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CARDIOMYOPATHIES: PATHOPHYSIOLOGY, CLASSIFICATION, AND CONTEMPORARY MANAGEMENT

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Abstract : Cardiomyopathies are a heterogeneous group of myocardial disorders characterized by structural and functional abnormalities of the heart muscle, often leading to heart failure, arrhythmias, and sudden cardiac death. Despite significant advances in cardiology, early diagnosis and optimal management remain challenging due to their diverse etiologies and overlapping clinical presentations. Cardiomyopathies are broadly classified into hypertrophic, dilated, restrictive, and arrhythmogenic forms, each with distinct genetic, molecular, and structural mechanisms. Advanced imaging techniques, including echocardiography and cardiac MRI, alongside genetic testing, have significantly improved diagnostic accuracy and risk stratification. Management strategies encompass pharmacologic therapy, device implantation, interventional procedures, and, in selected cases, heart transplantation. Emerging therapies targeting specific molecular pathways and gene defects show promise for personalized treatment. This review aims to provide a comprehensive overview of the current understanding of cardiomyopathies, focusing on their classification, pathophysiology, diagnostic strategies, and contemporary management approaches based on recent literature.

Keywords : Cardiomyopathy; hypertrophic; dilated; restrictive; arrhythmogenic; heart failure; diagnosis; management; genetics

Cardiomyopathies constitute a diverse group of myocardial disorders associated with structural and functional abnormalities of the heart muscle, often leading to significant morbidity and mortality. These conditions are a leading cause of heart failure, arrhythmias, and sudden cardiac death across all age groups, with variable prevalence depending on the subtype and underlying etiology. The clinical spectrum of cardiomyopathies ranges from asymptomatic individuals with mild structural changes to patients with severe heart failure or life-threatening ventricular arrhythmias.Historically, cardiomyopathies were primarily classified based on gross morphological features, such as ventricular wall thickness and chamber dilation. However, advances in molecular cardiology, imaging modalities, and genetic testing have substantially refined the understanding of their pathophysiology and heterogeneity. Contemporary classification integrates structural, functional, and genetic factors, enabling more accurate diagnosis, risk stratification, and personalized management strategies.Despite these advances, cardiomyopathies remain diagnostically challenging due to overlapping phenotypes, incomplete penetrance of genetic mutations, and variable disease progression. Early recognition is critical, as timely intervention can improve clinical outcomes, reduce the risk of sudden cardiac death, and enhance quality of life. Moreover, the advent of precision medicine and targeted therapies offers new opportunities for individualized treatment, highlighting the importance of integrating molecular insights into clinical practice.This review aims to provide a comprehensive overview of cardiomyopathies, focusing on their classification, molecular and structural pathophysiology,

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diagnostic innovations, and contemporary management strategies. By synthesizing current evidence from the literature, this article seeks to inform clinicians, researchers, and healthcare professionals about optimal approaches to diagnosis, risk assessment, and treatment of these complex disorders.

Cardiomyopathies are traditionally classified based on structural and functional myocardial abnormalities, with contemporary frameworks also incorporating genetic, molecular, and clinical features. The major categories include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and other less common forms such as left ventricular noncompaction and metabolic cardiomyopathies. Each subtype exhibits distinct pathophysiological mechanisms, clinical manifestations, and prognostic implications.

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy is the most common inherited cardiomyopathy, with a prevalence of approximately 1:500 in the general population. It is characterized by unexplained left ventricular hypertrophy, often involving the interventricular septum, in the absence of secondary causes such as hypertension or valvular disease. Most cases result from autosomal dominant mutations in sarcomeric genes, including MYH7, MYBPC3, TNNT2, and TNNI3, which encode key contractile proteins. These mutations lead to myocyte disarray, myocardial fibrosis, and diastolic dysfunction, predisposing patients to heart failure and sudden cardiac death.

Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy is defined by left ventricular dilation and systolic dysfunction, often resulting in progressive heart failure. Etiologies are heterogeneous and include genetic, infectious, toxic, and idiopathic causes. Familial DCM, accounting for up to 40% of cases, is frequently linked to mutations in TTN, LMNA, and DES genes. Secondary causes include viral myocarditis, alcohol or chemotherapy-induced cardiotoxicity, metabolic disorders, and peripartum cardiomyopathy. The clinical course is variable, ranging from asymptomatic ventricular enlargement to end-stage heart failure requiring transplantation.

Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy is characterized by impaired ventricular filling with preserved systolic function, often leading to severe diastolic heart failure. Etiologies include infiltrative diseases such as cardiac amyloidosis, sarcoidosis, and hemochromatosis, as well as idiopathic or familial forms. Fibrotic or infiltrative changes increase myocardial stiffness, resulting in elevated filling pressures, biatrial enlargement, and exercise intolerance.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is a genetically mediated cardiomyopathy predominantly affecting the right ventricle, with fibro-fatty replacement of the myocardium. It is strongly associated with mutations in desmosomal genes such as PKP2, DSG2, DSC2, and DSP. Patients are at high risk for

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ventricular arrhythmias and sudden cardiac death, often presenting in adolescence or early adulthood.

Other Rare Forms

Other less common cardiomyopathies include:

- Left ventricular noncompaction (LVNC): Characterized by prominent trabeculations and deep intertrabecular recesses, often associated with genetic mutations affecting sarcomeric or mitochondrial proteins.
- Metabolic and storage cardiomyopathies: Resulting from lysosomal storage disorders (e.g., Fabry disease), glycogen storage diseases, or mitochondrial defects.

Etiologic Considerations

Etiologically, cardiomyopathies arise from a complex interplay of genetic predisposition, environmental factors, and systemic diseases. Genetic mutations often lead to structural and functional abnormalities at the molecular and cellular levels, while acquired insults—including infections, toxins, and metabolic disturbances—can precipitate or exacerbate disease manifestations. Understanding the underlying etiology is essential for risk stratification, prognostication, and tailoring individualized therapeutic strategies.

Pathophysiology

The pathophysiology of cardiomyopathies reflects the interplay between genetic, molecular, and environmental factors, resulting in structural and functional myocardial abnormalities.

- Hypertrophic cardiomyopathy (HCM): Mutations in sarcomeric proteins cause myocyte disarray, myocardial fibrosis, and impaired relaxation, leading to diastolic dysfunction and increased arrhythmic risk.
- Dilated cardiomyopathy (DCM): Genetic defects, toxins, or infections result in myocyte injury, ventricular dilation, and systolic dysfunction. Progressive remodeling and fibrosis exacerbate heart failure and arrhythmias.
- Restrictive cardiomyopathy (RCM): Infiltrative or fibrotic processes increase ventricular stiffness, impair diastolic filling, and elevate atrial pressures.
- Arrhythmogenic right ventricular cardiomyopathy (ARVC): Desmosomal mutations lead to fibro-fatty replacement of myocardium, disrupting electrical conduction and predisposing to ventricular arrhythmias.
- Other forms (LVNC, metabolic cardiomyopathies): Structural abnormalities and metabolic defects impair myocardial contractility and compliance.

Overall, these mechanisms culminate in heart failure, arrhythmias, and, in severe cases, sudden cardiac death. Understanding the underlying pathophysiology is critical for targeted diagnosis, risk stratification, and therapy.

Management Strategies

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Management of cardiomyopathies aims to alleviate symptoms, prevent disease progression, reduce arrhythmic risk, and improve long-term outcomes. Therapeutic approaches are tailored to the specific subtype, severity, and underlying etiology.

Pharmacologic Therapy

- Heart failure management: ACE inhibitors, ARBs, ARNIs, beta-blockers, and diuretics improve symptoms and survival in dilated and restrictive forms.
- Arrhythmia control: Antiarrhythmic agents and rate-control medications reduce the risk of atrial fibrillation and ventricular arrhythmias.
- Symptom relief: In HCM, beta-blockers or calcium channel blockers alleviate exertional dyspnea and chest discomfort.

Device Therapy

- Implantable cardioverter-defibrillator (ICD): Indicated for primary or secondary prevention of sudden cardiac death in high-risk patients.
- Cardiac resynchronization therapy (CRT): Used in select patients with DCM and conduction abnormalities to improve ventricular synchrony and cardiac output.

Surgical and Interventional Approaches

- Septal myectomy or alcohol septal ablation: Effective in HCM patients with significant left ventricular outflow tract obstruction.
- Heart transplantation: Considered in end-stage cardiomyopathies refractory to medical and device therapy.

Emerging and Targeted Therapies

- Gene therapy, small molecule modulators, and precision medicine approaches are under investigation, particularly in genetically mediated cardiomyopathies.
- Enzyme replacement therapy is applicable in metabolic forms such as Fabry disease.

Lifestyle and Supportive Care

- Regular exercise tailored to functional capacity
- Dietary modifications and avoidance of alcohol or cardiotoxic agents
- Psychological support and long-term follow-up for symptom monitoring and risk assessment

Conclusion: Cardiomyopathies represent a heterogeneous group of myocardial disorders with diverse genetic, molecular, and environmental etiologies. They are associated with significant morbidity and mortality due to heart failure, arrhythmias, and sudden cardiac death. Advances in imaging, genetic testing, and molecular understanding have improved diagnosis, risk stratification, and personalized management strategies. Effective treatment requires a multidisciplinary approach, integrating pharmacologic therapy, device implantation, surgical

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interventions, and supportive care tailored to the specific cardiomyopathy subtype and patient characteristics. Emerging targeted and gene-based therapies hold promise for further improving outcomes, particularly in genetically mediated forms.Early recognition, accurate classification, and individualized management are essential to mitigate complications, enhance quality of life, and reduce long-term mortality in patients with cardiomyopathies. Continued research into molecular mechanisms and novel therapeutic strategies is expected to drive future advances in precision cardiology.

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