JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 8, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Further Refining Risk in Hypertrophic Cardiomyopathy With Late Gadolinium Enhancement by CMR*

Christopher M. Kramer, MD,[a] Stefan Neubauer, MD[b]

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease, affecting 1 in 500 individuals and is associated with an increased risk of sudden cardiac death (SCD) and heart failure (1). With contemporary management strategies including implantable cardioverter-defibrillators (ICDs) in patients at increased risk of SCD and other therapies, including medications, myectomy, alcohol septal ablation, and heart transplantation in appropriate patients, the prognosis for HCM has improved over the last several decades (2). However, risk stratification remains a significant challenge (1) and selecting patients appropriately for ICD therapy can be problematic.

The U.S. and European approaches to SCD risk stratification in HCM have some important differences. Clearly identified risk factors in the most recent U.S. guidelines include: 1) personal history of aborted SCD, ventricular fibrillation, or sustained ventricular tachycardia; 2) family history of SCD; and 3) syncope (3). Markers with less robust evidence behind them include nonsustained ventricular tachycardia on monitoring, extreme increase in left ventricular (LV) wall thickness (>30 mm), and hypotensive response to exercise (3). A European consortium more recently developed a HCM Risk-SCD Calculator that includes variables such as age, extent of LV hypertrophy, left atrium size, LV outflow tract gradient, family history of SCD, nonsustained ventricular tachycardia, and unexplained syncope to predict 5-year SCD risk (4). A recent study aimed to validate this risk calculator (5). The calculator performed well at lower and higher levels of risk, but less well at intermediate risk levels. The 1,524 patients (71%) at the lower end of risk (<4%) had an observed 5-year SCD incidence close to that predicted. The 326 patients (15%) with an intermediate calculated risk of 4% to 6% had an actual event rate just >2%. The 297 patients (14%) with a predicted risk of ≥6% had an observed SCD incidence of 8.9% at 5 years (5). There is room for improvement, especially in the intermediate risk group where risk may be overestimated. This finding is especially important due to the risk of implanting ICDs in those who do not need them in terms of inappropriate shocks and potential complications (6).

Over the past several years, late gadolinium enhancement (LGE) on cardiac magnetic resonance as a marker of replacement fibrosis has emerged as a risk marker for adverse outcomes in HCM. Approximately one-half of patients with HCM may have LGE with a characteristic pattern of patchy involvement, particularly at the right ventricular septal insertion sites and in those walls with the greatest hypertrophy. A meta-analysis of 5 studies involving 2,993 patients with a median follow-up of 3 years demonstrated that the presence of LGE was associated with a 3.4-fold increase in risk for SCD, a 1.8-fold increase in all-cause mortality, a 2.9-fold increase in cardiovascular mortality, and a trend to increase in heart failure death (7). However, the presence of LGE alone cannot be used as an indication for an ICD because at least one-half of patients would then be candidates and the risk of SCD is below 1% per year. A 4-center study of

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the [a]Departments of Medicine and Radiology and the Cardiovascular Imaging Center, University of Virginia Health System, Charlottesville, Virginia; and the [b]Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, Oxford, United Kingdom.
Drs. Kramer and Neubauer are supported by U01HL117006-01A1. Dr. Kramer is a consultant for Bayer.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.05.063

1,293 patients followed for 3.3 years showed that LGE of ≥15% of an LV mass was associated with a 2-fold increase in SCD event risk (8). The meta-analysis discussed herein showed that, after adjusting for baseline characteristics, the extent of LGE was strongly associated with the risk of SCD with a hazard ratio of 1.36 per increase in LGE extent of 10% (7). Thus, the extent of LGE may be a more potent marker than its presence alone.

SEE PAGE 857

Despite these data regarding LGE, neither the U.S. guidelines nor the HCM Risk-SCD Calculator include it as a risk marker as of yet. Meanwhile, data with regard to its importance continue to accrue. In this issue of the *Journal*, Mentias et al. (9) from the Cleveland Clinic present data from 1,423 patients with HCM who were recruited from their institution over an 8-year period and deemed to be low to intermediate risk. There were 965 patients (68%) with obstructive disease, with a mean LV outflow tract gradient of 70 ± 55 mm Hg by transthoracic echocardiography, and 71% of these underwent myectomy (just fewer than one-half of the overall group). One-half of the patients had any LGE and mean LGE was 8.4 ± 1.2% of the total LV mass. The composite endpoint used was SCD and appropriate ICD discharge. Similar to the study by Chan et al. (8), the present study demonstrates higher risk of the primary endpoint with LGE of ≥15% of LV mass with or without obstruction. In those with obstruction, LGE of ≥15% was associated with a 3-fold increase in the primary endpoint, whereas myectomy was associated with a greater than 50% decrease. In those patients who underwent myectomy, the percent LGE cutoff that increased the risk was higher at 25% of LV mass. Adding both LGE and myectomy to the U.S. guideline risk factors and the HCM-SCD risk calculator improved their discriminatory power.

This is the first paper to extend the importance of the LGE findings into both obstructive and nonobstructive subgroups, as well as to examine it in the context of those patients who go on to myectomy. The latter group is not specifically considered in presently used guidelines and risk scores. Myectomy seemed to mitigate somewhat the risk associated with the presence of LGE. This finding is not surprising, because myectomy has been known for some time to improve prognosis in HCM, such that post-myectomy patients have a similar prognosis to nonobstructive patients (10).

The current study makes an important contribution to the field, but it also has its limitations. First, as a single-center cohort, it may not be representative of the HCM patient community at large, because the Cleveland Clinic is often specifically referred patients for myectomy, which accounts for the large proportion of patients who underwent this procedure in this study. The ongoing Hypertrophic Cardiomyopathy Registry (HCMR) should shed additional light here, because this population was recruited from 44 sites in 6 countries in North America and Europe (11) and will be more representative of clinical practice. Nearing the 2-year follow-up point in 2,764 patients, only approximately 10% of patients have undergone myectomy.

Second, replacement fibrosis may not be the only type of fibrosis that affects risk in HCM. Interstitial fibrosis is prevalent (12,13) and may also influence risk. T1 mapping by cardiac magnetic resonance with measurement of extracellular volume has demonstrated increases in interstitial fibrosis in HCM (14). T1 mapping has been incorporated into the HCMR study as an exploratory marker and will be examined for its association with adverse outcome in HCM.

In summary, our ability to prognosticate in this complex disorder is improving with the addition of imaging markers. The current study, prior reports, and availability of the upcoming HCMR registry data all suggest that they should be considered for inclusion in the next set of guidelines and risk calculators.

ADDRESS FOR CORRESPONDENCE: Dr. Christopher M. Kramer, University of Virginia Health System, Departments of Medicine and Radiology, Lee Street, P.K. Box 800170, Charlottesville, Virginia 2290. E-mail: ckramer@virginia.edu. Twitter: @uvahealthnews.

REFERENCES

1. Geske JB, Ommen SR, Gersh BJ. Hypertrophic cardiomyopathy: clinical update. J Am Coll Cardiol HF 2018;6:364–75.

2. Maron BJ, Rowin EJ, Casey SA, Maron MS. How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice. JAMA Cardiol 2016;1:98–105.

3. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: executive summary. J Am Coll Cardiol 2013;58:2703–38.

4. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM Risk-SCD). Eur Heart J 2014;35:2010–20.

5. O'Mahony C, Jichi F, Ommen SR, et al. International external validation study of the 2014 European Society of Cardiology Guidelines on Sudden Cardiac Death Prevention in Hypertrophic Cardiomyopathy (EVIDENCE-HCM). Circulation 2018;137:1015–23.

6. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of

sudden cardiac death in hypertrophic cardiomyopathy. JAMA 2007;298:405–12.

7. Weng Z, Yao J, Chan RH, et al. Prognostic value of LGE-CMR in HCM: a meta-analysis. J Am Coll Cardiol Img 2016;9:1392–402.

8. Chan RH, Maron BJ, Olivotto I, et al. Prognostic value of quantitative contrast-enhanced cardiovascular magnetic resonance for the evaluation of sudden death risk in patients with hypertrophic cardiomyopathy. Circulation 2014;130:484–95.

9. Mentias A, Raeisi-Giglou P, Smedira NG, et al. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. J Am Coll Cardiol 2018;72:857–70.

10. Ommen SR, Maron BJ, Olivotto I, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 2005;46:470–6.

11. Kramer CM, Appelbaum E, Desai MY, et al. Hypertrophic Cardiomyopathy Registry: the rationale and design of an international, observational study of hypertrophic cardiomyopathy. Am Heart J 2015;170:223–30.

12. Varnava AM, Elliott PM, Sharma S, McKenna WJ, Davies MJ. Hypertrophic cardiomyopathy: the interrelation of disarray, fibrosis, and small vessel disease. Heart 2000;84:476–82.

13. Ho CY, Lopez B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med 2010;363:552–63.

14. Ho CY, Abbasi SA, Neilan TG, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging 2013;6:415–22.

KEY WORDS fibrosis, gadolinium, hypertrophic cardiomyopathy, magnetic resonance imaging, myectomy