REVIEW

Management of Hypertrophic Cardiomyopathy

Alan D. Enriquez, MD, and Martin E. Goldman, MD

ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is clinically defined as unexplained myocardial hypertrophy, and it is an autosomal dominant disease of the cardiac sarcomere. It is present in 1 in 500 in the general adult population, making it the most common genetic cardiovascular disease. The pathophysiology of HCM is complex, leading to significant variability in clinical presentation. This, combined with the lack of randomized trials, makes the management of these patients difficult.

Findings: The majority of patients with HCM are asymptomatic without a substantial reduction in survival. However, a considerable portion of patients will experience significant symptoms and HCM-related death, and effective therapies are available for these patients. Patients may have symptoms of heart failure from outflow tract obstruction and/or restrictive physiology. Medical therapy targeted at the underlying pathophysiology should be used, and surgical myectomy or alcohol septal ablation is available for those with refractory symptoms. While the overall risk of sudden cardiac death (SCD) is low in HCM patients, some are at elevated risk for and experience SCD, a devastating outcome in young patients. Risk stratification for SCD and treatment with implantable cardioverter-defibrillators is paramount. Many HCM patients will also develop atrial fibrillation, and this is often poorly tolerated. A rhythm control strategy with antiarrhythmic drugs or catheter ablation is often necessary, and anticoagulation should be administered to reduce the risk of thromboembolism. Finally, family members of patients with HCM should be regularly screened with electrocardiography and echocardiography.

Conclusions: HCM is a complex disease with heterogeneous phenotypes and clinical manifestations. The management of HCM focuses on reducing symptoms of heart failure, preventing SCD, treating atrial fibrillation, and screening family members. Treatment should be tailored to the unique characteristics of each individual patient.

Keywords: alcohol septal ablation, genetic screening, hypertrophic cardiomyopathy, implantable cardioverter-defibrillators, sudden cardiac death, surgical myectomy

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is defined by the presence of myocardial hypertrophy in the absence of systemic disease (eg, aortic stenosis, amyloidosis) capable of producing the magnitude of hypertrophy.[1] It was first described in the late 1950s by Brock and Teare. In 1990, the first mutation in a gene encoding the β-myosin heavy chain in familial HCM was identified,[2] and it is now recognized that HCM is a genetic disease of the cardiac sarcomere with an autosomal dominant pattern of inheritance. The prevalence in the adult general population is 0.2% (1:500) with approximately 600,000 affected in the United States, making HCM the most common genetic cardiovascular disease.[1]

HCM is diagnosed when echocardiography or cardiac magnetic resonance (CMR) imaging reveals unexplained left ventricular hypertrophy (LVH), usually ≥15 mm.[3] Although asymmetric septal hypertrophy is most common, there is significant heterogeneity in the degree and pattern of LVH.[4] In addition, there is considerable variability in the clinical presentation, natural history, and prognosis in patients with HCM. Although HCM disease expression usually occurs during adolescence or young adulthood, it can occur at any time as late onset disease has been described with certain gene mutations.[5,6] Although the majority of patients are asymptomatic, others are afflicted with incapacitating dyspnea or suffer sudden cardiac death, a devastating outcome in young patients.[7] This heterogeneity combined with the limited exposure of clinicians to HCM has led to controversy in managing patients with HCM.[8,9] This review focuses on the current management of patients with HCM.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The majority of patients with HCM are asymptomatic, and the diagnosis is often made incidentally or during family screening.[10] Asymptomatic patients tend to do

From the Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY. Address correspondence to A.D.E.; e-mail: adenriquez@partners.org

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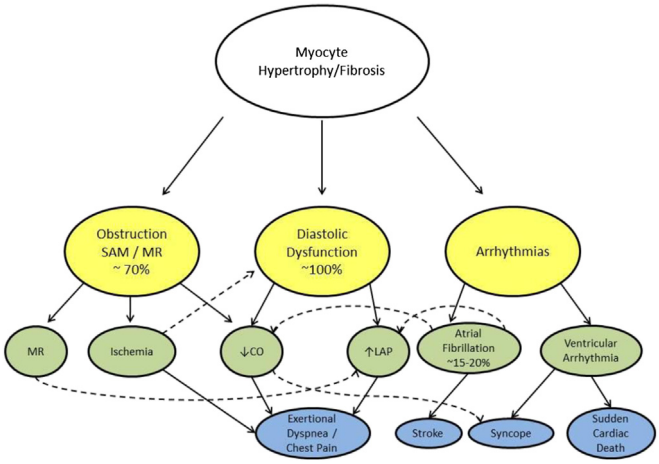

Figure 1. Pathophysiology (yellow, green) and clinical manifestations (blue) of hypertrophic cardiomyopathy. **Abbreviations**: CO, cardiac output; LAP, left atrial pressure; MR, mitral regurgitation; SAM, systolic anterior motion of the mitral valve.

very well with survival comparable to the general population.[7,11] However, up to 25% of patients will develop significant symptoms or HCM-related death.[7] Patients can present with multiple symptoms due to a complex interplay of multiple factors (Fig. 1), but there are primarily three pathways of clinical progression:

1. Heart failure with exertional dyspnea, chest pain, or a combination of the two. This is due to left ventricular outflow (LVOT) obstruction, diastolic dysfunction with restrictive physiology, or both.
2. Sudden cardiac death (SCD). Myocardial fibrosis combined with ischemia due to microvascular disease may predispose patients with HCM to ventricular tachyarrhythmias.[12,13] The incidence of SCD is ≤1% per year in the HCM population, but it is devastating as it generally occurs in asymptomatic or mildly symptomatic young patients without warning.
3. Atrial fibrillation (AF). AF develops in ~20% of patients with HCM and is associated with an increased risk for stroke, heart failure, and death.[14,15] More than 20% of these patients will suffer from thromboembolism.

MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

The management of patients with HCM is directed at control of heart failure symptoms, prevention of SCD, treatment of AF, and screening of family members. Figure 2 depicts treatment strategies for each clinical scenario in patients with HCM.

Heart Failure with LVOT Obstruction

Seventy percent of patients have dynamic LVOT obstruction at rest or provoked with exercise.[16,17] Of these patients, ~10% will progress to New York Heart Association (NYHA) class III/IV symptoms and require therapeutic intervention.[16,18]

Pharmacologic Therapy

β-Adrenergic antagonists, verapamil, and disopyramide are the mainstays of medical therapy in HCM with outflow tract obstruction.[3] These agents improve LVOT obstruction and symptoms by slowing the heart rate thereby improving left ventricular (LV) filling, decreasing myocardial oxygen demand, or through negative inotropic effects.

β-Adrenergic antagonists. It was first recognized that β-blockers are efficacious in patients with obstructive HCM in the 1960s.[19] Subsequent studies with propranolol demonstrated a reduction in outflow gradients (particularly with exercise), the alleviation of dyspnea, chest pain, palpitations, dizziness, and syncope.[20,21] β-Blockers are considered first-line therapy for the treatment of symptomatic patients with obstructive HCM.[3]

Calcium-channel blockers. Non-dihydropyridine calcium-channel blockers (CCBs) also improve symptoms in obstructive HCM. Verapamil is the most well-studied and most widely used CCB, and it decreases resting outflow gradients and improves diastolic function.[22,23] However, verapamil has vasodilatory effects, and adverse reactions such as hypotension, exacerbation of outflow gradients, and pulmonary edema have been reported.[24] Because of this, verapamil is only recommended as second-line therapy, and should be used with caution in patients with high LVOT gradients, pulmonary hypertension, or advanced heart failure.[3] Diltiazem is also used but has not been well studied.

Disopyramide. Disopyramide is a class 1a antiarrhythmic agent, and it exerts negative inotropic effects by altering Na^+-Ca^+ exchange.[25] It has been shown to alleviate resting outflow gradients and improve heart failure symptoms, perhaps to a greater degree than β-blockers.[26,27] Because disopyramide can increase atrioventricular (AV) nodal conduction leading to faster ventricular rates during