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Cardiac Hypertrophy: A Comprehensive Review from Molecular Mechanisms to Clinical Management

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ABSTRACT:

Cardiac hypertrophy, an increase in myocardial mass, represents an adaptive response to physiological or pathological stress. While physiological hypertrophy as seen in endurance-trained individuals is reversible and preserves cardiac function, pathological hypertrophy is characterized by maladaptive structural remodeling that predisposes to heart failure, arrhythmias, and sudden cardiac death. The divergent outcomes between these two forms stem from distinct molecular mechanisms and signaling pathways, including G-protein coupled receptors, mitogen-activated protein kinases (MAPKs), calcium-calcineurin signaling, and the PI3K/Akt axis. Pathological hypertrophy is often associated with fibrosis, oxidative stress, mitochondrial dysfunction, and reactivation of fetal gene programs. Advances in cardiac imaging, biomarker profiling, and genetic testing have improved diagnostic precision, while contemporary pharmacologic and device-based therapies have broadened treatment options. Emerging strategies including cardiac myosin inhibitors, gene-targeted therapies, and stem cell approaches offer promise for individualized and disease-modifying interventions. This review synthesizes current understanding of cardiac hypertrophy across molecular, diagnostic, and therapeutic domains and underscores future directions in precision medicine and regenerative therapies.

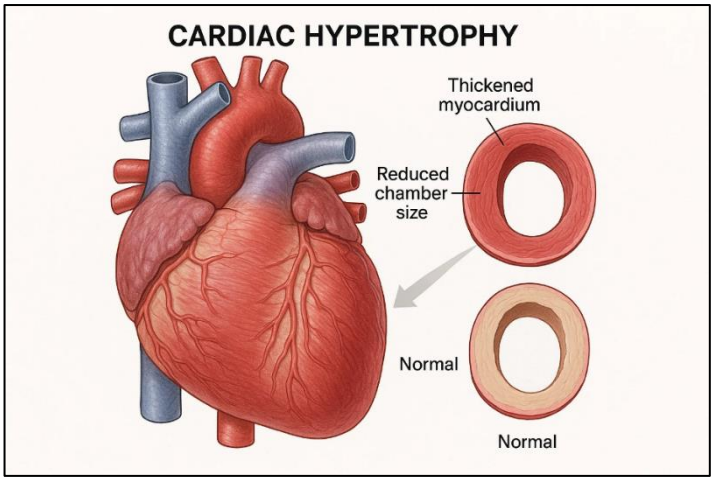
KEYWORDS: Cardiac hypertrophy, Signaling pathways; Fibrosis, Pressure overload, Therapeutic targets.

INTRODUCTION:

Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide, imposing a substantial burden on global public health. Among the myriads of cardiovascular pathologies, cardiac hypertrophy stands as a central and often insidious precursor to more severe conditions, particularly heart failure. Cardiac hypertrophy is fundamentally defined as an abnormal increase in the size of myocardial cells (cardiomyocytes), leading to an overall increase in heart muscle mass. This compensatory response is initially aimed at normalizing wall stress and maintaining cardiac output in the face of increased workload. However, the nature of this adaptation dictates its long-term outcome, distinguishing between a beneficial, physiological form and a detrimental, pathological form.

Physiological hypertrophy, exemplified by the "athlete's heart," is a reversible and adaptive process that enhances cardiac function without compromising myocardial integrity. In stark contrast, pathological hypertrophy, triggered by chronic stressors such as sustained hypertension, valvular heart disease, or underlying genetic mutations, is a maladaptive remodeling process. This pathological remodeling is characterized by structural disarray, increased

Figure 1. Structural Changes in Cardiac Hypertrophy



myocardial stiffness, fibrosis, and ultimately, a decline in contractile function, culminating in overt heart failure, arrhythmias, and an elevated risk of sudden cardiac death.

The purpose of this review is to synthesize recent advances in our understanding of cardiac hypertrophy. We will delve into the distinct characteristics of physiological and pathological hypertrophy, explore the intricate molecular and cellular mechanisms that govern these processes, discuss the latest diagnostic tools, and outline current and emerging therapeutic strategies. Furthermore, we will highlight future directions in research, including the promise of precision medicine and the identification of novel therapeutic targets, to address the ongoing challenges in preventing and treating this critical cardiac condition.

2. TYPES OF CARDIAC HYPERTROPHY

Cardiac hypertrophy is broadly categorized into two main types based on its underlying stimuli, structural characteristics, and functional outcomes: physiological and pathological. Understanding this distinction is crucial for both diagnosis and therapeutic intervention.

2.1. Physiological Hypertrophy

Physiological hypertrophy represents an adaptive and beneficial response of the heart to sustained increases in workload, most commonly observed in individuals undergoing chronic endurance or resistance training. This phenomenon is often referred to as "athlete's heart." It is an adaptive increase in heart muscle mass that occurs in response to regular, sustained physical activity, leading to enhanced cardiac performance. Physiological hypertrophy is characterized by a symmetrical increase in ventricular wall thickness and chamber size, maintaining a normal or even enhanced cardiac function. Crucially, it preserves myocardial contractility and relaxation properties. Histologically, it is distinguished by organized myocyte growth, increased angiogenesis (formation of new blood vessels), and the absence of interstitial fibrosis or cellular disarray. The primary stimulus is chronic endurance or resistance training, which imposes a sustained, balanced increase in both pressure and volume load on the heart. Distinct signaling pathways are activated in physiological hypertrophy, notably the Phosphoinositide 3-Kinase (PI3K)/Akt pathway. This pathway promotes protein synthesis and cell survival, contributing to healthy myocyte growth without inducing pathological remodeling. A hallmark of physiological hypertrophy is its reversibility; the heart typically regresses to its pre-training size and function upon cessation of regular intense exercise.

2.2. Pathological Hypertrophy

Pathological hypertrophy is a maladaptive response of the heart to chronic pathological stressors. Unlike its physiological counterpart, this form of hypertrophy is detrimental and often progresses to cardiac dysfunction and heart failure. It is a maladaptive increase in heart muscle mass triggered by chronic pathological conditions that impose excessive stress on the myocardium. Pathological hypertrophy typically involves asymmetrical growth, often leading to a disproportionate increase in wall thickness relative to chamber size (concentric hypertrophy, e.g., in pressure overload) or chamber dilation with some wall thickening (eccentric hypertrophy, e.g., in volume overload). It is associated with impaired cardiac function, increased myocardial stiffness, reduced compliance, and significant histological changes including myocyte disorganization, apoptosis, and extensive interstitial fibrosis. These changes collectively impair the heart's ability to pump and fill effectively. Chronic conditions that increase the resistance against which the heart must pump blood, such as systemic hypertension (high blood pressure) and aortic stenosis (narrowing of the aortic valve). This typically leads to concentric hypertrophy. Conditions that increase the amount of blood the heart must pump, such as valvular regurgitation (leaky heart valves) or shunts (abnormal blood flow pathways). This often results in eccentric hypertrophy. Hypertrophic Cardiomyopathy (HCM) is a prominent example of pathological hypertrophy caused by inherited genetic mutations. The most common mutations affect genes encoding sarcomeric proteins (e.g., β-myosin heavy chain, myosin-binding protein C), which are essential components of the heart's contractile machinery. Pathological hypertrophy is driven by the activation of distinct signaling pathways compared to physiological hypertrophy. Key pathways include G-protein Coupled Receptors (GPCRs) (e.g., activated by angiotensin II, endothelin-1, catecholamines), Mitogen-Activated Protein Kinase (MAPK) pathways (e.g., ERK, JNK, p38), and the calcium-dependent calcineurin/NFAT pathway. These pathways promote pathological gene expression patterns and cellular remodeling. Pathological hypertrophy is often progressive and, if the underlying stress is not alleviated, can lead to ventricular dilation, systolic dysfunction, and ultimately decompensated heart failure, which is typically irreversible without aggressive intervention.

3. MOLECULAR AND CELLULAR MECHANISMS OF CARDIAC HYPERTROPHY

The development and progression of cardiac hypertrophy, particularly its pathological form, are governed by a complex interplay of molecular and cellular events. These mechanisms involve intricate signaling networks, altered gene expression, and profound changes in cellular structure and function.

3.1. Signaling Pathways

Various signaling pathways act as critical transducers of hypertrophic stimuli, leading to changes in cardiomyocyte size and function.

- **G-protein Coupled Receptors (GPCRs):** Activation of GPCRs by neurohumoral factors plays a pivotal role. Angiotensin II (via AT1 receptors), Endothelin-1 (via ETA receptors), and catecholamines (via α1-adrenergic receptors) all activate GPCRs, initiating downstream signaling cascades that promote cardiomyocyte growth and pathological remodeling.

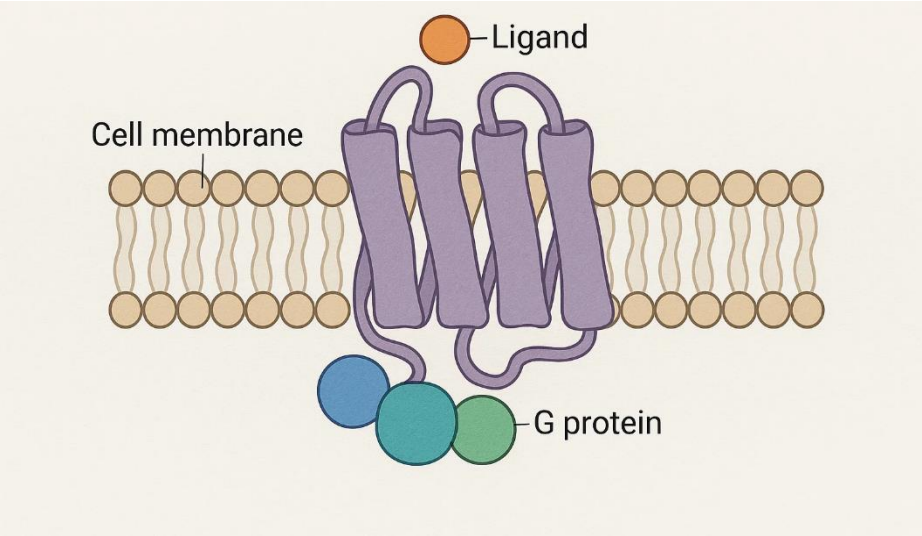


Fig 2. G-protein Coupled Receptors (GPCRs)

- **MAP Kinase Pathways:** The Mitogen-Activated Protein Kinase (MAPK) family, including Extracellular signal-Regulated Kinase (ERK), c-Jun N-terminal Kinase (JNK), and p38 MAPK, are crucial mediators. While ERK activation is often associated with both physiological and pathological hypertrophy, JNK and p38 are more strongly implicated in stress-induced pathological remodeling, apoptosis, and fibrosis.

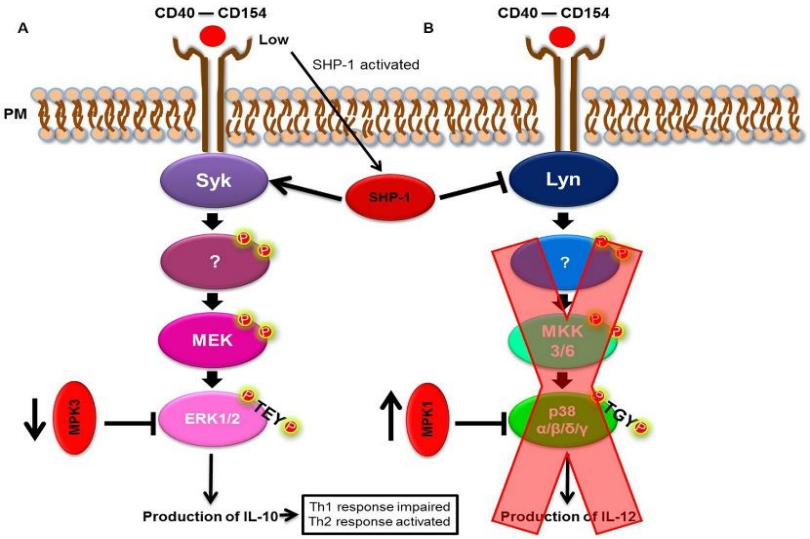
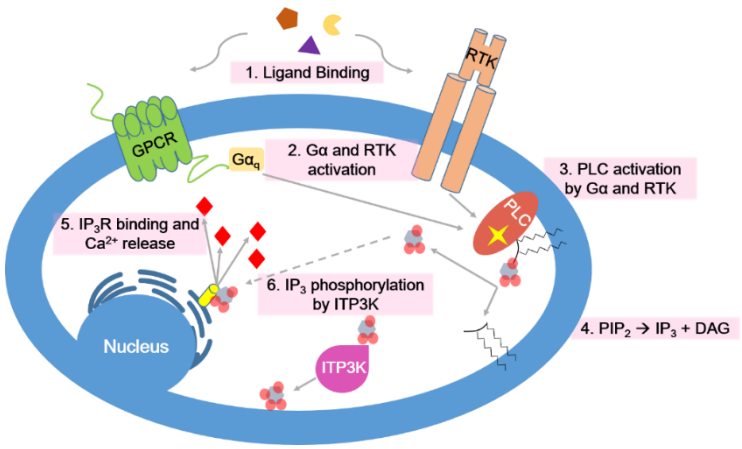


Fig 3. MAP Kinase Pathways

Calcium-Dependent Signaling: Intracellular calcium homeostasis is fundamental to cardiac function, and its dysregulation contributes to hypertrophy. The calcineurin/NFAT (Nuclear Factor of Activated T-cells) pathway is a key calcium-dependent signaling cascade. Sustained increases in intracellular calcium activate calcineurin, a phosphatase, which dephosphorylates NFAT, allowing its translocation to the nucleus to activate pro-hypertrophic gene expression.

Fig 4. Calcium-Dependent Signaling Pathway



- **PI3K/Akt/mTOR Pathway:** The Phosphoinositide 3-Kinase (PI3K)/Akt/mTOR (mammalian Target of Rapamycin) pathway holds a dual role. In physiological hypertrophy, activation of the PI3K/Akt arm is crucial for adaptive growth and protein synthesis. However, in pathological settings, dysregulation or sustained activation of certain components of this pathway can contribute to maladaptive remodeling.

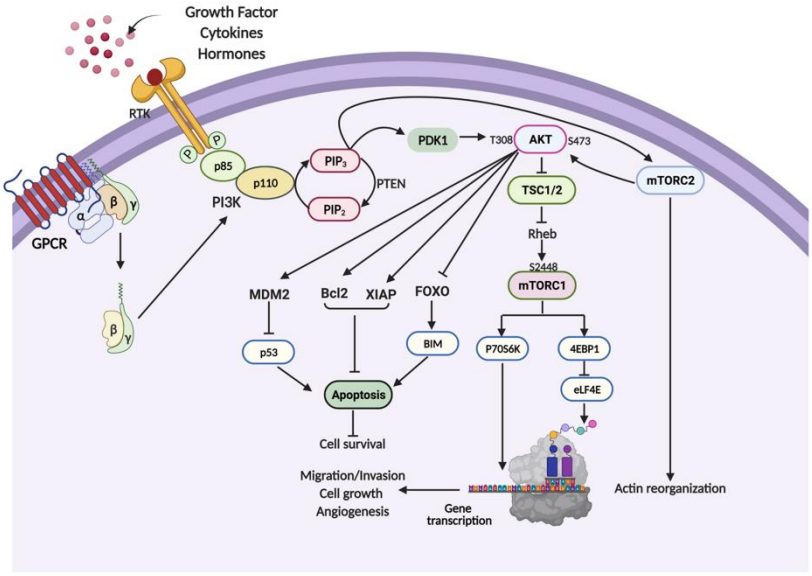


Fig 5. PI3K/Akt/mTOR Pathway

- **Other Pathways:** Emerging research highlights the involvement of other pathways, such as the Hippo pathway (regulating organ size and cell proliferation), Wnt signaling (involved in cell growth and differentiation), and Notch signaling (critical for cell fate determination and development), all of which contribute to the intricate network controlling cardiac hypertrophy.

3.2. Gene Expression and Transcriptional Regulation

Hypertrophic stimuli induce profound changes in gene expression, leading to the "fetal gene program" reactivation and altered protein synthesis.

- **Reactivation of Fetal Gene Program:** A hallmark of pathological hypertrophy is the re-expression of genes typically active during embryonic development but silenced in the adult heart. This includes the upregulation of Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) – important biomarkers of cardiac stress – and the switch from α-Myosin Heavy Chain (α-MHC) to β-Myosin Heavy Chain (β-MHC). β-MHC has slower ATPase activity, which is less energy-efficient but more force-generating, a characteristic of the fetal heart.
- **Transcription Factors:** Key transcription factors orchestrate these gene expression changes. GATA4, Myocyte Enhancer Factor 2 (MEF2), NFAT, and Serum Response Factor (SRF) are among the most studied, acting as master regulators of cardiac gene expression in response to hypertrophic signals.
- **Epigenetic Modifications:** Beyond direct transcriptional regulation, epigenetic modifications play a significant role. These include histone modifications (e.g., acetylation, methylation), DNA methylation, and the regulation by non-coding RNAs, particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs). These epigenetic changes can alter chromatin structure and gene accessibility, influencing the hypertrophic phenotype.

3.3. Cellular Processes

At the cellular level, cardiac hypertrophy involves a series of integrated processes that contribute to the overall remodeling of the myocardium.

- **Myocyte Growth and Remodeling:** Individual cardiomyocytes undergo significant hypertrophy, increasing in size and protein content. This involves the synthesis of new sarcomeres (the basic contractile units of muscle) and their assembly, leading to an increase in the cross-sectional area of the cells.
- **Fibrosis:** Interstitial fibrosis, the excessive deposition of extracellular matrix proteins (primarily collagen) by activated fibroblasts, is a critical component of pathological hypertrophy. This fibrosis increases myocardial stiffness, impairs diastolic function, and provides a substrate for arrhythmias. Transforming Growth Factor-β (TGF-β) signaling is a major driver of cardiac fibrosis.
- **Apoptosis and Necrosis:** In advanced stages of pathological hypertrophy and during the transition to heart failure, programmed cell death (apoptosis) and necrosis of cardiomyocytes can occur. This loss of functional myocardial cells further contributes to contractile dysfunction and chamber dilation.
- **Mitochondrial Dysfunction:** Mitochondria are the powerhouses of the cell, and their dysfunction is a key feature of pathological hypertrophy. Impaired energy metabolism, reduced ATP production, and altered mitochondrial dynamics contribute to the energy deficit and functional decline of hypertrophied hearts.

4. DIAGNOSIS OF CARDIAC HYPERTROPHY

Accurate and timely diagnosis of cardiac hypertrophy is essential for appropriate management and to prevent progression to more severe cardiac conditions. A combination of clinical evaluation, imaging techniques, and biomarker analysis is typically employed.

4.1. Clinical Evaluation- The initial diagnostic steps involve a thorough assessment of the patient's medical history and a physical examination.

- **Patient History:** This includes inquiring about symptoms such as shortness of breath, chest pain, fatigue, dizziness, fainting, and palpitations. A detailed family history is particularly important, especially if hypertrophic cardiomyopathy (HCM) is suspected, as it is often an inherited condition.
- **Physical Examination:** A physical examination may reveal signs suggestive of cardiac hypertrophy or its complications, such as abnormal heart sounds (e.g., heart murmurs, particularly in obstructive HCM), signs of fluid overload (e.g., peripheral edema, elevated jugular venous pressure), or an abnormal apical impulse.

4.2. Imaging Techniques- Imaging modalities are central to confirming the presence of cardiac hypertrophy, assessing its extent, and evaluating cardiac function.

- **Echocardiography:** This non-invasive ultrasound technique is considered the gold standard for diagnosing cardiac hypertrophy. It provides real-time images of the heart, allowing for precise measurement of ventricular wall thickness, chamber dimensions, and assessment of global and regional cardiac function (e.g., ejection fraction, diastolic function). It can also identify valvular abnormalities and outflow tract obstruction.
- **Cardiac CT (Computed Tomography):** While less commonly used as a primary diagnostic tool for hypertrophy itself, cardiac CT can be useful for assessing cardiac structure, coronary arteries, and calcification, providing complementary information in certain clinical scenarios.

4.3. Electrocardiography (ECG)- The electrocardiogram (ECG) can provide initial clues suggestive of cardiac hypertrophy, particularly left ventricular hypertrophy (LVH).

- **Signs of Left Ventricular Hypertrophy (LVH) Patterns:** ECG criteria for LVH often include increased QRS voltage, ST-T wave abnormalities (e.g., strain pattern), and left atrial enlargement. However, ECG has limitations in sensitivity and specificity, and milder forms of hypertrophy may not be detected.

4.4. Biomarkers- Circulating biomarkers can aid in the diagnosis, risk stratification, and monitoring of cardiac hypertrophy and its progression.

- **Natriuretic Peptides (BNP, NT-proBNP):** Brain Natriuretic Peptide (BNP) and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) are released from the heart in response to increased wall stress and volume overload. Elevated levels are indicative of cardiac dysfunction and can be used to assess the severity of heart failure associated with hypertrophy.
- **Troponins:** Cardiac troponins (T and I) are markers of myocardial injury. While not specific to hypertrophy, chronically elevated or acutely rising levels can indicate ongoing cardiomyocyte damage or ischemia, which can be a complication of hypertrophy.
- **Emerging Biomarkers:** Research is ongoing to identify more specific biomarkers for cardiac hypertrophy and fibrosis, including circulating microRNAs (miRNAs) and various fibrosis markers (e.g., procollagen type I aminoterminal propeptide [PINP], matrix metalloproteinases [MMPs]). These may offer insights into disease activity and prognosis.

4.5. Genetic Testing- Genetic testing is increasingly important, especially in the diagnosis and management of inherited forms of cardiac hypertrophy.

- **For Suspected Hypertrophic Cardiomyopathy (HCM) and Familial Forms:** Given that HCM is often caused by genetic mutations (e.g., in sarcomeric protein genes), genetic testing can confirm the diagnosis, identify specific mutations, and facilitate cascade screening of family members to identify at-risk individuals before symptom onset.

5. THERAPEUTIC STRATEGIES FOR CARDIAC HYPERTROPHY

The management of cardiac hypertrophy aims to alleviate symptoms, prevent disease progression, reduce the risk of complications, and improve patient outcomes. Therapeutic strategies range from pharmacological interventions to device-based therapies, invasive procedures, and crucial lifestyle modifications.

5.1. Pharmacological Interventions

Medications are the cornerstone of treatment for many forms of cardiac hypertrophy, particularly those secondary to hypertension or other systemic conditions.

- **Blood Pressure Control:** For hypertrophy driven by hypertension, strict blood pressure control is paramount. ACE Inhibitors (Angiotensin-Converting Enzyme Inhibitors) and ARBs (Angiotensin II Receptor Blockers): These agents widen blood vessels, lower blood pressure, and

can help regress left ventricular hypertrophy by reducing cardiac afterload and inhibiting pro-hypertrophic signaling pathways. Beta-blockers: Reduce heart rate and myocardial contractility, thereby decreasing cardiac workload and oxygen demand. They are also effective in controlling blood pressure. Calcium Channel Blockers: Relax the heart muscle and widen blood vessels, reducing blood pressure and improving myocardial relaxation. Diuretics: Reduce fluid volume in the body, which helps to lower blood pressure and alleviate symptoms of fluid overload.

- **Heart Rate Control:** Beta-blockers and calcium channel blockers are often used to slow the heart rate, allowing more time for ventricular filling and reducing myocardial oxygen consumption.
- **Myocardial Relaxation:** Calcium channel blockers can improve diastolic function by promoting myocardial relaxation, which is often impaired in hypertrophied hearts.
- **Novel Therapies for HCM:** For hypertrophic cardiomyopathy, new medications specifically target the underlying pathophysiology. **Cardiac Myosin Inhibitors (e.g., Mavacamten, Aficamten):** These drugs reduce hypercontractility and improve myocardial relaxation by modulating myosin-actin interactions. They represent a significant advance in treating obstructive HCM by reducing left ventricular outflow tract (LVOT) gradients.
- **Anti-fibrotic Agents:** Mineralocorticoid receptor antagonists (e.g., spironolactone, eplerenone) can reduce myocardial fibrosis, which is a key contributor to stiffness and dysfunction in pathological hypertrophy.

5.2. Device-Based Therapies

For patients at high risk of life-threatening arrhythmias or with specific conduction abnormalities, device-based therapies are crucial.

- **Implantable Cardioverter-Defibrillators (ICDs):** ICDs are recommended for patients with cardiac hypertrophy, particularly HCM, who are at high risk for sudden cardiac death due due to ventricular arrhythmias. The device continuously monitors heart rhythm and delivers an electrical shock to restore a normal rhythm if a dangerous arrhythmia is detected.
- **Pacemakers:** In some cases, pacemakers may be used to manage certain types of arrhythmias or conduction abnormalities associated with hypertrophy.

5.3. Invasive Procedures

When pharmacological and device-based therapies are insufficient, invasive procedures may be necessary to alleviate obstruction or repair structural defects.

- **Septal Myectomy:** This open-heart surgical procedure is the gold standard for patients with severe symptomatic obstructive HCM that is refractory to medical therapy. It involves the surgical removal of a portion of the thickened interventricular septum, which obstructs blood flow from the left ventricle to the aorta, thereby improving outflow and symptoms.
- **Alcohol Septal Ablation:** A less invasive, catheter-based procedure where a small amount of alcohol is injected into a septal coronary artery to induce a controlled infarction (localized tissue death) in the thickened septal muscle. This reduces the septal thickness and relieves outflow tract obstruction. It is an alternative for patients who are not candidates for surgical myectomy.
- **Valve Repair/Replacement:** If cardiac hypertrophy is secondary to significant valvular heart disease (e.g., severe aortic stenosis or mitral regurgitation), surgical repair or replacement of the affected valve can alleviate the underlying stress on the heart and potentially lead to regression of hypertrophy.

5.4. Lifestyle Modifications

Lifestyle changes are fundamental to the comprehensive management of cardiac hypertrophy, regardless of its etiology.

- **Dietary Changes (Low Sodium):** Reducing dietary sodium intake helps to control blood pressure and minimize fluid retention, thereby reducing cardiac workload.
- **Regular, Appropriate Exercise:** While excessive exercise can induce pathological hypertrophy in susceptible individuals, moderate and appropriate physical activity, as advised by a physician, is generally beneficial for cardiovascular health and can help manage underlying conditions like hypertension.
- **Weight Management:** Achieving and maintaining a healthy weight reduces the overall burden on the cardiovascular system and can contribute to better blood pressure control.

- **Smoking Cessation, Alcohol Moderation:** Smoking is a significant risk factor for cardiovascular disease and should be ceased. Excessive alcohol consumption can also negatively impact heart health and should be moderated or avoided.

6. FUTURE DIRECTIONS AND CHALLENGES

Despite significant advancements in understanding and managing cardiac hypertrophy, several challenges remain, paving the way for exciting future research directions.

9.1. Precision Medicine- The future of cardiac hypertrophy treatment lies in precision medicine, where therapies are tailored to the individual patient. Tailoring Therapies Based on Individual Patient Characteristics: This involves considering a patient's unique genetic profile, specific hypertrophic pathways activated, and individual response to treatments. Genetic testing will become even more integral, guiding therapeutic choices and predicting disease progression.

9.2. Novel Therapeutic Targets- A deeper understanding of molecular mechanisms is continuously revealing new therapeutic targets beyond traditional approaches. Targeting Specific Signaling Molecules: Research is focused on developing drugs that specifically modulate key kinases, phosphatases, or other signaling components involved in pathological hypertrophy, aiming for more targeted and effective interventions with fewer side effects. Gene Therapy and RNA-based Therapies: Approaches like gene therapy (e.g., using viral vectors to deliver therapeutic genes) and RNA-based therapies (e.g., using miRNAs or CRISPR/Cas9 technology to modulate gene expression) hold promise for correcting underlying genetic defects or altering maladaptive pathways.

9.3. Regenerative Medicine- The concept of repairing or regenerating damaged myocardial tissue is a long-term goal. Stem Cell Therapies for Myocardial Repair: While still largely experimental for hypertrophy, stem cell therapies are being explored for their potential to replace lost cardiomyocytes or to secrete paracrine factors that promote tissue repair and reduce fibrosis.

9.4. Early Detection and Risk Stratification- Improving the ability to detect hypertrophy early and identify patients at highest risk for adverse outcomes is critical. Development of More Sensitive and Specific Biomarkers: The discovery of novel circulating biomarkers that can accurately reflect the presence, severity, and progression of hypertrophy, as well as predict the risk of heart failure, is an ongoing priority. Advanced Imaging Techniques for Early Detection of Maladaptive Remodeling: Further refinement of imaging modalities, such as advanced cardiac MRI sequences or novel echocardiographic techniques, could allow for the detection of subtle maladaptive changes before overt hypertrophy or functional decline.

9.5. Understanding Transition to Heart Failure- A major challenge is to fully elucidate the mechanisms that drive the transition from compensated hypertrophy to decompensated heart failure. Elucidating the Mechanisms Driving Decompensation: Research is focused on identifying the "tipping points" and molecular switches that lead to the breakdown of compensatory mechanisms and the onset of systolic dysfunction and overt heart failure.

9.6. Challenges

Translating scientific discoveries into clinical practice presents several inherent challenges.

- **Translational Hurdles from Bench to Bedside:** Bridging the gap between promising preclinical findings and successful clinical trials remains a significant hurdle.
- **Identifying Optimal Timing for Interventions:** Determining the ideal window for initiating specific therapies to prevent or reverse pathological remodeling is crucial for maximizing patient benefit.
- **Addressing Heterogeneity in Patient Response:** Patients with cardiac hypertrophy, even with similar diagnoses, can exhibit diverse responses to therapies. Understanding the basis of this heterogeneity is essential for developing more personalized and effective treatment strategies.

10. CONCLUSION

Cardiac hypertrophy represents a complex and multifaceted cardiovascular condition that can range from a beneficial physiological adaptation to a detrimental pathological process leading to heart failure. A clear understanding of the distinct types, their underlying molecular and cellular mechanisms, and the intricate signaling pathways involved is fundamental to its effective management. Advances in diagnostic imaging techniques and the identification of novel biomarkers have significantly improved our ability to detect and characterize hypertrophy.

Current therapeutic strategies involve a combination of pharmacological interventions, device-based therapies, and invasive procedures, alongside crucial lifestyle modifications, all aimed at alleviating symptoms, controlling underlying causes, and preventing disease progression. The emergence of novel therapies, particularly cardiac myosin inhibitors for HCM, underscores the progress in targeting specific disease mechanisms. Looking ahead, the field is poised for transformative advancements. Precision medicine, driven by genetic insights and personalized approaches, holds immense promise for tailoring treatments to individual patients. The identification of novel therapeutic targets, advancements in gene and RNA-based therapies, and the potential of regenerative medicine offer exciting avenues for future interventions. While challenges such as translational hurdles and patient heterogeneity persist, continued research into the intricate biology of cardiac hypertrophy will undoubtedly lead to more effective prevention, earlier diagnosis, and ultimately, improved outcomes for patients affected by this critical cardiac condition.

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