Novel MRI Tools for Hypertrophic Cardiomyopathy Risk Stratification

Subjects: Cardiac & Cardiovascular Systems

Contributor: Fahad Alajmi , Mehima Kang , James Dundas , Alexander Haenel , Jeremy Parker , Philipp Blanke , Fionn Coghlan , John King Khoo , Abdulaziz A. Bin Zaid , Amrit Singh , Bobby Heydari , Darwin Yeung , Thomas M. Roston , Kevin Ong , Jonathon Leipsic , Zachary Laksman

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder with a well described risk of sudden cardiac death; however, risk stratification has remained a challenge. Recently, novel parameters in cardiac magnetic resonance imaging (CMR) have shown promise in helping to improve upon current risk stratification paradigms.

hypertrophic cardiomyopathy | cardiac magnetic resonance imaging | prognosis

1. Introduction

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder characterized by increased thickness of the left ventricular wall, not attributable to increased afterload [1]. Sudden cardiac death (SCD) is a feared complication of HCM, as outlined in the European Society of Cardiology (ESC) 2022 and 2023 guidelines, which describe an annual mortality rate of 1% to 2% and an annual rate of SCD or appropriate implantable cardioverter defibrillator therapy of 0.8% [2][3]. SCD is defined as sudden and unexpected death, presumed due to either cardiac arrythmia or hemodynamic collapse [4], occurring either within an hour of symptom onset, or being found dead within 24 h of an asymptomatic period. Known risk factors for SCD in HCM, as proposed by the American Heart Association/American College of Cardiology (AHA/ACC) and outlined in **Table 1**, include a family history of sudden cardiac death, left ventricular hypertrophy ≥30 mm, and extensive late gadolinium enhancement ≥15% of left ventricular mass [5].

Table 1. Demonstrates known risk factors for SCD in HCM, as proposed by the American Heart Association/American College of Cardiology (AHA/ACC) [5].

Risk Factors for Sudden Cardiac Death (SCD) in Hypertrophic Cardiomyopathy
1. Family history of sudden death in HCM
2. Massive left ventricular hypertrophy (LVH) ≥ 30 mm

Risk Factors for Sudden Cardiac Death (SCD) in Hypertrophic Cardiomyopathy
3. Unexplained syncope
4. HCM with left ventricular dysfunction < 50%
5. Presence of left ventricular apical aneurysm
6. Extensive late gadolinium enhancement (LGE) on CMR imaging (≥15% of left ventricular mass)
7. Non sustained ventricular tachycardia (VT) on ambulatory monitoring

Ikonomidis, I. Hypertrophic cardiomyopathy: An updated review on diagnosis, prognosis, and treatment. Heart Fail. Rev. 2019, 24, 439–459.

2. Arbelo, E.; Protonotarios, A.; Gimeno, J.R.; Arbustini, E.; Barriales-Villa, R.; Basso, C.; Bezzina, C.R.; Bilinska, Z.; Burke, M.; De Bortoli, M.; et al. ESC Scientific Document Group. 2023 ESC Guidelines for the management of cardiomyopathies. Eur. Heart J. 2023, 44, 3503–3626.

3. Zeppenfeld, K.; Tfelt-Hansen, J.; de Riva, M.; Winkel, B.G.; Behr, E.R.; Blom, N.A.; Charron, P.; Corrado, D.; Dagres, N.; de Chillou, C.; et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur. Heart J. 2022, 43, 3997–4126.

4. Jazayeri, M.A.; Emert, M.P. Sudden Cardiac Death: Who is at Risk? Med. Clin. N. Am. 2019, 103, 913–930.

5. Writing Committee Members; Ommen, S.R.; Mital, S.; Burke, M.A.; Day, S.M.; Deswal, A.; Elliott, P.; Evanovich, L.L.; Hung, J.; Joglar, J.A.; et al. Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy. Circulation 2020, 142, E558–E631. Available online: https://www.ahajournals.org/doi/abs/10.1161/CIR.0000000000000937 (accessed on 30 November 2022).

6. Flett, A.S.; Hayward, M.P.; Ashworth, M.T.; Hansen, M.S.; Taylor, A.M.; Elliott, P.M.; McGregor, C.; Moon, J.C. Equilibrium contrast cardiovascular magnetic resonance for the measurement of diffuse myocardial fibrosis: Preliminary validation in humans. Circulation 2010, 122, 138–144.

7. Wang, K.; Zhang, W.; Li, S.; Jin, H.; Jin, Y.; Wang, L.; Li, R.; Yang, Y.; Zheng, J.; Cheng, J. Noncontrast T1ρ dispersion imaging is sensitive to diffuse fibrosis: A cardiovascular magnetic resonance study at 3T in hypertrophic cardiomyopathy. Magn. Reson. Imaging 2022, 91, 1–8. Available online: https://pubmed.ncbi.nlm.nih.gov/35525524/ (accessed on 21 October 2022).

2. Novel Magnetic Resonance Imaging Tools for Hypertrophic Cardiomyopathy Risk Stratification

2.1. T1 Mapping and Extracellular Volume

Longitudinal T1 relaxation times are an intrinsic property of biological tissues in a magnetic field and describe the time required for protons within tissues to recover back into alignment with the static B_0 field of the MRI scanner following excitation with a radiofrequency energy pulse. Different tissues (e.g., fat, myocardium, blood) have different inherent T1 relaxation times, and these are further modified by administration of gadolinium-based contrast agents or the presence of disease states, such as the development of fibrosis within the myocardium. Measurement of true myocardial T1 relaxation curves is impractically time-consuming; however, they can be estimated using multiple available sequences (MOLLI, shortened MOLLI, SASHA, SAPPHIRE) with reasonable accuracy. T1 mapping denotes the estimation of pre-contrast (native) T1 times at the individual pixel level, allowing quantitative assessment of diffuse pathology (e.g., interstitial fibrosis) without requiring contrast administration. T1 mapping of both blood pool (correcting for hematocrit) and myocardium before and after administration of gadolinium contrast allows estimation of the myocardial extracellular volume (ECV) fraction [6]. Disease states such as extensive fibrosis and infiltrative pathologies such as cardiac amyloidosis particularly expand the extracellular space and so increase ECV.

Multiple studies have highlighted that higher T1 and ECV values in the HCM population compared to a control group were correlated with myocardial fibrosis, refs. [7][8][9][10][11][12] suggesting these parameters are useful diagnostically to help differentiate HCM from other causes of massive left ventricular hypertrophy (LVH), such as athletic remodeling, where minimal myocardial fibrosis is expected.

2.2. T2-Weighted CMR Imaging and T2 Mapping

T2 is another intrinsic property of tissue in a magnetic field and represents the decay of lateral magnetization (as opposed to longitudinal magnetization in T1). T2 delay is prolonged in tissue with increased water content, so T2-weighted imaging sequences (e.g., short-tau inversion recovery, STIR) have long been used for the qualitative assessment of myocardial edema. Similar to T1 mapping, T2 mapping sequences are now also used for quantitative edema evaluation [13]. While myocardial edema is not specific to HCM and is traditionally associated with acute pathologies such as acute myocardial infarction or myocarditis, there has been recent interest in the utility of T2-weighted imaging in chronic cardiomyopathies such as HCM.

Cramer et al. [14] identified an association between post-exercise troponin elevation and high T2 signals in hypertrophic cardiomyopathy patients. They described elevated T2 signal as the only independent predictor of troponin rise (odds ratio 7.9; 95% CI 2.7–23.1; p < 0.001), meaning that T2-weighted imaging can recognize a subset of vulnerable patients with active disease who may be at risk during exercise. This could be of particular use given the paucity of evidence [15][16] supporting common recommendations to reduce or avoid exercise in HCM due to perceived SCD risk.

2.3. CMR Feature Tracking and Other Strain Methods

Feature tracking (FT) is an emerging tissue-tracking technique using post-processing of CMR cine sequences already acquired for ventricular morphology and function. Similar to the now widely used speckle-tracking strain analysis in echocardiography, this technique involves quantitative evaluation of myocardial deformation, generating indices such as strain and strain rate for cardiac longitudinal, radial, and torsional (circumferential) motion. Given the good spatial resolution of balanced steady-state free precession (bSSFP) cine imaging with whole-heart coverage, these indices can be generated for individual LV myocardial layers (e.g., epicardial vs. endocardial strain) as well as applied to the thin-walled atria and right ventricle. Strain can be calculated in 2D (with reference to fixed LV geometry) or in 3D, with the latter potentially superior in complex and unusual anatomy. The concept that strain analysis might provide additional information beyond traditional global and segmental functional analysis is widely acknowledged in the current literature [17].

Xu et al. report that CMR-FT can be used to recognize myocardial dysfunction in HCM patients even with normal LV wall thickness and preserved LVEF [17]. Furthermore, they propose that the differences in epicardial and endocardial global circumferential strain can reflect HCM disease status, including both preclinical and overt. Xu et al. found that impaired left ventricular strain in HCM patients could be correlated with poor cardiac outcomes in terms of cardiovascular mortality and HF.

Heart failure with preserved ejection fraction (HFpEF) is common in HCM and is associated with adverse outcomes, including all-cause mortality [18]. Shi et al. used CMR-FT to determine the association between HFpEF and left atrial function in HCM patients. Left atrial phasic strain was able to differentiate between HCM patients with heart failure with preserved ejection fraction (HFpEF) and those without and could further categorize the severity of patients with HFpEF, whereas, in their population, LV global longitudinal strain could not [19]. LA reservoir (β = 0.90 [0.85–0.96]), conduit (β = 0.93 [0.87–0.99]), and booster (β = 0.86 [0.78–0.95]) strain were all independently

8. Thompson, E.W.; Kamesh Iyer, S.; Solomon, M.P.; Li, Z.; Zhang, Q.; Piechnik, S.; Werys, K.; Swago, S.; Moon, B.F.; Rodgers, Z.B.; et al. Endogenous T1ρ cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J. Cardiovasc. Magn. Reson. 2021, 23, 1–9. Available online: https://jcmr-online.biomedcentral.com/articles/10.1186/s12968-021-00813-5 (accessed on 21 October 2022).

9. Vullaganti, S.; Levine, J.; Raiker, N.; Syed, A.A.; Collins, J.D.; Carr, J.C.; Bonow, R.O.; Choudhury, L. Fibrosis in Hypertrophic Cardiomyopathy Patients with and without Sarcomere Gene Mutations. Heart Lung Circ. 2021, 30, 1496–1501.

10. Sunthankar, S.; Parra, D.A.; George-Durrett, K.; Crum, K.; Chew, J.D.; Christensen, J.; Raucci, F.J.; Xu, M.; Slaughter, J.C.; Soslow, J.H. Tissue characterisation and myocardial mechanics using cardiac MRI in children with hypertrophic cardiomyopathy. Cardiol. Young 2019, 29, 1459–1467. Available online: https://pubmed.ncbi.nlm.nih.gov/31769372/ (accessed on 21 October 2022).

11. Huang, L.; Ran, L.; Zhao, P.; Tang, D.; Han, R.; Ai, T.; Xia, L.; Tao, Q. MRI native T1 and T2 mapping of myocardial segments in hypertrophic cardiomyopathy: Tissue remodeling manifested prior to structure changes. Br. J. Radiol. 2019, 92, 20190634. Available online: https://pubmed.ncbi.nlm.nih.gov/31613647/ (accessed on 21 October 2022).

12. Treibel, T.A.; Fridman, Y.; Bering, P.; Sayeed, A.; Maanja, M.; Frojdh, F.; Niklasson, L.; Olausson, E.; Wong, T.C.; Kellman, P.; et al. Extracellular Volume Associates with Outcomes More Strongly Than Native or Post-Contrast Myocardial T1. JACC Cardiovasc. Imaging 2020, 13, 44–54. Available online: https://pubmed.ncbi.nlm.nih.gov/31103587/ (accessed on 21 October 2022).

13. Kim, P.K.; Hong, Y.J.; Im, D.J.; Suh, Y.J.; Park, C.H.; Kim, J.Y.; Chang, S.; Lee, H.J.; Hur, J.; Kim, Y.J.; et al. Myocardial T1 and T2 Mapping: Techniques and Clinical Applications. Korean J. Radiol. 2017, 18, 113–131.

14. Cramer, G.E.; Gommans, D.F.; Dieker, H.J.; Michels, M.; Verheugt, F.; de Boer, M.J.; Bakker, J.; Fouraux, M.A.; Timmermans, J.; Kofflard, M.; et al. Exercise and myocardial injury in hypertrophic cardiomyopathy. Heart 2020, 106, 1169–1175. Available online: https://heart.bmj.com/content/106/15/1169 (accessed on 21 October 2022).

15. Maron, B.J.; Roberts, W.C.; Epstein, S.E. Sudden death in hypertrophic cardiomyopathy: A profile of 78 patients. Available online: https://www.ahajournals.org/doi/abs/10.1161/01.CIR.65.7.1388 (accessed on 1 November 2022).

16. Liao, Y.W.; Redfern, J.; Somauroo, J.D.; Cooper, R.M. Hypertrophic Cardiomyopathy and Exercise Restrictions: Time to Let the Shackles Off? Br. J. Cardiol. 2020, 27, 64–66.

17. Xu, J.; Yang, W.; Zhao, S.; Lu, M. State-of-the-art myocardial strain by CMR feature tracking: Clinical applications and future perspectives. Eur. Radiol. 2022, 32, 5424–5435.

2.4. Other CMR Parameters

Mahmod et al. undertook CMR in 290 HCM patients with LVEF ≥ 55% and 30 age- and sex-matched controls, with clinical follow-up for a median of 4.4 years and a repeat CMR in a sub-group of 63 patients [20]. They found that RV longitudinal strain was an independent predictor of non-sustained ventricular tachycardia (NSVT) [HR 1.05 (95% CI 1.01–1.09), $p = 0.029$] and that right ventricular ejection fraction was a predictor for non-sustained ventricular tachycardia and other cardiovascular events, including heart failure outcome and cardiovascular death. An association between global longitudinal strain and NSVT was also demonstrated.

Abnormalities in myocardial trabeculation, including hypertrabeculation [21] and multiple myocardial crypts [22], are well-described in hypertrophic cardiomyopathy, although their significance remains unclear. Wang et al. investigated the prognostic significance of myocardial trabecular complexity using fractal analysis in 378 individuals with HCM and 100 age- and gender-matched healthy controls [23]. Standard bSSFP cine sequences were post-processed to quantitatively estimate the fractal dimension (FD), a unitless measure of trabecular complexity that ranges from 1 to 2. They found that increased LV maximal apical FD ≥ 1.325 was associated with both the primary endpoint (composite of all-cause mortality and aborted SCD) and the secondary endpoint of heart failure hospitalization in participants with HCM.

2.5. Summary

CMR techniques have the potential to provide improved prognostic information for patients with HCM. T1 and extracellular volume have been shown to be markers of myocardial fibrosis in HCM patients and to have an association with adverse outcomes. Importantly, both T1 and ECV predicted MACE, but also specifically SCD, even in patients without LGE.

Abnormalities in T2 in HCM were associated with serum biomarkers of myocardial injury. These studies are of interest, particularly because they may suggest a more active disease process than has been traditionally postulated in HCM. Theoretically, this may represent a therapeutic target for novel agents, but it might also identify patients who could benefit from measures to reduce SCD (e.g., exercise restriction during periods of active disease/myocardial injury) without exposing the wider HCM population to the downsides of these interventions. However, given that the studies included here only compared myocardial T2 to serum troponin values, it remains unclear whether T2 can provide additive information over troponin measurement alone, especially given the extremely high sensitivity of modern troponin assays as well as their lower cost and greater availability compared to CMR.

Regarding strain measurements from CMR feature tracking, not only were there associations with histological fibrosis and increased risk of ventricular arrythmias, but there were also significant findings of early atrial and

18. Liu, J.; Wang, F.; Ruan, J.; Wu, C.; Xue, H.; Jiang, W.; Wang, J.; Sun, X.; Kang, L.; Song, L. Identification of heart failure with preserved ejection fraction in hypertrophic cardiomyopathy using cardiac MRI radiomics. BMC Med. 2022, 20, 21.

19. Shi, R.; Shi, K.; Huang, S.; Li, X.; Xia, C.C.; Li, Y.; He, S.; Li, Z.L.; He, Y.; Guo, Y.K.; et al. Association between Heart Failure with Preserved Left Ventricular Ejection Fraction and Impaired Left Atrial Phasic Function in Hypertrophic Cardiomyopathy: Evaluation by Cardiac MRI Feature Tracking. J. Magn. Reson. Imaging 2022, 56, 248–259. Available online: https://pubmed.ncbi.nlm.nih.gov/34799953/ (accessed on 21 October 2022).

20. Mahmod, M.; Raman, B.; Chan, K.; Sivalokanathan, S.; Smillie, R.W.; Abd Samat, A.H.; Ariga, R.; Dass, S.; Ormondroyd, E.; Watkins, H.; et al. Right ventricular function declines prior to left ventricular ejection fraction in hypertrophic cardiomyopathy. J. Cardiovasc. Magn. Reson. 2022, 24, 36. Available online: https://pubmed.ncbi.nlm.nih.gov/35692049/ (accessed on 21 October 2022).

21. Casanova, J.D.; Carrillo, J.G.; Jiménez, J.M.; Muñoz, J.C.; Esparza, C.M.; Alvárez, M.S.; Escribá, R.; Milla, F.B.; de la Pompa, J.L.; Raya, Á.; et al. Trabeculated Myocardium in Hypertrophic Cardiomyopathy: Clinical Consequences. J. Clin. Med. 2020, 9, 3171.

22. Maron, M.S.; Rowin, E.J.; Lin, D.; Appelbaum, E.; Chan, R.H.; Gibson, C.M.; Lesser, J.R.; Lindberg, J.; Haas, T.S.; Udelson, J.E.; et al. Prevalence and Clinical Profile of Myocardial Crypts in Hypertrophic Cardiomyopathy. Circ. Cardiovasc. Imaging 2012, 5, 441–447.

23. Wang, J.; Li, Y.; Yang, F.; Bravo, L.; Wan, K.; Xu, Y.; Cheng, W.; Sun, J.; Zhu, Y.; Zhu, T.; et al. Fractal Analysis: Prognostic Value of Left Ventricular Trabecular Complexity Cardiovascular MRI in Participants with Hypertrophic Cardiomyopathy. Radiology 2021, 298, 71–79. Available online: https://pubmed.ncbi.nlm.nih.gov/33078997/ (accessed on 21 October 2022).

24. Maron, M.S. Clinical utility of cardiovascular magnetic resonance in hypertrophic cardiomyopathy. J. Cardiovasc. Magn. Reson. 2012, 14, 13.

Retrieved from https://encyclopedia.pub/entry/history/show/125301

ventricular dysfunction prior to the development of LGE or reduced ejection fraction. Some studies also validated simplified, easier-to-implement strain techniques, such as three-point fast LA long-axis strain, which may help overcome the downside of strain parameters that require more complex and time-consuming post-processing.

While some of the studies included did not specifically address the primary question of SCD risk, they may still be able to contribute to decision-making for HCM patients. For example, development of either HFpEF or atrial fibrillation is associated with worse outcomes but not with SCD; therefore, if left atrial strain and epicardial adipose tissue parameters can predict these complications, they could further inform patient and clinician decision-making. Small to moderate apical aneurysms, especially those with a thin wall, have been underdiagnosed and missed with the use of echocardiography. CMR has provided an advantage in the detection and diagnosis of these apical aneurysms [24]. In the era of novel HCM therapeutics such as mavacamten and future potential disease-modifying drugs, these imaging biomarkers may be used for patient selection or monitoring for response, so more data correlating their relationship with patient-centered clinical outcomes will be useful.

Of key importance, all of the main technique groups are relatively easily translated into modern CMR practice. The CMR-FT, fractal analysis, and EAT tools are all post-processed from standard workhorse cine sequences used for volumetric assessment of LV function. In line with other facets of CMR interpretation, some of these analyses are increasingly simplified and partially or fully automated with AI assistance using commercially available software. If only a single septal segment is to be analyzed, T1, ECV, and T2 mapping images can be acquired in three short breath-holds (one breath-held acquisition for each), adding minimal scan time to a standard CMR protocol. For a more comprehensive assessment, 16 AHA-segment coverage is feasible in nine breath-holds (three short-axis slices each at the base, mid-chamber, and apex).

While image acquisition is entirely feasible, the post-processing and reporting will be time-consuming where numerous parameters are being calculated, so understanding their relative value is likely to be crucial for widespread adoption. Additionally, the value of individual measures may vary at different stages of disease; for example, measures that are able to predict risk prior to the development of overt LGE may lose value later in the disease process when there is a high burden of LGE or significant systolic impairment. Building and validating a multi-modality risk prediction model is a key research question and one that could benefit from a machine-learning approach.