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Evaluation of Sudden Cardiac Death, Using Cardiovascular Magnetic Resonance

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Abstract

Coronary artery disease is the most frequent cause of SCD in individuals over the age of 30, while hypertrophic cardiomyopathy in those below 30 years of age. Cardiac magnetic resonance (CMR), a noninvasive, non-radiating technique, can reliably perform evaluation of 1) cardiac function through assessment of ventricular volumes and ejection fraction and 2) tissue characterization through oedema, fat and fibrotic substrate assessment. The presence of scar has been linked to ventricular arrhythmias, which is believed to be the major cause of SCD in both ischemic and nonischemic cardiomyopathy.

The extent of late gadolinium enhancement (LGE) in hypertrophic cardiomyopathy is correlated with risk factors of SCD. In idiopathic dilated cardiomyopathy, the presence of midwall fibrosis, assessed by CMR, also predicts SCD. In coronary artery disease, infarct size is the strongest predictor of SCD. LGE around infundibular patch and RV anterior wall, among other functional parameters, also play an important role in SCD prediction in repaired Tetralogy of Fallot (TOF). Finally, in treated transposition of great arteries (TGA), the extent of LGE in systemic RV also correlates with SCD development.

Keywords: Cardiac arrest; Sudden death; Cardiac magnetic resonance

Introduction

Sudden cardiac death (SCD) is responsible for 5.6-15% of annual mortality in USA [1] and represents the major cause of mortality in heart failure and coronary heart disease. Prediction of sudden cardiac death (SCD) still remains a major challenge for Cardiology. Coronary artery disease is the most frequent cause in individuals over the age of 30, while hypertrophic cardiomyopathy in those below 30 years of age [2]. Medication and/or implantable cardioverter defibrillator (ICD) is the treatment of choice in patients at high risk of SCD [2]. According to MADIT-II and SCD-HeFT trials [3], current guidelines recommend an AICD implantation as a class I indication for primary prevention of SCD in patients with a left ventricular ejection fraction (LVEF) ≤ 30% and in those with LVEF ≤ 35% that are New York Heart Association (NYHA) heart failure class II or III [4]. Although current guidelines recommend the LVEF as the best index for patients risk stratification for AICD implantation [4], the majority of patients receiving an AICD for primary prevention do not utilize this high cost therapy [5]. In contrary, patients with LVEF > 35% may develop lethal ventricular arrhythmias. Therefore, there is a need for better risk stratification of patients at high risk for SCD by evaluating other indexes that may play a role independently or in parallel with LVEF [6-8] in SCD prediction.

Accurate identification of patients at high risk for SCD still remains a diagnostic dilemma. In non-ischemic cardiomyopathy (NISC) with heart failure, female gender, age, lack of statin therapy and increased creatinin are independent risk factors for malignant arrhythmias [9]. In a recent prospective, longitudinal study of 472 patients with dilated cardiomyopathy referred to a UK center for CMR imaging, it was documented that the assessment of midwall fibrosis, using late gadolinium enhanced cardiovascular magnetic resonance imaging (LGE) provided independent prognostic information beyond LVEF in patients with nonischemic dilated cardiomyopathy [10]. Residual ischemia, reduced left ventricular ejection fraction (LVEF), electrical instability, frequent ventricular ectopic activity and impaired autonomic status are conventional risk factors for SCD prediction in coronary artery disease (CAD). However, CAD patients with EF < or = 30%, but no other risk factors, have low predicted mortality risk, in contrary to those with EF > 30% and other risk factors, who have higher mortality and higher risk of sudden death, than those with EF < or = 30% [11,12].

There is increasing evidence suggesting a relationship between myocardial scar and arrhythmogenicity [13-16]. Scar can be accurately visualized using LGE and there is a proven histopathological correlation for this link. The presence and extend of a scar may provide a substrate for ventricular arrhythmias [17,18]. Recently, the presence, location and morphology of scar, assessed by LGE, were proved of value in the identification of SCD background. Subendocardial and/or transmural LGE, following the distribution of coronary arteries, indicates the presence of CAD. Intramyocardial and/or subepicardial LGE, unrelated with the distribution of coronary arteries, is indicative of myocarditis and /or cardiomyopathy. LGE, located in the free wall of right and possibly left ventricle, is characteristic of arrhythmogenic right ventricular cardiomyopathy (ARVD/C) [19]. Furthermore, the percentage of LGE was proved a powerful factor of SCD prediction. Data from one hundred thirty-seven patients undergoing evaluation for possible ICD placement during a median follow-up of 24 months, proved that in patients with LVEF > 30%, the presence of significant scarring (> 5% LV) identifies a high-risk cohort similar in risk to those with LVEF ≤ 30%. Conversely, in patients with LVEF ≤ 30%, minimal or no scarring identifies a low-risk cohort, similar to those with LVEF > 30% [20]. In this study, LGE imaging was predictive of overall

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mortality as well as SCD, suggesting that LGE may not be specific for SCD prediction [20]. However, in other studies, the extent of LV scar, characterized by LGE, was strongly associated with the occurrence of spontaneous ventricular arrhythmias, but not with all-cause mortality [21]. In patients with LV dysfunction, myocardial scar, assessed by LGE, was the only significant predictor of inducible sustained monomorphic VT [22]; additionally, in a group of 373 patients with sustained or nonsustained ventricular tachycardia and normal left ventricular ejection fraction, LGE was an independent predicting factor of adverse outcomes in patients with ventricular arrhythmia [23]. Furthermore, LGE heterogeneity was an important parameter for risk stratification of patients, considered for primary prevention AICD implantation [22,23].

Risk Stratification and Prevention of SCD

Risk stratification and prevention of SCD is of tremendous importance [24]. Although CAD, NYHA III class and LVEF have been considered as independent, statistically significant predictive factors of mortality [25], there is still lack of powerful tools for screening patients at high risk for SCD. The current diagnostic algorithms recommend the routine performance of transthoracic echocardiography and invasive coronary angiography with the optional use of additional imaging, such as cardiac magnetic resonance (CMR) [26]. However, according to recent data, CMR has the great capacity to identify relevant, but clinically unsuspected, disease in patients with SCD, such as acute myocarditis and acute ischemic injury [27].

The clinical adoption of CMR in the tertiary care contributed to 50% improvement in the identification of relevant myocardial disease, leading to a robust 75% diagnostic yield, due to more sensitive detection of acute and healed ischemic or nonischemic myocardial disease [27]. Furthermore, CMR tissue characterization should include the evaluation of irreversible (scar) tissue injury using LGE and the identification of current or recent myocardial injury, using T2-weighted (oedema) imaging. The combination of these techniques allows the differentiation between acute or chronic injury [27]. The pattern and distribution of injury can offer a reliable assessment of disease aetiology [28], whereas the extent of irreversible tissue injury has been associated with future risk of SCD in both ischemic [29] and nonischemic [30] cohorts. In addition, fatty replacement of myocardium, identified by T1-weighted imaging, can support the diagnosis of arrhythmogenic right ventricular cardiomyopathy (ARVD/C) [31]. The combination of these 3 tissue imaging sequences together with CMR cine imaging, the gold standard for cardiac function, offers a robust tool for the identification of SCD substrate [27]. According to recent data published by our group, CMR, by performing tissue characterisation, can add unique information in the diagnostic work-up of patients with family history of SCD, normal coronaries and normal LVEF, missed by echocardiography [32]. However, at the moment the number of patients and the number of events described in these studies is very low and this raises a severe criticism about the diagnostic power of these studies, even in commonly evaluated diseases, such as dilated, hypertrophic and ischemic cardiomyopathy.

Published studies have used different primary and secondary end-points for SCD (VT, inducible VT in electrophysiology, cardiac arrest, appropriate ICD therapy, and appropriate shock). However, they are neither surrogate for SCD, nor interchangeable. It was proved that appropriate ICD shocks are not a reliable surrogate for SCD and overestimate the incidence of SCD in patients with nonischemic cardiomyopathy, because the ICD shocks experienced twice as many appropriate shocks as the number of fatal events. Therefore, counting ICD shocks is not equivalent to counting lives saved by ICD therapy. These data suggest that ICD shocks overestimate the efficacy of ICD, because many episodes of tachycardia terminate spontaneously. The PAIN-FREE II trial also demonstrated that at least 1/3 of very fast monomorphic VT terminated spontaneously before anti-tachycardia pacing therapy [33]. Additionally, current data show that in patients with nonischemic cardiomyopathy, many episodes of polymorphic VT and VF also terminate spontaneously [34]. Therefore, studies regarding surrogates about SCD should be evaluated with great precaution.

The role of CMR in the SCD prediction during different cardiac pathologies is presented below.

A. Cardiomyopathies

1. **Hypertrophic cardiomyopathy (HCM):** Hypertrophic cardiomyopathy (HCM) is characterized by a great diversity in clinical course, including the most common cause of SCD in young people and a determinant of heart failure (HF). CMR, due to high spatial resolution and tomographic imaging, has emerged as a technique well suited to identify unique phenotypic markers of affected genetic status in the absence of LV hypertrophy, including myocardial crypts, elongated mitral valve leaflets and LGE [35]. The available evidence proved that the extent of LGE was associated with both progression to heart failure and SCD [36] and has incremental value in addition to traditional risk factors for risk stratification of HCM [37,38] (Figure 1). Furthermore, the extent of LGE in HCM correlated with risk factors of SCD and the likelihood of inducible VT [39]. In a population of largely low or asymptomatic HCM, the presence of scar, indicated by LGE, was an independent predictor of all-cause and cardiac mortality [40]. Hanlon et al. proved that the extent of fibrosis and non sustained VT were univariate predictors for arrhythmic end points; non sustained VT remained an independent predictor of arrhythmic end points after multivariate analysis, but the extent of fibrosis did not [41]. However, not only the presence, but also the quantification of LGE is of important value. In a recent study, LGE measured at 4 SD and 5 SD was found to have the closest approximation to the extent of total fibrosis measured by the histopathological standard of reference and this finding has important clinical implications for the association of CMR

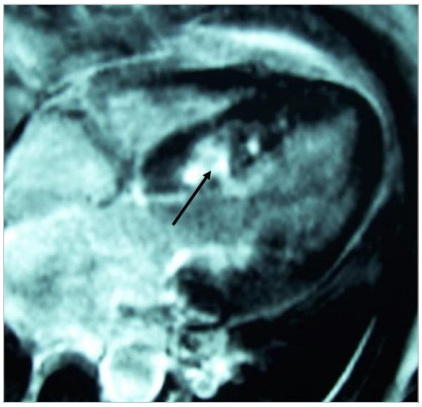

Figure 1: Extensive LGE in the interventricular septum of LV from a patient with HCM and SCD.

with important clinical endpoints in HCM, including sudden cardiac death [42,43].

2. **Dilated cardiomyopathy (ischemic and nonischemic):** Dilated cardiomyopathy is the end point of both ischemic (ICM) and nonischemic (DCM) heart disease. Scar quantification, using LGE, identifies patients at higher risk of future events, both in ICM and DCM. LGE can predict arrhythmic events in patients evaluated for ICD eligibility, irrespectively of cardiomyopathy aetiology [44,45]. In idiopathic DCM, cardiac index and RVEDV derived from CMR imaging in addition to QRS duration > 110 ms from conventional surface ECG and diabetes mellitus provide prognostic impact for SCD [46]. Furthermore, in DCM, the presence of CMR assessed midwall fibrosis has an additive predictive value for SCD/VT [10].

3. **Arrhythmogenic right ventricular dysplasia (ARVD):** Arrhythmogenic right ventricular cardiomyopathy (ARVD/C) is a familial heart muscle disease characterized by progressive fibro-fatty replacement of the right ventricular (RV) myocardium (Figure 2). Clinical presentation includes RV origin arrhythmia and/or SCD. Left ventricular (LV) involvement was present on histology in > 75% of cases in a multi-center pathology study [47- 49]. CMR is an important non-invasive diagnostic modality that allows both functional evaluation and tissue characterisation of RV - LV. The identification of RV myocardial fibro-fatty changes using LGE predicts inducible VT on programmed electrical stimulation [50-52].

4. **Left ventricular non compaction (LVNC):** Left ventricular non compaction (LVNC) is a cardiomyopathy associated with sporadic or familial disease, the latter having an autosomal, dominant mode of transmission. The clinical features associated with LVNC vary from asymptomatic to symptomatic patients, with the potential for heart failure, supraventricular and ventricular arrhythmias, thromboembolic events and sudden cardiac death. The literature reports the incidence of malignant ventricular arrhythmias in as many as 47% of the patients and sudden cardiac death in almost 50% of them [53]. Although multicenter CMR studies on LVNC are missing, the presence of extensive LGE should motivate ICD implantation [54,55].

5. **Neuromuscular disorders:** Positive LGE is a common finding in muscular dystrophinopathies and inflammatory myopathies [56-58]. However, further studies are needed in order to identify, if LGE is an independent predictive factor for sudden death in these patients.

6. **Autoimmune and immune mediated diseases:** Positive LGE has been already identified in many autoimmune diseases like systemic lupus erythematosus, scleroderma, rheumatoid arthritis, vasculitis etc [59-62]. However, at the moment there is no evidence that LGE can predict sudden cardiac death in these patients. In contrary, in sarcoidosis, an immune mediated disease, the presence of LGE is considered as a useful method for the early identification of cardiac sarcoidosis. Furthermore, the presence of LGE is a significant predictor of SCD and poor outcome in these patients [63].

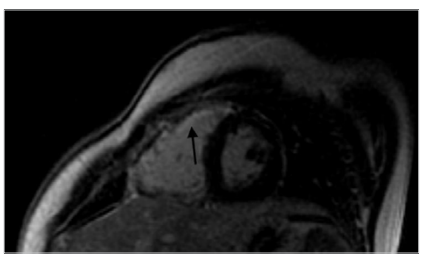

Figure 2: Extensive LGE, due to fibrosis in a patient with ARVD and SCD.

B. Myocarditis

SCD can complicate viral myocarditis both during the acute and chronic phase. Biopsy-proven viral myocarditis was associated with a long-term mortality of up to 19.2% in 4.7 years and LGE was the best predictor of all-cause mortality and of cardiac mortality [64].

In chronic Chagas myocarditis, the presence of two or more contiguous segments with transmural fibrosis was an independent predictor of VT (4.1-fold greater VT risk) [65]. However, there are not enough data supporting the role of LGE for SCD prediction in viral or autoimmune myocarditis.

C. Coronary artery disease

CMR has a growing application in the diagnostics of myocardial infarction (MI). In a single study, it allows assessment of morphology, function (volumes-ejection fraction), oedema, microvascular obstruction (MVO), fibrosis and also complications that can not be easily diagnosed by other imaging techniques, such as myocardial hemorrhage or thrombus. An obvious advantage of CMR is the possibility to differentiate between acute and chronic MI and the assessment of area at risk [66].

LGE has high sensitivity and specificity to detect and quantify fibrotic tissue, due to MI. Additionally, LGE characteristics are of predictive value for the occurrence of SCD in ICM [66]. In patients with chronic myocardial infarction scheduled for primary preventive ICD implantation, infarct transmurality, as defined by LGE, identifies a subgroup with increased risk for life-threatening arrhythmias and SCD [67]. Furthermore, the amount of myocardial scar, identified by LGE, predicts all-cause mortality in a range of patients groups, including those with a previous MI, ICM and vascular risk factors, but without clinical evidence of a prior MI [66-68]. In patients with HF after MI, scar quantification predicts both the occurrence [68-73] and the inducibility of VT on electrophysiological study, identifying patients susceptible for SCD. Infarct mass and infarct surface area were the strongest predictors of SCD. The mechanistic relationship between scar and arrhythmogenecity is well established and there are some postmortem studies suggested that scar burden reflects the susceptibility to SCD [74-77]. However, although scar percentage was associated with the occurrence of appropriate ICD therapy, the strongest correlation was documented with the number of myocardial segments with full-thickness (76% to 100%) scar [77] (Figure 3).

Additionally, post-infarction scars on CMR are characterized by differentiating the core infarct and the infarct border zone (peri-infarct or grey zone=PIZ) based on the spatial distribution of signal intensity (SI). Yan et al. [78] identified that a large peri-infarct zone was a powerful predictor of mortality. PIZ was defined as area with an SI between 2 and 3 SD above SI of remote myocardium, normalized as a percentage of total infarct zone (area with an SI of > 2 SD above remote myocardium). Roes et al. [79] found that PIZ was the strongest predictor for spontaneous VT. Based on the potential limitation of using the peak SI of remote myocardium to define PIZ, core infarct and

PIZ were based exclusively on the maximum SI in the hyperenhanced area (core SI ≥ 50% of maximal SI, grey zone 35% ≤ SI < 50% of maximum SI) [80,81]. However, at the moment there are no data about the definite role of PIZ in the SCD prediction.

D. Congenital heart disease

Congenital heart disease is one of the most frequent causes of SCD in individuals below 30 years of age [1]. Although there are not enough data, in a heterogeneous group of adult congenital heart disease, it was documented that prolonged QRS duration, diminished exercise capacity and ventricular fibrosis, identified by LGE, were associated with SCD prediction and might improve patients' selection for further screening [82].

In operated on for TOF, the presence of LGE around infundibular patch and RV anterior wall represents surgically damaged regions with fibro-fatty replacement. The coexistence of scar and viable myocardium promotes electrical re-entry and predisposes to SCD [83,84]. Finally, patients treated for transposition of great arteries (TGA), by atrial redirection surgery, have RV that sustains systemic pressures. LGE, due to myocardial fibrosis that occurs in the systemic RV of TGA correlates with age, ventricular dysfunction and SCD [85].

To summarize the value of CMR findings in the evaluation of SCD the following questions should be addressed.

1. Is the incremental information gained by CMR with LGE imaging at this point sufficient to alter clinical practice guidelines?

Both LVEF and amount of myocardial damage, as assessed by CMR, are independent predictors of all-cause mortality. Even in patients with near-normal LVEF, significant damage identifies a cohort with a high risk for early mortality [10]. Therefore, LGE must be included in the evaluation of SCD, as a new independent parameter for the assessment of patients with cardiomyopathies (DCM or HCM) and coronary artery disease [10,40,77].

2. How should we quantify scar? Visual assessment or semi-automated software?

According to recent studies a quantification of scar is an independent prognostic factor for patients' classifications; therefore, it should be considered as a powerful index for the evaluation of all cardiac patients in conjuction with LVEF [20].

3. Which are the potential technical limitations of CMR and LGE imaging in predicting the occurrence of VT and SCD?

While the use of LGE to identify myocardial fibrosis is very sensitive, the accurate quantification of the amount of fibrosis is limited, because LGE signal differs in different studies and as a consequence, a direct comparisons cannot be made [86]. Additionally, LGE is influenced by technical parameters, including the threshold set to differentiate normal from fibrotic myocardium [87]. This resulted in variability of myocardial fibrosis in different cardiomyopathies. Last but not least, LGE typically images only focal macroscopic fibrosis and not microscopic fibrosis. As large signal intensity differences between fibrotic and normal myocardium may not exist when the fibrosis is diffuse, LGE is of limited value in the assessment of diffuse interstitial fibrosis. To overcome this problem, T1 mapping was proposed. T1-mapping has the potential to differentiate both interstitial and replacement fibrosis from normal myocardium but not one type of fibrosis from another [88]. T1-mapping allows fibrosis quantification on a standardized absolute scale and represents a more accurate method to quantify total fibrotic amount than LGE.

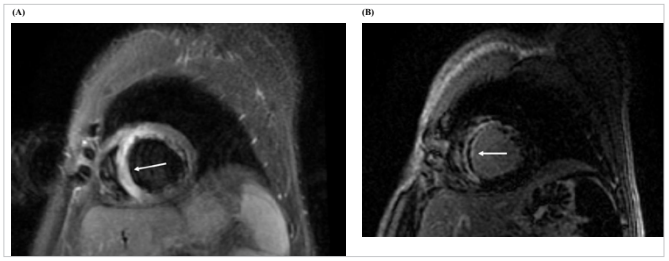

Figure 3: Transmural oedema (A) and LGE (B) in intravascular septum of LV from a patient with transmural myocardial infarction and SCD.

History of SCD or aborted SCD	
History of Diabetes Mellitus	
History of Coronary artery disease	
History of Cardiomyopathy	
NYHA > II	
LVEF < 40%	
LGE > 5%LV	
In nonischemic cardiomyopathy	In ischemic cardiomyopathy
Female gender	Residual ischemia
Age	Reduced LVEF
Lack of statin therapy	Electrical instability
Increased serum creatinin	Frequent ventricular ectopic activity
	Impaired autonomic status

Table 1: Clinical and CMR parameters that should be carefully evaluated in assessment of patients with SCD.

Clinical and CMR parameters that should be carefully evaluated in assessment of patients with SCD are presented in Table 1.

Conclusion

In conclusion, CMR, through the combination of function assessment and tissue characterization has a significant predictive value for SCD in both nonischemic (HCM and DCM) and ischemic cardiomyopathy. Infarct's size and transmurality are the strongest predictors for SCD in ischemic heart disease. In myocarditis, definite data about LGE, as a predictive factor for SCD, are available only in Chagas myocarditis. In repaired TOF, LGE around infundibular patch and RV anterior wall is a SCD predictor.

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