Prediction of ventricular arrhythmias using cardiovascular magnetic resonance

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Ventricular tachycardia (VT) is the commonest cause of sudden cardiac death (SCD) in developed countries. Coronary artery disease (CAD) is the most frequent cause of VT in individuals over the age of 30, while hypertrophic cardiomyopathy (HCM), myocarditis and congenital heart disease in those below 30 years of age. Cardiac magnetic resonance (CMR), a non-invasive, non-radiating technique, can reliably detect the changes in ventricular volumes and the ejection fraction that can be predictive of VT/SCD. Furthermore, the capability of CMR to perform tissue characterization and detect oedema, fat and fibrotic substrate, using late gadolinium enhanced images (LGE), can predict VT/SCD in both ischaemic and non-ischaemic cardiomyopathy. The extent of LGE in HCM is correlated with risk factors of SCD and the likelihood of inducible VT. In idiopathic-dilated cardiomyopathy, the presence of midwall fibrosis, assessed by CMR, also predicts SCD/VT. Additionally, in arrhythmogenic right ventricle (RV) dysplasia/cardiomyopathy, CMR has an excellent correlation with histopathology and predicted inducible VT on programmed electrical stimulation, suggesting a possible role in evaluation and diagnosis of these patients. A direct correlation between LGE and VT prediction has been identified only in chronic Chagas' heart disease, but not in viral myocarditis. In CAD, infarct size is the strongest predictor of VT inducibility. The peri-infarct zone may also play a role; however, further studies are needed for definite conclusions. Left ventricle, RV, right ventricular outflow tract (RVOT) function, pulmonary regurgitation and LGE around the infundibular patch and RV anterior wall play an important role in the VT prediction in repaired Tetralogy of Fallot. Finally, in treated transposition of great arteries, the extent of LGE in the systemic RV correlates with age, ventricular dysfunction, electrophysiological parameters and adverse clinical events, suggesting prognostic importance.

Keywords Ventricular arrhythmia • Sudden death • Cardiac magnetic resonance

Introduction

Ventricular arrhythmia remains the most common cause of sudden cardiac death (SCD) in developed countries occurring in 1–2:1000 inhabitants per year.1 Prediction of SCD, due to ventricular arrhythmia (VT), still remains a major challenge for cardiology. Coronary artery disease (CAD) comprises the most frequent cause of VT/SCD in individuals over the age of 30, while hypertrophic cardiomyopathy (HCM), myocarditis and congenital heart disease are the most frequent causes in individuals below 30 years of age.1 The majority of patients with ventricular arrhythmia presents with SCD, as the first demonstration of underlying cardiac disease.2 Medication and/or implantable cardioverter defibrillator (ICD) is the treatment of choice in patients at high risk of VT.

The benefits of primary prophylactic implantable ICD are actually debated, as some drawbacks become more apparent and the natural history of underlying cardiac disease may be improved. Additionally, the clinical course of both ischaemic and non-ischaemic heart disease, treated with a primary prophylactic ICD, is similar with respect to mortality and to appropriate and inappropriate ICD interventions, in spite of a younger age at baseline of non-ischaemic cardiomyopathy.3 ICDs are routinely used to prevent SCD in selected HCM patients. However, HCM with ICD had a significant cardiovascular mortality and were exposed to frequent inappropriate shocks and implant complications. This suggests that new strategies are required to improve patients’ selection for ICDs and to prevent disease progression in those receiving a device.4

Accurate identification of patients at high risk of SCD remains a challenging problem. A variety of clinical, imaging and laboratory parameters has been used to address this issue. In non-ischaemic cardiomyopathy (NISC) with heart failure (HF), female gender,
age, lack of statin therapy and increased creatinine represent independent risk factors for malignant arrhythmias.\(^5\) Residual ischaemia, depressed left ventricular ejection fraction (LVEF), electrical instability, frequent ventricular ectopic activity and impaired autonomic status are conventional risk factors for SCD prediction in CAD. However, according to recent data, CAD patients with an EF $\leq 30\%$, but no other risk factors, have a low predicted mortality risk, in contrary to those with an EF $>30\%$ and other risk factors, who have higher mortality and higher risk of sudden death, than those with the EF $\leq 30\%$.\(^6,7\)

Recently, the presence, location and morphology of scar, as assessed by late gadolinium enhanced (LGE) images, were proved to be of value in the identification of pathophysiological background behind VT/SCD. Subendocardial and/or transmural LGE, following the distribution of coronary arteries, indicates the presence of CAD. Intramyocardial and/or subepicardial LGE, unrelated to the distribution of coronary arteries, is indicative of myocarditis and/or cardiomyopathy. LGE, located in the free wall of the right and possibly the left ventricle, is characteristic of arrhythmogenic RV dysplasia/cardiomyopathy (ARVD/C).\(^8\) Furthermore, the percentage of LGE was proved a powerful factor of SCD prediction. Data from 137 patients undergoing evaluation for possible ICD placement during a median follow-up of 24 months, proved that in patients with an LVEF $>30\%$, the presence of significant scarring ($>5\%$ LV) identifies a high-risk cohort similar in risk to those with an LVEF $\leq 30\%$. Conversely, in patients with the LVEF $\leq 30\%$, the minimal or no scarring identifies a low-risk cohort, similar to those with the LVEF $>30\%$.\(^9\) Although the clinical significance of LGE in the evaluation of SCD has been established, current clinical guidelines do not recommend implantable cardiac defibrillators for patients with unstable ventricular arrhythmias in the setting of acute myocardial injury.\(^10\)

### Risk stratification of SCD

Risk stratification and prevention of SCD is of tremendous importance. Although CAD, NYHA III class and LVEF have been considered as independent, statistically significant predictors of mortality,\(^11\) 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), a non-invasive technique capable to perform tissue characterization.\(^12\) However, according to recent data, CMR has the great capacity to identify relevant, but clinically unsuspected, disease in patients with SCD or sustained monomorphic ventricular tachycardia, such as acute myocarditis and acute ischaemic injury.\(^13\) 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 ischaemic or non-ischaemic myocardial disease.\(^13\) 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 of distinct patterns of acute or chronic injury.\(^13\) The pattern and distribution of injury can offer a reliable assessment of disease aetiology,\(^14\) whereas the extent of irreversible tissue injury has been associated with future arrhythmia risk in both ischaemic\(^15\) and non-ischaemic\(^16\) cohorts. In addition, fatty replacement of myocardium, identified by T1-weighted imaging, can be a diagnostic tool for the detection of ARVD/C.\(^17\) The combination of these three tissue imaging sequences with CMR cine imaging, a gold standard for cardiac morphology and function, offers a robust tool for the identification of arrhythmogenic substrate.\(^13\)

### Role of CMR for ventricular tachycardia prediction in cardiomyopathies

#### Hypertrophic cardiomyopathy

HCM is characterized by genetic and phenotypic heterogeneity, leading to a great diversity in clinical course, including the most common cause of SCD in young people and a determinant of 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.\(^18\)

The available evidence proved that myocardial scar, demonstrated by LGE, is an important predictor of cardiac mortality in HCM. The extent of LGE was proved to be associated with both progression to heart failure and SCD.\(^19\) LGE has incremental value in addition to clinical risk factors for risk stratification and management of HCM\(^20,21\) (Figure 1). Furthermore, the extent of LGE in HCM correlated with risk factors of SCD and the likelihood of inducible VT.\(^22\) In a population of largely low or asymptomatic HCM, the presence of scar, indicated by LGE, was a good independent predictor of all-cause and cardiac mortality.\(^23\) O’Hanlon et al.\(^24\) proved that the extent of fibrosis and non-sustained VT were univariate predictors for arrhythmic endpoints. However, non-sustained VT remained an independent predictor of arrhythmic endpoints after multivariate analysis, but the extent of fibrosis did not. Recently, the LGE signal intensity (LGE-SI) in HCM was proved of important value in VT prediction. In this context, the intermediate LGE-SI ($SI \geq 4$ but $<6$ SD above the mean SI of normal myocardium) was a better predictor of VT than high LGE-SI (LGE with $SI \geq 6$ SD).\(^25\) According to these findings, the LGE plays a crucial role for VT prediction in HCM. However, further multicentre studies are needed to assess the clinical implications of LGE type, location and extent for VT prediction in different subgroups of HCM.

#### Dilated cardiomyopathy (ischaemic and non-ischaemic)

Dilated cardiomyopathy is the endpoint of both ischaemic (ICM) and non-ischaemic (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. Additionally, the presence, size and heterogeneity of myocardial scar can predict VT and identify patients appropriate for ICD, between those referred for cardiac resynchronization treatment. In idiopathic DCM, the 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. Furthermore, in DCM, the presence of CMR-assessed midwall fibrosis has an additive predictive value for SCD/VT. In another study comparing the electrophysiological background and the CMR findings in a cohort of non-ischaemic cardiomyopathy, the predominance of scar distribution involving 26–75% of wall thickness was significantly predictive of inducible VT and remained independently predictive in the multivariable model after adjustment for LVEF.

Arrhythmogenic right ventricular dysplasia

Arrhythmogenic right ventricular (RV) cardiomyopathy (ARVD/C) is a familial heart muscle disease characterized by progressive fibro-fatty replacement of the RV myocardium. Clinical presentation includes RV origin arrhythmia and SCD. Left ventricular (LV) involvement was present on histology in >75% of cases in a multicentre pathology study. According to the standardized diagnostic criteria, proposed by the Study Group on ARVD/C of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies, the diagnosis of ARVD/C is based on the presence of major and minor criteria encompassing structural, histological, electrocardiographic, arrhythmic, and family history factors. Currently, ICDs are routinely used to prevent SCD in ARVC.

Figure 1 Contrast-enhanced CMR images of the left ventricle in short axis at equatorial (A), basal (B), and apical levels (C) and in a two-chamber long-axis view (D). Images show the areas of delayed enhancement at the level of the interventricular septum and the free wall, indicating the presence of extensive and transmural fibrosis. (adapted from Bongioanni S et al., Circ Cardiovasc Imaging 2009;2:349–350).
CMR is an important non-invasive diagnostic modality that allows both functional evaluation and tissue characterization (fibrosis detection) of RV–LV (Figure 2). The identification of RV myocardial fibro-fatty changes in ARVD/C, using LGE, has an excellent correlation with histopathology and predicts inducible VT on programmed electrical stimulation.\textsuperscript{17,32–34} Disease variants recognition with early and/or predominant LV involvement, using CMR, allows better risk stratification.\textsuperscript{34} In a recent study, scar characterization by LGE was in agreement with the electroanatomic voltage maps for VT prediction.\textsuperscript{35}

Myocarditis

VT can complicate viral myocarditis both during the acute and chronic phases. During the acute phase, myocarditis can be presented as acute coronary syndrome, raised troponin and VT with epi- or intramyocardial LGE and normal coronary angiography\textsuperscript{36} (Figure 3). After evaluation of 79 patients referred for CMR following an admission with presumed ACS and raised serum troponin in whom no culprit lesion was detected, 13% had unrecognized myocardial infarction (MI) and 6% takotsubo cardiomyopathy and the remainder (81%) were diagnosed with myocarditis (five of them with VT and normal LVEF).\textsuperscript{37} Additionally, 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.\textsuperscript{38} In a recent evaluation of 13 children with tachycardia originating from the RV outflow tract of apparently normal hearts, endomyocardial biopsy and CMR revealed acute myocarditis in 38%, fatty infiltration of RV in 15% and minor histologic abnormalities in 23%.\textsuperscript{39} Finally, 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).\textsuperscript{40} However, there are not enough data supporting the role of LGE for VT prediction in viral or autoimmune myocarditis.

Role of CMR for ventricular tachycardia prevention after MI

CMR has a growing application in the diagnosis of MI. In a single study, it allows the assessment of morphology, function (volumes-ejection fraction), oedema, microvascular obstruction, fibrosis and also complications that cannot 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 (AAR).\textsuperscript{41}

LGE has high sensitivity and specificity to detect and quantify fibrotic tissue due to MI. There is evidence that LGE predicts unfavourable LV remodelling after acute MI and therefore it might be considered as an index of LV dysfunction, alternative to LVEF or LV end-systolic volume. Pathophysiological correlations between LGE and LVEF seem to be supported by studies
However, although scar percentage was associated with VT inducibility during electrophysiological study, identifying patients susceptible for such re-entrant sites, but not to histopathology. Improvement in LGE spatial resolution and validation of LGE-derived scar characteristics in experimental models with histopathologic correlation might overcome these limitations.

T1 mapping, an index of diffuse fibrosis, has been recently applied in the evaluation of fibrotic substrate of both ischaemic and non-ischaemic cardiac diseases. In acute MI, pre-contrast T1 mapping allows the assessment of the extent of myocardial damage. T1-mapping might become an important complementary technique to LGE and T2W for identification of reversible myocardial injury and prediction of functional recovery in acute MI. Additionally, for determining AAR after acute MI, non-contrast T1 mapping and T2 mapping sequences yield similar quantitative results and both are in agreement with microspheres. However, at the moment there are no data about the role of T1 mapping in VT prediction.

Figure 4 Transmural LGE, due to myocardial infarction, in the apical part of the septum, apex and in the apical part of lateral wall from a patient with myocardial infarction and VT.

showing that LGE inclusion in multivariate models often leads to substantial blunting of the well-known prognostic power of LVEF. However, according to recent data, LGE is a strong prognostic factor in unselected patients with stable CAD, showing a complementary role with respect to LVEF. Furthermore, LGE is of value in the detection of unrecognized MI (UMI). In a community-based cohort of older individuals, the prevalence of UMI by CMR was higher than the prevalence of recognized MI (RMI) and was associated with increased mortality risk. Additionally, LGE characteristics are of predictive value for the occurrence of VT in ICM. In patients with chronic MI scheduled for primary preventive ICD implantation, infarct transmurality, as defined by LGE, identifies a subgroup with increased risk for life-threatening arrhythmias and SCD. Furthermore, the amount of myocardial scar, identified by LGE, predicts all-cause mortality in a range of patient groups, including those with a previous MI, ICM and vascular risk factors, but without clinical evidence of a prior MI. In patients with HF after MI, scar quantification predicts both the occurrence of VT and the inducibility of VT on electrophysiological study, identifying patients susceptible for sustained VT. Bello et al. quantified scar, using LGE, in 48 patients with CAD and reduced LVEF, undergoing electrophysiological study. Eighteen of them had inducible monomorphic VT. Infarct mass and infarct surface area were the strongest predictors of VT inducibility. The mechanistic relationship between ventricular scar and arrhythmogenesis is well established, and postmortem studies have suggested that scar burden may reflect the susceptibility to VT. 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 (76–100%) scar (Figure 4).

The majority of previous LGE studies have classified myocardium as scar or normal (remote) myocardium; however, few studies have used a more graduated approach. 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 SI. Yan et al. identified that a large peri-infarct zone (PIZ) was a powerful predictor of mortality. PIZ was defined as the 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). Schmidt et al. demonstrated that infarct tissue heterogeneity, expressed as PIZ, but not the total infarct size, correlated with inducibility of monomorphic VT during electrophysiology. In this study, the core infarct was defined as areas with SI >50% of maximal SI in the hyperenhanced area and the PIZ as the myocardium with SI >peak SI of remote myocardium but <50% of the maximum SI. However, inducibility of VT does not necessarily correlate with the occurrence of spontaneous VT. Roes et al. 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 the maximal SI, grey zone 35% ≤ SI < 50% of the maximum SI). However, it seems unlikely that these different semi-automated methods can result in a similar quantification of heterogeneous infarct tissue. Furthermore, none of them has been compared with histopathology. Recently, Woie et al. defined the core infarct as the area with the highest SI minus 2 SD of the visually determined scar, but it was not completely clear, if this evaluation was performed for each slice separately that would imply the potential variation in the infarct core SI per slice.

In another study it was documented that PIZ is a complex tissue substrate that changes its composition and decreases in mass, following myocardial reperfusion. The difference in tensile strain forces, between the infarct scar and the PIZ, is reached ~30 days after MI. After this time, the underlying tissue substrate is mainly composed of viable myocytes and clear defined collagen tissue. Myocardial strain characteristics, combined with PIZ for the assessment of LGE images, may provide important clinical information for the development of life-threatening arrhythmias, as well as SCD post-MI.

We should also emphasize that the currently in vivo used LGE techniques have inferior resolution and are unlikely to visualize the exact 3D scar geometry. A 3D infarct structure, using high-spatial resolution LGE techniques in a swine infarct model, was related to VT re-entrant sites, but not to histopathology. Improvement in LGE spatial resolution and validation of LGE-derived scar characteristics in experimental models with histopathologic correlation might overcome these limitations.
Role of CMR for ventricular tachycardia prevention in congenital heart disease

Congenital heart disease is a frequent cause of ventricular arrhythmia in individuals below 30 years of age. Although there are not enough data in this field, 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 significantly associated with VT prediction and might improve patients’ selection for further screening.69

The repair in TOF results in pulmonary regurgitation, contributing to RV dilatation and VT development.70 Pulmonary valve replacement in TOF repair and chronic pulmonary regurgitation leads to stabilization of QRS duration and, in conjunction with intraoperative cryoablation, to a decrease in the incidence of pre-existing atrial and ventricular tachyarrhythmia.71 LV, RV and right ventricular outflow tract (RVOT) function play an important role in VT development in repaired TOF. A tissue tracking, applied to CMR images, identified LV synchrony predisposing to malignant arrhythmia in repaired TOF.72 Furthermore, severe LV, RV and RVOT dysfunction, assessed by CMR, predicted major adverse clinical events.73,74

The presence of LGE around the infundibular patch and RV anterior wall was proved in agreement with low voltage areas, identified by the electro-anatomical mapping in repair TOF. In patients operated on for TOF, these areas represent surgically damaged regions, due to infundibulotomy and ventriculotomy, with the consequent of fibro-fatty replacement. The coexistence of scar and viable myocardium promote electrical re-entry and predisposes to VT formation.75,76

Finally, patients treated for transposition of great arteries (TGA)s, by atrial redirection surgery, have RV that sustains systemic pressures. LGE, due to myocardial fibrosis, occurs in the systemic RV of TGA after atrial redirection surgery. The extent of LGE correlates with age, ventricular dysfunction, electrophysiological parameters and clinical events, suggesting prognostic importance.77

Take home messages

(1) LGE has a predictive value for VT/SCD in both ischaemic and non-ischaemic cardiomyopathy.
(2) LGE can accurately predict VT/SCD only in chronic Chagas’ myocarditis, but not in viral or autoimmune myocarditis. However, CMR can diagnose myocarditis with normal LVEF, presented as VT/SCD.
(3) In CAD, infant’s size and transmurality are the strongest predictors for VT/SCD.
(4) PIZ may play a role in VT inducibility; however, further studies are needed for definite conclusions.
(5) Pulmonary regurgitation, severe LV, RV, RVOT dysfunction and LGE around the infundibular patch and RV anterior wall are VT predictors in repair TOF.

Conflicts of interest: none declared.

References

Successful repair of obstructed pulmonary venous confluence by the descending aorta in a 43-year-old patient: pre- and post-operative images

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A 43-year-old female patient presented with a 3-year history of progressive dyspnoea (NYHA III). She underwent pulmonary artery banding at the age of 6 months followed by ventricular septal defect repair at 6 years and mitral valve repair at the age of 7 years. On physical examination, the patient was dyspnoeic on mild effort with a soft pansystolic murmur over lower left sternal edge.

Transthoracic echocardiography revealed severe tricuspid valve regurgitation and turbulent flow at the site of entrance of the pulmonary veins (PVs) in the left atrium (LA). (Panel A). Contrast-enhanced CT scanning revealed abnormal PV drainage with obstruction at the level of both left-sided PVs and PV confluence connection to the LA (Panels B and C). A small persistent left superior vena cava (LSVC) drained into the LA (Panel D). Surgical correction involved enlargement of the left-sided PV ostium and of the confluence to the LA, ligation of LSVC, and repair of the tricuspid valve. CT scanning 1 month after surgery revealed wide open pulmonary connection to the LA (Panels D and E). The patient was symptom free at the 6-month follow-up.

(A) Apical four chambers view of transthoracic the echocardiography showing stenosed common orifice of the PVs and turbulent blood flow at the site of entrance in LA. (B and C) Pre-operative CT with axial and reconstructed images showing that both the left superior and the inferior PVs join together forming a narrow compressed channel that joins another right common channel, both open by a narrow opening with the LA. (D) Pre-operative coronal image showing persistent LSVC. (E and F) Post-operative axial and reconstructed images showing wide open entry of all PVs into the LA.