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Update on Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a primary disease of cardiac myocytes, characterized mainly by cardiac and myocyte hypertrophy. It is diagnosed clinically by the presence of cardiac hypertrophy in the absence of altered loading conditions that would fully account for the problem.[1] Typically, the left ventricle is not dilated and the left ventricular ejection fraction is increased.[1] Human HCM is the prototypic and genetic form of pathologic cardiac hypertrophy.

The clinical diagnosis of HCM is neither sufficiently specific (because of the presence of phenocopy) nor completely sensitive (because of incomplete penetrance of the causal mutations). Phenocopies are often indistinguishable from true cases of HCM. The incidence of phenocopy in patients with the clinical diagnosis of HCM is unknown but is estimated at 10%. The distinction between HCM and phenocopy is important, because the treatments of the conditions differ significantly.

Hypertrophic cardiomyopathy is an archetypical single-gene disorder. More than a dozen causal genes and several hundred mutations have been identified in patients and families with HCM.[2] The known causal genes encode sarcomeric proteins. Therefore, HCM is commonly recognized as a disease of sarcomeric proteins. The 2 most common genes—each accounting for approximately 25% of cases—are *MYH7* and *MYBPC3*, which encode the β-myosin heavy chain and myosin-binding protein C, respectively. *TNNT2, TNNI3, TPM1,* and *ACTC1* collectively account for about 10% of cases; other causal genes, such as the Z disk proteins *MYOZ2* and *TCAP*, encoding myozenin 2 and telethonin, respectively, are less common. Overall, the causal mutations in approximately two thirds of all patients with HCM have been identified.

Advances in molecular genetics have enabled a genetic-based diagnosis. Genetic screening leads to identification of the causal mutations in approximately half of the cases. In familial cases and in certain clinical situations, genetic testing can provide valuable information, but its impact is diminished in sporadic cases. The value of genetic testing in risk stratification and prognostication is similarly weakened by the involvement of a large number of determinants, in addition to the causal mutation, in the pathogenesis of the phenotype.

Hypertrophic cardiomyopathy is a relatively benign disease. In young athletes, however, HCM is the most common cause of sudden cardiac death (SCD) and is responsible for almost half of all cases.[3] Sudden cardiac death is often the first manifestation of HCM in apparently healthy, young individuals.[3] Several predictors of the risk of SCD have been identified, including a history of sudden cardiac arrest, a history of recurrent syncope (due to cardiac arrhythmias), and sustained or repetitive nonsustained ventricular tachycardia. The presence of these risk factors warrants the implantation of a defibrillator. A strong family history of SCD (more than 1 family member) and severe cardiac hypertrophy are also important risk factors for SCD that are taken into consideration in evaluating patients for defibrillator implantation.

The fundamental question in HCM, since its modern description about 50 years ago, has been whether cardiac hypertrophy and fibrosis, once established, can be reversed or prevented. The current pharmacologic treatment of human HCM is largely empirical, and none has yet prevented, attenuated, or reversed cardiac hypertrophy or altered the prognosis in cases of HCM. β-Blockers are the mainstay of therapy and are effective for symptomatic relief but not for the reversal of cardiac phenotype. The clinical usefulness of calcium channel blockers is hampered by the risk of hypotension and syncope, at rest or (particularly) during exercise. Likewise, their effectiveness in the reversal of cardiac phenotype remains unestablished.

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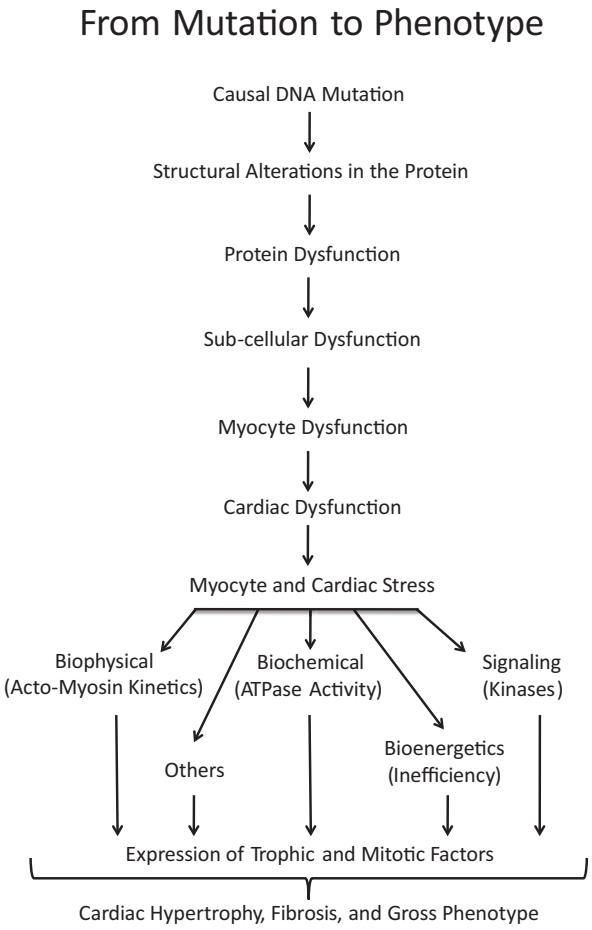

Fig. 1 *Pathogenesis of hypertrophic cardiomyopathy. The causal mutations alter the structure and function of the sarcomeres and impart various stresses on cardiac myocytes (mechanical, biochemical, bioenergetic, and others). The stress leads to the activation of signaling molecules that mediate the induction of cardiac myocyte hypertrophy, fibrosis, and other aspects of the gross cardiac phenotype.*

Mechanistic studies suggest that the genetic mutations cause functional defects that activate pro-growth and pro-fibrotic signaling molecules; this signaling leads to cardiac hypertrophy and fibrosis (Fig. 1).[4] We have shown that cardiac hypertrophy and fibrosis can be prevented, attenuated, and reversed through genetic and pharmacologic interventions in animal models of HCM.[5-9] The most promising among the experimental therapies is N-acetylcysteine (NAC), because it completely reverses cardiac hypertrophy and fibrosis.[8,9] The potential usefulness of NAC in the treatment of human HCM requires testing.

In summary, HCM is a relatively common disease and is the most common discernible cause of SCD in young athletes. Sudden cardiac arrest in a patient's history, or recurrent syncope, or ventricular tachycardia—any of these is an important risk factor for SCD. Cardiac hypertrophy is an important determinant of the risk of morbidity and death, including the risk of SCD in HCM. None of the currently used pharmacologic therapies attenuates cardiac hypertrophy and fibrosis, prevents SCD, or reduces the mortality rate of HCM. Experimental therapies, such as NAC, can prevent, reverse, or attenuate cardiac hypertrophy and fibrosis in HCM, but their clinical usefulness in human beings remains to be tested.

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