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Noninvasive imaging markers associated with sudden cardiac death

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ABSTRACT

Sudden cardiac death (SCD) accounts for approximately 15–20% of all deaths worldwide. While the majority of SCDs occur in adults, children, and adults <35 years (<1%) may also be affected. Currently the most effective strategy for both primary and secondary prevention of SCD is the implantable cardioverter-defibrillator (ICD). However, identification of patients who will benefit from ICD implantation remains challenging. Left ventricular ejection fraction (LVEF) is the most frequent imaging parameter used to select patients for ICD implantation for primary prevention. However, LVEF has shown to be suboptimal for prediction of benefit. Non-invasive cardiac imaging permits characterization of the arrhythmogenic substrate, including dispersion of electromechanical activation, presence of myocardial scar, and cardiac innervation status. The arrhythmogenic substrate may change across the different underlying diseases. While in ischemic cardiomyopathy, differentiation and characterization of infarct core and peri-infarct zone have been shown to refine the risk stratification of patients, in non-ischemic cardiomyopathies, the substrate may be more heterogeneous and tissue characterization assessing focal and diffuse fibrosis and inflammation processes may be more relevant. Furthermore, in channelopathies, assessment of mechanical dispersion between myocardial layers may identify the patients with increased risk of ventricular arrhythmias. Finally, potential triggers of ventricular arrhythmias such as myocardial ischemia can be evaluated. The role of noninvasive imaging in the risk stratification of SCD and the selection of candidates for ICD will be discussed in this article.

Keywords: Cardiovascular imaging, Sudden cardiac death.

Introduction

Sudden cardiac death (SCD) is defined by the World Health Organization as an unexpected death that occurs within 1 h from the onset of symptoms in witnessed circumstances, or within 24 h from when the individual was last observed alive and asymptomatic—in the case when death occurs in unwitnessed circumstances [1].

The occurrence of SCD as a result of cardiac arrest (mainly due to ventricular tachycardia or fibrillation [VT/VF]) is responsible for about one-fifth of all global deaths. Despite universally improving outcomes of resuscitation, most individuals experiencing a sudden cardiac arrest expire. While SCD occurs most frequently in older individuals with acquired structural cardiac disease, it may also occur in younger persons in whom it is often due to inherited

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disorders. The most common cause of SCD is coronary heart disease, followed by cardiomyopathies, inherited arrhythmia-related syndromes, and valvulopathies [2].

The implantable cardioverter-defibrillator (ICD) is the most effective strategy for the prevention of SCD, associated with 50% relative risk reduction in arrhythmia-related death in secondary prevention [3], and 54% relative risk reduction in primary prevention [1].

An LVEF $\leq$ 35% is currently the imaging-based variable to select patients who may benefit from an ICD [4,5]. However, LVEF has been shown to be an insensitive marker to predict SCD. By solely relying on this parameter, 65% of SCD victims would not receive an ICD [6]. Furthermore, among patients with an LVEF $\leq$ 35%, up to 65% of recipients of an ICD will not have had appropriate therapy 3 years after insertion [7–9]. The preeminent reason for LVEF being nonspecific is that it also predicts non-SCD events [10]. LVEF in isolation is therefore a suboptimal risk-stratifier, necessitating superior strategies to select the most appropriate candidates for ICD implantation [9].

An improved methodology for risk stratification is required not only for the cost-effective use of ICDs, but also to limit exposure of recipients of these devices to inappropriate electrical shocks and potential infections. Noninvasive imaging techniques, e.g., echocardiography, cardiac magnetic resonance (CMR) imaging, and nuclear imaging, have emerged as promising modalities to assess the arrhythmogenic substrate and identify the patients who will benefit from an ICD implantation. These modalities may be used, in addition to electrophysiological parameters and genetic markers of SCD.

Imaging underlying mechanisms of SCD

A contemporary view of the pathophysiology of SCD, holds that arrhythmogenic substrates are acted upon by certain triggers to cause life-threatening arrhythmias (Fig. 1) [2]. Examples of these arrhythmogenic substrates are the presence of scar tissue (especially when interspersed with viable myocardium), myocardial hypertrophy, and channelopathies; whereas triggers include transient ischemia, mechanical stretch, sympathetic activity (and an abnormal response to stimulation), electrolyte disturbances, myocardial inflammation, and the time of day [2,11]. An example of this interaction between an underlying arrhythmogenic substrate and a trigger is the presence of scar tissue from a previous myocardial infarct, which *per se* is electrically inactive, and which then interacts with ischemia in the peri-infarct zone [12,13]. Exercise is a common trigger, for example, in arrhythmogenic, right ventricular cardiomyopathy, and in type 1 long-QT-syndrome, while emotional stress or auditory stimuli can provoke dysrhythmias in type 2 long-QT-syndrome. All the foregoing effects probably reflect autonomic nervous system activity [1,14]. In addition, in hypertrophic cardiomyopathy, an afternoon, and evening circadian periodicity of VT has been described in contrast to the early morning pattern described in ischemic heart disease [15]. Specific factors that transcriptionally control the circadian expression of ion channels may explain the different diurnal patterns of VT and SCD for each underlying substrate [16].

Many of these arrhythmogenic substrates and triggers can be characterized with current imaging techniques.

Imaging pathophysiology of SCD

Coronary artery disease and SCD

SCD can occur by means of scar-related VT/VF, ischemia-induced polymorphic VT, mechanical complications (e.g., myocardial free wall rupture) in the aftermath of a myocardial infarction (especially in the first month post-infarction), and pump failure/brady-arrhythmias in chronic, ischemic cardiomyopathy [2].

Ischemia acts as a trigger of reentry in a peri-infarct zone that is anatomically and functionally integrated with an area of post-infarct scar formation. Ischemia can also function as the immediate cause of arrhythmias (mostly polymorphic VT) in an area of viable myocardium. Therefore, assessment of extent and characteristics of myocardial scar and the factors that may change the myocardial scar properties are the endpoints of non-invasive imaging for risk stratification of patients with ischemic heart disease (Table 1).

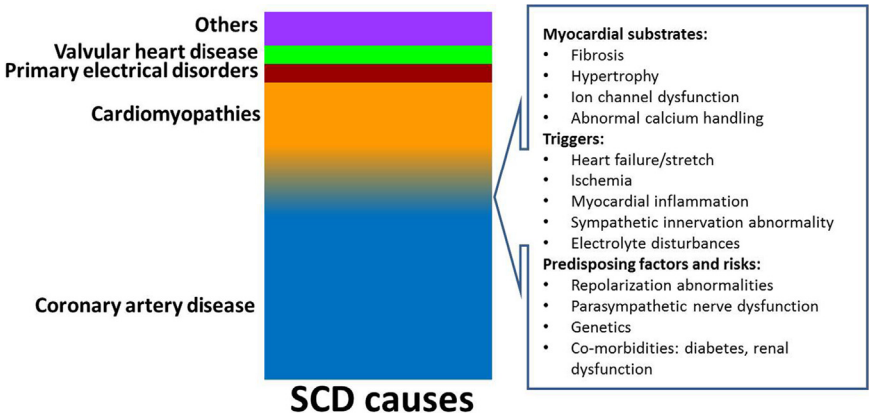

Fig. 1 – Causes of sudden cardiac death, myocardial substrate and substrate modulators. Coronary artery disease is the most frequent cause of SCD. Myocardial fibrosis is a common arrhythmogenic substrate to many SCD causes. (Adapted from Hayashi et al. [2].)