Is It Possible to Predict the Onset of “Heart Failure” in Hypertrophic Cardiomyopathy?

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Hypertrophic cardiomyopathy (HCM) is a common inherited disease with diverse phenotypic and genetic expression, clinical presentation and natural history. To date, a large number of genetic studies have established that HCM is caused by mutations in the genes encoding the thick and thin myofilament protein components of the sarcomere or adjacent Z-disc.1 However, the vast genetic heterogeneity of HCM has limited the role of mutation analysis in predicting prognosis or phenotypic expression for individual patients.

HCM is characterized by unexplained myocardial hypertrophy, and approximately 10% of the patients have severe left ventricular hypertrophy (LVH), defined as maximal left ventricular (LV) wall thickness ≥30 mm.2 Maron et al have indicated that this level of hypertrophy is relatively common in young patients and rare among elderly patients.3 This age-related difference is mainly explained by young patients with severe LVH not surviving into middle age and beyond, because of the high incidence of sudden cardiac death. An alternative explanation is that patients with severe LVH undergo LV wall thinning during their clinical course. Although previous studies have reported the progression of wall thinning observed in up to 15% of patients with HCM, Thaman et al demonstrated that wall thinning ≥5 mm occurred in 58% of patients with severe LVH.4 Cardiac remodeling is a possible mechanism responsible for LV wall thinning, but the precise mechanism for the remodeling in HCM is unknown. It is conceivable that myocardial ischemia, necrosis, apoptosis, increased collagen synthesis and fibroblast proliferation might occur, which is similar to dilated cardiomyopathy.5

HCM is unique among cardiovascular diseases because of its clinical presentation and progression during all phases of life from infancy to advanced age. This long period of
observation can itself impede complete understanding of the natural history of HCM over the any decade of life. The age of the patient is an important determinant of HCM-related event rates and clinical course. For example, sudden death event is most common in young patients (eg, <30 years of age), but paradoxically, uncommon in patients of more advanced age (eg, >60 years of age).\textsuperscript{9}

Reported HCM-related mortality risk has undergone substantial revision over time. Recently, mortality in adult patients has decreased to approximately 0.5\% per year because of treatment interventions, particularly implantable cardioverter-defibrillators (ICD) and heart transplantation.\textsuperscript{7} Furthermore, because the sudden death rate in HCM patients has decreased as a result of increasing usage of ICDs, death from heart failure is emerging as the predominant mode of demise.

In this issue of the Journal, Hamada et al\textsuperscript{10} followed HCM patients (54±12 years old), including both obstructive and non-obstructive cardiomyopathy, for 20 years. They found abnormal elevations of CK-MB in 64\% of the patients, and compared the cumulative event-free rate and survival rate between high CK-MB patients (group H) with low CK-MB patients (group L). They showed that both were significantly lower in group L than in group H, suggesting that serum levels of cardiac enzymes might predict the prognosis of patients with HCM. They also speculate that persistent elevation of cardiac enzymes in HCM patients might indicate ongoing myocardial injury and result in death from heart failure. A very recent report by Maron et al\textsuperscript{11} demonstrates the natural history of HCM in midlife adults. Clinical outcomes was evaluated in 1,000 HCM patients, aged 30–59 years (mean 45±8 years), who were followed for 7.2 years. In their study, considering the difference in the frequency of the treatment option of heart transplantation and relatively short follow-up period, both the reported incidence of death and events related to heart failure were relatively low.

For some time, the risk for heart failure death in HCM patients was defined as follows: (1) SV+RVs <3.5 mV by ECG, (2) %FS <35\%, (3) LV outflow-tract obstruction, and (4) atrial fibrillation.\textsuperscript{9} Recently, late gadolinium enhancement on contrast-enhanced cardiovascular magnetic resonance and fragmented QRS complex on the ECG were reported as additional independent predictors of adverse prognosis in Japanese HCM patients.\textsuperscript{10,11}

Although the initial %FS and frequency of hypertrophic obstructive cardiomyopathy (HOCM) in group L were similar to group H, SV+RVs was significantly greater in group H. During 20 years of observation, %FS significantly decreased, and the frequency of atrial fibrillation increased in group H. These results are not compatible with previously reported risks. As mentioned before, the clinical presentation and progression greatly differ according to whether the HCM patients were young or advanced age. The difference might be related to the population of study subjects, as this cohort had a mean age of 54 years and included 34–39\% of HOCM patients.

Although the majority of nonobstructive HCM patients experience a relatively stable clinical course without significant symptoms, some will experience progressive, limiting heart failure symptoms predominantly caused by diastolic dysfunction.\textsuperscript{12} Some degree of heart failure occurs in approximately 50\% of HCM patients, in the presence of preserved systolic function.\textsuperscript{13} The most advanced form of heart failure within the HCM spectrum is the endstage phase occurring in a distinctive subset of patients with nonobstructive HCM (prevalence, <3\%\textsuperscript{14}). The presence and contribution of heart failure with preserved systolic function in the current study is unknown. The progression of heart failure is associated with conversion to systolic dysfunction and adverse LV remodeling with extensive myocardial scarring, often resulting in regression of hypertrophy and cavity enlargement (Figure).

Although an elevated serum level of CK-MB and severe LVH might predict the onset of heart failure in HCM patients, there seemed to be no possible and effective medication to prevent or prolong the onset of heart failure. Almost 70–80\% of patients in both groups were treated with β-blockers and calcium antagonists and the frequency of the use of these drugs was similar.

The 20 years of follow-up of HCM patients with relatively advanced age demonstrated the usefulness of measuring the serum levels of cardiac enzymes for the prediction of the prognosis of the patients. However, there is a great demand for additional study to clarify the treatment strategy to prevent heart failure deaths, mainly in advanced-age HCM patients.

References