Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 56, No. 11, 2010
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.06.004

EDITORIAL COMMENT

Prognosis in Hypertrophic Cardiomyopathy With Contrast-Enhanced Cardiac Magnetic Resonance

The Future Looks Bright*

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Hypertrophic cardiomyopathy (HCM) is the most common genetic cause of heart disease and the most frequent cause of sudden cardiac death (SCD) in young people (1). Determining which patients are at higher risk of the development of adverse outcomes, particularly SCD, remains challenging. The current accepted risk factors for primary prevention therapy with implantable cardioverter-defibrillators (ICDs) include: 1) family history of HCM-related SCD; 2) unexplained recent syncope; 3) massive left ventricular (LV) hypertrophy (thickness >30 mm); 4) nonsustained ventricular tachycardia on 24-h Holter monitor; and 5) hypotensive or attenuated blood pressure response to exercise (1). However, these risk factors are only supported by observational studies, and some patients without risk factors die of SCD.

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Cardiac magnetic resonance (CMR) is emerging as a powerful tool for the diagnosis and risk stratification in HCM. CMR is widely accepted as a gold standard method for assessment of myocardial function as well as LV mass, which has been shown to be a sensitive predictor of adverse outcomes in HCM (2). In a study comparing echocardiography and CMR in patients with known or suspected HCM, echocardiography failed to demonstrate LV hypertrophy in 6% of patients, underestimated hypertrophy in the anterolateral free wall, and underestimated the presence of hypertrophy >3 cm in 10% of the patients (3). The diagnosis of apical-variant HCM can also be missed by echocardiography, but correctly identified by CMR (4). In a study of 1,299 patients with HCM, 28 demonstrated apical aneurysms by CMR, but only 16 (57%) of these were detected by echocardiography (5). Myocardial tagging with CMR has demonstrated regional impairment in intramyocardial deformation and increased myocardial torsion in patients with HCM despite globally preserved ejection fraction in many of these patients (6,7).

As myocardial fibrosis may provide the underlying arrhythmogenic substrate in HCM, there has been significant interest in determining whether late gadolinium enhancement (LGE) by CMR is in independent risk factor for predicting SCD and other adverse outcomes. Multiple studies have demonstrated a high prevalence of LGE, predominantly in a patchy, multifocal mid-wall distribution in regions of hypertrophy (8,9). LGE has been shown to be associated with nonsustained ventricular tachycardia as well as with other risk factors for SCD (9–12). However, few previous studies have evaluated hard end points of cardiovascular death, sudden cardiac death, or heart failure death.

In this issue of the *Journal*, Bruder et al. (13) prospectively enrolled 243 patients with HCM who were followed for an average of 3 years after CMR for the primary end points of all-cause and cardiac mortality. The patients were predominantly asymptomatic and had to have a nondilated hypertrophied ventricle with a maximal wall thickness >15 mm. LGE was seen in 67% of the patients, ranging from 1% to 40% of LV mass, despite the fact that nearly 75% of the patients had no risk factors for SCD. They found that the presence of LGE was associated with an odds ratio of 5.47 for all-cause mortality and 8.01 for cardiac mortality. This odds ratio was greater than that associated with the presence of 2 clinical risk factors for SCD and held up as a strong predictor of the primary end points in multivariate analysis. There were no events during the first 1,825 days of follow-up in those without LGE. Notably, 20 of the 22 patients who died during follow-up did not have previous symptoms, and clinical risk factors for SCD were only present in 3 patients who died of SCD during follow-up. The presence of LGE was the only significant predictor of the primary outcome besides patient age and LV mass. However, LGE did not reach statistical significance for predicting SCD. This study is one of the first of its kind to demonstrate that the presence of fibrosis/scar as detected by LGE is a significant predictor of death in HCM patients.

In a second study in this issue of the *Journal*, O'Hanlon et al. (14) studied 217 HCM patients using CMR and prospectively followed them for a mean duration of 3.1 years for the primary composite end point, which included cardiovascular death, unplanned cardiovascular admission, sustained ventricular tachycardia/ventricular fibrillation, or appropriate ICD discharge. Although the patients' LV

*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.

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function was similar to that of the study population of Bruder et al. (13), the mean patient age was 5 years younger, more than half of the subjects had New York Heart Association functional class of ≥2, and nearly one-half had at least 1 clinical risk factor for SCD. Similar to the study by Bruder et al., the majority of patients (63%) had LGE.

LGE was associated with a hazard ratio of 3.4 for the primary composite end point, and the risk increased with the extent of LGE. The extent of LGE was also independently predictive of worsening heart failure (unplanned heart failure admission, progression to class III/IV congestive heart failure, or heart failure death) and of the arrhythmic end points (sustained ventricular tachycardia/ventricular fibrillation, appropriate ICD discharge, SCD). However, in multivariate analysis, nonsustained ventricular tachycardia remained an independent predictor of SCD, whereas LGE did not. Although 83% of the major arrhythmic events occurred in the LGE group, the study was underpowered to detect a significant difference for this end point. Again, none of the other standard clinical risk factors were predictive of SCD events.

The primary end point was largely driven by unplanned cardiovascular admissions (29 of the 40 primary end points), and in their cohort, the individual end points of cardiovascular death and ventricular tachycardia/ventricular fibrillation and SCD were not independently predicted by LGE. However, this is likely due to the relatively small number of these events (9, 9, and 2, respectively). Longer follow-up in larger cohorts will be necessary to have adequate numbers of events to achieve statistical significance.

In one of the few previous studies looking at outcomes with LGE in HCM, Maron et al. (15) studied 202 patients (mean age 42 years) over an average of 1.9 years for the adverse cardiovascular event rate (including progressive heart failure, SCD, and appropriate ICD shock) and failed to show a difference in the annualized event rate between patients with (5.5%) and without (3.3%) LGE. However, this negative result could have been due to the duration of follow-up or the younger age of their cohort. More recently, Rubinshtein et al. (16) followed 424 patients with HCM (mean age 55 years) over 3.6 years and demonstrated a strong association of LGE with SCD and appropriate ICD discharges even after controlling for other variables.

Thus, the studies in this issue of the *Journal* add to the growing body of literature suggesting that LGE should be considered as an independent predictor of adverse cardiac outcomes. However, a large, prospectively designed study is still needed to definitively establish LGE as a predictor of SCD and cardiac death in HCM. Due to the relatively small number of patients with HCM at any 1 center, a multicenter collaborative clinical trial would be the best way to definitively answer this question. Randomizing HCM patients with LGE without standard clinical indications for ICD therapy or no therapy could be one way of designing such a study. Understanding how well today's accepted clinical risk factors predict ICD discharge with the use of a registry would also help in this regard. The time has come for LGE by CMR to be examined carefully as a potential risk marker in this deadly disease.

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Key Words: cardiovascular magnetic resonance ■ hypertrophic cardiomyopathy ■ late gadolinium enhancement ■ myocardial fibrosis ■ sudden cardiac death.