most common cause of fixed conduction block. Furthermore, the interposition of bundles of scar/fibrous tissue within layers of viable myocytes enhances the degree of non uniform anisotropy, favors electric uncoupling, and creates

areas of unidirectional conduction block and slow conduction. In addition, cellular hypertrophy and changes in the density and distribution of gap junction channels impact strongly on cellular coupling contributing to abnormal conduction and favoring reentrant and focal arrhythymias. (Tomaselli and Marbán, 1999) In addition, transient factors that influence the arrhythmogenic substrate may increase the electric heterogeneity. Myocardial ischemia may enhance regional electric heterogeneity of the myocardium by prolongation of the action potential duration, alteration of calcium handling and myocyte membrane properties, reduced cellular coupling, and redistribution of connexines. (Tomaselli and Zipes, 2004) Furthermore, the association between altered sympathetic innervation and arrhythmia susceptibility is well established. (Zipes and Rubart, 2006) In pathological conditions such as heart failure or long QT syndrome, sympathetic stimulation enhances dispersion of repolarization or induces after-depolarizations contributing to arrhythmogenesis. Also, in ischemic cardiomyopathy, the extent of denervated ventricular myocardium is strongly related to increased arrhythmogenicity. (Cao *et al*., 2000)

Ventricular arrhythmias (VA) have been associated with mortality in idiopathic dilated cardiomyopathy (IDCM). All 3 main mechanisms of arrhythmogenesis - reentry, trigger activity, and automatism - have been implicated. Arrhythmogenic substrates in IDCM favor these mechanisms and are often potentiated by electrolyte imbalance secondary to diuretic treatment, by antiarrhythmic drugs, or by bradycardia, leading to polymorphic ventricular tachycardia (VT). Myocardial macroreentry is the mechanism most frequently responsible for monomorphic VT in IDCM; however, focal activation and His-Purkinje macroreentry are often responsible and, especially in the latter case, are frequently unrecognized. Clinical suspicion and final recognition by electrophysiologic testing have important therapeutic consequences, because both focal activation and His-Purkinje macroreentry can be treated effectively by catheter ablation. On the other hand, the frequent recurrences of myocardial macroreentrant VT after ablation require this therapy to be used in combination with drugs or an implantable cardioverter defibrillator (ICD).

Beta-Adrenoceptor antagonists (beta-blockers) have a beneficial effect for primary prevention of VA in IDCM, type III antiarrhythmics have a neutral effect on mortality and type I antiarrhythmics should be avoided. Treatment of nonsustained VT in IDCM is controversial because it often presents without symptoms and is linked more to overall mortality than to arrhythmic mortality. Empiric treatment with amiodarone or electrophysiologically guided sotalol are preferred to the use of other drugs for secondary prevention of sustained VA. ICDs should be implanted in patients who have been resuscitated from cardiac arrest due to VA, or in those with poorly tolerated VT and severe left ventricular dysfunction. Empiric treatment with amiodarone or electrophysiologically guided class III antiarrhythmics may also be alternatives for patients with IDCM and no severe left ventricular dysfunction, especially if VT is well tolerated. (Merino, 2001) In the last years, noninvasive imaging has provided important insight into the identification of patients at risk of SCD by characterizing the arrhythmogenic substrate and its interaction with different transient factors that modulate mechanisms of arrhythmia. Current noninvasive imaging modalities, such as MRI and nuclear imaging provide important information on extent and location of myocardial fibrosis. However, the role of noninvasive imaging modalities to evaluate the relative contribution of other molecular and cellular determinants of abnormal conduction remains unexplored.

Myocardial scar

Myocardial scar is often an area where collagen weaves around islands of varying degree of viable myocytes, and is a strong substrate for arrhythmogenesis. It creates tissue in-homogeneity, allows slow conduction and re-entrant currents that underlie malignant arrhythmias. (Bello *et al*., 2005) Not surprisingly, risk of SCD in both IHD and non IHD patients tracks scar burden and scar tissue heterogeneity measured with cardiac magnetic resonance. (Bello *et al*., 2005) Scar can be assessed by any number of methods including Echo & nuclear imaging studies, but late gadolinium enhancement on cardiac magnetic resonance (LGE-CMR) is currently the 'gold-standard' in imaging for myocardial scar. (Bello *et al*., 2005) LGE has been validated to represent fibrosis and an expansion of extracellular volume in ischemic as well as non-ischemic heart disease While an attractive parameter, measuring scar is tricky (Flett *et al*., 2011) and there is no consensus on the standard method for myocardial scar quantification.

Most predictive CMR techniques, for SCD risk stratification, are based on the fact that the signal intensity (SI) of an infracted area or fibrotic area (scar) post Gadolinium (late gadolinium enhancement -LGE) is higher than that of the normal myocardium. LGE is expressed as signal intensity and there are various ways of differentiating abnormal from normal. A simple schema uses LGE SI > 2SDofa remote non-involved myocardium, while another used between 2 and 3 SD, but even higher SD cut off values have also been used. (Flett *et al*., 2011) Peri-infarct gray zones have been defined variably: peri-infarct and core-infarct zones as LGE-SI between 2 and 3 SD and greater than 3 SD of the reference myocardial segment respectively or as having SI that is between normal myocardium and <50% of infarct core SI. Scar heterogeneity has also been studied in non-ischemic cardiomyopathies like HCM, where one strategy used values 4SD but < 6 SD above the mean signal intensity of normal myocardium for intermediate LGE-SI while threshold of 6 SD above normal myocardium was considered high LGE-SI. Scar has been quantified by manual or automated techniques for tracing regions of interest.

Identification of structural heart disease

Structural heart disease portends an increased risk for SCD and imaging provides the best ability to map and characterize cardiac structure. Thus identification of cardiac structure is often the first step in trigging for SCD risk; however, while abnormal structure is predictive of SCD, most of the population-attributable risk (PAR) of SCD is in subjects without any known structural abnormalities. This makes it a less productive method in general screening for SCD. Both, ventricular viability and LV dyssynchrony, are associated with

increased risk of ventricular arrhythmias and cardiac resynchronization therapy (CRT) has been shown to reduce this risk. (Kutyifa *et al*., 2013; Cleland *et al*., 2013) Both viability and dyssynchrony can be best characterized through imaging and remain targets in the evaluation for SCD However, just as with structural heart disease in general, its population based efficacy for screening remains poor.

Anatomic and electrophysiologic substrate for ventricular tachyarrhythmias leading to SCD in patients with an ICM

In the course of time after the onset of myocardial infarction, the loss of myocardium and the associated loss of contractile function are compensated by cardiac hypertrophy. Eventually, this may result in failure.

Heart failure is associated with an increased risk of sudden death caused by ventricular tachyarrhythmias. The role of altered repolarization in the formation of arrhythmogenic substrates and triggers has been studied at multiple levels of integration, including molecular, cellular, tissue, and organ levels. Numerous studies have focused on conduction abnormalities in the context of ischemic heart disease and left ventricular dysfunction after myocardial infarction. However, ischemia alone, independent of left ventricular dysfunction, alters conduction by depressing membrane excitability and increasing tissue resistivity (Akar and Tomaselli, 2005)

Left-ventricular systolic dysfunction, or heart failure (HF), is a chronic, progressive condition with a poor prognosis. Approximately 50% of deaths, especially in mild to moderate cases, are sudden. Most sudden deaths are thought to be due to ventricular tachycardia; however, premature ventricular contractions and couplets parallel severity of HF and have been associated with increased mortality risk as opposed to dysrhythmic death. Ventricular arrhythmogenesis results from many mechanisms (afterdepolarizations, reentry, and enhanced automaticity) and preconditions (electrophysiologic abnormalities, neuroendocrine activation, electrolyte imbalances, scar from an ischemic event in ischemic cardiomyopathy, fibrosis in dilated cardiomyopathy, hemodynamic abnormalities, and HF medical management. (Albert, 2004)

Catheter ablation is less likely to result in arrhythmia prevention if the substrate is based on a wandering rotor in a substrate of fine fibrosis. The challenge for clinical cardiology is to identify the type of structural remodeling in each patient with heart failure and thereby to identify the best therapeutic options. Apart from the key requirements for arrhythmogenesis, many modulatory factors play a role (Coumel, 1987). Examples of the modulation of the triggering and substrate are the influence of the autonomic nervous system, pharmacological treatment, mechanical action of the heart and diet.

Wall motion

Heart failure is a common consequence of myocardial infarction and often involves abnormal wall motion in some parts of the heart. Abnormal wall motion is a strong predictor of sudden cardiac death (Tracy *et al*., 1987). Myocardial stretch and dilatation are associated with opening of stretch sensitive ion channels and with arrhythmias (Wang *et al*., 1994). Kamkin *et al*. have demonstrated that myocytes from human, guinea pig and rat hearts show membrane depolarization upon stretching, action potential prolongation and spontaneous activity. The membrane current underlying these changes was inhibited by Gadolinium, and the changes were more outspoken in hypertrophied myocytes (Kamkin *et al*., 2000). In a recent paper, Opthof *et al*. have reported on the role of wall motion abnormalities on dispersion in repolarization in patients (with and without previous myocardial infarction) undergoing cardiac surgery (Opthof *et al*., 2012). Local unipolar electrograms were obtained from up to 72 left ventricular epicardial sites and activation recovery intervals (ARIs) were measured as an index of action potential duration. Wall motion was measured simultaneously with esophageal echocardiography in 9 left ventricular regions of the heart. It appeared that in the presence of wall motion abnormalities the difference of ARIs between the 9 regions of the heart was larger than in patients without wall motion abnormalities, independent of the presence of myocardial infarction. Importantly, the overall increased dispersion in ARIs was caused by increased dispersion of ARIs within the normally moving myocardium. The dispersion in ARIs also was associated with dispersion in repolarization time, which forms one of the required substrates for the initiation of reentry (Coronel *et al*., 2009) . In summary, these data suggest that wall motion abnormalities may directly create or increase the substrate for reentrant arrhythmias. (Opthof *et al*., 2012)

Right ventricular failure

Right ventricular (RV) failure develops as a consequence of a variety of pathological condition such as RV infarction, pulmonary hypertension, genetic disorders (e.g. arrhythmogenic right ventricular cardiomyopathy (ARVC)), or in the context of corrected congenital cardiac disease such as surgical repair of Tetralogy of Fallot (TOF). It can also occur secondary to left-sided heart failure. RVs regardless of the anatomical origin (left or right side) of heart failure (Lou *et al*., 2012) suggesting that the RV might be involved in arrhythmia generation and maintenance independent of the ventricular origin of heart failure.

Although RV arrhythmias and sudden cardiac death are common features of these pathological conditions (Zipes *et al*., 2006), the electrophysiological remodeling and the mechanisms involved in arrhythmia generation in the failing RV remain relatively understudied compared to the left ventricle (LV). APD prolongation, a hallmark of LV heart failure, has also been consistently observed in the failing RV myocardium (Lambert *et al*., 2010). On the ECG of patients with RV dysfunction, this prolongation is typically reflected by an increased duration of the QT-interval (Turrini *et al*., 2001) although a concomitant electrophysiological remodeling of the LV is also likely to contribute to this effect (Hardziyenka *et al*., 2012). In the pressure-overloaded RV of the rat, the APD prolongation appeared to be related to a decrease in the expression of the main potassium channels (Benoist *et al*., 2011). APD dispersion is also increased in the failing RV when measured in isolated ventricular myocytes (Umar *et al*., 2012) and at the RV epicardial surface of

perfused isolated hearts where the right ventricular out flow tract shows the longest APD (Benoist *et al*., 2012). Conduction abnormalities are commonly found in right heart failure and are linked not only to changes in the expression, localization and phosphorylation of gap junctions (Uzzaman *et al*., 2000), altered sodium current properties (Kaplan *et al*., 2004), and fibrosis (Cerrone *et al*., 2012) but also to scars in ARVC and TOF patients after corrective surgery (Marra *et al*., 2012). Indeed, an increased duration of the QRS interval of patients with repaired TOF or ARVC reflects activation delays (Steriotis *et al*., 2009) and loss of synchronicity (Tops *et al*., 2009). The presence of QRS fragmentation, which is related to scar size, is a good predictor of arrhythmias in these pathological conditions (Shanmugam, *et al*., 2013). Electrical maladaptation to a change rate observed in the failing RV in the form of steep APD and conduction velocity (CV) restitution curves, could lead to alternans, an established predictor of sudden cardiac death (Benoist *et al*., 2012). As in LV failure, altered calcium homeostasis is also likely to play an important role in RV dysfunction and arrhythmogenesis. Sarcoplasmic reticulum (SR) calcium leak has been described in ARVC where it has been shown to be related to mutations of the ryanodine receptor (Tiso *et al*., 2001). SR calcium leak was also described in failing RV myocytes of pulmonary hypertensive rats but the underlying mechanisms were different and involved a SR calcium overload likely to be related to (i) an increased calcium entry due to the APD prolongation and (ii) a decreased sodium/calcium exchanger function (Benoist *et al*., 2012). In the latter study calcium transient alternans was commonly observed at high pacing rates (9 Hz). This may contribute to or result from electrical alternans observed in vivo and ex vivo (Coronel *et al*., 2013)

The specific shape and thickness of the RV make it sensitive to changes in diastolic volume and the failing RV is typically dilated and thus exposed to a greater level of stretch than its left counterpart. RV stretch consecutive to chronic pulmonary regurgitation has been shown to contribute to arrhythmia generation by decreasing APD (unlike the APD increase commonly observed in models of pulmonary hypertension), increasing APD dispersion and slowing conduction velocity (Gray *et al*., 2003) via the activation of mechanosensitive channels (White, 2006) for review). In patients with repaired TOF, a good correlation has been found between RV dilatation, QRS duration and the incidence of ventricular tachycardia (Gatzoulis *et al*., 1995) and RV mechanical dispersion was increased in ARVC patients presenting with life-threatening arrhythmias (Sarvari *et al*., 2011)

Anatomic and electrophysiologic substrate for ventricular tachyarrhythmias leading to SCD in patients with a NICM

We will focus primarily on idiopathic dilated cardiomyopathy (IDCM) with additional sections on hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC)

Idiopathic dilated cardiomyopathy (IDCM)

IDCM is a term used to represent both genetic and non-genetic disorders characterized by impaired ventricular systolic function and enlargement of the ventricular cavity size in the absence of obstructive coronary artery disease or prior myocardial infarction as well as other well known causes of cardiac dysfunction such as valvular and hypertensive heart disease (Buxton *et al*., 2006). It is now well accepted that the arrhythmogenic substrate in NICM is characterized by patchy, layered fibrosis and irregular myocyte disarray usually in a perivalvular distribution with a propensity for the mid-myocardial and epicardial layers. (Unverferth *et al*., 1986)

Conduction abnormalities in nonischemic dilated cardiomyopathy: basic mechanisms and arrhythmic consequences. (Akar and Tomaselli, 2005)

In the heart, impulse conduction depends on several factors, including intrinsic membrane excitability, intra- cellular and extracellular resistivities, and cell-to-cell coupling. Evidence for conduction slowing in human HF has emerged over the years (Hombach, 2002). In early studies, it was recognized that some HF patients exhibited a prolonged QRS duration and/or a delay in the low-frequency terminal portion of the QRS complex of their signal-averaged electrocardiograms (SAECG). Such delays indicated presence of ventricular late potentials (LPs) that were associated with myocardial conduction slowing. Importantly, prolonged QRS and LP have been described in patients who have both ischemic and nonischemic causes of HF. Thus, ventricular conduction delay appears to be an integral part of the electrophysiological substrate in both etiologies of HF (Middlekauff *et al*., 1990)

By definition, anisotropic propagation, a hallmark of myocardial conduction, refers to the fact that the speed of impulse propagation varies depending on the direction in which it is traveling. For example, CV along myocardial fibers is significantly faster than that across fibers, thereby resulting in an elliptical rather than a circular spread of membrane depolarization away from a point stimulus, such as a pacing electrode or an insertion point of the His-Purkinje network into the myocardium. The fast axis of impulse propagation is oriented along cardiac fibers where tissue resistivity is lowest, whereas slow propagation is oriented across fibers. In the heart, overall tissue anisotropy varies depending on age, tissue type (i.e., crista terminalis vs. ventricular myocardium), and presence or absence of disease. Interestingly, in diseased hearts, regional changes in tissue properties result in nonuniform anisotropy of impulse propagation (Peters and Wit, 1998), which can promote reentrant arrhythmias (named anisotropic reentry). This occurs when impulse conduc- tion proceeds slowly but safely (low likelihood of conduction block) in the transverse direction and rapidly but unsafely (higher likelihood of conduction block) in the longitudinal direction. Under these circumstances, conduction block can readily form parallel to cardiac fibers where tissue resistivity is low and the loss of net depolarizing charge to downstream cells (i.e., electrotonic sink) is high (Spach *et al*., 1988)

A prominent role for conduction slowing in the genesis of arrhythmias and sudden death in HF has emerged over the past two decades. Clinically, the presence of highly fractionated electrograms and LPs in high-risk patients is a hallmark of slowed conduction, which predisposes to reentrant arrhythmias. The nature of conduction slowing appears to vary depending on the etiology of the disease. Whereas in ischemic

hearts conduction slowing is localized at the border zone of the MI, in nonischemic cardiomyopathic hearts, there is evidence for global conduction slowing involving both ventricles. The anisotropy of conduction also depends on the disease etiology.Whereas anisotropy is heterogeneous across the ischemic failing heart, predisposing to anisotropic reentry, it is not altered in at least three different models of nonischemic HF. The principal cellular and molecular determinants of conduction in ventricular myocardium are the availability of Na current, the size and shape of ventricular myocytes, the quantity and distribution of fibrous tissue, and cell- to-cell coupling. The contribution of each of these to conduction slowing varies between ischemic and nonischemic models and within each disease etiology. However, changes in the expression, distribution, and function of the principal ventricular gap junction protein, Cx43, appear to play a significant functional role in conduction abnormalities and arrhythmias in both ischemic and nonischemic cardiomyopathies. Therefore, a better understanding of the fundamental mechanisms controlling the degree of cellular coupling, including the critical signaling cascades that influence gap junction structure, function, and distribution, is necessary. Finally, the relative contributions of changes in the interstitium, myocyte dimensions, and ion channels to conduction slowing will be required for a more comprehensive understanding of arrhythmias in HF. (Akar and Tomaselli, 2005)

Initially developed to detect necrosis caused by myocardial infarction, cardiac MRI has shown distinct scar patterns in patients with NICM (Wu *et al*., 2001). Although echocardiography is the most widely used modality for assessing cardiac function and CMRI is more helpful for characterizing structural abnormalities. Others authors have found this modality useful for prognostication. (Gulati *et al*., 2013)

Hypertrophic cardiomyopathy (HCM)

HCM is a genetically determined disorder of the heart muscle, most frequently associated with mutations of the sarcomere. Clinically, HCM is characterized by pathologic left ventricular hypertrophy, which can lead to a variety of dynamic obstructive patterns.

Histopathologic hallmarks of HCM include myocyte hypertrophy with regions of myocyte disarray, variable fibrosis and small-vessel disease. (Davies, 1984; Anderson *et al*., 1979) Disorganization of the gap junctions has been found, with dispersion of intercellular proteins around the myocytes leading to altered electromechanical coupling and ultimately, ventricular arrhythmias. There is also marked increase in interstitial collagen leading to areas of dense scarring, often worse in the septum compared to the free wall. (Hughes, 2004) These structural abnormalities are not apparent on echocardiography but may be seen by CMRI, which has become a useful adjunctive imaging modality for this condition. Arrhythmogenic substrate in HCM is considered to be the conduction delay due to the myocyte disarray and interstitial fibrosis. Extent of fibrosis is one of the important predictors of arrhythmic events and delayed contrast-enhancement cardiac magnetic resonance (CMR) has been shown to be useful to provide information on the extent and distribution of fibrosis. Delayed enhancement abnormalities (DEA) on CMRI can be seen in 40-80% of these patients and when present, DEA are often patchy, mid-myocardial and multifocal. (To *et al*., 2011) Confluent areas of septal scarring have also been observed and, in our experience, patients with HCM have a high prevalence of mid-myocardial scarring. It should also be noted, that a subset of patients with HCM may develop progressive LV failure and dilation, and ultimately possess a phenotype that overlaps with IDCM. (Ueda *et al*., 2012)

It has been proved pathologically that the extent of late gadolinium enhancement had good relation with distribution of collagen tissue. (Moon *et al*., 2004) Previous reports presented the apical wall thinning and fibrotic changes at the origin of VT in patients with mid-ventricular obstruction or apical hypertrophy. (Lim *et al*., 2009) Ueda and al reported that the VT circuits in the DHCM patients were located at the basal septum or the basal anterior to anterolateral LV, which are quite different from other HCM subsets (Inada *et al*., 2011). Santangeli *et al.* (Santangeli *et al*., 2010) reported that the most common location of reentry circuits were the LV–RV junction in patients with HCM without apical hypertrophy. Other pathological or radiographical studies on fibrosis distribution were also similar to our results. (Satoh *et al*., 2009) Also, these arrhythmogenic lesions tended to appear to exist not endocardially but epicardially or deeply intramural, which would explain the difficult (Ueda *et al*., 2012)

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is a genetically determined heart muscle disorder characterized by fibrofatty replacement of the ventricular myocardium. (Marcus *et al*., 2010) While the RV is most commonly affected, involvement of the LV can also occur (Sen-Chowdhry *et al*., 2008). Hearts of patients with ARVC manifest RV dilation, wall thinning and ventricular microaneurysms. Histopathology studies have shown that the myocardium is atrophied and replaced with fibrofatty material, largely affecting the midand epicardial layers (Corrado *et al*., 1997). When the clinical suspicion is high, CMRI imaging is commonly employed during our workup looking for pathognomonic changes of the myocardium. These may be best visualized by using T1-weighted imaging and fast spin-echo MRI combined with fat suppression (Sen-Chowdhry *et al*., 2006; Tandri *et al*., 2005). The mechanism underlying VT in these patients is usually reentry and ablation can be effective therapy, although it may require more than one attempt to adequately target the circuits fromthe endocardium and epicardium.

Conclusion

SCD is a major health problem worldwide. The mechanism underlying SCD is frequently ventricular arrhythmias and these are more common in patients with structural heart disease. NICM is an important and perhaps globally under-recognized form of structural heart disease that may be a significant contributor to SCD. The optimal strategy for risk stratification is yet to be determined in patients with NICM,

particularly those with IDCM, HCM or ARVC. ICD therapy has been shown to be useful for reducing arrhythmic death in patients with ICD and NICM. However, long-term management of devices, especially in patients with NICM can be challenging because of the younger population age and related issues.The implantable cardioverter defibrillator (ICD) is the most effective therapy for the prevention of sudden cardiac death (SCD) in adults with life threatening ventricular tachyarrhythmias.

Recent clinical trials have shown a mortality benefit from the prophylactic implantation of ICDs in patients with coronary artery disease and left ventricular systolic dysfunction. However, despite the mortality benefit conferred by ICDs, even appropriate ICD shocks may cause significant psychological effects, most commonly depression and anxiety, which may worsen patients' quality of life. Studies have also suggested that patients who receive ICD therapy are at an increased risk of developing non-sudden cardiac death. These factors emphasize the need for improved selection of patients who would benefit most from the ICD. Better risk-stratification tools are needed to identify the best candidates for implantable cardioverter defibrillator implantation. Since the risk of SCD in an individual may change with time, serial testing using one or more of the above modalities may be indicated.Nevertheless, a multifaceted and systematic approach comprising careful analysis of 12-lead ECG, advanced imaging techniques such as CMRI and invasive electroanatomic mapping, can often help delineate and characterize the arrhythmogenic substrate in these patients. Infarct characterization by cardiac magnetic resonance (CMR) has become an evolving potential tool for risk stratification.

Despite decades of progress, further research is necessary for refining our ability to risk stratify these patients in order to minimize SCD in those considered at high risk. Finally, better tools are needed to identify and target the arrhythmogenic substrate that underlies ventricular arrhythmias in this unique patient population.

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