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EDITORIAL

The Bright Side of Myocardial Edema

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Sudden cardiac arrest (SCA) is the abrupt cessation of cardiac activity in the absence of a clear noncardiac cause (drowning, trauma, electrocution, drug overdose, etc). Sudden cardiac death, the gravest of potential consequences, is defined as death occurring within 1 hour of the onset of symptoms. Sudden cardiac death poses a significant public health problem, representing ≈50% of all cardiovascular deaths—≈300 000 deaths per year in the United States alone. Although the highest risk of sudden cardiac death occurs among patients with systolic heart failure and a left ventricular ejection fraction <30%, the largest absolute number of events occur in the previously healthy. In nearly one quarter of victims, sudden cardiac death is the incident symptomatic cardiac event.[1]

See Article by Zorzi et al.

Predicting who will suffer from recurrent SCA events is difficult, yet the stakes could not be higher. Without clear identification of the underlying cause for SCA, therapeutic ambiguity will undoubtedly exist. Additionally, although the management of SCA associated with acute myocardial infarction or underlying cardiomyopathies[1–3] is well established, evidence-based guidance is limited for patients with other causes of SCA. Patients without preexisting cardiac conditions represent an increasing proportion of SCA events.[1]

T2-weighted imaging is a widely used and versatile magnetic resonance imaging technique with varied clinical applications. Within cardiology, T2-weighted imaging accurately detects myocardial edema (ME) in ischemic and nonischemic diseases. This technique is a critical component for the formal cardiac magnetic resonance (CMR) diagnosis of myocarditis[4] and delineates the myocardium at risk immediately after acute myocardial infarction that may be salvaged by revascularization.[5,6] Identification of ME enhances the diagnostic yield in myocardial infarction with nonobstructed coronary arteries,[7] adds prognostic information in amyloid light-chain amyloidosis,[8] and is the most sensitive CMR technique for the detection of acute allograft rejection in recipients of heart transplants.[9]

Early CMR improves the diagnostic yield in myocardial infarction with nonobstructed coronary arteries[7] and myocarditis, as ME typically resolves within a few weeks after presentation.[4] The persistence of ME 6 months after the diagnosis of acute myocarditis imparts a favorable prognosis, as edema-associated late gadolinium enhancement is more likely to resolve.[10] Thus, apart from infiltrative cardiomyopathies (such as amyloidosis), ME assessed by T2-weighted imaging may indicate reversible myocardial injury.

In this issue of the *Journal of the American Heart Association (JAHA)*, Zorzi et al[11] present a multicenter, retrospective cohort study of survivors of out-of-hospital cardiac arrest (OHCA) over an 11-year period at 9 Italian centers. Survivors of OHCA without acute myocardial infarction or other clinically apparent cause for SCA were included and underwent "early CMR" (within 1 month post-SCA; median 11 days). The authors hypothesized that early evidence of ME may represent reversible injury of the myocardial substrate and thus may portend a favorable prognosis in SCA. The cohort of 101 survivors of OHCA was representative of

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SCA epidemiology with middle-aged men comprising the largest demographic (median age 47 years, 71% male). Interestingly, 16% of the cohort suffered SCA during sports participation. All the subjects underwent invasive coronary angiography except for the 10% of the cohort that had a clearly identifiable nonischemic cause of SCA. No patients were lost to follow-up (median 47 months). The final cause for SCA was determined to be due to structural (50%), ischemic (21%), or primary arrhythmogenic/inherited channelopathy (29%).

T2-short tau inversion recovery imaging (all on 1.5 T magnets) was the basis for CMR ME assessment and was made by 2 readers at each site blinded to the clinical data with a third reader at the core laboratory serving as a tiebreaker. ME was defined as myocardial T2 signal intensity greater than twice that of skeletal muscle. Nearly one fifth (18%) of the cohort had ME; 11/18 were classified as ischemic injury and 7/18 inflammatory (only 4 meeting modified Lake Louise criteria[4] for myocarditis). The presence of ME was associated with a higher survival free from appropriate implantable cardioverter-defibrillator (ICD) therapy (89% versus 73%, P=0.04) and was an independent predictor of better arrhythmic outcome. ME was present to an equal extent between ischemic (N=8) and nonischemic substrate (N=8) in those without appropriate ICD therapy at follow-up. The 2 patients with ME who experienced appropriate ICD interventions had underlying ischemic cardiomyopathy with left ventricular ejection fraction <35%, significant late gadolinium enhancement burden, and ischemia-induced SCA with no revascularization targets. An entirely normal CMR (without ME or late gadolinium enhancement) identified a population in which genetic testing for channelopathies was high yield (34% were identified to have long QT or Brugada syndromes). The authors therefore concluded that ME, as identified by T2-weighted CMR imaging, confers a positive prognosis for survivors of OHCA.

We congratulate the authors for this large study of survivors of OHCA that adds to a growing body of literature supporting the role of CMR in this population. OHCA survivorship is rare (merely 10%), and more than half of survivors have obstructive coronary lesions on angiography.[1] This study is relevant for the minority of survivors of OHCA without clear angiographic explanation for SCA (15% of the 684 eligible survivors of OHCA), but an important group in whom secondary prevention ICD is currently recommended.[1] Although guidelines do not advocate the routine use of CMR in survivors of OHCA, this technology may elucidate the underlying cause for SCA, detect potentially reversible myocardial injury, and identify high-risk features and/or irreversible damage. CMR has been shown to enhance diagnostic certainty in survivors of OHCA[12–14] and confers additional prognostic information. As with most diseases, the presence and extent of late gadolinium enhancement predicts adverse events in this population.[15] ME has previously been shown to be a favorable prognostic factor among survivors of OHCA at a single center in a smaller cohort of patients with shorter follow-up and in whom secondary ICD was not uniformly deployed.[16]

This study suggests that ME on CMR is an imaging biomarker of a transient arrhythmogenic substrate and thus its presence is a favorable finding associated with a reduced risk of recurrent arrhythmogenic events. It is postulated that the demonstration of ME discriminates between patients with reversible ischemia (with or without the presence of obstructive CAD, and thus at lower risk for subsequent SCA after appropriate medical therapy and/or percutaneous coronary intervention), transient nonischemic ME (myocarditis, Takotsubo cardiomyopathy; lower risk) from higher risk myocardial pathology without ME (replacement fibrosis, idiopathic ventricular fibrillation). The authors correctly state that their work is hypothesis generating; larger studies must be performed to confirm these findings before identification of ME can be formally incorporated into risk stratification of survivors of SCA. Given the exceptional stakes, supreme diagnostic confidence in the demonstration of ME (and the associated clinical diagnosis) will be required to imply a lower future risk of SCA and potentially withhold ICD therapy.

The basis for CMR ME assessment in this study was T2-short tau inversion recovery imaging, not T2 parametric mapping. Although the authors took care to avoid bias by having 2 independent, blinded CMR reads at each site, the inherent subjectivity of more qualitative and binary T2-short tau inversion recovery sequence assessment may limit the real-world generalizability of these results. T2 mapping has increasingly replaced T2-short tau inversion recovery imaging methods owing to its feasibility, image quality, reproducibility, and quantitative detection of ME.[17] However, this technique is not without its own challenges. Comprehensive analysis (with multiple short- and long-axis views and/or whole-heart mapping) may be necessary to provide the highest diagnostic confidence. Parametric mapping ideally requires the establishment of normative values specific for each individual magnet.[18] Even when this is achieved, the editorial authors suspect a high level of interobserver and interinstitutional variance in the interpretation of this technique. Identification of regional abnormalities may be somewhat arbitrary. What is the appropriate size/location of a region of interest to sample? What statistical deviation from normal defines pathology? Societal guidance is needed to define optimal methods for standardized analysis and interpretation of parametric mapping in the clinical and research arenas.

The evolution of whole-heart CMR parametric mapping, machine learning in image analysis, and larger scale OHCA registries will certainly influence our ability to comprehensively phenotype cardiac structure and function and permit the deployment of precision medicine for patient-level ICD decisions. CMR is an efficient, safe, and comprehensive imaging technique that augments the diagnostic and prognostic assessment in an ever-expanding variety of cardiac conditions. Larger studies using modern techniques should be encouraged to further refine the relevance of myocardial edema, inflammation, and fibrosis in survivors of SCA and other cardiac diseases.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e210–e271. doi: 10.1161/CIR.0000000000000548
2. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;127:e362–e425. doi: 10.1161/CIR.0b013e3182742cf6
3. Lemkes JS, Janssens GN, van der Hoeven NW, Jewbali LSD, Dubois EA, Meuwissen M, Rijpstra TA, Bosker HA, Blans MJ, Bleeker GB, et al. Coronary angiography after cardiac arrest without st-segment elevation. *N Engl J Med*. 2019;380:1397–1407. doi: 10.1056/NEJMoa1816897
4. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72:3158–3176. doi: 10.1016/j.jacc.2018.09.072
5. Bulluck H, White SK, Fröhlich GM, Casson SG, O'Meara C, Newton A, Nicholas J, Weale P, Wan SMY, Sirker A, et al. Quantifying the area at risk in reperfused ST-segment-elevation myocardial infarction patients using hybrid cardiac positron emission tomography-magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2016;9:e003900. doi: 10.1161/CIRCIMAGING.115.003900
6. Aletras AH, Tilak GS, Natanzon A, Hsu LY, Gonzalez FM, Hoyt RF Jr, Arai AE. Retrospective determination of the area at risk for reperfused acute myocardial infarction with T2-weighted cardiac magnetic resonance imaging: histopathological and displacement encoding with stimulated echoes (DENSE) functional validations. *Circulation*. 2006;113:1865–1870. doi: 10.1161/CIRCULATIONAHA.105.576025
7. Vago H, Szabo L, Dohy Z, Czimbalmos C, Toth A, Suhai FI, Barczi G, Gyarmathy VA, Becker D, Merkely B. Early cardiac magnetic resonance imaging in troponin-positive acute chest pain and non-obstructed coronary arteries. *Heart*. 2020;106:992–1000. doi: 10.1136/heartjnl-2019-316295
8. Kotecha T, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, Knight DS, Zumbo G, Rosmini S, Maestrini V, et al. Myocardial edema and prognosis in amyloidosis. *J Am Coll Cardiol*. 2018;71:2919–2931.
9. Han D, Miller RJH, Otaki Y, Gransar H, Kransdorf E, Hamilton M, Kittelson M, Patel J, Kobashigawa JA, Thomson L, et al. Diagnostic accuracy of cardiovascular magnetic resonance for cardiac transplant rejection: a meta-analysis. *JACC Cardiovasc Imaging*. 2021:S1936-878X(21)00427-7. in press. doi: 10.1016/j.jcmg.2021.05.008
10. Aquaro GD, Ghebru Habtemicael Y, Camastra G, Monti L, Dellegrottaglie S, Moro C, Lanzillo C, Scatteia A, Di Roma M, Pontone G, et al. Prognostic value of repeating cardiac magnetic resonance in patients with acute myocarditis. *J Am Coll Cardiol*. 2019;74:2439–2448.
11. Zorzi A, Mattesi G, Baldi E, Toniolo M, Guerra F, Cauti FM, Cipriana A, De Lazzari M, Muser D, Stronati G, et al. Prognostic role of myocardial edema as evidenced by early cardiac magnetic resonance in survivors of out-of-hospital cardiac arrest: a multicenter study. *J Am Heart Assoc*. 2021;10:e021861. doi: 10.1161/JAHA.121.021861
12. Neilan TG, Farhad H, Mayrhofer T, Shah RV, Dodson JA, Abbasi SA, Danik SB, Verdini DJ, Tokuda M, Tedrow UB, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. *JACC Cardiovasc Imaging*. 2015;8:414–423. doi: 10.1016/j.jcmg.2014.11.017
13. Baritussio A, Zorzi A, Ghosh Dastidar A, Susana A, Mattesi G, Rodrigues J, Biglino G, Scatteia A, De Garate E, Strange J, et al. Out of hospital cardiac arrest survivors with inconclusive coronary angiogram: impact of cardiovascular magnetic resonance on clinical management and decision-making. *Resuscitation*. 2017;116:91–97. doi: 10.1016/j.resuscitation.2017.03.039
14. Wu KC. Sudden cardiac death substrate imaged by magnetic resonance imaging: from investigational tool to clinical applications. *Circ Cardiovasc Imaging*. 2017;10:e005461. doi: 10.1161/CIRCIMAGING.116.005461
15. Baritussio A, Biglino G, Scatteia A, De Garate E, Dastidar AG, Palazzuoli A, Harries I, Strange JW, Diab I, Bucciarelli-Ducci C. Long-term outcome of myocardial scarring and deformation with cardiovascular magnetic resonance in out of hospital cardiac arrest survivors. *Eur Heart J Cardiovasc Imaging*. 2021;22:1149–1156. doi: 10.1093/ehjci/jeaa293
16. Zorzi A, Susana A, De Lazzari M, Migliore F, Vescovo G, Scarpa D, Baritussio A, Tarantini G, Cacciavillani L, Giorgi B, et al. Diagnostic value and prognostic implications of early cardiac magnetic resonance in survivors of out-of-hospital cardiac arrest. *Heart Rhythm*. 2018;15:1031–1041. doi: 10.1016/j.hrthm.2018.02.033
17. Salerno M, Kramer CM. Advances in parametric mapping with CMR imaging. *JACC Cardiovasc Imaging*. 2013;6:806–822. doi: 10.1016/j.jcmg.2013.05.005
18. Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: a consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017;19:75. doi: 10.1186/s12968-017-0389-8