REVIEW

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Misconceptions and Facts About Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy is the most common genetic heart disease. Once considered relentless, untreatable, and deadly, it has become a highly treatable disease with contemporary management. Hypertrophic cardiomyopathy is one of cardiology's "great masqueraders." Mistakes and delays in diagnosis abound. Hypertrophic cardiomyopathy commonly "masquerades" as asthma, anxiety, mitral prolapse, and coronary artery disease. However, once properly diagnosed, patients with hypertrophic cardiomyopathy can be effectively managed to improve both symptoms and survival. This review highlights some of the misconceptions about hypertrophic cardiomyopathy. Providers at all levels should have awareness of hypertrophic cardiomyopathy to promptly diagnose and properly manage these individuals.

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Hypertrophic cardiomyopathy is one of the success stories in modern cardiovascular medicine. Once funneled into the appropriate subspecialty care, patients with hypertrophic cardiomyopathy can be effectively managed, not only to reduce symptoms, but also to improve survival. At the same time, appropriate recognition and referral of these patients depend on provider awareness and physician education. This review addresses some common misconceptions about hypertrophic cardiomyopathy that still persist among practicing physicians.

MISCONCEPTION #1: HYPERTROPHIC CARDIOMYOPATHY IS A RARE DISEASE RELEVANT ONLY TO SUBSPECIALTY CARE

The prevalence of hypertrophic cardiomyopathy has been studied over the last 2 decades using 2-dimensional (2D) echocardiography screening in distinctly different populations ranging from Japanese health workers to Tanzanian hospital patients to American urban communities.[1-4] Surprisingly, these studies yielded similar results with estimated hypertrophic cardiomyopathy prevalence of 0.2% (1 in every 500).[4] In a metropolitan area similar to New York, with 20 million inhabitants, this translates to about 40,000 patients with hypertrophic cardiomyopathy. Importantly, most of the individuals identified in these studies were asymptomatic. Among 7 patients identified by 2D echocardiography in the Coronary Artery Risk Development in Adults (CARDIA) Study, only 1 had suggestive cardiac symptoms.[3] While these studies provide important insight into the prevalence of hypertrophic cardiomyopathy, there is a concern that they may underestimate the true disease burden in the population.[4] First, although 2D echocardiography is the primary modality for diagnosing hypertrophic cardiomyopathy, it still may fail to identify certain hypertrophic cardiomyopathy phenotypes, such as localized hypertrophy of certain left ventricular segments. Second, the variability of phenotypic expression in genotype-positive patients is not completely understood. In a study examining sarcomere gene variants in the Framingham and Jackson Heart Study cohorts, 11.2% of subjects carried at least one rare nonsynonymous sarcomere variant, and 0.6% of subjects carried mutations considered to be pathogenic based on conservative criteria.[5] A majority of these study

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subjects had no clinical diagnosis of hypertrophic cardiomyopathy, although in the Framingham Heart Study cohort, sarcomere variants were associated with an increased risk for adverse cardiovascular events.[5] Therefore, based on the current data, hypertrophic cardiomyopathy is among the most common genetic heart diseases and probably even more prevalent than previously estimated.[4] Providers at all levels should have awareness of hypertrophic cardiomyopathy to diagnose and properly manage these individuals.

CLINICAL SIGNIFICANCE

- Hypertrophic cardiomyopathy is probably more prevalent than previously estimated.
- Sudden cardiac death can be the first manifestation of hypertrophic cardiomyopathy.
- Abnormalities of the mitral valve apparatus are seminal in pathophysiology of obstructive hypertrophic cardiomyopathy.
- Hypertrophic cardiomyopathy is a highly treatable disease provided it is recognized early and appropriately referred to subspecialty care.

MISCONCEPTION #2: HYPERTROPHIC CARDIOMYOPATHY IS A DISEASE OF CARDIAC MUSCLE ONLY

Hypertrophic cardiomyopathy is a genetic disease that is attributed to a variety of sarcomere gene mutations and typically described as nonphysiologic left ventricular muscle thickening without an apparent clinical cause. Hypertrophic cardiomyopathy phenotype may become apparent at any age; indeed, delayed development of clinical phenotype even in the elderly has been widely described.[6] The hypertrophied cardiac muscle has distinct pathologic features such as cardiomyocyte disarray with areas of fibrosis. The basal and mid-interventricular septum is commonly involved, predisposing to the most commonly known feature of hypertrophic cardiomyopathy: dynamic obstruction of the left ventricular outflow tract due to systolic anterior motion of the mitral valve and mitral-septal contact.[7,8] While myocardial hypertrophy is an essential part of the hypertrophic cardiomyopathy phenotype, another important pathologic feature, abnormal mitral valve apparatus, is underappreciated. The mitral apparatus in patients with hypertrophic cardiomyopathy commonly shows some distinct abnormalities.[9] First, there is abnormal anterior papillary muscle position in the left ventricular cavity. Second, mitral valve leaflets are elongated and redundant, with increased residual leaflet protrusion into the left ventricle, beyond the coaptation point of the leaflets.[10] These abnormalities of the mitral apparatus predispose to systolic anterior motion, resulting in dynamic left ventricular outflow obstruction. Indeed, some patients with dynamic obstruction due to systolic anterior motion of the mitral valve have these distinct pathologic features of the mitral apparatus but no significant left ventricular hypertrophy.[11] Understanding the contribution of the mitral valve apparatus abnormalities to pathophysiology of dynamic left ventricular outflow obstruction is essential. Multiple studies using Doppler echocardiography have demonstrated that systolic anterior motion of the mitral valve results not from a Venturi effect, as previously believed, but rather from an early systolic flow interaction with the abnormally elongated anterior mitral valve leaflet pushing it into the left ventricular outflow tract.[7,10] This interaction is not observed in normal controls and in nonobstructed patients. Based on these observations, many believe that repair of the mitral valve, plication of the anterior leaflet, and release of abnormal papillary muscle attachments should be a routine part of the septal myectomy procedure for drug-resistant symptomatic hypertrophic cardiomyopathy patients.[12] This approach is designed to repair all aspects of the obstructive pathology and to effectively relieve dynamic obstruction.

Hypertrophic cardiomyopathy patients may also have narrowing of the intramural small coronary arteries ("small vessels") caused by intimal and medial hypertrophy of the smooth muscle cells in their walls.[13] This can contribute to ischemia, even in the absence of atherosclerotic narrowing of the epicardial coronary arteries.

MISCONCEPTION #3: HYPERTROPHIC CARDIOMYOPATHY PATIENTS CARRY A HIGH MORTALITY RATE

For many years, hypertrophic cardiomyopathy has been perceived as a deadly, untreatable disease: early records from subspecialty referral centers indicated an annual mortality rate of 3%-6%.[14] Over the last several decades, hypertrophic cardiomyopathy management strategies have evolved and matured due to better understanding of the disease, including pathophysiology of systolic anterior motion of the mitral valve, and advances in therapy. Initial management of hypertrophic cardiomyopathy patients includes proper education, risk stratification for sudden cardiac death, and family screening (**Figure 1**).[15,16] Automatic implantable cardioverter-defibrillator, an effective tool to prevent sudden cardiac death, is offered to patients with prior cardiac arrest or sustained ventricular arrhythmias. Importantly, primary prevention of sudden death is often offered to the larger group of individuals at high risk for such events, such as patients with massive hypertrophy, recent syncope, or family history of sudden death in a first-degree relative.[15] Symptomatic patients commonly benefit from a beta-blocker (or verapamil, if intolerant of beta-blockers). In persistently symptomatic patients with left ventricular outflow tract obstruction disopyramide, a strongly negative inotropic agent can reduce the degree of obstruction and bring symptomatic relief.[17] In patients with

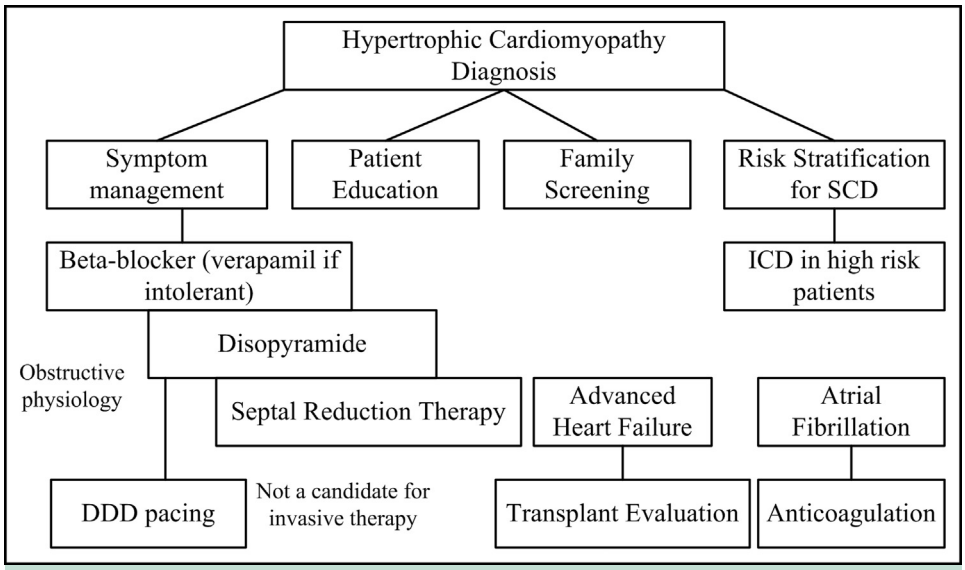

Figure 1 Outline of hypertrophic cardiomyopathy patient management. ICD = implantable cardioverter defibrillator; SCD = sudden cardiac death.

refractory symptoms despite medical therapy, septal reduction therapy with septal myectomy is the gold standard for relief of resistant obstruction; alcohol septal ablation is reserved for patients who are not candidates for surgery due to advanced age or frailty.[15] Anticoagulation is used in patients with atrial fibrillation to decrease the risk of embolic events. Hypertrophic cardiomyopathy patients have high embolic risk when atrial fibrillation occurs, and the traditional thromboembolic risk stratification tools do not apply to these patients.[15] Physicians simply have to remember to anticoagulate hypertrophic cardiomyopathy patients with atrial fibrillation even if they have none of the conventional risk factors. Patients with transformation into left ventricular systolic dysfunction or very severely impaired diastolic dysfunction benefit from heart transplantation.[15] These systematic management strategies resulted in substantial improvement of prognosis in patients with hypertrophic cardiomyopathy: recent studies of "midlife" hypertrophic cardiomyopathy patients reported annual mortality of 0.5%-1%, comparable with that of the general population.[14,18] Therefore, with appropriate management, hypertrophic cardiomyopathy has become a highly treatable disease. While management of these patients requires skilled subspecialty care, early recognition is necessary at all health care provider levels. It is not uncommon for young hypertrophic cardiomyopathy patients to be asymptomatic or have subtle symptoms, and sudden cardiac death can be the first manifestation of hypertrophic cardiomyopathy. Therefore, a high degree of suspicion (because of murmur, cardiac symptoms, abnormal electrocardiogram) is required from primary care

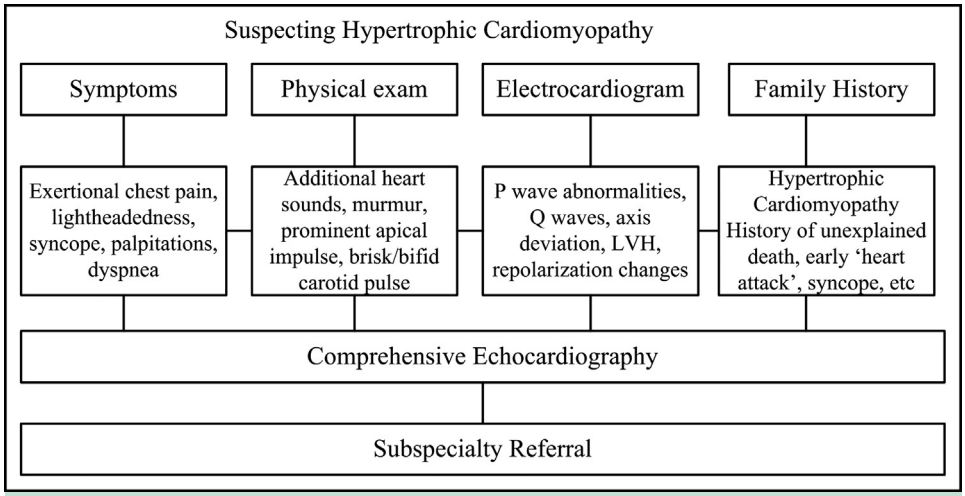

Figure 2 Appropriate early identification of hypertrophic cardiomyopathy patients at all provider levels. LVH = left ventricular hypertrophy.

providers to recognize the disease and refer to appropriate subspecialty care (**Figure 2**). Hypertrophic cardiomyopathy is cardiology's "great masquerader." Mistakes and delays in diagnosis abound. Hypertrophic cardiomyopathy commonly "masquerades" as asthma, anxiety, mitral valve prolapse, and coronary artery disease. Internists should be aware of the phenomenon of latent obstruction − where there is no obstruction at rest (and no murmur), but where significant obstruction can occur after provocation with Valsalva maneuver, standing, eating, or after exercise.[19-21]

MISCONCEPTION #4: HYPERTENSIVE PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY SHOULD BE TREATED WITH TRADITIONAL FIRST-LINE ANTIHYPERTENSIVE AGENTS

Hypertension is highly prevalent in the general population (approximately 30% in mid-life), and patients with hypertrophic cardiomyopathy are not exempt. Treatment of patients with co-existing hypertrophic cardiomyopathy and hypertension can be challenging.[15] Direct vasodilators such as dihydropyridine calcium channel blockers and renin-angiotensin system blockers are among the most efficacious and well-tolerated first-line medications for the treatment of hypertension in general. However, these drugs can exacerbate outflow tract obstruction in patients with obstructive hypertrophic cardiomyopathy (especially those with latent obstruction) and may be potentially harmful, even in some nonobstructed patients with small left ventricular cavity.[22] We recently aimed at establishing a general framework for treating hypertrophic cardiomyopathy patients with hypertension.[23] In obstructed patients, symptom control with a traditional stepwise therapy for gradient relief was prioritized (**Figure 1**); this included discontinuation of potent peripheral vasodilators. In patients with persistent hypertension despite optimal symptom-control therapy, oral clonidine or a low-dose thiazide diuretic (12.5 to 25 mg of hydrochlorothiazide with triamterene) was used for blood pressure control. This strategy led, not only to significant symptom reduction, but also better hypertension control despite discontinuation of vasodilators in most patients. The long-term outcomes of this approach were favorable, with a low incidence of adverse cardiovascular events.[23] However, no large-scale placebo-controlled outcome data are available to identify the most effective therapeutic strategy in hypertensive hypertrophic cardiomyopathy patients.

MISCONCEPTION #5: MOST PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY REQUIRE SEPTAL REDUCTION THERAPY (SURGERY OR ALCOHOL SEPTAL ABLATION)

Accumulating data suggest that most patients diagnosed with hypertrophic cardiomyopathy can be managed without surgical intervention.[14] Medical therapy (usually starting with a beta-blocker) is effective in relieving symptoms. Disopyramide as a step-up therapy in patients with persistent symptoms and left ventricular outflow obstruction is not associated with an increased risk of sudden death.[15,17] In a multicenter study of disopyramide, two-thirds of patients could be successfully managed without the need for septal reduction intervention.[24] In these patients, resting gradients were reduced by half, with a concomitant relief of symptoms. Moreover, there was a trend toward better survival in disopyramide-treated patients. Sudden death in the disopyramide-treated patients was low, 1% per year, which was lower than non-disopyramide-treated patients.[24] In a more recent study using higher-dose disopyramide that was more effective for gradient reduction, the incidence of sudden cardiac death or aborted sudden cardiac death was <0.5%/year.[18] In a recent review of 1001 consecutive "midlife" hypertrophic cardiomyopathy patients from 2 institutions, less than a third ultimately required intervention: septal myectomy in 226 (23%), alcohol septal ablation in 27 (3%), and heart transplant in 25 (3%).[14] It is also important to emphasize that in contemporary practice, septal myectomy is associated with low perioperative mortality (0.5%-0.8% in experienced centers) and results in marked improvement of symptoms.[14,18,25] In summary, most patients with hypertrophic cardiomyopathy can be effectively managed without septal reduction therapy. But when surgery is necessary, it is highly effective and can be done safely at experienced centers.

CONCLUSION

Many patients with hypertrophic cardiomyopathy are asymptomatic or have subtle symptoms. Others may be misdiagnosed with other conditions, not uncommonly due to lack of provider awareness. Sudden cardiac death can be the first manifestation of hypertrophic cardiomyopathy. Proper provider education may help in early diagnosis of these patients and timely referral to specialized care.

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