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Physiological and Pathological Hypertrophic Cardiomyopathy

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) refers to the abnormal thickening of the heart muscle, primarily affecting the left ventricle, and can occur due to both physiological and pathological causes. Physiological hypertrophy is an adaptive, reversible response to increased physical demand, as seen in athletes or pregnancy. It is characterized by proportional thickening of the ventricular walls, increased chamber size, and enhanced cardiac function, without fibrosis or myocyte disarray. This form of hypertrophy is beneficial and reversible when the increased workload is reduced, posing minimal health risks.In contrast, pathological hypertrophy arises due to genetic mutations or chronic conditions such as hypertension and hypertrophic cardiomyopathy. It often results in asymmetric thickening, particularly of the interventricular septum, and can lead to left ventricular outflow tract obstruction (LVOTO). Pathological hypertrophy is accompanied by fibrosis, myocyte disarray, and impaired diastolic function, which can progress to heart failure, arrhythmias, or sudden cardiac death. Unlike physiological hypertrophy, pathological forms are typically irreversible and associated with significant morbidity and mortality. The Physiological hypertrophy enhances cardiac performance and is reversible, pathological hypertrophy leads to adverse outcomes and requires medical intervention. Differentiating between these forms is particularly important in athletes and individuals with a family history of heart disease to prevent potential complications.

KEYWORDS: Hypertrophic cardiomyopathy, Mavacamten, Physiological hypertrophy, Pathological hypertrophy, Beta blockers, Endocarditis

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic heart disorder characterized by the abnormal thickening (hypertrophy) of the heart muscle, primarily affecting the left ventricle[1]. Unlike other forms of heart enlargement caused by factors like high blood pressure or valve disease, HCM occurs independently of such conditions and is often the result of mutations in genes responsible for heart muscle proteins[2].

The thickened heart muscle in HCM can lead to a variety of complications, including obstruction of blood flow from the heart, impaired relaxation and filling of the heart, and increased risk of arrhythmias (irregular heartbeats). In some cases, this can result in symptoms like chest pain, shortness of breath, dizziness, or even sudden cardiac death, particularly in young athletes[3].

HCM is one of the most common inherited heart diseases, with a prevalence of about 1 in 500 people worldwide. It is highly variable in its presentation, ranging from asymptomatic individuals to those with severe heart failure[4]. Understanding HCM is crucial, as early detection and management can significantly improve outcomes and reduce the risk of life-threatening complications.

SIGNS AND SYMPTOMS

Hypertrophic cardiomyopathy (HCM) presents with a range of signs and symptoms, which can vary greatly among individuals. Some people with HCM might not experience any symptoms, while others may develop severe manifestations[5]. Common signs and symptoms include: Shortness of Breath (Dyspnea) , Chest Pain (Angina), Palpitations, Dizziness, Fainting, Fatigue, Swelling (Edema)[6].

EPIDEMIOLOGY

Hypertrophic cardiomyopathy (HCM) is one of the most common genetic heart diseases, with a prevalence estimated to be about 1 in 500 individuals in the general population, which equates to roughly 0.2%. This makes HCM the most frequently occurring inherited cardiomyopathy, affecting people of all ages, genders, and ethnicities[7].

Key Epidemiological Aspects:

1. **Genetics:** HCM is often inherited in an autosomal dominant manner, meaning a child has a 50% chance of inheriting the condition if one parent has it. More than 1,500 mutations in genes encoding heart muscle proteins have been associated with HCM, making the genetic profile quite diverse.
2. **Age of Onset**: Although HCM can be diagnosed at any age, it often becomes apparent during adolescence or early adulthood. Some individuals may be asymptomatic until much later in life, while others might experience symptoms as early as childhood[8].
3. **Gender Distribution**: HCM affects both men and women, though studies have shown that men are diagnosed more frequently, possibly due to more pronounced symptoms or higher engagement in physical activities that trigger symptom onset.
4. **Ethnicity:** HCM occurs across all ethnicities; however, studies suggest that certain populations, such as African Americans, may have a higher risk of developing more severe forms of the disease or experiencing worse outcomes[9].
5. **Mortality and Morbidity**: While many individuals with HCM live normal lives, it is a leading cause of sudden cardiac death, especially among young athletes. However, advances in early detection, medical management, and lifestyle modifications have improved survival rates[10].

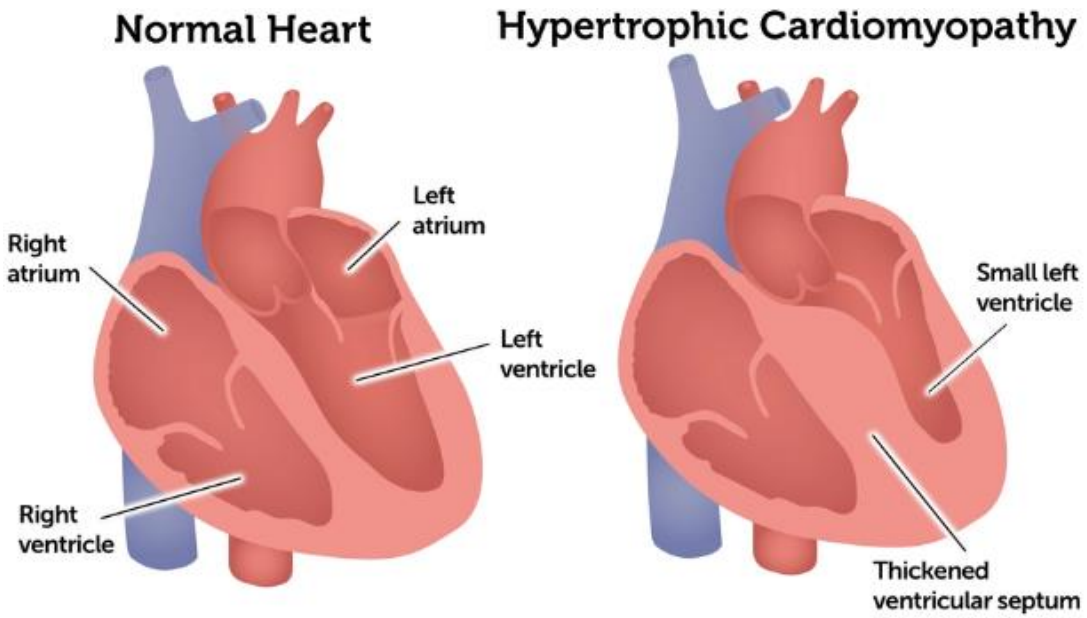

Fig no:1 Normal heart vs Hypertrophic cardiomyopathy

COMPLICATIONS

Hypertrophic cardiomyopathy can cause many complications, including abnormal heartbeat, stroke, heart failure, and sudden cardiac arrest.

1. **Arrhythmia:** Arrhythmias, abnormal heart rhythms, are a common complication of HCM. Several types of arrhythmia affect heart rate and heart function. Atrial fibrillation (AFib) is the most common arrhythmia that people with HCM may develop[11]. Heart palpitations, Irregular heartbeat, Shortness of breath, Lightheadedness, Fatigue ,Chest pain
2. **Mitral Valve Disease :** HCM can affect the heart's mitral valve, which allows blood to flow from the left atrium into the left ventricle. HCM may cause abnormalities in the mitral valve that allow blood flow to move backward into the left atrium. Mitral valve disease can cause a heart murmur without any symptoms, or it can cause fatigue, shortness of breath, and an irregular heartbeat. If your disease is severe, you may need surgery or a heart valve replacement[12].
3. **Infective Endocarditis:** Infective endocarditis (IE) is an infection of the lining of the heart, usually the heart valves. HCM affects the mitral valve, putting people with HCM at higher risk of IE of the mitral valve. IE can cause fever and symptoms of infection[13], along with chest pain and shortness of breath. Intravenous antibiotics are medicines delivered directly into a vein, can effectively treat IE.
4. **Heart Failure:** HCM rarely leads to heart failure, a condition that happens when damage to the heart makes it unable to provide oxygen-rich blood to the body. Heart failure can make you feel tired, short of breath, and have trouble breathing. It can also cause a cough, swelling in your legs, arrhythmia, and other symptoms. Heart failure can be deadly, but it can often be managed by medication, surgery, or an implantable cardioverter defibrillator. Some people may need a heart transplant[14].
5. **Dilated Cardiomyopathy:** Dilated cardiomyopathy, causes the heart's ventricles to stretch out, making the chambers weak. This condition can make it harder for your heart to pump blood throughout your body.

6. **Sudden Cardiac Death:** Sudden cardiac death (SCD) — also called sudden cardiac arrest — rarely happens with HCM. However, some people with HCM are at higher risk. SCD can occur in young people — usually athletes — and in adults. Even if HCM is not causing any noticeable symptoms, it can increase the risk of SCD[15].

DIAGNOSIS

Echocardiogram is the test usually used to make a diagnosis. An echocardiogram often is used to diagnose hypertrophic cardiomyopathy. Sound waves are used to create images of the beating heart. This test shows how well the heart's chambers and valves are pumping blood.

Other commonly used diagnostic tests include:

Cardiac magnetic resonance imaging (MRI) uses radio waves and strong magnets to create pictures of your heart and show how it's working.

Electrocardiogram (ECG) This quick and painless test measures the electrical activity of the heart. Sticky patches called electrodes are placed on the chest and sometimes the arms and legs. Wires connect the electrodes to a computer, which prints or displays the test results. An ECG can show irregular heartbeats and signs of heart thickening[16].

Holter monitor This small, portable ECG device records the heart's activity. It's worn for a day or two while you do your regular activities.

Cardiac CT scan Rarely, this test is done to diagnose hypertrophic cardiomyopathy. But it may be suggested if an MRI can't be used. A cardiac CT scan uses X-rays to make pictures of the heart and chest. It can show the size of the heart.

Stress test A stress test often involves walking on a treadmill or riding a stationary bike while the heart is monitored. Exercise stress tests help reveal how the heart responds to physical activity.

Cardiac MRI This test uses powerful magnets and radio waves to create images of the heart. It provides information about the heart muscle and how the heart and heart valves work[17]. This test often is done with an echocardiogram.

TREATMENT

Part of treatment will include helping you adopt a heart-healthy lifestyle by getting good nutrition and appropriate exercise. Medication, surgical and nonsurgical procedures, and implantable devices are available, as well based on their needs. Several medicines, including beta blockers and calcium channel blockers, can reduce HCM symptoms.

Mavacamten is a newer medicine approved by the Food and Drug Administration to treat HCM in select patients. It works by regulating how hard the heart pumps and has been shown to prevent the need for future surgeries. This medication is restricted to specialized cardiologists and is not widely available outside HCM clinics[18].

Beta blockers such as metoprolol, propranolol, atenolol.

Calcium channel blockers such as verapamil, diltiazem.

Heart rhythm medicines such as amiodarone, disopyramide.

Blood thinners such as warfarin, dabigatran, rivaroxaban. Blood thinners can help prevent blood clots if you have atrial fibrillation or the apical type of hypertrophic cardiomyopathy. Apical HCM can raise the risk of sudden cardiac death[19].

Surgery and other Procedures are available to treat cardiomyopathy or its symptoms. They include:

Septal myectomy This open-heart surgery might be recommended if medicines don't improve symptoms. It involves removing part of the thickened, overgrown wall between the heart chambers. This wall is called the septum. Septal myectomy helps improve blood flow out of the heart. It also reduces backward flow of blood through the mitral valve[20].

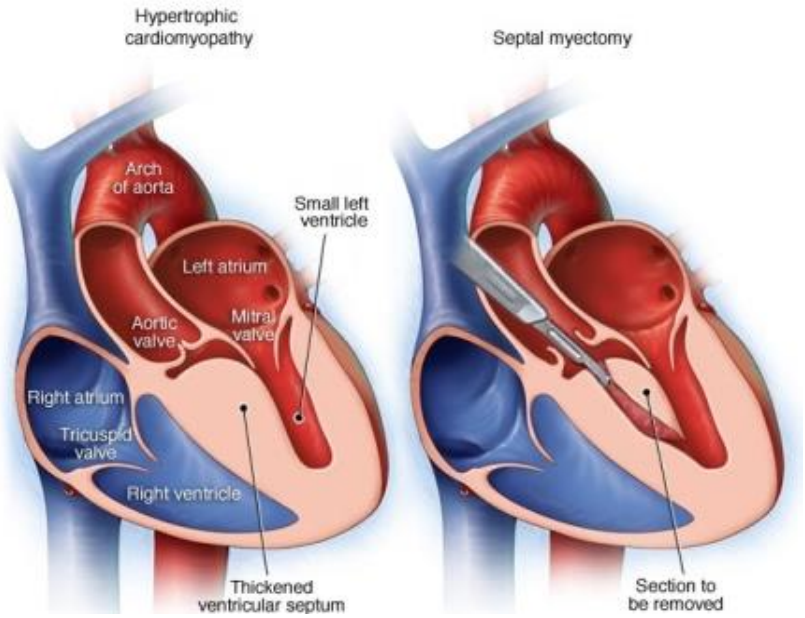

Fig no:2 Septal myectomy

The surgery can be done using different approaches, depending on the location of the thickened heart muscle. In one type, called **Apical myectomy**, surgeons remove thickened heart muscle from near the tip of the heart. Sometimes the mitral valve is repaired at the same time.

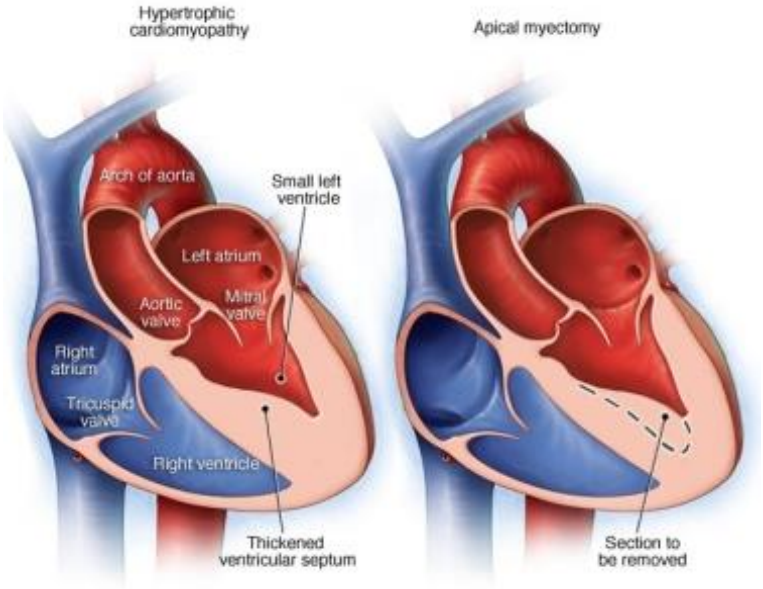

Fig no:3 Apical myectomy

Septal ablation This procedure use alcohol to shrink the thickened heart muscle. A long, thin tube called a catheter is placed into an artery that supplies blood to the affected area. Alcohol flows through

the tube. Changes in the heart's electrical signaling system, also called a heart block, is one complication. A heart block must be treated with a pacemaker. The small device is placed in the chest to help control the heartbeat.

Implantable cardioverter-defibrillator (ICD) This device is placed under the skin near the collarbone. It continuously checks the heart rhythm. If the device finds an irregular heartbeat, it sends out low- or high-energy shocks to reset the heart's rhythm. Use of an ICD has been shown to help prevent sudden cardiac death, which occurs in a small number of people with hypertrophic cardiomyopathy.

Cardiac resynchronization therapy (CRT) device Rarely, this implanted device is used as a treatment for hypertrophic cardiomyopathy. It can help the chambers of the heart squeeze in a way that's more organized and efficient[20].

Ventricular assist device (VAD) This implanted device also is rarely used to treat hypertrophic cardiomyopathy. It helps blood flow through the heart.

Heart transplant This is surgery to replace a diseased heart with a donor's healthy heart. It can be a treatment option for end-stage heart failure when medicines and other treatments no longer work.

Types of Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) has several subtypes, which are classified based on the pattern and location of the thickened heart muscle. The main types include:

1.Asymmetric Septal Hypertrophy (ASH)

The most common type, where the thickening occurs predominantly in the interventricular septum (the wall separating the left and right ventricles). This often leads to obstruction of blood flow from the left ventricle. This type is often associated with symptoms like shortness of breath, chest pain, and fainting, especially during exertion

2. Apical Hypertrophic Cardiomyopathy

In this subtype, the thickening occurs mainly at the apex (tip) of the heart. It is more prevalent in certain populations, such as in Japan. Patients may present with symptoms similar to other types, though some remain asymptomatic for long periods.

3. Midventricular Hypertrophy

In this type, the thickening occurs in the mid-portion of the left ventricle, sometimes leading to a narrowed or "hourglass-shaped" chamber. This type can result in the formation of an apical aneurysm and carries a risk of arrhythmias and thromboembolism[21].

4. Concentric Hypertrophic Cardiomyopathy

This rarer form involves uniform thickening of the entire left ventricle, leading to reduced chamber size. Patients may experience symptoms like fatigue, shortness of breath, and exercise intolerance due to impaired heart function.

5. Non-Obstructive Hypertrophic Cardiomyopathy

In this form, there is no significant obstruction to blood flow out of the left ventricle despite the thickening. The thickened muscle doesn't interfere with blood ejection but still affects heart function. Patients may still experience symptoms such as chest pain, palpitations, or shortness of breath, although some may remain asymptomatic

6. Obstructive Hypertrophic Cardiomyopathy (oHCM) is a subtype of hypertrophic cardiomyopathy characterized by the obstruction of blood flow from the left ventricle to the aorta due to the thickening of the heart muscle, particularly the interventricular septum. This obstruction can lead to significant clinical

implications and symptoms for affected individuals. Common symptoms of oHCM include: Shortness of Breath (Dyspnea), Chest Pain (Angina), Syncope: Fainting spells, Palpitations[22].

Lifestyle and home remedies

Lifestyle changes can lower the risk of complications related to hypertrophic cardiomyopathy. Exercise, Eat a healthy diet, Don't smoke. Stay at a healthy weight, Limit or stay away from alcohol. Control blood pressure and cholesterol, Get regular health checkups, Practice good sleep habits.

Hypertrophic cardiomyopathy encompasses both physiological and pathological forms, with significant differences in their underlying mechanisms, clinical manifestations, and outcomes. Physiological hypertrophy is a benign and reversible adaptation to increased workload, while pathological hypertrophy is a genetic disorder associated with severe complications such as heart failure and sudden cardiac death.

1. PHYSIOLOGICAL HYPERTROPHIC CARDIOMYOPATHY

Physiological hypertrophy is an adaptive and reversible form of heart muscle enlargement that typically occurs in response to increased workload or demand, such as regular exercise or pregnancy. This type of hypertrophy is commonly seen in athletes, where the heart adapts to sustained physical training by increasing the size of cardiac muscle fibers, thus enhancing the heart's ability to pump blood[23].

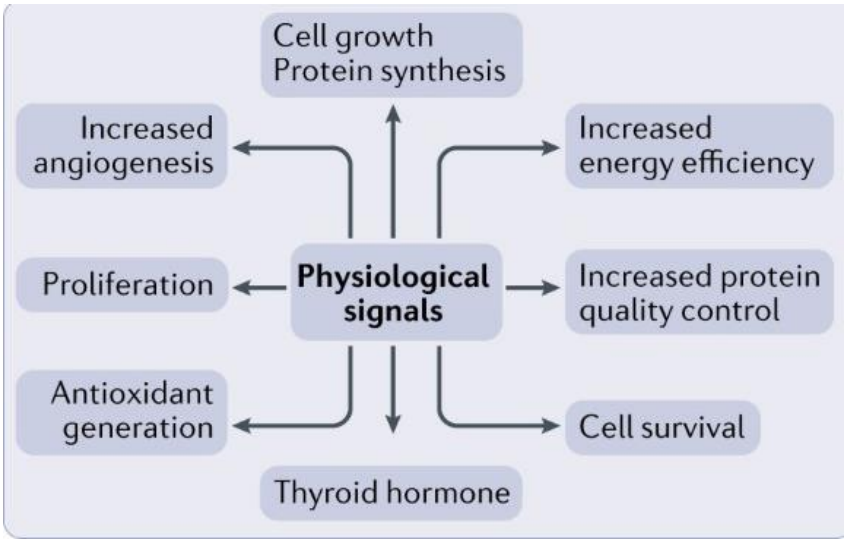

Fig no:4 Physiological hypertrophy

Mechanism

Physiological hypertrophy occurs as a response to increased cardiac demand, driven primarily by hemodynamic stimuli such as volume or pressure overload. Exercise induces a state where the heart needs to pump more blood to meet the increased oxygen demand of muscles, leading to an increase in cardiac output. To accommodate this, the heart adapts by growing larger and more efficient, a process regulated by growth factors and mechanical stress on the cardiac muscle fibers.

The heart's response to these stimuli involves the activation of signaling pathways like the insulin-like growth factor-1 (IGF-1) and Akt pathways. These pathways stimulate cardiomyocyte growth, but without the fibrotic or necrotic changes typically associated with pathological hypertrophy. Furthermore, physiological hypertrophy maintains normal or even enhanced cardiac function, allowing athletes to sustain higher levels of physical performance.

In physiological hypertrophy, the wall thickening is typically symmetrical and proportional to the increased chamber size, ensuring adequate ventricular filling and systolic function. Moreover, this adaptation is reversible; if the increased workload (such as exercise) ceases, the heart can return to its normal size and function without permanent structural changes[24].

Features of Physiological Hypertrophy

Proportional Chamber Enlargement: The increase in left ventricular wall thickness is accompanied by a proportional increase in chamber size, allowing for sustained normal diastolic function.

Enhanced Cardiac Function: Physiological hypertrophy often results in better cardiac performance, with an increased stroke volume and improved ventricular function.

Reversibility: The hypertrophic changes are reversible if the stimulus (such as intense athletic training) is removed.

Absence of Fibrosis: Physiological hypertrophy is not accompanied by the fibrosis or scar tissue formation that is seen in pathological conditions.

Normal Genetic Basis: Unlike pathological HCM, which is often inherited, physiological hypertrophy is typically not associated with genetic mutations[25].

2. PATHOLOGICAL HYPERTROPHIC CARDIOMYOPATHY

Pathological hypertrophic cardiomyopathy, on the other hand, is a genetic disorder that leads to asymmetric thickening of the heart muscle, particularly the interventricular septum, which can impair the heart's ability to pump blood effectively. It is one of the most common causes of sudden cardiac death, particularly in young athletes.

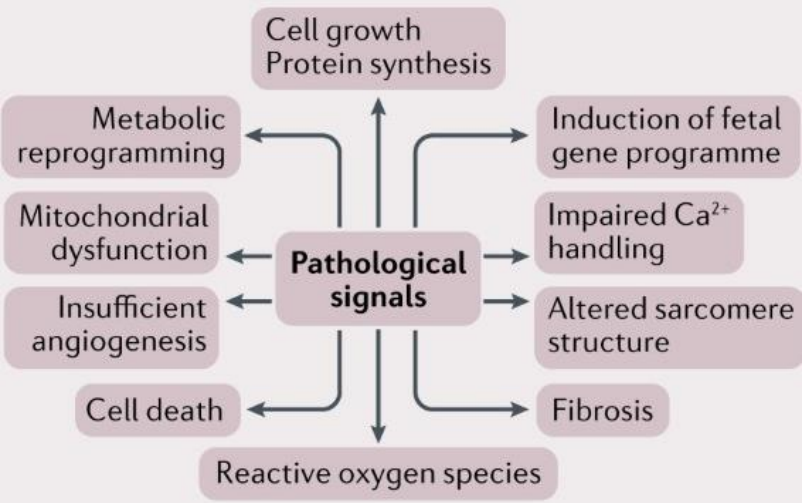

Fig no:5 Pathological hypertrophy

Mechanism

Pathological HCM is primarily caused by mutations in genes encoding proteins of the cardiac sarcomere, such as β-myosin heavy chain, myosin-binding protein C, and troponin. These genetic abnormalities lead to altered myocyte function and impaired force generation, which results in inappropriate growth of cardiac muscle fibers. The heart responds by thickening its walls, but unlike physiological hypertrophy, this adaptation is maladaptive and can lead to clinical complications.

The hypertrophy in pathological HCM is typically asymmetric, with disproportionate thickening of the septum compared to the left ventricular free wall. This abnormal geometry can obstruct blood flow from the left ventricle into the aorta, known as left ventricular outflow tract obstruction (LVOTO), which can result in symptoms like chest pain, dyspnea, syncope, and increased risk of sudden cardiac death.
Pathological hypertrophy also triggers secondary changes in the heart, including fibrosis, disarray of muscle fibers, and small vessel disease. These alterations contribute to increased ventricular stiffness, impaired relaxation, and diastolic dysfunction, as well as arrhythmias, which can be life-threatening[26].

Features of Pathological Hypertrophy

Asymmetric Thickening: The hypertrophy in pathological HCM is usually localized, most often affecting the interventricular septum. This can result in left ventricular outflow tract obstruction.
Impaired Diastolic Function: The thickened heart muscle becomes stiff, leading to impaired relaxation and filling of the left ventricle, which can cause diastolic dysfunction and symptoms of heart failure.
Fibrosis and Myocyte Disarray: Unlike physiological hypertrophy, pathological HCM involves fibrosis and disarray of myocytes, which contributes to arrhythmias and structural abnormalities.
Genetic Predisposition: Pathological HCM is inherited in an autosomal dominant manner and is caused by mutations in sarcomeric proteins. Family history is a key risk factor for developing the disease.
Irreversible Changes: The hypertrophy in pathological HCM is not reversible and often progresses, leading to complications such as heart failure, arrhythmias, and sudden cardiac death.
Increased Risk of Sudden Cardiac Death: One of the most feared complications of pathological HCM is sudden cardiac death, particularly in young individuals and athletes.

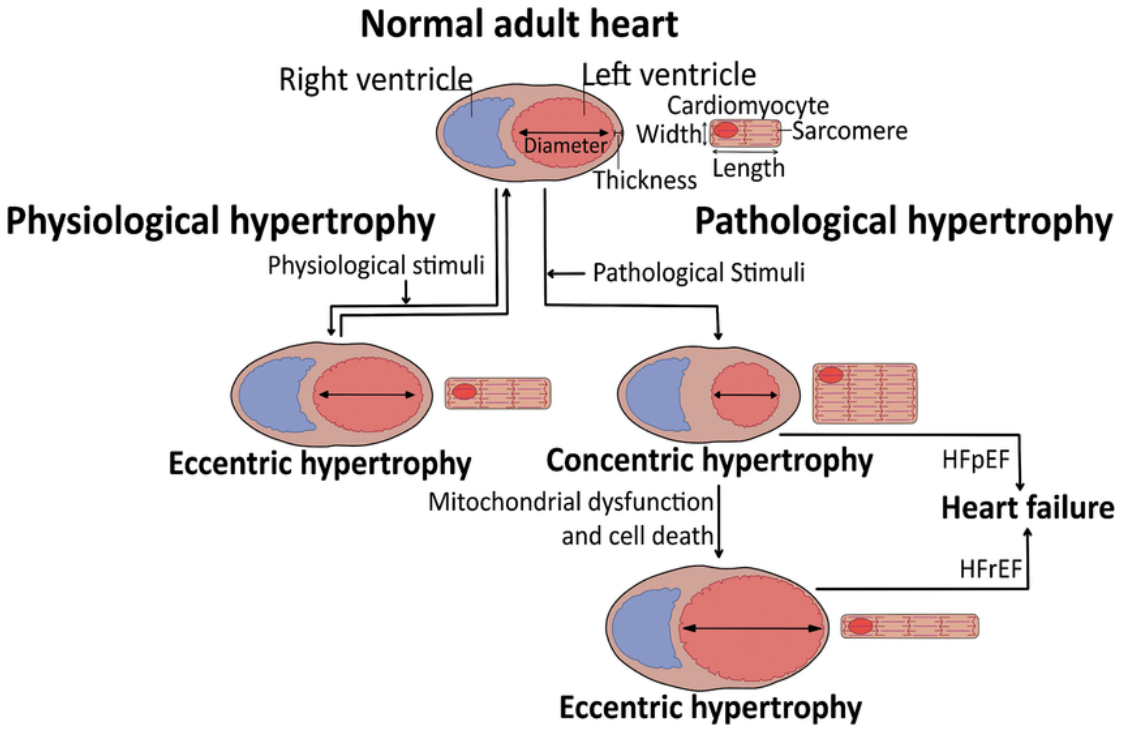

Fig no: 6 Overview of Physiological and Pathological Hypertrophy

CONCLUSION

Hypertrophic cardiomyopathy (HCM) is a complex condition that manifests as abnormal thickening of

the heart muscle, primarily affecting the left ventricle. This thickening can result from either physiological or pathological causes, with significant differences in outcomes. Physiological hypertrophy is a beneficial and adaptive response to increased physical demands, such as intense exercise or pregnancy, and is reversible when the stimulus is removed. It enhances cardiac performance without causing structural or functional harm. On the other hand, pathological hypertrophy, often seen in conditions such as hypertrophic cardiomyopathy and chronic hypertension, is characterized by asymmetric thickening, fibrosis, and myocyte disarray. This form of hypertrophy is associated with adverse clinical outcomes, including diastolic dysfunction, arrhythmias, and an increased risk of sudden cardiac death. Pathological hypertrophy is typically irreversible and progressive, requiring medical intervention to manage symptoms and prevent complications. The ability to differentiate between physiological and pathological hypertrophy is crucial for patient care, particularly in athletes and those with a family history of HCM, where early detection can prevent life-threatening events.

Advances in genetic testing, imaging techniques, and personalized medicine offer new opportunities for early diagnosis and tailored treatment strategies. Understanding the underlying mechanisms of HCM is vital for improving outcomes, as timely intervention can mitigate risks and enhance quality of life for affected individuals.

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