The Role of Cardiovascular Magnetic Resonance in Sudden Death Risk Stratification in Hypertrophic Cardiomyopathy

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KEYWORDS

• Hypertrophic cardiomyopathy • Cardiovascular magnetic resonance • Sudden death
• Myocardial fibrosis • Late gadolinium enhancement

KEY POINTS

- Hypertrophic cardiomyopathy (HCM) is the leading cause of sudden death in young patients; although current risk factor strategy is very effective, not all high-risk patients are identified.
- Contrast-enhanced cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) can identify areas of myocardial fibrosis where potentially life-threatening ventricular arrhythmias originate.
- HCM patients with LGE have a 7-fold greater risk for nonsustained ventricular tachycardia compared with patients without LGE.
- Extensive LGE (≥15% of left ventricular [LV] mass) is an emerging risk marker for sudden death events, even in HCM patients without conventional risk factors.
- The absence of LGE in patients with HCM is associated with low risk and is a measure of reassurance for patients.
- Other high-risk HCM subgroups can be reliably identified with CMR, including patients who develop LV apical aneurysm and those with massive LV hypertrophy.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease and the leading cause of sudden death in young people, including competitive athletes.[1,2] Recently, cardiovascular magnetic resonance (CMR), with its high spatial resolution and tomographic imaging capability, has emerged as an important complementary imaging technique to echocardiography with the opportunity to provide unique clinical information.[3–6] For example, CMR can precisely characterize the location, distribution, and extent of left ventricular (LV) hypertrophy, and can be superior to echocardiography for HCM diagnosis by identifying areas of segmental hypertrophy not reliably visualized by echocardiography (or underestimated in terms of extent), which can improve diagnostic strategies.[7–9]

However, over the last decade it is the unique capability of contrast-enhanced CMR with late gadolinium enhancement (LGE) to identify myocardial fibrosis, the structural nidus for the generation of potentially life-threatening ventricular arrhythmias,[10] which has generated the greatest enthusiasm for the notion that LGE may enhance risk stratification in HCM.[6] These

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observations underscore an important role for CMR in the contemporary assessment of patients with HCM, providing important information that affects diagnosis and risk stratification.

CURRENT RISK STRATIFICATION STRATEGY IN HYPERTROPHIC CARDIOMYOPATHY

Sudden death remains the most devastating consequence of HCM and the most frequent cause of sudden death in competitive athletes in the United States.[1,2] Sudden death in HCM occurs most commonly in young patients and significantly less in patients of advanced ages (≥60 years), and is often the initial clinical manifestation of HCM.[1] However, intense vigorous exertional activity, such as with most organized competitive sports, is also associated with an increased risk of sudden death in patients with HCM.[2,11] The mechanism of sudden death is primary ventricular tachycardia/fibrillation (VT/VF) originating from an unstable electrophysiologic substrate, which includes an abnormal arrangement of hypertrophied myocytes, with an expanded extracellular space composed of interstitial fibrosis and replacement scar resulting from bursts of silent microvascular ischemia (caused by structurally abnormal intramural coronary arteries).[1,10]

Over the last 5 decades, several noninvasive risk markers have emerged to comprise a primary prevention risk stratification model, in an effort to identify HCM patients at highest risk for potentially life-threatening VT/VF.[2,12] These risk factors include: (1) family history of premature HCM-related sudden death, in close or multiple relatives; (2) unexplained syncope judged nonneurocardiogenic, particularly if recent and in young patients; (3) nonsustained VT on serial ambulatory electrocardiogram (ECG), particularly when bursts are multiple, repetitive, or prolonged; (4) hypotensive or attenuated blood pressure response to exercise; and (5) extreme LV hypertrophy (wall thickness ≥30 mm).[2,12] Secondary prevention with an implantable cardioverter-defibrillator (ICD) is indicated in patients with a history of prior cardiac arrest or spontaneous, sustained VT.[1,12]

Risk for sudden death is increased in proportion to the absolute number of risk factors.[12] However, one risk factor alone may be sufficient to increase the risk enough in an HCM patient for that individual to be considered for life-saving therapy with primary prevention ICD, particularly in a patient with 1 of the 3 strongest risk markers: massive LV hypertrophy, family history of sudden death, or recent unexplained syncope.[13] For those patients considered at high risk (ie, patients with 1 or more of the previously stated primary risk factors) the ICD has proved efficacious at preventing sudden death (**Fig. 1**).[1,2,13] In a recent multicenter study with more than 500 HCM patients, the ICD delivered an appropriate shock for VT/VF in 20% of patients, who were implanted for primary or secondary prevention, over a follow-up period of less than 4 years.[13] Appropriate device interventions occurred at 11% per year for secondary prevention and 4% per year for those patients implanted for primary prevention. The current risk stratification strategy and the ICD seem to have substantially affected the natural history of HCM, with HCM-related mortality rates decreasing to very low and less than those of the pre-ICD treatment era.[1]

LIMITATIONS OF RISK STRATIFICATION IN HYPERTROPHIC CARDIOMYOPATHY

Although the noninvasive clinical risk markers have proved to be highly effective in identifying many HCM patients at increased risk for sudden death who will benefit from primary prevention ICDs, the HCM risk algorithm is incomplete.[14] For example, sudden death risk in patients without conventional risk markers is 0.5% per year, meaning that a minority of high-risk patients remains unrecognized with the current risk stratification algorithm.[14] In addition, nearly half of clinically identified HCM patients have 1 or more risk factors so a substantial proportion of the HCM patient population could be considered at risk, leading to overtreatment with ICDs in some patients.[12] Furthermore, high-risk stratus remains ambiguous (ie, "gray zone") in a subgroup of patients (particularly those with 1 risk factor), making decision making about ICDs complex. These observations underscore the need for additional strategies to improve risk prediction for sudden death.

CONTRAST-ENHANCED CARDIOVASCULAR MAGNETIC RESONANCE

Following the intravenous injection of gadolinium, contrast-enhanced CMR images can detect areas of high signal intensity LGE in the LV myocardium (**Fig. 2**). Several observations support the principle that LGE represents the arrhythmogenic substrate of myocardial fibrosis in HCM. For example, in ventricular septal tissue removed from HCM patients at the time of surgical myectomy, there is a strong association between the extent of fibrosis assessed by histologic examination and LGE (as determined from preoperative contrast-enhanced CMR studies).[15] In addition, CMR findings of LGE correlate to areas of myocardial fibrosis by histologic evaluation in HCM patients undergoing transplant.[16]