Recent Progress in End-Stage Hypertrophic Cardiomyopathy

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Abstract: Within the diverse spectrum of hypertrophic cardiomyopathy (HCM), a unique subgroup characterized by left ventricular enlargement and systolic dysfunction has emerged (defined as end-stage HCM [ES-HCM]). This underestimated entity provides challenging treatment strategies for extremely high risk of refractory heart failure and sudden cardiac death. Over the last 2 decades, the clinical features of ES-HCM have expanded and the underlying mechanisms gradually elucidated. Moreover, there is increasing evidence for early recognition of ES-HCM. New insights into early prevention and management will improve the clinical outcomes of this entity.

Key Indexing Terms: Hypertrophic cardiomyopathy; Systolic dysfunction; End stage. **[Am J Med Sci 2015;349(5):448–453.]**

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiac disease with a prevalence of 1:500 in the general population and is defined as a hypertrophied and nondilated ventricular cavity in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy.[1] The majority of affected individuals survive with normal or supernormal systolic function until their 70s or 80s. However, severe systolic dysfunction is observed in 2.4% to 5.7% of patients with HCM,[2–6] ending with refractory heart failure and cardiac death. This condition is termed burnt-out, dilated phase or end-stage HCM (ES-HCM). Awareness of ES-HCM has markedly increased since initial reports in the 1980s.[6] Increasing evidence on the role of multiple gene mutations has been drawn from a number of confusing data, especially after the development of appropriate animal models. Modifier factors that advance the progression of ES-HCM have been gradually recognized. In addition, the notable feature is no longer confined to a dilated pattern. Finally, there have been important advances in early recognition of patients with ES-HCM. Herein, the authors provide a review of the current understanding of the diagnosis, pathogenesis and treatment of ES-HCM.

PREVALENCE

To date, there are no data on the prevalence of ES-HCM in the general population, with the majority of studies based on referral HCM populations. The reported prevalence of HCM varies from 2.4% to 15.7%.[2–6] This diversity largely results from the retrospective nature and heterogeneity of patients with respect to ethnicity, definition of ES-HCM, age and follow-up period. New incident patients during follow-up seem homogeneous, with a relatively uniform annual incidence of 0.5% to 1.5% in HCM.[2–4,7] These findings suggest that ES-HCM is not rare in patients with HCM and provide significant implications for investigation of this entity.

DIAGNOSIS

As not all patients with HCM progress into end stage phase, an accurate definition is needed. In contrast to the classic phenotype, ES-HCM is characterized by a markedly dilated ventricular cavity, a relatively thin wall and a severe systolic dysfunction. The morphologic features are heterogeneous,[8] and a left ventricular end-diastolic diameter >55 mm (50%) is not a suitable definition. Furthermore, fraction shortening $\leq 25\%$ is too low, leading to an underestimate of ES-HCM.[3] Left ventricular ejection fraction (LVEF) $<50\%$ on echocardiography is a relatively better definition of systolic dysfunction and has been widely accepted as a cutoff level for ES-HCM.[2,4,7] However, in some patients with ES-HCM who have already presented with a dilated and hypokinetic left ventricle it is difficult to differentiate from dilated cardiomyopathy (DCM) (Table 1). In such cases, previous echocardiography, other documentation of left ventricular (LV) asymmetric hypertrophy or family history is always required. Other indicators including retained focal hypertrophy, relative small cavity and high LVEF and myocyte disarray on pathological findings are useful to confirm diagnosis.[9,10] Recently, a few reports demonstrated that cardiac magnetic resonance (CMR) and positron emission tomography (PET) are useful for differentiating ES-HCM from DCM.[11–14] For example, mean myocardial flow reserve in PET in ES-HCM was significantly lower than that in DCM.[12] In addition, late gadolinium enhancement (LGE) in ES-HCM is more widely distributed into all LV segments, whereas LGE in DCM is localized mainly in the interventricular septum.[11,13]

Interestingly, a less frequent restrictive-hyperkinetic morphology was also reported in ES-HCM.[8,15] This pattern is characterized by an extremely small LV cavity, restrictive filling and mild to moderate systolic dysfunction. This pattern strongly resembles primary restrictive cardiomyopathy (RCM). As some cases of RCM even have mild to moderate impaired systolic dysfunction and LV hypertrophy,[16] echocardiography does not provide differential diagnosis. In this case, a family history of HCM and myocyte disarray at explants or autopsy would contribute to distinguishing ES-HCM from RCM.

Early recognition of patients with ES-HCM from general HCM is important for early prevention, although this is challenging. Initial studies suggest that patients with HCM who develop end-stage phase always exhibit a younger age at diagnosis, greater wall thickness and higher frequency of family history, syncope, nonsustained ventricular tachycardia (VT) and abnormal blood pressure on exercise.[2,4] However, these factors do not help to identify the ideal tipping point separating reversible from irreversible stages of dysfunction for an individual with HCM. In a recent prospective cohort study of patients with HCM (absence of coronary artery disease), a dipyridamole myocardial blood flow ([Dip]-MBF) <1.1 $mL \cdot min^{-1} \cdot g^{-1}$ and an end-diastolic LV dimension >45 mm were independent

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TABLE 1. Comparison of clinical characteristics in end-stage HCM and dilated cardiomyopathy

	End-stage HCM (dilated pattern)	Dilated cardiomyopathy
Family history of HCM	Present	Absent
Morphologic characteristics		
LVFW/IVS thickness	Normal or ↑	Normal or ↓
Left ventricular end-diastolic diameter	Normal or ↑	Usually ↑↑
Left atrial diameter	↑↑	↑
Endocardial and/or interstitial fibrosis	Present	Present
Myocyte hypertrophy	Present	Present
Myocyte disarray	Usually present	May be present
Small vessel disease	Usually present	May be present
Functional characteristics		
Cardiac compliance (diastolic filling)	mild↓	normal
Left ventricular ejection fraction	↓	↓↓
Thrombosis	Common	Common
Microvascular function		
Myocardial blood flow	↓	↓
Myocardial flow reserve	↓↓	↓

HCM, hypertrophic cardiomyopathy; IVS, interventricular septum; LVFW, left ventricular free wall; ↓, decrease; ↑, increase.

predictors of systolic dysfunction of development into end stage phase.[17] In addition, a recent stress CMR study reported early identification of patients with ES-HCM, although more quantitative data are required.[11] Furthermore, it is difficult to perform PET or stress CMR for all patients with HCM. Another opinion has been proposed regarding strengthening the awareness of the early stage of ES-HCM (LV remodeling), when the patients are still presented with mild to moderate symptom and EF reduction (~50%–65%).[18] This is beneficial for early therapy and prognostic improvement.

PATHOPHYSIOLOGY

Awareness of the clinical phases of HCM in individual patients aids in understanding the pathogenesis of progression to end stage phase. Olivotto et al[19] proposed a simple framework for systematic clinical staging of HCM: nonhypertrophic HCM, classic phenotype, adverse remodeling and overt dysfunction (ie, end stage phase). A hypertrophic phenotype tends to manifest during the 2nd decade of life or later and is generally absent in the majority of newborn or very young children. More than three quarters of patients with HCM retain long periods of clinical stability in the classic phenotype stage (LVEF >65% and little or absence of extensive fibrosis). Adverse remodeling (LVEF between 50% and 65% and increasing LV fibrosis) can occur in middle age, along with LV wall thickness regression (~1–2 mm/yr), LV cavity enlargement (~1–4 mm/yr) and decreased LVEF.[20] Over approximately 5 to 6 years, end-stage (LVEF <50% and extreme degrees of fibrosis) develops in 5% to 10% of patients with HCM.[4,19] Adverse remodeling has a profound influence on the clinical course and management of ES-HCM and has important implications for the investigation of its causes.

Myocardial ischemia is a recognized but underappreciated pathophysiologic mechanism of adverse remodeling in HCM.[21] Small vessel disease, characterized by increased number of small intramural coronary arteries with thickened walls and narrowed lumens, is the most likely anatomical substrate of myocardial ischemia in patients with HCM.[22,23] These structurally abnormal intramural coronary arteries are responsible for the reduced vasodilator capacity and blunted MBF during stress (termed microvascular dysfunction).[17] Recurrent increased diastolic wall tension and enhanced myocardial oxygen requirement can induce myocardial ischemia. In addition, reduced myocardial capillary density contributes to myocardial ischemia in the disease process. As a result, there is progressive death of myocardial cells (necrosis or apoptosis)[24] and replacement fibrosis. This process is gradual because acute clinical events occur only rarely. Thus, the authors speculate that the pathophysiologic course involves small vessel disease–mediated myocardial ischemia and fibrosis, with LV remodeling and promotion of end-stage phase progression.

This hypothesis is supported by 2 recent studies. First, impaired MBF after stress in HCM was reported to be associated with adverse LV remodeling and LV systolic dysfunction.[17] Furthermore, a stress CMR study reported that blunted MBF is related to the degree of LGE (representation of fibrosis) in patients with ES-HCM.[25] These observations suggest an association between myocardial ischemia, myocardial fibrosis, LV remodeling and ES-HCM (Figure 1).

Etiopathogenesis

HCM is a cardiovascular genetic disease mainly caused by mutations in sarcomere genes.[26] Although a certain genotype-phenotype correlation has not been established,[27] an observational cohort study reported that the presence of double or triple sarcomere gene mutations was associated with HCM in end-stage phase.[28] There is also increasing evidence to suggest that multiple gene mutations are a primary factor activating end-stage formation. For example, patients with HCM with triple sarcomere gene mutations result in a marked increase in the risk of end-stage progression and adverse outcomes.[29,30] Moreover, patients with ES-HCM exhibit a higher rate of multiple mutations (13%) than general patients with HCM (5%).[31–33] More recently, double-mutant (TnI-203/MHC-403) mice have been developed as an appropriate model of ES-HCM. TnI-203/MHC-403 mice developed a significantly increased heart weight to body weight ratio, marked interstitial myocardial fibrosis at 14 days of age, rapid