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Review Article

Sudden cardiac death in patients with nonischemic cardiomyopathy

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ABSTRACT

Sudden cardiac death (SCD) is an important cause of mortality worldwide. 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. 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. Herein, we aim to discuss the current understanding of the anatomic and electrophysiologic substrate underlying ventricular arrhythmias and highlight features that may be associated with a higher risk of SCD in these 3 conditions.

1. Introduction

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.[1] 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.[2] However, in at least 5% of patients presenting with SCD, a cardiac abnormality remains undetected.[3] 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.[4,5] In contrast, studies of in-hospital arrest suggest that as many as 80% of these events are asystole or PEA and only 20% are VT/VF.[6] 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.[7–9] Interestingly, despite the advances in the management of cardiovascular disease, the overall prevalence of SCD has remained largely unchanged.

There have been long-standing efforts to treat those who have previously experienced lethal ventricular arrhythmias

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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.[10] 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.[11–16] 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.[17] More recently, cardiac magnetic resonance imaging (CMRI) has been put forth as a highly sensitive and specific non-invasive diagnostic modality for delineating myocardial scar in the setting of NICM.[18,19] 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.

In this review, we aim to discuss the 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). Our goals are to illuminate clinical features that may be associated with a higher risk of SCD and to provide commentary on challenging electrophysiologic features in these scenarios that may have implications for further risk stratification.

2. Idiopathic dilated cardiomyopathy (IDCM)

2.1. *Background*

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.[20] Its prevalence is estimated to be 1:2500 with up to 35% considered familial in origin and the remainder occurring secondary to infection, toxins, autoimmune, neuromuscular and nutritional disorders.[8,20] Some studies estimate that 50% of cardiomyopathy cases are without an identifiable cause and are therefore labeled “idiopathic”.[21] Non-sustained ventricular arrhythmias and ventricular premature depolarizations (VPDs) are common in this patient population but sustained VT is less frequent, reported in only 5%.[22–24] However, it is possible that these estimates are flawed and the prevalence of sustained VT may be higher. In landmark primary prevention ICD trials, rates of appropriate ICD therapy for sustained VT/VF have ranged from 18 to 31% in this population.[16,25,26]

2.2. *Anatomic and electrophysiologic substrate*

Limited data from small necropsy series of patients with IDCM reveal both areas of grossly visible scar and regions of irregular/patchy fibrosis intertwined with surviving myocytes.[27–29] These studies helped to shape our initial understanding of the VT substrate in IDCM, which has been further enhanced by cardiac MRI studies. Initially developed to detect necrosis caused by myocardial infarction, cardiac MRI has shown distinct scar patterns in patients with NICM.[30,31] 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.[29]

Catheter-based substrate mapping and ablation of ventricular arrhythmias in NICM was modeled after the technique used in ICM.[32,33] In a seminal paper by Marchlinski et al, initial voltage criteria for normal and abnormal tissue were established and a linear ablation strategy for interrupting the VT circuit was proposed. The electroanatomic substrate abnormalities were commonly found in the basal-lateral/perivalvular region with an unusual predilection for the mid-myocardial and epicardial layers (Fig. 1).[34–36] Early observations during percutaneous epicardial electroanatomic mapping showed the presence of fat in the perivalvular region could mimic scar and thus more specific signal criteria were established to distinguish the two.[37,38] It is important to note that the interventricular septum can also harbor the substrate for VT in IDCM and may be missed by routine catheter mapping due to a rim of healthy adjacent tissue (Fig. 2).[39] Recently, our group has demonstrated that delayed conduction across the interventricular septum may be an additional method for identifying intramural substrate abnormalities.[40]

The importance of the routine surface 12-lead ECG in deciphering the underlying arrhythmogenic substrate should be emphasized. The ECG markers of delayed activation may be subtle in patients with IDCM. Nevertheless, research by our group has shown that basic QRS measurements during sinus rhythm may help identify patients with IDCM manifesting basal-lateral VT substrate.[41] A simple three-step algorithm (including lateral lead QRS fragmentation, absence of inferior Q waves, and lead V6 S wave to R wave ratio) may also be useful for distinguishing the presence of nonischemic from ischemic VT substrate in a similar distribution.[42]

2.3. *High-risk features*

Risk stratification of SCD often includes an assessment of 1) myocardial substrate 2) repolarization abnormalities and 3) the autonomic nervous system (Table 1). In terms of myocardial substrate abnormalities, reduced LV ejection fraction has been repeatedly shown to be the most robust