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EDITORIAL COMMENT

Hypertrophic Cardiomyopathy

There Is Much More to the Recipe Than Just Outflow Obstruction*

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For decades, cardiologists have maintained a keen fascination with hypertrophic cardiomyopathy (HCM), resulting in a robust body of literature. By and large the pathophysiologic mechanisms, consequences, and treatment of left ventricular outflow tract obstruction have garnered a large proportion of the published reports. In fact, population-based studies shed light on the fact that the nonobstructive variants of HCM are more common than the obstructive forms. That sudden cardiac death can be a prominent feature in some families, that atrial fibrillation manifests severe clinical disability in subsets of HCM patients, and that hundreds of mutations in the genetic code for cardiac sarcomeric proteins have been implicated in the pathogenesis of the disease all underscore the marked variability in the complex entity that is HCM. In this issue of the *Journal,* Biagini et al. (1) highlight another important facet of HCM: the possibility of progression to an end-stage or "burned out" dilated phase.

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Previous investigations and anecdotal reports have suggested that late wall thinning and chamber dilation will develop in approximately 5% of patients with HCM. The new data reported in this issue confirm this prevalence, but also introduce the incident rate of new cases of this dilated phase (0.5% per year). These data suggest that those in whom hypertrophy manifests at a younger age, those with the greatest amount of hypertrophy, and those with a significant family history of HCM are more likely to have wall thinning and left ventricular cavity dilatation in the long term. Although the number of patients in this study is small (reflecting the rarity of dilated-phase HCM) and does not allow clear prospective identification of those at increased risk for dilation, these findings need to be considered in the context of the genetic and metabolic recipe of HCM.

Beginning with the sentinel descriptions of mutations in the genetic codes for cardiac sarcomeric proteins, investigators have sought to uncover the molecular pathogenesis by which these mutations actually produce left ventricular hypertrophy. Abnormal sarcomere structure, calcium handling, and decreased or increased sarcomeric unit function have all been implicated in the development of the inappropriate myocyte disarray, fibrosis, and hypertrophy that typify HCM (2,3). There remains a lack of consensus on a unifying pathogenetic model for either the initial development of hypertrophy or the rare occurrence of late regression of hypertrophy.

Myocardial fibrosis is common in the histologic examination of the hearts of patients with HCM. Those patients with late wall thinning show a gross overrepresentation of this fibrosis, leading to the reasonable hypothesis that myocardial ischemia may play a role in the process (4). An increased myocardial oxygen demand caused by the hypertrophy and abnormal loading conditions, coupled with abnormal capillary density, would favor ischemia as an important factor in HCM. Numerous studies have shown abnormal perfusion and decreased coronary flow reserve in the hearts of patients with HCM (5,6). The magnitude of the decrement in flow reserve has also been correlated with increasing systolic dysfunction (7). The implication is that either the heart that is undergoing transition to dilatation is dipping into its flow reserve, or the microvascular impairment actually causes the fibrosis and dilatation. In either scenario, these hearts seem to be in or on the brink of crisis.

The tenuous biochemical environment in HCM is furthered by evidence of down-regulated beta-adrenergic receptors, heightened sympathetic activity, and increased cardiac catecholamine levels (8,9). The potential deleterious effects of a prolonged hyperadrenergic state can be drawn from patients with primary idiopathic dilated cardiomyopathy (DCM). It seems plausible that an environment favoring ischemia and with elevated sympathetic neurotransmitter levels could lead to fibrotic transition. Certainly there also are other commonalities between HCM and DCM. Mutations in some of the same sarcomeric proteins can cause either type of cardiomyopathy. In fact, there are remarkable similarities in vast gene expression arrays and energy use between patients with DCM and late-stage dilatation HCM (10–13).

The study by Biagini et al. (1), with the suggestion that patients with clear hypertrophy at a young age with a greater magnitude of hypertrophy, seems to support the concept that energetic crisis and ultimate energetic failure may lead to late-stage transformation. Perhaps these patients with early and more complete disease expression represent those that reach the energetic brink more readily. Possibly, the early expression or rapid progression results in increased metabolic demands and more inefficiency, which ultimately leads to cell death and fibrotic replacement. Whether specific therapies targeted at delaying the progression of hypertrophy or at counteracting the effects of catecholamines will have any benefit will be difficult to show given the rarity of dilated-phase HCM.

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In the making of fine wines, the basic ingredients are the same, but it is the environment, the handling, the timing, and the exposure to other impurities that ultimately results in the enjoyment (or not) of the final product. Perhaps the commonly proclaimed heterogeneity in the expression of HCM is the result of a "vinification" of the cardiac myocyte such that sarcomeric mutations, modifier gene polymorphisms (14), local loading conditions, and as-yet-undetermined factors all combine in the right sequences and concentrations to produce each variety of clinical HCM. Cardiologists need to continue to try to understand this very complex condition.

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