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Review Article

Cardiac imaging in evaluating patients prone to sudden death

Ashenafi Tamene [a], *Venkatakrishna N. Tholakanahalli* [a], *Y. Chandrashekhar* [a,b,*]

[a] *Division of Cardiology, University of Minnesota and VA Medical Center, Minneapolis, MN 55417, USA*
[b] *Professor of Medicine, University of Minnesota, Division of Cardiology (111c), 1, Veterans Drive, Minneapolis, MN 55417, USA*

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ABSTRACT

Identifying subjects who are at risk for SCD and stratifying them correctly into low or high-risk groups is the holy grail of Cardiology. While imaging shows a lot of promise, it is plagued by the fact that most SCD occurs in relatively healthy subjects, a massive group who would not ordinarily be subjected to imaging. Left ventricular ejection fraction (LVEF) currently is our primary parameter for risk stratification for sudden cardiac death but is a poor marker with low sensitivity and specificity. Current data shows that sophisticated imaging with techniques, mainly Cardiac magnetic resonance Imaging (CMR), have the potential to identify novel high-risk markers underlying SCD, beyond ejection fraction. Imaging seems to further refine risk in patients with low LVEF as well as in those with normal EF; this is a major strength of advanced imaging. Clinical application has been slow and not fully prime time. It is important to remember that while promising, imaging techniques including CMR, have not been tested in rigorous prospective studies and thus have not as yet replaced EF as the gatekeeper to ICD implantation.

1. Introduction

Sudden cardiac death (SCD), unexpected cardiac death usually within an hour after the onset of symptoms, remains a major health problem.[1] Estimates in the US range widely but it accounts for approximately 50% of deaths from cardiovascular diseases.[2] Predicting who will die suddenly from ventricular arrhythmias is extremely difficult and predicting sudden death, proximate to the event, is nearly impossible with current technology. Presence of structural heart disease, especially LV dysfunction, is predictive of risk for long term SCD. Unfortunately, the majority of patients presenting with SCD often have normal LV function and death is often the first symptom of heart disease.[3] Risk stratifying for SCD is thus a challenge – the deaths are by definition sudden and more importantly, unexpected in most cases; worsening heart disease is a strong predictor of SCD, but this becomes less useful since most of the deaths occur in subjects with no heart disease. Current indices to risk stratify SCD are thus sub optimal and we urgently need newer and novel methods to identify and characterize substrate that can trigger SCD. Imaging can

* *Corresponding author*. Tel.: +1 612 467 3484.
E-mail address: shekh003@umn.edu (Y. Chandrashekhar).

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play a role here and recent advances in imaging have helped us refine our thinking about who will have sudden cardiac death. Traditional cardiac imaging identifies increased risk of SCD mainly via its ability to show structural substrates like EF, hypertrophy, scar and scar heterogeneity.[4] Newer imaging modalities, especially molecular imaging, might allow us to image channels and interstitial connections and even conduction itself but these are in the research arena at this time. Imaging can also assess triggers that impart increased risk of ventricular arrhythmias (e.g. cardiac autonomic abnormality, pattern of innervation, etc). In this article, we will briefly review the role of multi-modality imaging techniques in identifying patients at risk for sudden cardiac death and illustrate how imaging aids in therapeutic decision making in disorders known to lead to SCD. Purely research methodologies and those not freely available like molecular imaging techniques will not be discussed in this review.

The etiology of SCD differs depending on the age group studied. In adults, SCD is most often seen over a background of coronary artery disease.[1,4] Non-ischemic cardiomyopathies account for 10–15%, whereas other cardiac disorders, including valvular heart disease, congenital heart defects and channelopathies, account for the remainder. Our current, albeit incomplete, understanding of the mechanism of SCD postulates a complex interaction between multiple factors including genetic predisposition (e.g. channelopathies), anatomic substrates (e.g. coronary artery disease, coronary artery anomalies, myocardial scar), and functional triggers (such as ischemia, neurohormonal factors, metabolic perturbations as well as, hemodynamic changes). Most of the time, the final common pathway is presumed to be a fatal ventricular arrhythmia; ventricular fibrillation is the first recorded rhythm in 75–80% of patients presenting with sudden cardiovascular collapse, although, with better monitoring[5] and change in therapies,[6] a bradycardiac death is being recognized more often now than before. Moreover, our ability to diagnose the etiology of SCD is also sub optimal and a significant proportion of patients of presumed to have arrhythmic SCD end up to have other non-arrhythmic causes.[7] Thus imaging, while promising, should be considered in light of SCD etiologies, current successful therapies that arose from clinical trials that did not need complex stratification with advanced imaging and finally, its applicability to the general low risk population where SCD is the commonest.

2. Imaging targets in sudden cardiac death

While a traditional review can address multimodality imaging in each of the cardiac conditions associated with SCD, all current imaging seems to address only a few mechanistic targets, namely structure of the heart, its function, presence of scar and in a few cases, state of the cardiac autonomic system. Vulnerable plaque and ischemia often underlie SCD and are excellent targets for imaging – in fact, CMR seems to be identifying sub clinical myocardial infarction in many cases presenting with unexplained SCD both in life (SCD survivors) and in death (post mortem) CMR forensics –.[8] However, ischemia and evaluation for vulnerable plaque is not usually a directly proximate stratifying marker for SCD. Noninvasive risk-stratification techniques for identifying patients with coronary artery disease at risk for SCD also do not emphasize these as markers as primary targets.[4]

2.1. *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[9] – 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[10] 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,[11] patients with EF ≤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 ≤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.[11] Furthermore, most SCD events (in terms of absolute number of cases) occur in patients with preserved left ventricular ejection fraction[4,9] – 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.[12] 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.

2.2. *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 inhomogeneity, allows slow conduction and re-entrant currents that underlie malignant arrhythmias.[13] Not surprisingly, risk of SCD in both IHD and non IHD patients tracks scar burden and scar tissue heterogeneity measured with cardiac magnetic resonance.[13,14] 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.[13–15] 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[15] 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 >2 SD of a remote non-involved myocardium, while another used between 2 and 3 SD, but even higher SD cut off values have also been used.[15] 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 ≥4 SD 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.

2.3. *Abnormal cardiac autonomic activity*

Abnormalities in cardiac autonomic activity are considered to be contributory factors or triggers in SCD. Radiotracers that are picked up into the cardiac adrenergic synapse, using a mechanism similar to catecholamines, are used to measure cardiac adrenergic activity. ^{123}Iodine-metaiodobenzylguanidine (^{123}I-MIBG) and ^{11}C-meta-hydroxyephedrine (^{11}C-HED) can be used for this purpose and have been successful in predicting adverse outcomes in cardiomyopathies.[16]

2.4. *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 triaging 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.[17,18] 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.

3. Specific imaging modalities in the evaluation for sudden cardiac death

3.1. *Echocardiography*

Echocardiography is commonly used in the evaluation of patients with suspected structural heart disease who present with syncope, ventricular arrhythmia, hemodynamic instability, ischemia/infarction or heart failure. Echocardiography is an excellent modality for myocardial structure and with its fast frame rate, for regional and global function. Ventricular volumes, thickness and mass are surrogates for all adverse events including arrhythmic death. Scar size, thickness and viability are measured but other modalities, like CMR, have replaced echo for this purpose. Echo has a particularly important role in triaging for SCD in HCM. LV thickness ≥3.0 cm on echocardiography is an important adverse marker of outcome.[19] Echo studies have also shown that LV mass may be more important for SCD than wall thickness.[20] Finally, the pattern of hypertrophy in HCM is a strong determinant of events. Those with a reversed S shaped HCM have little outflow obstruction but an association with sarcomeric HCM and a high arrhythmic event rate with MHY7 mutation.[21]

Echocardiography, due to its ease of use and widespread availability, is one of the primary tools used to assess left ventricular ejection fraction (LVEF). 3D is better for quantifying EF and volumes compared to 2D echo with or without contrast but most of our SCD data are based on 2D echo information. Thus, while 3D echo will give us a more accurate EF, it is not known if this as yet translates to better prediction of SCD. However, it is important to understand the limitations of EF measurements. EF prediction shows great inter observer variability in the very mild and very severe LV dysfunction. For example, an EF measurement at the ICD guideline cut off can vary up to ± 3.3% on 2D study using the Simpson's formula and ±1.7% on 3D measurement; interval EF measurements can also change due physiological changes, differences in how the study was acquired, and interobserver variability – 5–6% with non contrast 3D and 10–13% with 2D techniques.[22] Not surprisingly, only a minority of patients chosen for ICDs on the basis of EF cut offs show appropriate shocks on follow up suggesting that while EF is currently the best practice standard for triaging for SCD, it remains a very crude and poor parameter.

LVEF is useful for predicting need for ICD but it is not clear if this is a property of "reduced contractility" or a reflection of "degree of injury/scar". Nevertheless, more precise methods of regional and global contractility (function), like deformation imaging (strain, strain rate etc), are being explored to predict SCD (Fig. 1). Myocardial strain curves quantify regional myocardial contraction, dispersion and timing, and are better than EF in predicting LV function as well as ventricular arrhythmias.[23] Global longitudinal strain (GLS – the average of peak negative strain of 16 left ventricular segments greater than or equal to −12% by speckle tracking) as well as mechanical dispersion which is a surrogate of electrical heterogeneity in the myocardium (SD of time from the peak of R-wave on electrocardiography to peak systolic strain in 16 left ventricular segments) have been found to be an independent predictor of arrhythmic events in prospective studies in large numbers of patients following acute myocardial infarction[23,24]; this was independent of and better than EF measurement.[23] While low LVEF was associated with arrhythmic events it was not as good in patients with lesser degree of LV dysfunction while GLS was more predictive for arrhythmic events than LVEF while remaining useful also in patients with EF >35%.[24] Combining GLS and mechanical dispersion (MD)

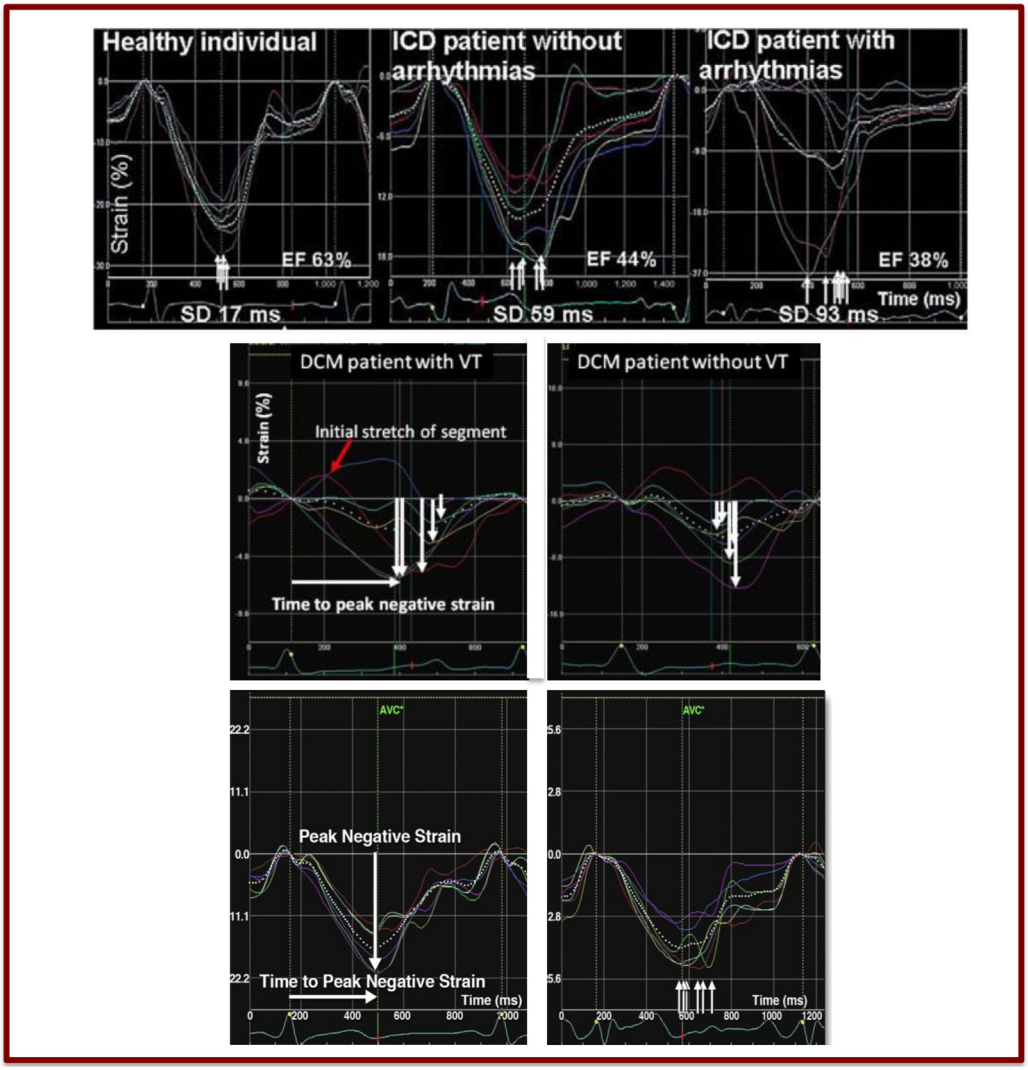

Fig. 1 – Deformation imaging and risk of SCD. Top Panel: Normal individuals show little dispersion in peak myocardial strain timing but abnormal ventricles show significant mechanical dispersion that was prominent in patients with arrhythmias. Middle Panel: In patients with DCM, Global longitudinal strain and LVEF are reduced in both patients with and without VT but worse contraction dispersion was seen in a patient with VT. Bottom Panel: Similarly, dispersion is worse in post MI patients who have arrhythmic events. Modified from Haugaa et al. *J Am Coll Cardiol Img* 2010;3:247–256; JASE 2012;25,667–673; *J Am Coll Cardiol Img* 2013;6:2013 841–850.

improved predictability. GLS and MD might have a role in the early window post MI – traditionally, ICD placement is not recommended in the first 40 days post MI since a benefit was not shown. However, there is a significant risk of SCD in this period. A recent study showed that GLS measured in the very early post MI period predicted long term SCD better than EF and other echo parameters. Interestingly, MD was difficult to evaluate in the peri MI period and failed to show additive benefit over GLS unlike in the period late after MI.[25] GLS thus might be an important and easily obtainable parameter in predicting risk in patients early after MI, especially in those with EF >35% or those with EF <35% but thought to be at low risk for an arrhythmic event by other current stratification guidelines.

Dilated cardiomyopathy (DCM) and ischemic cardiomyopathy (ICM) have many similar final pathway mechanisms for SCD including scarring and mechano-electrical dyssynchrony; DCM is associated with SCD and patients with low EF are recommended for an ICD. Just as in ICM, EF is a poor predictor of ICD events in DCM and deformation imaging, which uses multiple segments across the whole cardiac cycle and is a better reflector of scar heterogeneity, might perform better. Indeed a recent study[26] showed that mechanical dispersion was a strong predictor of ventricular arrhythmias in patients with DCM independent of LVEF most likely since regional myocardial deformation could be a surrogate of electromechanical interactions.

Mechanical dispersion reflects myocardial contraction variability, and in turn scar heterogeneity, and has been used to demonstrate finer abnormalities in syndromes associated with SCD. Mechanical dispersion is a surrogate of electromechanical dispersion and strain imaging shows increased

dispersion of myocardial contraction in patients with long-QT syndrome and predicts adverse arrhythmic outcome better than QTc alone.[27] Arrhythmogenic right ventricular cardiomyopathy (ARVC) causes SCD in previously healthy young individuals with and even without obvious signs of RV structural disease. Traditional diagnosis is based on RV dilatation and dysfunction but this would not identify asymptomatic carriers of desmosomal mutations. Mechanical dispersion heterogeneity and decreased myocardial strain is prominent in patients with ARVC showing arrhythmias and could be used for risk stratification of patients as well as asymptomatic mutation carriers. While MRI is excellent for detecting structural abnormalities in ARVC, it appears that newer echo techniques can detect ventricular abnormalities in asymptomatic mutation carriers with normal MRI. In addition its use in the risk stratification of patients with CAD, global longitudinal strain has a similar role in hypertrophic cardiomyopathy,[28] and systemic sclerosis.[29] It is important to realize that while early studies seem to show promise for advanced echo techniques, including some that seem to show advantage over EF alone in small studies, none have yet reached a clinical stage where they can be used for stratification of SCD. For echo, the ability to measure EF still remains the gold standard for triaging patients for risk of SCD. Clinical trials using GLS etc to predict SCD are eagerly awaited.

Athletes, often young, have an excess risk of SCD and this population most commonly is asymptomatic. Primary prevention is mainly based on screening before participation but the yield is low and accompanied by a high occurrence of false negative tests, given low pre test probability in the population. Multimodality imaging might be useful.[30] Echo has been considered a screening modality in young athletes since it identifies a different subset (cardiomyopathies like HCM and ARVC and aortic pathology) than with EKG alone (mainly channelopathies). Whether Echo should be used at all is controversial with some sport organizations requiring it even without robust data. Some have advocated using it only in cases with abnormal EKGs. There is some overlap between physiologic hypertrophy in athletes and pathological hypertrophy in HCM and ventricular remodeling of the RV can overlap with milder forms of ARVC; this make the test less specific in a group with low pre test probability. In one screening study, echo found suspicious disease in 0.7% of subjects and did not seem to add much over and above EKG screening.[31] Tissue Doppler and deformation imaging may be marginally better but rigorous studies with outcomes are lacking.

Other Echocardiographic variables associated with risk of SCD include increased ventricular thickness and mass, remodeling [e.g. ratio of septal thickness to left ventricular diastolic diameter >0.5] and extreme left ventricular hypertrophy (≥30 mm) in hypertrophic cardiomyopathy[32] and increased left ventricular mass index in patients with stable coronary artery disease. Left atrial size in patients with chronic heart failure also seems to predict SCD, probably as a function of the severity of heart failure.

3.2. *Nuclear imaging and SCD*

Nuclear techniques including most commonly, Single Photon Emission Computer Tomography Myocardial Perfusion Imaging (SPECT-MPI), can predict high risk of cardiovascular events, including SCD. It provides information beyond EF measurement on gated studies; it can assess ischemia, viability and scar tissue that are predictors of death or recurrent ventricular arrhythmias.[33] Perfusion and scar remain useful even in SCD events that occur in patients with preserved EF. Piccini et al, retrospectively analyzed 4865 patients with known CAD and EF >35%; summed stress score of >8 predicted increased risk of sudden death[34] even after adjustment for EF and relevant clinical factors.

Cardiac Positron Emission Tomography (Cardiac PET) exquisitely assesses myocardial blood flow, perfusion, function and metabolism. For example, ^{82}Rubidium PET myocardial perfusion strongly predicts adverse cardiovascular outcomes.[35] However, it is not clear if there is any unique benefit to using cardiac PET for stratification of patients at risk of SCD. Nuclear techniques to assess sympathetic activity and sympathetic denervation might have better success.[36] Abnormal uptake and wash out of MIBG, a compound that mimics neuronal synapse catechol uptake in the heart, is associated with adverse outcomes, including SCD, in patients with chronic heart failure. This technique is becoming readily available and might have a role in triaging for SCD in patients with known heart disease. Cardiac MIBG performed better than many traditional techniques used to stratify risk of SCD (e.g. SAECG, HRV, or QT dispersion) and remained a powerful predictor of SCD in patients with mild-to-moderate CHF, independently of LVEF.[37] MIBG uptake predicts VT induction at EP studies[38] and appropriate discharges in patients with an ICD.[39] Not surprisingly, the ADMIRE HF study showed that "arrhythmic" events were significantly more common in subjects with Heart/Mediastinum uptake ratio <1.6[40] Favalito et al studied patients with ischemic cardiomyopathy eligible for ICD for primary prevention of SCD.[41] In this prospective study, increased sympathetic denervation, as assessed by ^{11}C-meta-hydroxyephedrine PET imaging, predicted SCD independent of infarct volume and LVEF. Cardiac PET has advantages in defining inflammation and this may have prognostic potential in predicting SCD in conditions like cardiac sarcoidosis where SCD is common and cardiac arrest can be the initial manifestation even in patients with preserved EF. ^{18}F-fluorodeoxyglucose defects are markers of active disease and portend poor prognosis and may improve triage for ICDs, given the currently sub optimal results in these patients.[42] Nuclear techniques are thus useful in the risk stratification for SCD independent of EF but more robust validation studies are needed. Its role in population screening is likely to be very limited given the risk of radiation and its inability to predict SCD with great refinement compared to other rapidly developing techniques like CMR.

3.3. *Cardiac multidetector computed tomography*

Cardiac Computed Tomography (Cardiac MDCT) is an excellent modality for ventricular structure and function and can thus be of help in evaluating patients with substrate for SCD. A risk of radiation has limited its use but that is changing given newer technologies that minimize radiation exposure. While findings on CTA can predict prognosis, there is little

data on the predictive ability of CTA for primarily SCD. Coronary calcium is strongly predictive of adverse events but whether it can uniquely predict SCD is not clear. CTA's best role is in diagnosing coronary artery anomalies.[43] However, these are often causes of SCD in student athletes and radiation is a significant limitation in cost effective screening this population with CT. Furthermore, it is not known if it adds more than what we can find with traditional imaging like Echo. In the young adult athlete, hypertrophic cardiomyopathy, congenital coronary abnormalities, channelopathies/abnormal conduction pathways, aortic rupture, and arrhythmogenic right-ventricular cardiomyopathy are the top 5 reasons for SCD and echo can is very useful in at least 3 of these conditions and CTA's unique abilities may be limited to coronary anomalies.

3.4. *Cardiac magnetic resonance imaging (CMR)*

CMR can provide the most comprehensive information about patients destined for SCD – It is an excellent technique, probably the gold standard, for morphology (EF, Volume, Thickness and Mass), and may be even better than nuclear perfusion studies for inducible ischemia.[44] Its main strength, however, lies in its ability to accurately show viability and scar in the myocardium (Fig. 2). CMR detected scar is predictive of SCD in heart failure with both, preserved as well as reduced EF, ischemic and non-ischemic cardiomyopathy as well as in syndromes like HCM, ARVC and infiltrative diseases.[45] The extent of LGE on CMR is a strong predictor of ventricular arrhythmic events. Total scar burden as well as, peri-infarct scar predicts SCD or ventricular arrhythmias in ICM. Apart

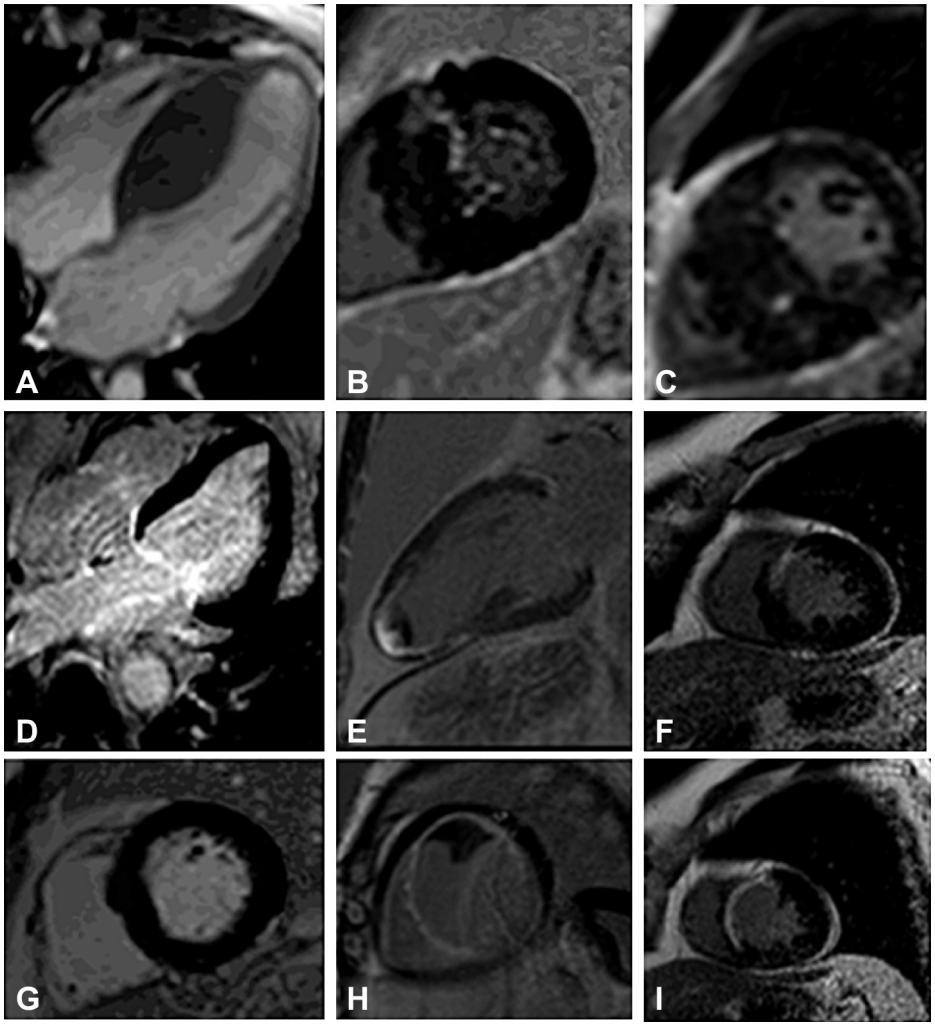

Fig. 2 – CMR and risk stratification for SCD. The Top Panel shows patients with HCM with severe asymmetric septal hypertrophy (A) and LGE in the septum, especially near RV insertion (B). No LGE is seen in the other walls. Another HCM with severe LVH but a lesser degree of LGE (C). Both severe LVH (>30 mm) and extent of LGE predict SCD risk. Middle & Lower Panel: Shows normal heart with no LGE (D, G) and varieties of scar (E, F, H, I). Apical scar (E) and anterio septal scar (F) with mild heterogeneity, while H and I shows varying extent and thickness – H is a full thickness scar in most of the septum and this is non viable myocardium. I shows a partial thickness scar with islands of tissue that is not scar – these might be substrates for arrythmia. Presence of scar and scar heterogeneity predict arrhythmic events better than current parameters like EF etc. There is a good-sized LV apical clot (E and H). LGE- Late Gadolinium Enhancement.

from scar, CMR can further differentiate between infarct and peri infarct zone and identify the characteristics of the peri infarct zone (presumably a mixture of dead and living cells with variable degree of viability and thus an arrhythmogenic substrate) and the "gray area" zone region, both of which area strongly associated with arrhythmic events.[46] Such gray area or peri infarct morphology seems to predict arrhythmia and SCD better than infarct size and EF in the post MI period. Total scar is also an independent predictor of arrhythmic endpoints in DCM with mid wall fibrosis, [seen in about a third of patients with DCM], being an independent predictor of sudden death and ventricular tachycardia.[47] Not surprisingly, a recent meta-analysis showed that the effect is independent of reduced LVEF; (about 4 fold increase in risk over patients with little scar).[48] However, most studies in this area involve small samples and have varying criteria scar quantification and end-points.

CMR Scar size is the most exciting marker for SCD and but its unique strength seems to be that it can further stratify patients with both low and higher EF (group that has the highest population attributable risk for SCD but who are not traditionally considered candidates for ICD therapies in current guidelines). Klem et al showed the power of CMR in predicting SCD in this group – patients with LVEF >30% and scar >5% had more events (death and ICD discharges as well as SCD) and behaved like those with EF <30%; in contrast, those with EF ≤30% and minimal scar (<5%) behaved like patients with EF >30% in terms of events.[45] Scar could thus reclassify approximately a third of the patients into more precise groups better than what an electrophysiologic study could do. It is likely that such information might be useful in refining who should get an ICD using criteria over and above EF alone.

CMR is thus a very promising test modality for triaging for SCD and is likely to get better with time. Having said that, it is important to recognize that a number of uncertainties remain that limit its widespread use in regular clinical practice. Nearly all of the data are from small observational studies – presence or extent of scar is predictive of more arrhythmia and arrhythmic deaths; however, there is less data in prospectively studied patients. CMR scar characteristics, like other stratifying techniques, predict worse outcome as a group but are not robust enough to predict which particular individual will have an event and do not identify how soon an event will occur. It is not clear how much better it would be than other stratifying techniques (e.g. an EP study, risk scores or a combination of scores + biomarkers). Finally, there are no intervention studies based on CMR data to prove that the predictive value is sufficient to make a clinically meaningful change in practice. Most studies have been in patients with LV dysfunction and it is not clear how CMR will perform in the group with the highest risk for SCD – those without significant LV dysfunction in the general population. It is not clear what is the best way to characterize scar size and multiple methods are in use. It is also not clear which feature of a scar conveys the highest risk (size, thickness, grayness, viability in scar etc) and extent of scar needed to predict risk in different subsets (cut off) is still unclear. Its test performance characteristics (positive and negative predictive value) are not well known in many sub groups and cost effectiveness may be suboptimal in the group with preserved EF (where most of the SCD deaths occur). Finally, Late Gadolinium Enhancement (LGE) on CMR may be indicative of overall bad prognosis and not just arrhythmic death.[45]

Myocarditis is a special subset of heart failure with variable recovery and a high mortality that is often due to SCD. LGE has been shown to be a very powerful predictor of outcome independent of degree of failure as measured with LV size or function. In the study by Grun et al, no patient with biopsy proven myocarditis but without LGE died on follow up; this was irrespective of LV size and function.[49] On the other hand, the presence of LGE had a 12.8 fold hazard ratio for cardiac death. Interestingly, LGE did not correlate well with EF or recovery of EF suggesting that it had a unique effect on predicting SCD.

HCM, an autosomal dominant disease with variable penetrance is the most common cause of SCD in patients <40 years with a risk of about 1% per year. Predicting SCD is difficult and current approaches use algorithms that pool multiple risk factors. A multivariable SCD risk score has low positive predictive value, and CMR may help refine this. Many studies have shown that an association of malignant arrhythmia and SCD with LGE (total scar, nature of scar and its extent). Presence of CMR detected myocardial scar was predictive of inducible sustained ventricular arrhythmias, SCD or cardiac death.[50,51] However, the effect, while better than many other markers, is not in itself strong enough to influence therapy in the absence of other high-risk features. Scar is quite common in HCM and the type of scar (tissue heterogeneity reflected by regions of intermediate signal intensity of LGE) might be more predictive of future events in general and in HCM in particular.[46,52,53] A recent meta-analysis showed the predictive value of CMR for predicting SCD in HCM.[50] While this is exciting, it remains a research area not currently generating a Class I clinical recommendation[32] and we need strong clinical trial data, showing additive value and better clinical outcomes, to support its use in general Cardiac practice.[32]

CMR also has an important role in other cardiomyopathies. It shows RV morphology better than any of the current imaging modalities and is the imaging modality of choice for functional and structural assessment of the right ventricle in a variety of disorders associated with SCD including RV infarct and Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC). ARVC is an important cause of SCD in the young and athletes.[54] Right ventricular LGE predicts increased likelihood of inducible sustained ventricular tachycardia in patients with ARVC.[1,54] Presence of diffuse disease including left ventricular involvement with CMR, may call for considering an ICD for primary prevention of SCD.[1] Patients with sarcoid have a significantly higher risk of arrhythmia and SCD and LGE (sparing the subendocardium) suggests cardiac involvement and increased risk of cardiac death. A recent study showed that LGE is predictive of death and ICD discharge in patients with sarcoid.[55] This needs to be confirmed in larger studies before we use LGE decision making for primary prevention of SCD in such patients. Chagas disease is associated with cardiac involvement and fibrosis that is common in patients with SCD and may help triage of who will benefit from ICDs.[56] Finally, CMR is being studied in other cardiomyopathies including infiltrative diseases (amyloidosis,

hemochromatosis) and cardiomyopathies associated with muscular dystrophies; however, there is limited evidence for using this in stratification for SCD. CMR, with its exquisite detail, might be very important to risk stratify athletes but it is expensive, not easy to do and may find a place in evaluating athletes thought to have high risk from other screening modalities. It certainly is not likely to be a primary screening tool. In addition, we don't have good normal data and since many high-level athletes have spotty LGE we may not be able to use LGE (scar) as the primary parameter to screen for risk (unlike in other conditions like cardiomyopathy).[57]

4. Conclusion

Identifying subjects who are at risk for SCD and stratifying them correctly into low or high-risk groups is the holy grail of Cardiology. SCD is a major problem and Imaging is an exciting modality, but it is important to understand that imaging may not be a panacea even if we had a good screening tool in SCD imaging. While imaging shows a lot of promise, it is plagued by the fact that most SCD occurs in relatively healthy subjects, a massive group who would not ordinarily be subjected to imaging. EF currently is our primary parameter for risk stratification for sudden cardiac death but is a poor marker with low sensitivity and specificity. Current data shows that sophisticated imaging with techniques, mainly CMR, have the potential to identify novel high-risk markers underlying SCD, beyond ejection fraction. Imaging seems to further refine risk in patients with low EF as well as in those with normal EF; this is a major strength of advanced imaging. Clinical application has been slow and not fully prime time. It is important to remember that while promising, imaging techniques including CMR, have not been tested in rigorous prospective studies and thus have not as yet replaced EF as the gatekeeper to ICD implantation. Despite enthusiasm for imaging in predicting SCD, participation in rigorous clinical trials has been modest and one major effort could not even enroll enough patients to be successful.[58] It is, however, important to remember that even though risk stratification and prevention of sudden death through Imaging may be of value in certain selected groups, there is currently a lack of powerful tools for screening of the general population where the majority of sudden cardiac deaths occur. Rather than be a population-screening tool, the immediate focus of research in future imaging studies needs to be the following – (a). Refine the low EF population – i.e. finding which patients among the current MADIT II & SCD-HEFT population(s) benefits most from ICDs. (b). Identifying high-risk subjects in the preserved EF categories – a group where most of the SCD risk resides. At this time, at least till we have good clinical trials, sophisticated imaging might be limited to the groups with the highest risk (10 yr risk over 20% or more) and those with abnormalities found on standard screening techniques. Imaging targeting a combination of ischemia, scar and innervation with or without biomarker information, might in theory, refine risk prediction but the cost effectiveness of such a strategy remains to be proven before widespread applicability. Future advances will help better crystallize the role of Imaging in patients at risk for SCD.

Conflicts of interest

All authors have none to declare.

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