Review Article

Cardiac Magnetic Resonance in Primary Prevention of Sudden Cardiac Death

Giorgio Faganello, Aldostefano Porcari, Federico Biondi, Marco Merlo, Antonio De Luca, Giancarlo Vitrella, Manuel Belgrano[1], Lorenzo Pagnan[1], Andrea Di Lenarda, Gianfranco Sinagra

Departments of Cardiovascular and [1]Radiology, Azienda Sanitaria Universitaria Integrata of Trieste, University of Trieste, Trieste, Italy

Abstract

Sudden death accounts for 400,000 deaths annually in the United States. Most sudden deaths are cardiac and are related to arrhythmias secondary to structural heart disease or primary electrical abnormalities of the heart. Implantable cardioverter defibrillator significantly improves survival in patients at increased risk of life-threatening arrhythmias, but better selection of eligible patients is required to avoid unnecessary implantation and identify those patients who may benefit most from this therapy. Left ventricular (LV) ejection fraction (EF) measured by echocardiography has been considered the most reliable parameter for long-term outcome in many cardiac diseases. However, LVEF is an inaccurate parameter for arrhythmic risk assessment as patients with normal or mildly reduced LV systolic function could experience sudden cardiac death (SCD). Among other tools for arrhythmic stratification, magnetic resonance (CMR) provides the most comprehensive cardiac evaluation including *in vivo* tissue characterization and significantly aids in the identification of patients at higher SCD risk. Most of the evidence are related to late gadolinium enhancement (LGE), which was proven to detect cardiac fibrosis. LGE has been reported to add incremental value for prognostic stratification and SCD prediction across a wide range of cardiac diseases, including both ischemic and nonischemic cardiomyopathies. In addition, T1, T2 mapping and extracellular volume assessment were reported to add incremental value for arrhythmic assessment despite suffering from several technical limitations. CMR should be part of a multiparametric approach for patients' evaluation, and it will play a pivotal role in prognostic stratification according to the current evidence.

Keywords: Cardiac magnetic resonance, late gadolinium enhancement, primary prevention, prognostic stratification, sudden cardiac death

Introduction

Sudden cardiac death (SCD) is a major health problem affecting mainly young individuals without severe comorbidities during their working life and generally with a long life expectancy. Epidemiological studies report SCD affecting up to 400,000 people in the United States,[1] mainly due to malignant arrhythmias as ventricular tachycardia (VT) or ventricular fibrillation (VF). Among the potential causes, ion-channel diseases and nonischemic cardiomyopathies (NICM) represent the main conditions associated with SCD, especially in participants <40 years.[2] Ischemic heart disease (IHD) is a more relevant cause of SCD in the older population, despite rarely occurring in young individuals.[1] The progressive decline in SCD achieved in recent years derives from the implementation of dedicated strategies: (1) the introduction of nationwide systematic cardiac screening programs in young competitive athletes;[3] (2) development of pharmacologic treatments promoting ventricular reverse remodeling (beta-blockers [BBs] and angiotensin-converting enzyme inhibitors) and directly decreasing the risk of SCD (BBs, mineralocorticoid antagonists, and sacubitril/valsartan), especially in patients affected by heart failure (HF) with reduced left ventricular (LV) ejection fraction (EF);[4] and (3) the use of implantable cardioverter defibrillator (ICD). Nevertheless, SCD prevention remains a major issue even in the era of ICD therapy. Consequently, great efforts are required to identify participants at high SCD risk for primary prevention. In this setting, cardiac magnetic resonance (CMR) has emerged over the years as informative and reliable imaging technique

Access this article online

Quick Response Code:

Website: www.jcecho.org

DOI: 10.4103/jcecho.jcecho_25_19

Address for correspondence: Dr. Giorgio Faganello, Department of Cardiovascular, Azienda Sanitaria Universitaria Integrata of Trieste, University of Trieste, Via Pietro Valdoni 7, 34149, Trieste, Italy.
E-mail: giorgio.faganello@asuits.sanita.fvg.it

How to cite this article: Faganello G, Porcari A, Biondi F, Merlo M, Luca AD, Vitrella G, *et al*. Cardiac magnetic resonance in primary prevention of sudden cardiac death. J Cardiovasc Echography 2019;29:89-94.

thanks to the high spatial resolution and to the possibility of *in vivo* tissue characterization. Although not included in the current guidelines for SCD prediction, a consistent body of literature is growing supporting the incremental value of CMR for arrhythmic risk assessment.

The aim of the present review is to provide a summary of the potential advantages of CMR evaluation in the challenging setting of arrhythmic stratification.

Traditional Parameters in Prognostic Stratification for Sudden Cardiac Death

LVEF is the most commonly used parameter to evaluate LV systolic function[5] and the widest used predictor of long-term outcome.[6] The risk of cardiovascular events increases with the progressive decline in LVEF.[6] The latest HF classification[4] distinguishes three categories based on LVEF (preserved EF [HFpEF], midrange EF [HFmrEF], and reduced EF [HFrEF]) and current guidelines for SCD[7] recommend LVEF and New York Heart Association (NYHA) functional class as main criteria for arrhythmic stratification. However, these two parameters suffer from intrinsic limitations (i.e., NYHA class is a highly variable and subjective index) and novel tools, tailored on the specific patient rather than on study populations, are required on the path toward precision medicine.

The vast majority of contemporary understanding in arrhythmic stratification derives from the setting of HFrEF. In this group, ICD implantation for primary prevention could be considered in the presence of LVEF ≤35% despite ≥3 months of optimal medical therapy, but a distinction should be made between IHD and NICM.[4]

Although patients with above-mentioned characteristics and chronic IHD could be eligible for ICD therapy (Level of evidence I, Class A), device implantation should be delayed by 40 days from myocardial infarction (MI) as no improvement in prognosis has been demonstrated before that time. However, the incidence of major arrhythmic events is greatest in the early post-MI phase and patients could benefit from ICD therapy during this period. In addition, patients with NICM could receive device implantation despite with lower class of recommendation (Level of evidence I, Class B).[4] As NICMs are an heterogeneous population including cardiac diseases characterized by different intrinsic arrhythmic risk, the efficacy of ICD therapy for SCD prevention could be underestimated if evaluated in unselected populations of NICMs, regardless of the specific etiology (i.e., cardiac sarcoidosis vs. hypertensive cardiomyopathy), as demonstrated in the DANISH trial.[8]

HFmrEF, defined as LVEF in the range of 40%–49%, represents a "gray area," dynamic in nature, comprising patients previously diagnosed with HFrEF and HFpEF. Patients with HFrEF receiving evidence-based medical and device therapy can improve LVEF and be reclassified as HFmrEF. The same considerations hold true for patients with HFpEF experiencing MI or other progressive cardiac diseases with a decline in LVEF.

Transition from HFrEF to HFmrEF category is reasonably associated with a better prognosis compared to persistent HFrEF category, but LVEF could further decline over time. As recently reported, patients with dilated cardiomyopathy (DCM) and HFmrEF represent a subgroup diagnosed at an earlier stage of disease. Although having an apparent better long-term evolution, about 17% of these patients develop HFrEF despite medical therapy.[9]

Finally, HFpEF represents up to 50% of HF patients.[10] Most of them would not be candidates for ICD implantation based on above-mentioned recommendations,[4] despite SCD has been estimated to be a frequent cause of death in this population (about 25% of all deaths).[11] In the Oregon Sudden Unexpected Death Study, among individuals who experienced cardiac arrest, 65% of patients would not have qualified for a primary prevention ICD therapy.[12]

As for NICM, HFpEF includes a wide spectrum of cardiac diseases, in which estimation of SCD risk is particularly challenging both for the extreme phenotypic variability of patients and the significant amount of noncardiovascular deaths.[13] Hypertrophic cardiomyopathy (HCM), HCM phenocopies, cardiac amyloidosis, and constrictive pericarditis could have normal LVEF at presentation but still carry different arrhythmic risks. Considering these cardiac diseases as a single entity based on similar LVEF can only result in unsuccessful risk assessment.

These findings questioned the traditional concept of LVEF as an accurate prognostic parameter,[14] suggesting the need of individualized patient-tailored strategies for risk assessment, relying on other variables (i.e., etiologic characterization) beside LVEF. In this field, CMR could be a pivotal tool, providing not only a more accurate quantification of LVEF, frequently overestimated by echocardiography,[15] but also noninvasive tissue characterization.[16]

This imaging technique should be part of the comprehensive evaluation for arrhythmic stratification in different clinical scenarios (i.e., HCM, NICM, arrhythmogenic right ventricular cardiomyopathy [ARVC], IHD). Moreover, CMR parameters could improve the accuracy of current strategies for SCD prediction when considered in combination with available multiparametric scores, as in the case of HCM and ARVC.

Cardiac Magnetic Resonance: New Insights into Cardiac Muscle Beyond Left Ventricular Ejection Fraction

CMR provides the most comprehensive cardiac evaluation, including chamber size quantification, ventricular function and mass, myocardial wall thicknesses, segmental function, and identification of anomalous coronary arteries.[17] The

ability to obtain images in all plane directions, good temporal and spatial resolution, reliable endocardial border detection, and the independency of geometrical assumptions for the quantification of volumes and systolic function of both ventricles are the main advantages of this methodic compared to other imaging modalities.[18] CMR represents a valuable technique providing *in vivo* tissue characterization and identification of the arrhythmic substrate. Gadolinium-based contrast agents allow detection and quantification of the presence, location, size, and pattern of myocardial fibrosis.

Late gadolinium enhancement

Gadolinium is an extracellular agent that reveals the presence of fibrosis in the myocardium, which is considered an arrhythmic substrate and the final pathway of irreversible cardiac injury.[19] In recent years, late gadolinium enhancement (LGE) is emerging as a crucial parameter in arrhythmic stratification. The presence of LGE provides relevant diagnostic (IHD vs. NICM) and prognostic information aiding clinicians identify the best candidates for ICD implantation in primary prevention.

In a recent meta-analysis on the value of LGE in a population of 2850 patients with IHD and NICM,[20] the presence of LGE was a powerful predictor of life-threatening ventricular arrhythmias. LGE-positive patients met the composite arrhythmic endpoint (SCD, aborted SCD, VT/VF, appropriate ICD therapy) more frequently than LGE-negative patients (23.9% vs. 4.9%, respectively). Even when dealing with NICMs exclusively, LGE positivity proved to identify patients at increased overall mortality, HF hospitalization, and SCD/aborted SCD.[21] In this population, LGE has been demonstrated to add incremental value for prediction of major arrhythmic events not only in both LVEF >35%[22] and LVEF <35%.[23]

Nevertheless, the additional value of LGE quantification for risk assessment is still debated. LGE semi-quantitatively estimates the amount of irreversible myocardial damage, which is likely to be relevant for patients survival.[24] However, methods for LGE quantification are not standardized and suffer from high intra- and inter-observer variability. The potential correlation between the amount of scar and arrhythmic risk has been investigated with conflicting results. LGE extension was found to confer a significant increase in arrhythmic risk when exceeding 5% of LV volume[25] or even at lower percentages.[26] However, more studies are needed to derive solid information in this field.

LGE location is an additional feature to consider for SCD risk estimation. Specific LGE locations (anterior and septal) has been demonstrated to predict fatal and nonfatal arrhythmic events in specific NICMs,[22,27] but this parameter should complement other prognostic indexes to improve SCD stratification.

Furthermore, the potential value of the area surrounding LGE, namely "border zone," for SCD stratification has been investigated. It includes viable and nonviable myocytes separated by fibrotic tissue of the scar region.[28] The border zone mass is involved in the development of arrhythmias[29] and was demonstrated to predict VT inducibility on electrophysiological study (EPS),[30] appropriate ICD therapy,[31] and mortality.[32] Quantification of border zones could be included in arrhythmic stratification workup, but more studies and a consensus on the methodology of quantification are required.[33]

Although being very informative, LGE identification suffers from several limitations. Despite common assumptions, it seems a dynamic parameter with regard to several settings. The expansion of the extracellular volume (ECV) occurring early after cardiac injuries (i.e., myocytes necrosis and inflammation) leads to increased volume of gadolinium distribution, contrast agent local concentration, and therefore, hyperenhancement. At this stage, LGE reflects not only the presence of fibrosis but also the expansion of the interstitium. Moving away from the acute phase, cardiac inflammation regresses along with tissue edema and leukocytes infiltration,[34] and LGE matches more accurately cardiac fibrosis. Probably, with time, LGE reliably identifies myocardial scar as long as novel cardiac damages do not occur. In addition, LGE shows high diagnostic accuracy in case of localized cardiac phenomena. However, it may fail to detect cardiac fibrosis in the presence of diffuse heart muscle involvement [Figure 1].

Mapping techniques and extracellular volume

T1 and T2 mapping use a quantitative approach to assess cardiac tissue and reflect the magnetic properties of cardiac muscle based on its composition.[35] T1 and T2 mapping involve pixel-wise measurements of absolute T1 relaxation times on a quantitative map.

T1 mapping depicts diffuse fibrosis in both IHD[36] and NICM.[37] Recently, impaired T1 mapping emerged as independent predictor of appropriate ICD therapy or sustained VT in patients with IHD and NICM at a follow-up of 425 days.[38] In IHD, infarct core native T1 was found to inversely correlate with endpoints associated with arrhythmic risk as ventricular adverse remodeling, all-cause mortality, and HF hospitalization.[39]

T2-weighted sequences detect myocardial edema and aid clinicians characterizing acute phenomena (i.e., myocarditis). Traditional T2-weighted images have low signal-to-noise ratios and suffer from regions of signal inhomogeneities where edema could be more difficult to detect.[40] Conversely, T2 mapping allows direct measurement of myocardial T2 relaxation time providing quantification of phenomena. Robust data on T2 mapping for arrhythmic risk stratification are lacking, partially because this technique is currently limited by several technical issues and nonstandardized among different centers. However, initial evidence suggest the potential role of abnormal T2 mapping in predicting major adverse events including cardiac death, cardiac transplantation, and ventricular assist device implantation.[41]

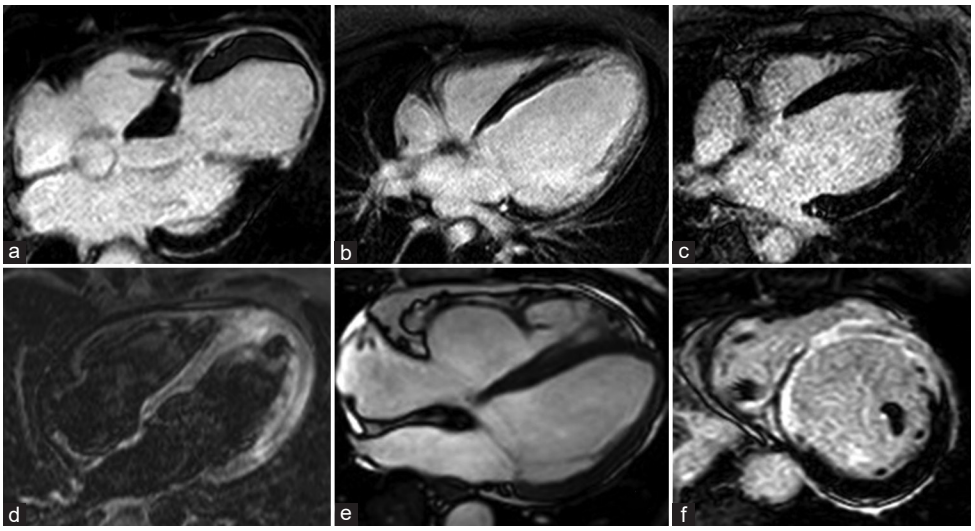

Figure 1: Examples of cardiac magnetic resonance applications in primary prevention: (a) Apical aneurysm of left ventricular with transmural late gadolinium enhancement positivity containing a stratified thrombus after acute myocardial infarction. (b) Diffuse intramyocardial and subepicardial late gadolinium enhancement positivity in a dilated left ventricular consistent with dilated cardiomyopathy. (c) Thickened left ventricular apex with mild late gadolinium enhancement positivity detecting apical hypertrophic cardiomyopathy. (d) Acute myocarditis with subepicardial and intramyocardial edema in a T2-weighted sequence revealing active inflammation. (e) Dilated right ventricular with bulging of the free wall in a patient with arrhythmogenic right ventricular dysplasia. (f) Transmural late gadolinium enhancement of the interventricular septum disclosing sarcoid lesions

Postcontrast T1 mapping techniques combined with native T1 and the patient's hematocrit allow to estimate ECV fraction,[42] a direct measurement of the myocardial interstitium. As many cardiac injuries cause myocardial fibrosis and abnormal substrate deposition into the extracellular space, an increased ECV fraction represents a marker of pathologic processes[43] and could add prognostic information across a wide range of cardiac diseases.[44,45] Being able to detect milder but global processes as widespread edema and fibrosis,[46] ECV could complement LGE evaluation as additional index. Myocardial fibrosis quantification by ECV was reported to be associated with hospitalization for HF and death.[41] Similar to T2 mapping, the potential role of ECV in SCD stratification requires more studies to be evaluated.

Unfortunately, these techniques suffer from major technical limitations that restrict their use in everyday clinical practice, precluding their reproducibility among different centers. Acquisition and processing of parametric maps require several technical steps that could be performed with variable methodologies, each one with different intrinsic risks of error in the final measurements. In particular, different sequences are available to perform T1 and T2 mapping and a consensus is needed to define the reference sequence to be used.

Deformation imaging

Deformation imaging is a novel, promising technique for cardiac function evaluation.[47] Global longitudinal strain (GLS) is the most studied parameter and initial evidence suggest its incremental value for diagnosis and prognostic stratification. GLS was reported to predict cardiac death, heart transplantation, and aborted SCD in DCM, with values ≥12.5% predicting the outcome even in patients with LVEF <35% or LGE positivity.[48] In a recent multicenter study on ischemic and nonischemic DCM, each 1% worsening in GLS conferred 89.1% increase in risk of death after adjustment for multiple risk factors, including LVEF and LGE.[49] Beside GLS, global circumferential strain was recently shown to predict LV reverse remodeling in patients with newly diagnosed nonischemic DCM.[50]

"In conclusion, recent evidence supports the use of GLS as additional prognostic parameter to complement LVEF and LGE assessment. Despite encouraging results, more multicenter studies investigating several strain subtypes are needed for routine use of this technique in clinical practice."

Limitation of cardiac magnetic resonance

CMR evaluation is not currently recommended in official guidelines as the first-line examination to support ICD implantation. Despite being a very informative imaging technique, several limitations exist, such as high costs, poor image quality in the presence of arrhythmias, and prior implantation of CMR noncompatible devices. Moreover, CMR requires a time-consuming learning curve to be mastered.

Impaired renal function represents a relative contraindication for gadolinium contrast-agents administration, especially in the presence of severely reduced glomerular filtration rate. Native T1 and T2 provide a direct tissue characterization without administration of contrast agents but present high variability and scarce reproducibility among different centers.

The limited accessibility of CMR represents a critical issue restricting its routine use, especially in the acute phases, where echocardiography represents the first-line imaging tool. However, CMR is gaining more and more value in clinical

practice, and its accessibility is expected to improve in the future.

Conclusion

Despite progresses in pharmacological and electrical therapies, SCD remains a relevant issue. LVEF and NYHA class are the widest used parameters to stratify the arrhythmic risk and current guidelines for primary prevention largely rely on it. However, they proved to be quite inadequate for SCD prediction. Indeed, arrhythmic risk assessment should be tailored on the single patient on the road to precision medicine.

Providing comprehensive assessment of heart function and *in vivo* tissue characterization, CMR significantly improves the identification of patients at high SCD risk. Cardiac fibrosis represents the most important arrhythmic substrate, providing genesis and perpetuation of life-threatening arrhythmias. Along with LGE, initial evidence suggests an incremental prognostic value of mapping techniques and ECV quantification, but significant technical limitations at the actual state-of-art restrict their use in current clinical practice. Furthermore, the use of CMR parameters to guide ICD implantation needs to be tested in large randomized clinical trials.

A multiparametric approach, including critical clinical thinking and the integrated use of different imaging and nonimaging techniques, will allow identification of at-risk patients in whom ICD implantation may be most beneficial.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, *et al.* American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: A scientific statement from the American Heart Association council on clinical cardiology committee on electrocardiography and arrhythmias and council on epidemiology and prevention. Circulation 2008;118:1497-518.
2. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al.* 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793-867.
3. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA 2006;296:1593-601.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American society of echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-3.9E+15.
6. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, *et al.* Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. Eur Heart J 2013;34:1404-13.
7. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, *et al.* 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric AND Congenital Cardiology (AEPC). Eur Heart J 2015;36:2793-867.
8. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, *et al.* Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221-30.
9. Merlo M, Gentile P, Artico J, Cannatà A, Paldino A, De Angelis G, *et al.* Arrhythmic risk stratification in patients with dilated cardiomyopathy and intermediate left ventricular dysfunction. J Cardiovasc Med (Hagerstown) 2019;20:343-50.
10. Vaduganathan M, Michel A, Hall K, Mulligan C, Nodari S, Shah SJ, *et al.* Spectrum of epidemiological and clinical findings in patients with heart failure with preserved ejection fraction stratified by study design: A systematic review. Eur J Heart Fail 2016;18:54-65.
11. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, *et al.* Mode of death in patients with heart failure and a preserved ejection fraction: Results from the irbesartan in heart failure with preserved ejection fraction study (I-preserve) trial. Circulation 2010;121:1393-405.
12. Stecker EC, Vickers C, Waltz J, Socoteanu C, John BT, Mariani R, *et al.* Population-based analysis of sudden cardiac death with and without left ventricular systolic dysfunction: Two-year findings from the Oregon sudden unexpected death study. J Am Coll Cardiol 2006;47:1161-6.
13. Donal E, Lund LH, Oger E, Hage C, Persson H, Reynaud A, *et al.* New echocardiographic predictors of clinical outcome in patients presenting with heart failure and a preserved left ventricular ejection fraction: A subanalysis of the ka (Karolinska) ren (Rennes) study. Eur J Heart Fail 2015;17:680-8.
14. Mele D, Nardozza M, Ferrari R. Left ventricular ejection fraction and heart failure: An indissoluble marriage? Eur J Heart Fail 2018;20:427-30.
15. Pontone G, Guaricci AI, Andreini D, Solbiati A, Guglielmo M, Mushtaq S, *et al.* Prognostic benefit of cardiac magnetic resonance over transthoracic echocardiography for the assessment of ischemic and nonischemic dilated cardiomyopathy patients referred for the evaluation of primary prevention implantable cardioverter-defibrillator therapy. Circ Cardiovasc Imaging 2016;9. pii: e004956.
16. Porcari A, De Angelis G, Romani S, Paldino A, Artico J, Cannatà A, *et al.* Current diagnostic strategies for dilated cardiomyopathy: A comparison of imaging techniques. Expert Rev Cardiovasc Ther 2019;17:53-63.
17. Faganello G, Doimo S, DI Nora C, DI Lenarda A. Cardiac imaging in patients with acute or chronic heart failure. Minerva Cardioangiol 2017;65:589-600.
18. Greupner J, Zimmermann E, Grohmann A, Dübel HP, Althoff TF, Borges AC, *et al.* Head-to-head comparison of left ventricular function assessment with 64-row computed tomography, biplane left cineventriculography, and both 2- and 3-dimensional transthoracic echocardiography: Comparison with magnetic resonance imaging as the reference standard. J Am Coll Cardiol 2012;59:1897-907.
19. Peters NS, Wit AL. Myocardial architecture and ventricular arrhythmogenesis. Circulation 1998;97:1746-54.
20. Disertori M, Rigoni M, Pace N, Casolo G, Masè M, Gonzini L, *et al.* Myocardial fibrosis assessment by LGE is a powerful predictor of ventricular tachyarrhythmias in ischemic and Nonischemic LV dysfunction: A meta-analysis. JACC Cardiovasc Imaging 2016;9:1046-55.
21. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in nonischemic cardiomyopathy: A systematic review and meta-analysis. Circ Cardiovasc Imaging 2014;7:250-8.

22. Halliday BP, Gulati A, Ali A, Guha K, Newsome S, Arzanauskaite M, *et al.* Association between midwall late gadolinium enhancement and sudden cardiac death in patients with dilated cardiomyopathy and mild and moderate left ventricular systolic dysfunction. Circulation 2017;135:2106-15.
23. Gutman SJ, Costello BT, Papapostolou S, Voskoboinik A, Iles L, Ja J, *et al.* Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. Eur Heart J 2019;40:542-50.
24. Mahrholdt H, Wagner A, Judd RM, Sechtem U, Kim RJ. Delayed enhancement cardiovascular magnetic resonance assessment of non-ischaemic cardiomyopathies. Eur Heart J 2005;26:1461-74.
25. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B, *et al.* Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. J Am Coll Cardiol 2012;60:408-20.
26. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, *et al.* Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. Circulation 2006;113:2733-43.
27. Aquaro GD, Perfetti M, Camastra G, Monti L, Dellegrottaglie S, Moro C, *et al.* Cardiac MR with late gadolinium enhancement in acute myocarditis with Preserved systolic function: ITAMY study. J Am Coll Cardiol 2017;70:1977-87.
28. Schuleri KH, Centola M, Evers KS, Zviman A, Evers R, Lima JA, *et al.* Cardiovascular magnetic resonance characterization of peri-infarct zone remodeling following myocardial infarction. J Cardiovasc Magn Reson 2012;14:24.
29. Demirel F, Adiyaman A, Timmer JR, Dambrink JH, Kok M, Boeve WJ, *et al.* Myocardial scar characteristics based on cardiac magnetic resonance imaging is associated with ventricular tachyarrhythmia in patients with ischemic cardiomyopathy. Int J Cardiol 2014;177:392-9.
30. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK, *et al.* Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. Circulation 2007;115:2006-14.
31. Jablonowski R, Chaudhry U, van der Pals J, Engblom H, Arheden H, Heiberg E, *et al.* Cardiovascular magnetic resonance to predict appropriate implantable cardioverter defibrillator therapy in ischemic and nonischemic cardiomyopathy patients using late gadolinium enhancement border zone: Comparison of four analysis methods. Circ Cardiovasc Imaging 2017;10. pii: e006105.
32. Yan AT, Shayne AJ, Brown KA, Gupta SN, Chan CW, Luu TM, *et al.* Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006;114:32-9.
33. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG, *et al.* Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for cardiovascular magnetic resonance (SCMR) board of trustees task force on standardized post processing. J Cardiovasc Magn Reson 2013;15:35.
34. Gräni C, Eichhorn C, Bière L, Murthy VL, Agarwal V, Kaneko K, *et al.* Prognostic value of cardiac magnetic resonance tissue characterization in risk Stratifying patients with suspected Myocarditis. J Am Coll Cardiol 2017;70:1964-76.
35. Klein C, Nekolla SG, Balbach T, Schnackenburg B, Nagel E, Fleck E, *et al.* The influence of myocardial blood flow and volume of distribution on late Gd-DTPA kinetics in ischemic heart failure. J Magn Reson Imaging 2004;20:588-93.
36. Messroghli DR, Walters K, Plein S, Sparrow P, Friedrich MG, Ridgway JP, *et al.* Myocardial T1 mapping: Application to patients with acute and chronic myocardial infarction. Magn Reson Med 2007;58:34-40.
37. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, *et al.* Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005;111:186-93.
38. Chen Z, Sohal M, Voigt T, Sammut E, Tobon-Gomez C, Child N, *et al.* Myocardial tissue characterization by cardiac magnetic resonance imaging using T1 mapping predicts ventricular arrhythmia in ischemic and non-ischemic cardiomyopathy patients with implantable cardioverter-defibrillators. Heart Rhythm 2015;12:792-801.
39. Carrick D, Haig C, Rauhalammi S, Ahmed N, Mordi I, McEntegart M, *et al.* Prognostic significance of infarct core pathology revealed by quantitative non-contrast in comparison with contrast cardiac magnetic resonance imaging in reperfused ST-elevation myocardial infarction survivors. Eur Heart J 2016;37:1044-59.
40. Friedrich MG, Sechtem U, Schulz-Menger J, Holmvang G, Alakija P, Cooper LT, *et al.* Cardiovascular magnetic resonance in myocarditis: A JACC white paper. J Am Coll Cardiol 2009;53:1475-87.
41. Spieker M, Haberkorn S, Gastl M, Behm P, Katsianos S, Horn P, *et al.* Abnormal T2 mapping cardiovascular magnetic resonance correlates with adverse clinical outcome in patients with suspected acute myocarditis. J Cardiovasc Magn Reson 2017;19:38.
42. Flett AS, Hayward MP, Ashworth MT, Hansen MS, Taylor AM, Elliott PM, *et al.* Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: Preliminary validation in humans. Circulation 2010;122:138-44.
43. Banypersad SM, Sado DM, Flett AS, Gibbs SD, Pinney JH, Maestrini V, *et al.* Quantification of myocardial extracellular volume fraction in systemic AL amyloidosis: An equilibrium contrast cardiovascular magnetic resonance study. Circ Cardiovasc Imaging 2013;6:34-9.
44. Luetkens JA, Homsi R, Sprinkart AM, Doerner J, Dabir D, Kuetting DL, *et al.* Incremental value of quantitative CMR including parametric mapping for the diagnosis of acute myocarditis. Eur Heart J Cardiovasc Imaging 2016;17:154-61.
45. Kuruvilla S, Janardhanan R, Antkowiak P, Keeley EC, Adenaw N, Brooks J, *et al.* Increased extracellular volume and altered mechanics are associated with LVH in hypertensive heart disease, not hypertension alone. JACC Cardiovasc Imaging 2015;8:172-80.
46. Radunski UK, Lund GK, Stehning C, Schnackenburg B, Bohnen S, Adam G, *et al.* CMR in patients with severe myocarditis: Diagnostic value of quantitative tissue markers including extracellular volume imaging. JACC Cardiovasc Imaging 2014;7:667-75.
47. Merlo M, Porcari A, Sinagra G. The (ultra) sound of a burning heart: A matter of speckles. Int J Cardiol 2018;259:132-3.
48. Buss SJ, Breuninger K, Lehrke S, Voss A, Galuschky C, Lossnitzer D, *et al.* Assessment of myocardial deformation with cardiac magnetic resonance strain imaging improves risk stratification in patients with dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging 2015;16:307-15.
49. Romano S, Judd RM, Kim RJ, Kim HW, Klem I, Heitner JF, *et al.* Feature-tracking global longitudinal strain predicts death in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy incremental to ejection fraction and late Gadolinium enhancement. JACC Cardiovasc Imaging 2018;11:1419-29.
50. Merlo M, Masè M, Vitrella G, Belgrano M, Faganello G, Di Giusto F, *et al.* Usefulness of addition of magnetic resonance imaging to echocardiographic imaging to predict left ventricular reverse remodeling in patients with nonischemic cardiomyopathy. Am J Cardiol 2018;122:490-7.