Hypertrophic Cardiomyopathy Medication

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Key points

- History of Hypertrophic cardiomyopathy (HCM)
- Introduction to HCM
- Symptoms of HCM
- Causes of hypertrophic cardiomyopathy
- Treatment of HCM
- Experiment and side effects of Mavacamten

The first modern description of hypertrophic cardiomyopathy (HCM) was provided in 1958 by Robert Teare, who published a series of cases of asymmetrical hypertrophy or muscular hamartoma of the heart in young individuals who experienced sudden cardiac death. During the early 1960s, Dr. Eugene Braunwald and his colleagues described the histological aspects, clinical presentation, and treatment of this condition. Epidemiological studies have estimated that HCM is as likely as one in 500 individuals. Moreover, it has been identified in 122 countries. Recent discoveries have shown that approximately 20 million individuals are affected by HCM each year; 10% of these cases are clinically identified, and 6% are symptomatic. Studies have shown that the majority of individuals with HCM have an ordinary or nearly normal life expectancy.1

Hypertrophic cardiomyopathy (HCM) is the most common heritable cardiovascular disorder worldwide. It's inherited as an autosomal dominant trait or can be caused by incomplete penetrance.2 HCM in simpler terms is a condition in which the heart muscle wall thickens and stiffens making it harder for the heart to pump blood to the body.4 The disease is characterized by marked variability in morphological expression as well as histopathological hallmarks, including myocyte enlargement, myocyte disarray, and myocardial

fibrosis, which can be identified using echocardiography or magnetic resonance imaging. These features can cause impaired diastolic function, left ventricular outflow tract obstruction (LVOTO), termed obstructive HCM (oHCM), and cardiac arrhythmias, leading to significant cardiac complications.1 Additionally, in obstructive HCM (oHCM) the thickened muscle also blocks blood flow from the heart to the rest of the body.4

HCM can presents itself as asymmetric septal hypertrophy or in other patterns like an apical, concentric, lateral wall and right ventricular forms.2 Symptoms of its oHCM form include exercise limitations, dyspnea, tiredness, palpations and chest pain. 4 The clinical course of this disorder varies greatly as many young individuals with HCM are asymptomatic or mildly symptomatic 2 until later in life, while some can experience complications during their childhood. Patients can suffer from either heart failure symptom 5 or their first clinical symptom can manifest as sudden cardiac death. 2 Significant insights into the genetic landscape of HCM have enhanced our understanding of molecular pathogenesis and empowered gene-based diagnostic testing to identify at-risk individuals.2

The pathology of HCM includes mutagenic variation in the sarcomere protein genes. These mutations (in sarcomere genes) can activate some signaling pathways via transcriptional activation and can influence non-cardiac cells such as fibroblasts. Additional factors, including environmental, genetic, and epigenetic can result in heterogeneous disease expression.5 Studies show that 40–50% of the myosin heads are in the 'off state'3 (also known as super-relaxed state or interacting heads motif) 6 with insignificant energy consumption in a healthy heart, however, in a heart suffering from HCM, 15–20% of the myosin heads are in this 'off state' the rest are in the 'on state'3 (also known as disordered-relaxed state)6 not only consume more energy in the form of adenosine triphosphate (ATP), but also primed to interact with actin. These effects combine to cause excess myosin–actin cross bridges during both systole and diastole which can lead to inefficient hyperdynamic contraction and diastolic dysfunction. This sustained sarcomere hyperactivity activates pro-hypertrophic, pro-inflammatory, and pro-fibrotic pathways leading to progressive myocardial remodeling, characterized by fibrosis, myofilament disarray, and elevated heart stresses.3 Because the left ventricular outflow tract obstruction (LVOTO) gradient in oHCM is dynamic, reflecting increases in obstructing or anteriorly displacing forces that can occur with fluctuations in heart rate, contractile force or loading conditions. In

contrast, in non-obstructive HCM (nHCM), the thickened heart muscle does not block blood outflow from the left ventricle, but causes impaired relaxation and diastolic dysfunction, which is the underlying basis of nHCM pathophysiology.3

Furthermore, medications for HCM include Mavacamten, an allosteric, selective, and reversible inhibitor of cardiac myosin3, the motor unit of the sarcomere. Mavacamten decreases the number of myosin heads that can bind to actin, thereby reducing the formation of cross-bridges in HCM. This shifts the overall myosin population towards an energy-sparing state. In healthy hearts, myofilaments become more sensitive to Ca2+ as cells are stretched. Mavacamten reduces the Ca2+ sensitivity of contraction. Without mavacamten, the Ca2+ sensitivity of force increased as the sarcomere length increases. This suggests that the length-dependent activation response can be maintained in the human myocardium by mavacamten. There were subtle effects of mavacamten on reducing force values under relaxed conditions, as well as slowing myosin cross-bridge recruitment and speeding cross-bridge detachment.6

In preclinical studies, mavacamten decreases overall ATP breakdown at the sarcomere level, reduces diastolic tensions, and promotes relaxation. As a result of these direct, salutary diastolic, systolic, and energy-sparing attributes, mavacamten increases the ventricular chamber size and reduces the velocity of myocardial contraction. This reduces anteriorly displacing forces that aid systolic anterior motion (SAM) therefore creating an optimal intraventricular mechanical environment to reduce LVOT obstruction.3 Mavacamten directly targets the cardiac sarcomere and restores its organization and function to a natural state. This allows us to confirm the role of the sarcomere and to refine our understanding of the pathology of HCM.3

In the experiment, EXPLORER-HCM trial, mavacamten was compared to placebo which is a pill with no medicinal or active substances in symptomatic people with oHCM. The study showed that mavacamten reduced the obstruction that restricts blood flow and improved symptoms, overall health, and ability to partake in the daily activities. However, side effects such as irregular heartbeat, palpitations, rapid heartbeat, and heart failure were observed in individuals who had taken either mavacamten or the placebo.4

In conclusion, Drugs that modulate myofilament function may be helpful for individuals suffering from cardiomyopathies. Moreover, a mechanosensitive thick-filament regulatory mechanism has also been discovered, by which myosin heads transition between 'off' and 'on states'. Heads in the 'off state' are unable to bind actin.6 Patients with oHCM are currently prescribed negative chronotropes (increases heart rate) and inotropes (decreases heart rate). Invasive therapies like alcohol septal ablation or myectomy can alleviate structural obstruction.3

References:

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