Is Regression of Left Ventricular Hypertrophy Really a Good Thing for Patients With Hypertrophic Cardiomyopathy?: The Emerging Mavacamten Story

The 60-year history of hypertrophic cardiomyopathy has been periodically encumbered by uncertainties regarding its very nature and pathophysiology, including popular myths about the disease, some of which have persisted to this day.[1] One such example is the belief that the clinical course of hypertrophic cardiomyopathy can be reversed by eliminating or substantially reducing left ventricular (LV) hypertrophy itself, the sine qua non and primary diagnostic and pathophysiologic feature of this complex inherited disease.[2−4] In the past, some investigators have been enamored with this concept and the expectation that it could offer a potential "cure" for all adverse consequences of the disease − that is, if hypertrophy is eliminated by some intervention so will be the overall pathologic disease process, albeit without sufficiently considering the potentially deleterious consequences of alterations in muscle structure.[2−4]

The LV hypertrophy regression hypothesis has been seriously entertained on at least 2 prior occasions in the modern history of the disease.[2−4] First, in the 1980s, the calcium channel blocker verapamil was introduced to control heart failure symptoms, with the possible mechanism of reducing LV wall thickness.[2] Subsequently, in the 1990s the questionable claim was advanced that LV wall thickness could be normalized in symptomatic hypertrophic cardiomyopathy patients by dual chamber pacing, instituted primarily for the purpose of relieving LV outflow obstruction.[3] Soon thereafter pacing was controversially proposed as a curative intervention for young asymptomatic children with nonobstructive disease.[4] Although neither verapamil nor pacing have been shown convincingly to alter the disease phenotype, the simplistic hypothesis that hypertrophy can (or should) be reversed has nevertheless survived in this disease.[5]

However, often lost in this dialogue is the critical point that the only representative example within the natural history of hypertrophic cardiomyopathy in which significant regression of LV hypertrophy occurs is: the highly unfavorable process of end-stage, ie, the triad of LV chamber enlargement, reduction in ejection fraction to <50%, and thinning of the LV wall from myocardial scarring (fibrosis) as a repair process following myocyte death in the setting of microvascular ischemia.[6,7] Notably, the end-stage is disproportionately responsible for disease-related mortality and morbidity in which irreversible LV remodeling with systolic dysfunction can lead to progressive heart failure symptoms requiring advanced treatments, including transplant in some patients. (Figure 1)

Pertinent to whether reducing LV thickness and mass in hypertrophic cardiomyopathy should be celebrated as a key management objective becomes particularly relevant with the possible introduction of mavacamten to this disease (MyoKardia; Bristol Myers Squibb).[8] Mavacamten is a selective allosteric inhibitor of cardiac myosin tailored to mitigate excessive actin-myosin cross-bridge interaction, thereby reducing cardiac contractility and acting clinically as a potent disopyramide-like negative inotropic drug targeting relief of outflow gradients.[8] Although mavacamten has not achieved FDA approval at the time of this writing, nevertheless preliminary enthusiasm for this drug is high in some quarters, perhaps an understandable reaction to the failure to introduce novel drugs for hypertrophic cardiomyopathy over the previous several decades.

Relevant to the evolving understanding of mavacamten, and also consistent with the myth in hypertrophic cardiomyopathy that regression of LV hypertrophy is a desirable clinical goal, a recent and highly visible substudy[5] from the EXPLORER-HCM randomized phase 3 trial reported serial cardiac magnetic resonance imaging observations in 35 selected patients. Saberi et al[5] reported profound regression in the magnitude of LV hypertrophy evidenced by thinning of ventricular septum ≥5 mm in 25% of patients (and up to 8 mm), and 25% reduction in calculated LV mass in 30% of patients, occurring over only the short treatment period of 30 weeks. This magnitude of LV regression exceeds what could have been expected from the incomplete relief of the outflow gradient attributable to mavacamten in the EXPLORER-HCM trial.

Although this extensive degree of the remodeling is largely unrecognized in hypertrophic cardiomyopathy,[9] a notable prime exception is the highly unfavorable end-stage process which over time can ultimately lead to irreversible heart failure.[6,7] We also wish to underscore the distinction between striking regression of LVH reported by Saberi et al. due to mavacamten in hypertrophic cardiomyopathy (a primary structural genetic abnormality), versus the mild regression of LVH possible with pharmacotherapy in patients with secondary forms of hypertrophy (eg, systemic hypertension), or following relief of outflow tract obstruction by surgical myectomy.[10]

In addition to this striking regression of LV hypertrophy reported in the EXPLORER-HCM substudy,[5] about 7% of patients treated with mavacamten in the overall study cohort experienced substantial transient decreases in ejection fraction to less than 50% (and as low as 35%), findings that meet the HCM definition of systolic dysfunction, as well as 2 patients with clinical heart failure.[6,7] If unrecognized over time (and not subject to reversal) this unintentional consequence of mavacamten could create a new subpopulation of patients with heart failure. Furthermore, this potential risk could expand as additional patients are treated for much longer periods outside the highly monitored short-term clinical trial setting, including more patients with borderline ejection fraction (50%−60%). Nevertheless, the authors of the mavacamten substudy[5] regard the striking regression of LVH, although reminiscent of the end-stage of hypertrophic cardiomyopathy, a favorable outcome and therapeutic objective.

In conclusion, it is important to appreciate the complexity of hypertrophic cardiomyopathy in judging new treatment innovations, by relying on the knowledge acquired in this disease over 60 years. For example, new powerful

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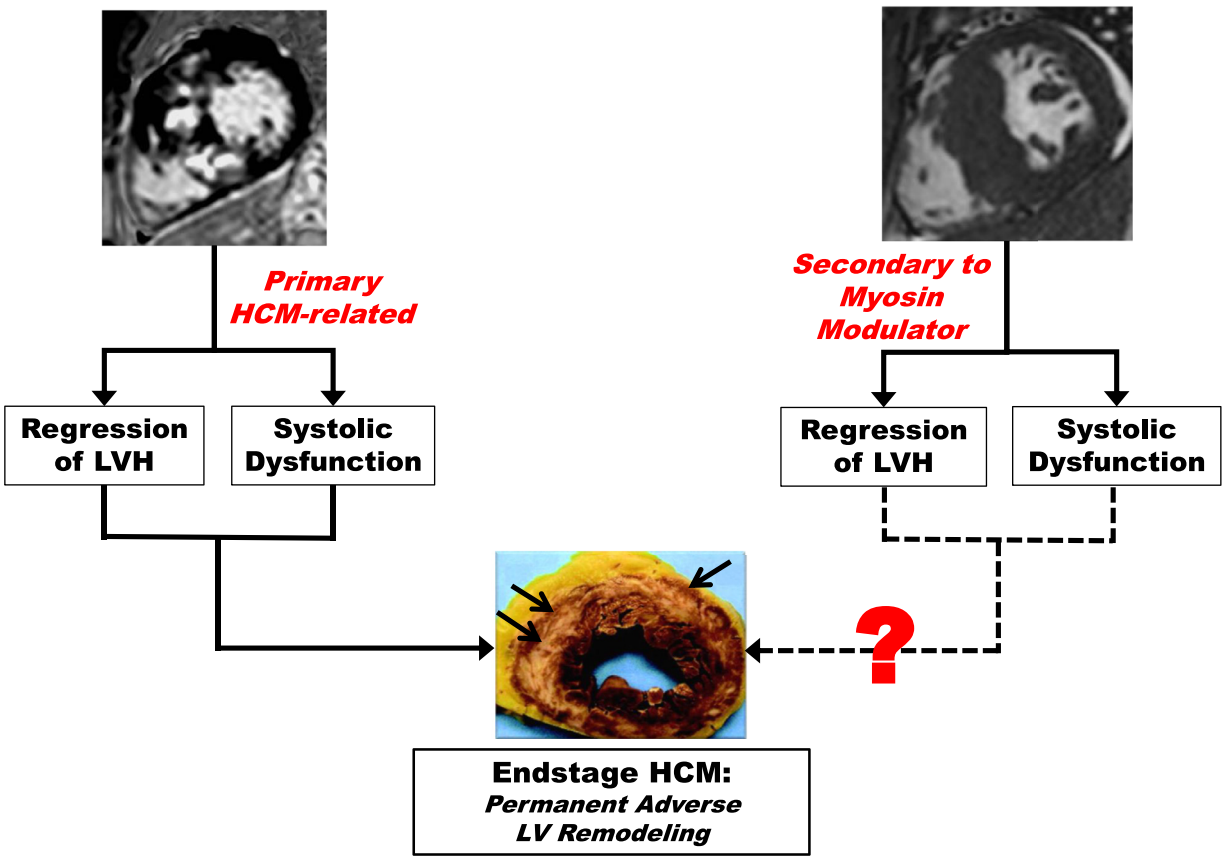

Figure 1. Spontaneous evolution to the end-stage of hypertrophic cardiomyopathy (HCM) occuring is a small subset of patients, compared with the possible unintended consequence of long-term therapy with a myosin modulator. LVH = left ventricular hypertrophy.

negative inotropic drugs such as mavacamten poised for introduction into the therapeutic armamentarium of hypertrophic cardiomyopathy, while capable of reducing outflow obstruction and symptoms in some patients also have the potential for excessively reducing LV contractility and promoting adverse remodeling, and therefore should be viewed prudently with caution.

Barry J. Maron, MD*
Ethan J. Rowin, MD
Martin S. Maron, MD
HCM Institute, Tufts Medical Center, Boston, Massachusetts
* Corresponding author.
(Barrymaron1@gmail.com).

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