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Cardiac Magnetic Resonance for Ventricular Arrhythmia Therapies in Patients with Coronary Artery Disease

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Abstract

Cardiac magnetic resonance (CMR) imaging is currently gold standard for myocardial tissue characterization and scar assessment. CMR serves potential prognostic information in patients with coronary artery disease (CAD) for both ventricular arrhythmia risk, as well as it may also be used for guiding VT ablation procedures. This review is focused on the usefulness of CMR for ventricular arrhythmia therapies in patients with CAD.

Introduction

Despite many cardiologists think that cardiac magnetic resonance (CMR) is a tool to diagnose arrhythmogenic right ventricular cardiomyopathy, nowadays for electrophysiologists; it is nearly a perfect tool for risk stratification and guiding complex ablation procedures, by its ability to characterize scar tissue. In this review, we focused on the usefulness of CMR in ventricular tachycardia therapies in ischemic heart disease.

Patients with prior MI are at risk of developing cardiovascular events, particularly ventricular arrhythmias. Differentiation of the patient at high risk to develop lethal ventricular arrhythmia is crucial.

Ventricular tachycardia (VT) is a life-threatening arrhythmia that is common to all forms of heart disease and also an important cause of sudden death. Ventricular scars due to previous myocardial infarction (MI) provide a substrate for reentry. Although dense, fibrous scars in the infarcted myocardium incapable of depolarization cannot alone cause arrhythmias, when surrounded by distorted bundles of surviving myocytes capable of depolarization in the infarct border zone, arrhythmogenic substrates for slow conduction and reentry phenomena may arise.[1-8] Histological examination of myocardial specimens from patients with chronic MI and medically refractory VT revealed heterogeneous area compound of isolated bundles of surviving myocytes interwoven with strands of fibrous tissue at the apparent arrhythmic focus.[3] It is critical to visualize scar tissue better for both understanding the arrhythmia mechanism and guiding therapies.

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None.

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CMR is the gold standard imaging modality to assess both the size and the characterization of scar tissue, as well as chamber sizes and volumes. Dense scar (DS) and the peri-infarct zone (PIZ) heterogeneity can be visualized by contrast-enhanced CMR (ce-CMR).

Several studies have evaluated the risk stratification potential of myocardial scar assessment by ce-CMR. These reports showed that extent of the left ventricular scarring, as well as the extent of the PIZ were independent predictors of ventricular tachyarrhythmia inducibility in ischemic cardiomyopathy. Also these scar characteristics have been linked to appropriate implantable cardioverter defibrillator (ICD) shocks in this patient group.[9-13]

CMR Based Risk Assessment in CAD

Current guidelines recommend insertion of ICDs for patients with reduced left ventricular ejection fraction (LVEF), but review of two major primary ICD prevention trials[14-15] showed that, only 20% of patients had appropriate therapy during four years follow-up.[16] According to MADIT II trial, in which patients had undergone only LVEF based ICD implantation, sixteen ICDs should be implanted to prevent one sudden cardiac death. Identification of patients with depressed LVEF who will benefit from costly and invasive procedure is an important task. On the other hand, the majority of sudden deaths occur in patients with only moderately reduced or preserved LVEF.[17] With rapid restoration of coronary flow by percutaneous intervention during acute MI being the standard of care, over 85% of survivors of acute MI have only mild or moderate reduction of LVEF in the recovered phase after infarction.[18] However, risk stratification of patients with preserved systolic functions is still controversial. In this review, we will focus to potential role of CMR in ischemic patients with reduced LVEF and preserved LV functions, separately.

Left ventricular systolic functions alone does not differentiate mortality due to pump failure or sudden death due to ventricular

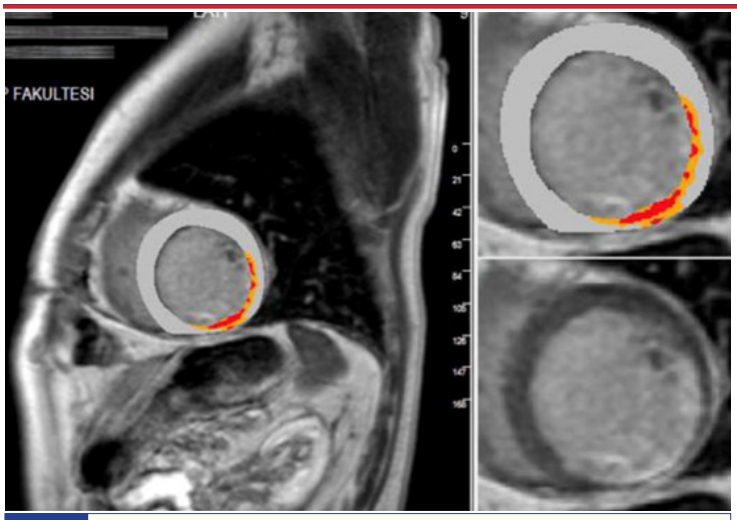

Figure 1: Custom developed software used for analyzing scar size and characteristics. Red indicates scar core and yellow indicates peri-infarction zone

arrhythmia.[19] LVEF, as measurement of scar size has low sensitivity. It can be influenced by autonomic functions, hemodynamic parameters; such as preload and afterload, drugs and post-MI remodeling. Additionally, it may not be always correlated with scar size.[20-21] For this reason, direct visualization and quantification of scar tissue may serve additional prognostic information.

Experience with CMR in ischemic patients with reduced LVEF includes studies with endpoint as VT inducibility or composite endpoint: mortality/ICD therapy. Bello et al.[9] studied 48 patients with CAD who were referred for programmed ventricular stimulation (PVS). Infarct surface area and mass, as measured by CMR, are better identifiers of patients who have a substrate for monomorphic VT than LVEF. A study also done by Bello et al.'s group[12] showed that, LVEF and infarct mass by ce-CMR were best predictors of mortality in CAD patients. By a more pathophysiologic approach heterogeneous tissue or PIZ (mixture of normal-appearing tissue and scar) was studied for VT inducibility and survival in CAD patients. Schmidt et al.[10] enrolled 47 patients with ischemic cardiomyopathy in whom primary ICD implantation was planned to their study. PIZ extent was found to predict VT inducibility. Similarly, Roes et al.[11] studied the relation between infarct tissue heterogeneity on CMR and the occurrence of spontaneous ventricular arrhythmias. Ninety-one patients with previous MI scheduled for ICD implantation underwent cine-CMR to evaluate left ventricular function and volumes and ce-CMR for characterization of scar tissue (infarct gray zone as measure of infarct tissue heterogeneity, infarct core, and total infarct size). Appropriate ICD therapy was documented in 18 patients (20%) during a median follow-up of 8.5 months (interquartile range, 2.1 to 20.3). Multivariable Cox proportional hazards analysis revealed that infarct gray zone was the strongest predictor of the occurrence of spontaneous ventricular arrhythmia with subsequent ICD therapy. Wu et al.[22] used infarct tissue heterogeneity and CRP levels to identify high and low risk subgroups in dilated cardiomyopathy patients. Patients in the lowest tertile for both PIZ and CRP were at particularly low risk (0.7%/year event rate) while those in the highest tertile for both PIZ and CRP had an event rate of 16.1%/year, p<0.001. In contrast to previous studies, Lin Y et al.[23] studied predictors of ventricular arrhythmias in patients with a LVEF lower than 50% and found no difference in PIZ% between groups with or without ventricular arrhythmias/mortality. Number of conductive channels, a more complicated marker derived from PIZ configuration, was the only CMR parameter identifying the endpoints.

Table 1: summarizes CMR based risk stratification studies in patients with CAD

Study	Cohort	Method	Result
Bello et al[9]	CAD (n=48)	LGE (>2SD)	Infarct mass and surface area predict monomorphic VT by PVS
Bello et al[12]	CAD (n=100)	LGE (Manual planimetric)	Infarct>24% and LVEF<30% predict death
Schmidt et al[10]	ICM (n=47)	PIZ (2-3 SD)	PIZ% predicts VT inducibility
Roes et al[11]	Post-MI (n=91)	FWHM (Total scar/PIZ)	PIZ was associated with spontaneous VTs
Wu et al[22]	ICM (n=137)	FWHM (TS/PIZ)	Combination of CRP and low PIZ identify low risk
Lin et al[23]	ICM (n=63)	PIZ (2-3SD)	#Conductive channels within PIZ was associated with VT/VF attacks
Yalin et al[24]	Post-MI mild systolic dysfunction and ns-VT (n=28)	PIZ (2-6SD)	PIZ% identified VT inducibility better than TS%
Yan et al[13]	CAD (n=144)	PIZ (2-3SD)	LV volume index and PIZ size were independent predictors of all cause and CV mortality
Watanabe et al[25]	CAD (n=301)	PIZ (2-3SD)	PIZ% was associated with all cause mortality and ICD/deaths. Association was stronger in patients with LVEF>35%
Klem et al[26]	ICM (n=73)	LGE (Manual planimetric)	LGE>5% predicts deaths or appropriate ICD discharges

As mentioned before, risk stratification of ischemic patients with preserved systolic functions is controversial. CMR may be useful tool to detect patients at high arrhythmic risk in this cohort. Our group[24] studied potential role of CMR in post-MI patients with mild systolic dysfunction and nonsustained VT (Figure-1). We compared CMR parameters between patients with (n=9) and without VT (n=19) inducibility during PVS. PIZ% and total scar% were independent predictors of monomorphic VT inducibility, whereas LVEF was similar between the groups. The study of Yan et al.[13] showed that the extent of PIZ defined by ce-CMR was an independent predictor of post-MI all-cause and cardiovascular mortality after adjusting for LV volumes or LVEF. The mean LVEF of all the patients was 44% (calculated by CMR). After a follow-up of 2.4 years, the patients with a median PIZ% were statistically at a higher total mortality risk compared with those with a lower PIZ%. However, they did not study arrhythmic causes of deaths. More recent study by Watanabe et al.[25] followed 301 patients with chronic CAD for median 4 years. Present study highlighted the significance of infarct heterogeneity in all-cause mortality and death/ICD therapies. The prognostic association was especially notable in patients with LVEF>35%. In addition, despite having an LVEF>35%, patients with a high degree of infarct heterogeneity experienced similar mortality as patients with severe systolic dysfunction (LVEF≤35%). This finding was consistent with hypothesis on scar sizing would be more sensitive than LVEF alone. Klem et al.[26] tested whether an assessment of myocardial scarring by CMR would improve risk stratification in patients evaluated for ICD implantation. In patients with LVEF > 30%, 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%. These two studies may be a candidate to reclassify patients

according to scar characteristics instead of LVEF.

Stress CMR is a useful imaging modality for ischemia assessment. Ischemia detected by CMR provides an incremental prognostic risk factor over other risk factors.[27] It is not known how ischemia around scar zone affects PIZ measurement and it is also unclear if the combination of stress and delayed enhanced CMR imaging may increase the prognostic accuracy.

CMR imaging is currently gold standard for myocardial tissue characterization and is a risk stratifying method in CAD patients (Table 1). The study is usually performed within <45 minutes without radiation exposure. Despite the role of CMR in risk stratification for SCD, it has several limitations in this field. CMR based risk stratification has been evaluated in multiple studies, in which the number of patients and events were low. In addition, all evidence was derived from retrospective or observational studies. DETERMINE study, a randomized trial to test the potential role of CMR based risk stratification in gray zone patients with CAD (LVEF 35%-50%), was designed.[28] Unfortunately, to reach the target randomization, approximately 10.000 patients would have to been screened with CMR. Due to slow enrollment, the study was halted. Taking into consideration of several other risk factors studied in patients with preserved LVEF, may decrease the number of patients needed for randomization and may help identifying patients with high mortality risk.

Furthermore, the risk for SCD is a dynamic process; patients might have worsening of their condition and new insults over time, whereas others might have significant recovery or improvement. Hence, assessment on the basis of first imaging alone might not be accurate, and follow-up evaluation might be warranted. Although CMR assessment of scar by late gadolinium enhancement (LGE) is an extremely robust technique, it has several limitations, including partial volume effect that may exaggerate PIZ%. Partial volume effect relates to the 3-dimensional spatial resolution of the image. If a given voxel at the infarct periphery contains an admixture of both infarcted (high signal intensity-SI) and noninfarcted (low SI) tissue, the 2 different SIs will be averaged, and this particular voxel will be represented by an intermediate SI (gray). However, this admixture of tissues causing intermediate SI can occur in 2 different ways. First, it could result merely from the volume-averaging effects of an area of uniformly fibrotic tissue (dense infarct scar) with an adjacent area of completely preserved, viable myocardium, particularly in situations in which spatial resolution is limited. In this case, anatomically, there would be a single border between fibrotic scar and viable myocardium, and the limited spatial resolution would render an apparent intermediate SI in that border region. However, a second possibility is that intermediate SI arises from the intermingling of discrete areas of preserved myocardium with bundles of fibrotic, infarcted scar within the same voxel. In this case, there would be a more gradual anatomic transition from dense, infarct core to preserved tissue beyond the infarct periphery. The latter mechanism is supported by pathological data.

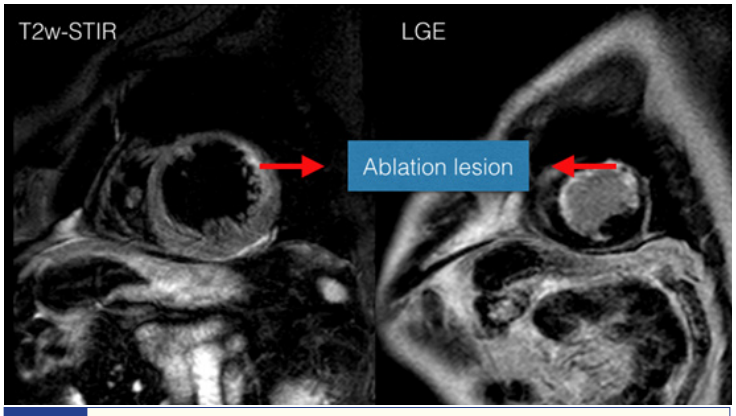

Figure 2: T2w-STIR shows myocardial eadema, whereas LGE shows dark no-reflow region on corresponding RF application site

Furthermore there remains controversy within the CMR literature regarding which post-processing criteria should be used to characterize the size of the PIZ. PIZ measurements differ among study protocols[9-13] (Table 1). de Haan et al.[29] compared the previously studied methods for PIZ measurement and found that additional estimation of scar core and/or PIZ size does not appear to increase the diagnostic accuracy over total scar size alone. Additionally, measurement of PIZ may not be reproducible. It has to be validated by histological specimens.

CMR Guided VT Ablation Procedures

CMR also has the potential to guide the treatment of scar based monomorphic ventricular tachycardia. Ventricular tachycardia ablation is an essential therapy for patients with frequent ICD shocks. Interruption of isthmuses of viable myocardium within scar may terminate the tachycardia.[30] Conventional mapping techniques require induction of the arrhythmia. In minority of post-MI patients with ventricular tachycardia, induction of clinical VT does not cause significant hemodynamic instability and allows mapping maneuvers. Activation mapping and entrainment mapping may identify critical isthmus. Success rates have been reported to be approximately 75% after successful mapping procedures.[31] In the majority of patients, however, induction of VT leads to severe hypotension, and entrainment and activation mapping during VT is not possible. Voltage mapping during sinus rhythm has been used to identify low-voltage areas (1.5 mV), which are presumed to be areas of a scar. A substrate based ablation strategy using linear lesions, deployed anatomically with reference to the myocardial scar/infarct zone has proved to be effective.[32] Late potentials, fragmented, and isolated potentials and slow conducting channels detected during scar mapping are highly sensitive and specific markers for critical isthmuses.[33-39] Ablation of conducting channels and late/isolated potentials identified by voltage mapping is safe and effective method.[40] Current voltage and EGM based mapping techniques can be difficult, however, because of ambiguities in correlating maps with anatomy, as well as possible missed critical sites due to the point-by-point endocardial sampling nature of current methods. Point by point mapping of the ventricle is time-consuming and increasing procedural time may cause serious complications. Thus, a need exists to develop alternative approaches to VT ablation that would provide an improved delineation of the arrhythmogenic substrate.

Desjardins et al.[41] studied 14 patients who underwent post-MI VT ablation. They conclude that CMR can accurately predict the electro-anatomic characteristics of corresponding subendocardial locations. Critical sites of post-infarction arrhythmias were confined to areas of late enhancement. The scar information on MRI can be selectively imported into an electro-anatomical mapping system to facilitate the mapping and ablation procedure.

Perez David E et al.[42] used delayed enhanced CMR based signal intensity mapping to determine conducting channels. They studied

18 patients with sustained monomorphic VT and 18 age, sex, infarct location and LVEF matched controls. Cohort underwent CMR, and patients underwent VT ablation procedure guided by electro-anatomical mapping system. Color-coded shells displaying CMR subendocardial signal intensity were generated (3-dimensional SI mapping). Merging the SI maps during EP study was not performed and the electrophysiologist performing the ablation procedure was blinded to CMR data. They compared with endocardial voltage maps and SI maps offline. Their study showed that channels of heterogeneous tissue are more commonly identified in sustained monomorphic VT than in control patients, and the CC detected by endocardial voltage mapping can be identified by 3D SI mapping. Gupta S et al.[43] used CMR based scar maps merged to EAM system during VT ablation. Registration accuracy and MRI/EAM correlations were assessed and critical areas for VA were correlated with the presence of scar. With a positional registration error of 3.8±0.8 mm, 86% of low voltage points of the EAM projected onto the registered scar. The CMR defined scar correlated with the area of low voltage (R=0.82, p<0.001). All sites critical to VTs projected on the registered scar. Selective identification and extraction of CMR defined scar followed by registration into a real-time mapping system is feasible and helps to identify and display the arrhythmogenic substrate in post-MI VTs. Bipolar only voltage mapping may not always detect scar accurately. CMR images have been used to target regions of scar for optimizing ablation strategy may not be appreciated from bipolar voltage maps and have demonstrated that a >2-mm rim of surviving endocardium was able to produce an electrogram >1.5 mV, such that this commonly employed bipolar voltage criteria of 1.5 mV would not detect this scar.[44] Verma et al.[45] also reported a series of patients in whom approximately 15% of ablation sites were outside of the bipolar LVA.

Despite, nearly perfect tissue characterization of CMR; the current techniques to guide VT ablation have several limitations. Positional error using surface registration may affect accuracy of the technique. Furthermore, partial volume effect may exaggerate peri-infarction zone measurement. This problem may be solved by high resolution MR imaging. Administration of gadolinium as a contrast medium in patients with chronic renal disease should be avoided (unless no other alternative is available), because of the risk of nephrogenic sclerosis. Usefulness of CMR in patients with advanced cardiomyopathy and decompensated heart failure prohibiting patients from lying flat during a CMR study is limited. The majority of patients referred for post-MI VT ablation have an implantable defibrillator. Current clinical ce-CMR scar imaging protocols produce ICD artifacts that affect >50% of the LV myocardium.[46] This may significantly limit the application of CMR for image guided VT ablation. Novel wideband late gadolinium CMR has been developed to allow for improved scar evaluation on patients with ICDs.[47]

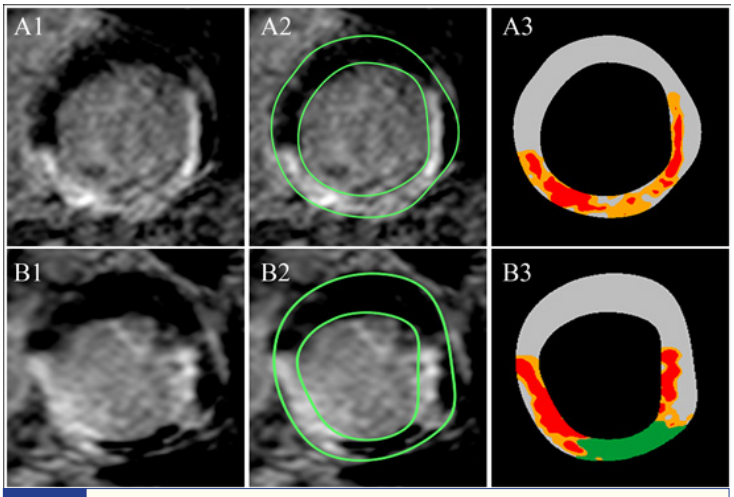

Figure 3: **Delayed-enhancement CMR before (A) and 24-hours after the ablation procedure (B)**

Another issue that is important to guide VT ablation is to detect epicardial VT circuits. The substrate of most VTs is located in the endocardium but some VT can only be ablated from the epicardium. A combined endo-epicardial substrate ablation approach reduces VT recurrences, however less than 30% of patients in whom the accuracy to delimit epicardial scars. Epicardial mapping and ablation is open for complications due to need for pericardial puncture. Therefore, epicardial RF delivery is limited by fat or associated with bleeding, extra-cardiac damages, coronary vessels and phrenic nerve injury. Alternative ablation approaches might be desirable. By this point, Arenal et al.[48] showed that CMR based SI mapping can identify epicardial VT substrate accuratly in animals. Unfortunately, to date this observation has not yet been proven in human. Detection of epicardial substrate without epicardial mapping may be important, because it has been shown that it is possible to eliminate epicardial LAVAs from endocardial site.[49]

Radiofrequency ablation lesions can be visualized by CMR (Figure-2). In our case[50] with ventricular tachycardia and previous MI, we performed substrate modification including late potential and fragmented potential ablation. Preablation CMR data showed large area of PIZ (CMR data was blinded to ablation performing physician), post-ablation CMR 24 hours later, showed dark-"no-reflow" points reaching into previously observed PIZ (Figure-3). Characteristics of MR based ablation lesion visualization in a general VT ablation cohort has been studied by Vunnan R, et al.[51] They concluded that, current delayed enhanced CMR protocols can detect ablation lesions in 1/3 patients after VT ablation; ischemic heart disease, higher transmurality of scar and presence of ICD may negatively impact the ability to visualize RF lesions. In their study, they performed CMR imaging relatively late, than we did. In our institution, we have four post-MI patients that we have pre- and postablation (within 24 hours) CMR data. In all patients CMR visualized RF ablation lesions. We attribute this discrepancy to time of CMR after ablation procedure. Another task of this study is to identify ability of CMR in evaluation of RF lesions. In our patients successful ablation lesions were in areas of peri-infarction zone. It seems that ablation in peri-infarction zone may eliminate VTs and may provide prognostic information. Our study in this field is ongoing. Prognostic role of postablation CMR imaging has to be investigated. It may become an alternative endpoint of the VT ablation procedure rather than checking the inducibility.

Conclusion

CMR imaging is a noninvasive method that allows visualization and quatification of scar tissue. Despite its limitations CMR based risk stratification and possible reclassifying of patients are hopeful. Randomized prospective trials of CMR with well-accepted end-points may change current LVEF based prevention strategy. Today, use of CMR before and during VT ablation procedure may render an opinion where to concentrate mapping. After only-SI mapping guided VT ablation studies and postablation CMR studies with

follow-up data may supersede point-by-point EAM systems and VT inducibility after ablation as an end-point of the procedure.

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