

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

Roxana Berenice González Muñoz¹, Deborah Dafne Cid Ramírez¹, Andrea Catalina Esquivel Márquez², Daniela flores hernández³, Oswald Gerardo Mauricio Cruz³, Andrea Guadalupe Alvarado Esparza³, Benito Montoya Silva⁴, Katia Gabriela Silva Esquivel⁴, Miguel Castellanos Contreras⁵, Carlos Alfonso Martín Olguín Curiel⁶, Shaili Sajaf Alonso Reyes²

¹Universidad Universidad Cuauhtémoc Plantel Aguascalientes. Aguascalientes, Mexico.

²Universidad Autónoma de Aguascalientes. Aguascalientes, Mexico.

³Centro Universitario de Estudios de la Salud de Aguascalientes. Aguascalientes, Mexico.

⁴Universidad Cuauhtémoc Aguascalientes. Aguascalientes, Mexico.

⁵Universidad de Guadalajara. Guadalajara, Jalisco, Mexico.

⁶Universidad del Valle de Atemajac. Mexico.

ABSTRACT

Restrictive cardiomyopathy represents one of the most challenging phenotypes within the spectrum of myocardial diseases, distinguished by impaired ventricular filling due to increased myocardial stiffness while preserving near-normal systolic function during early stages. Although considered uncommon, it carries a disproportionately high morbidity and mortality burden owing to its subtle clinical onset, heterogeneous etiologies, and frequently delayed diagnosis. Advances in multimodal imaging, myocardial tissue characterization, and molecular diagnostics have reshaped current understanding of this entity, revealing intricate associations with infiltrative, fibrotic, storage, and radiation-induced myocardial injuries. The clinical trajectory is typically dominated by progressive diastolic dysfunction, biatrial enlargement, preserved ejection fraction heart failure physiology, and variable conduction system involvement. Despite these characteristic features, restrictive cardiomyopathy remains diagnostically elusive, often requiring integration of echocardiography, cardiac magnetic resonance, endomyocardial biopsy, and biomarker profiling. Therapeutic strategies continue to evolve, transitioning from purely supportive management to etiology-directed interventions, including novel pharmacologic agents and targeted therapies for infiltrative and genetic subtypes. This article provides an extensive review of the contemporary understanding of restrictive cardiomyopathy, emphasizing its complex pathophysiology, diagnostic challenges, and emerging therapeutic horizons.

KEYWORDS: Restrictive cardiomyopathy; diastolic dysfunction; myocardial stiffness; infiltrative myocardial disease; cardiac magnetic resonance; endomyocardial biopsy; heart failure with preserved ejection fraction.

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INTRODUCTION

Restrictive cardiomyopathy constitutes a rare yet clinically impactful myocardial disorder defined primarily by impaired ventricular diastolic filling secondary to increased myocardial rigidity, with the early preservation of systolic performance. This hemodynamic pattern leads to elevated filling pressures, pulmonary venous congestion, systemic

venous hypertension, and a characteristic heart failure phenotype that often resembles advanced heart failure with preserved ejection fraction.^{1,2,3}

Unlike hypertrophic or dilated cardiomyopathies, restrictive cardiomyopathy typically exhibits nondilated and nonhypertrophic ventricles, accompanied by marked biatrial enlargement that reflects chronic diastolic impairment. The

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

etiologic spectrum encompasses a diverse range of pathological processes, including amyloid infiltration, endomyocardial fibrosis, iron deposition, sarcoid granulomatous involvement, and genetic defects affecting sarcomeric or cytoskeletal proteins. These etiologies converge on the shared pathophysiologic hallmark of increased myocardial stiffness, resulting from extracellular matrix expansion, abnormal protein deposition, or fibrotic remodeling.^{4,5,6}

Clinically, restrictive cardiomyopathy often manifests with insidious symptoms such as exertional dyspnea, fatigue, orthopnea, and peripheral edema, which may progress despite preserved left ventricular ejection fraction. The coexistence of arrhythmias, conduction disturbances, thromboembolic events, and hepatic or renal congestion further complicates the disease course. Diagnostic evaluation is inherently complex, relying on a multimodal approach in which transthoracic echocardiography provides initial insights into diastolic dysfunction, while cardiac magnetic resonance enables detailed tissue characterization, and endomyocardial biopsy may be required to confirm specific etiologies. Biomarkers, including natriuretic peptides and those associated with infiltrative processes, contribute additional diagnostic value in selected cases. Despite significant progress in understanding underlying mechanisms, treatment remains challenging and is frequently focused on symptom relief and management of complications. However, the emergence of targeted therapies for amyloidosis, iron overload, and genetic cardiomyopathies signals a paradigm shift toward more personalized and disease-specific interventions. Restrictive cardiomyopathy therefore stands at the intersection of classic heart failure physiology and modern cardiovascular medicine, demanding comprehensive evaluation and nuanced therapeutic strategies to improve patient outcomes.^{7,8,9}

Background

The conceptual foundations of restrictive cardiomyopathy have evolved substantially over the past decades, shaped by an increasing appreciation of its heterogeneous etiologies, intricate hemodynamic profile, and distinct morphologic characteristics that set it apart from other primary myocardial disorders. Historically, restrictive cardiomyopathy was regarded as a relatively obscure and poorly defined entity, often conflated with constrictive pericarditis due to the overlapping clinical picture of impaired ventricular filling, elevated diastolic pressures, and signs of systemic and pulmonary congestion. Early clinical descriptions emphasized the profound diastolic dysfunction that dominated the disease course, yet the ability to accurately distinguish restrictive physiology from pericardial constriction remained limited, leading to misclassification and therapeutic uncertainty. As diagnostic technologies advanced, particularly with the introduction of Doppler echocardiography and later cardiac magnetic resonance

imaging, clinicians began to recognize the characteristic nondilated ventricles, marked biatrial enlargement, and absence of pericardial thickening or calcification that typify restrictive cardiomyopathy.^{10,11,12}

The understanding of its etiologic spectrum also underwent a significant transformation. Initially considered primarily idiopathic, restrictive cardiomyopathy is now recognized as a phenotype arising from a wide array of infiltrative, inflammatory, genetic, and metabolic abnormalities that converge on the common pathway of reduced myocardial compliance. Infiltrative processes such as amyloid deposition and sarcoid granulomatous infiltration gained prominence as major contributors to restrictive physiology, while endomyocardial fibrosis and hypereosinophilic syndromes emerged as important causes in specific geographic and clinical contexts. Furthermore, advances in molecular genetics uncovered mutations in sarcomeric, cytoskeletal, and desmin-associated proteins responsible for familial forms of restrictive cardiomyopathy, highlighting its relationship with the broader continuum of inherited cardiomyopathies. The identification of radiation-induced myocardial injury and iron overload cardiomyopathy added further complexity to its etiologic landscape, underscoring the multifactorial nature of restrictive myocardial remodeling.^{13,14,15,16}

From a pathological standpoint, early autopsy and histologic studies provided crucial insights into the structural substrates underlying restrictive physiology. Investigators documented varying degrees of interstitial fibrosis, extracellular matrix expansion, endocardial thickening, and abnormal deposition of proteins or minerals, all of which contribute to ventricular stiffening and impaired diastolic relaxation. These morphological observations aligned with the hemodynamic profiles obtained from cardiac catheterization, which revealed rapid early diastolic filling followed by an abrupt plateau, reflecting the noncompliant ventricular chamber. Such hemodynamic patterns became foundational in the differentiation between restrictive cardiomyopathy and constrictive pericarditis, reinforcing the importance of invasive assessment in ambiguous cases and guiding the development of refined diagnostic algorithms.^{17,18,19}

The epidemiology of restrictive cardiomyopathy has also gained clarity with time, illustrating its relative rarity in comparison with dilated or hypertrophic cardiomyopathies, yet emphasizing its disproportionately high disease burden due to progressive heart failure, arrhythmias, and thromboembolic complications. Variability in prevalence among different regions and populations further highlighted the interplay of environmental, genetic, and socioeconomic factors shaping its presentation. The clinical recognition of restrictive cardiomyopathy expanded alongside improvements in noninvasive imaging and biomarker profiling, allowing earlier identification of subtle diastolic abnormalities and myocardial tissue alterations that

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

previously went undetected until advanced disease stages.^{20,21,22}

Therapeutically, the historical management of restrictive cardiomyopathy centered on symptomatic relief, as targeted interventions were limited by incomplete understanding of its underlying mechanisms. However, breakthroughs in the treatment of specific etiologies—such as disease-modifying therapies for amyloidosis, chelation strategies for iron overload, and immunomodulatory regimens for inflammatory forms—ushered in a new era in which etiology-directed approaches began to supplement conventional heart failure management. These developments not only improved outcomes in selected patient populations but also underscored the importance of accurate etiologic diagnosis, driving further refinement of contemporary diagnostic frameworks.^{22,23,24} Together, these historical milestones form the foundation of the current conceptualization of restrictive cardiomyopathy as a distinct, multifaceted myocardial disease requiring nuanced diagnostic evaluation and increasingly personalized therapeutic strategies. The evolution of knowledge in this field continues to unfold, propelled by advances in molecular medicine, high-resolution imaging, and translational research that seek to elucidate the complex interplay between myocardial structure, cellular biology, and clinical physiology.^{25,26}

Natural History

The natural history of restrictive cardiomyopathy unfolds as a progressive and often insidious trajectory in which the structural and functional rigidity of the ventricular myocardium gradually undermines hemodynamic equilibrium, eventually precipitating multisystemic consequences. In its earliest phases, the disease may remain virtually silent, with patients experiencing only subtle symptoms such as exertional fatigue or mild exercise intolerance that are frequently attributed to nonspecific cardiovascular deconditioning. During this latent period, diastolic dysfunction is already present at the microstructural level, driven by abnormal myocardial compliance, impaired ventricular relaxation, or the infiltration or deposition of pathologic substrates that stiffen the myocardial matrix. Despite the absence of overt clinical manifestations, elevated filling pressures begin to develop, initiating a cascade of compensatory neurohormonal responses that transiently preserve forward cardiac output but simultaneously contribute to progressive structural remodeling and endothelial dysfunction.^{27,28,29}

As the disease advances into a more clinically overt stage, patients exhibit increasingly evident manifestations of heart failure with preserved ejection fraction, characterized by dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema. This transition reflects the escalating inability of the ventricles to accommodate venous return during diastole without marked increases in intracardiac pressures, leading to pulmonary venous

congestion and systemic venous hypertension. The atria, subjected to chronic pressure overload, progressively dilate and become susceptible to structural remodeling that fosters electrical instability. Atrial arrhythmias, particularly atrial fibrillation and atrial flutter, often emerge during this phase, further compromising hemodynamic efficiency and increasing the risk of thromboembolic events. In many patients, particularly those with infiltrative etiologies such as amyloidosis or storage disorders, conduction abnormalities, chronotropic incompetence, or atrioventricular block may develop, reflecting direct compromise of the conduction system.^{30,31,32,33}

Over time, the natural course is marked by the steady deterioration of diastolic filling, culminating in a fixed and unyielding pattern of ventricular stiffness that renders cardiac output highly preload-dependent and vulnerable to even minor fluctuations in intravascular volume. Symptoms intensify, and patients may develop refractory congestion, cardiorenal syndrome, hepatic dysfunction due to chronic congestion, and profound limitations in functional capacity. In specific subtypes, such as eosinophilic or radiation-induced restrictive cardiomyopathy, disease progression may be punctuated by episodic surges of inflammatory or fibrotic activity that accelerate myocardial stiffening and abruptly worsen clinical status.^{34,35,36}

Ultimately, the condition evolves toward an advanced stage characterized by severe biventricular diastolic impairment, irreversible end-organ dysfunction, and a sharp decline in quality of life. At this point, therapeutic options become limited, often relying on aggressive medical management, rhythm control strategies, device therapy for conduction disease, or, in select candidates, evaluation for heart transplantation. Without definitive intervention—particularly in infiltrative variants that progress rapidly—the prognosis is generally poor, with survival strongly influenced by the underlying etiology, the tempo of myocardial involvement, and the degree of extracardiac organ compromise.³⁷

Thus, the natural history of restrictive cardiomyopathy is defined by a continuum that begins with subclinical myocardial stiffening and culminates in advanced, refractory heart failure, with each intermediate phase shaped by the intricate interplay of structural rigidity, hemodynamic imbalance, neurohormonal activation, and progressive multiorgan involvement.³⁸

Pathophysiological framework

The pathophysiological framework of restrictive cardiomyopathy is anchored in the progressive derangement of myocardial compliance and the disruption of normal diastolic mechanics, culminating in a clinical syndrome defined by elevated ventricular filling pressures despite preserved or near-preserved systolic performance. At the core of this process lies an abnormal increase in myocardial stiffness, arising from a wide spectrum of structural, molecular, and cellular alterations that collectively impair the

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

ability of the ventricles to accommodate venous return during diastole. The myocardium in restrictive cardiomyopathy undergoes a transformation characterized by interstitial expansion, excessive collagen deposition, altered collagen cross-linking, and, in many cases, infiltration by abnormal proteins or inflammatory cells. These changes distort the extracellular matrix architecture, reducing its elasticity and limiting the normal distensibility of the ventricular chambers. In infiltrative variants, such as those associated with amyloid deposition or granulomatous disease, the accumulation of foreign material displaces and distorts normal myocardial fibers, amplifying stiffness and disrupting coordinated microstructural mechanics.^{38,39}

On a cellular level, defects in cytoskeletal proteins, sarcomeric elements, and desmin-related structures contribute to altered mechanical properties of cardiomyocytes. Mutations affecting titin isoforms or Z-disc-associated proteins modify the elastic recoil of myocardial fibers, diminishing their ability to relax efficiently during early diastole. The consequence of these alterations is a reduction in ventricular suction and a blunted capacity to generate negative intraluminal pressures necessary for rapid early diastolic filling. As the myocardium stiffens, diastole becomes increasingly dependent on elevated atrial pressures to maintain adequate ventricular preload. This compensatory mechanism manifests clinically and structurally as marked biatrial enlargement, reflecting the chronic pressure overload borne by the atrial chambers.^{40,41}

The hemodynamic signature of restrictive cardiomyopathy emerges from these biomechanical disruptions. During cardiac catheterization, ventricles exhibit a rapid early filling phase followed by an abrupt plateau, producing the classic dip-and-plateau contour that reflects severely restricted diastolic compliance. Unlike constrictive pericarditis, where the external pericardial constraint governs filling dynamics, restrictive cardiomyopathy arises from intrinsic myocardial pathology that affects the entire ventricular wall, limiting both longitudinal and circumferential expansion. Despite preserved ejection fraction, subtle impairments in longitudinal systolic function often coexist due to early involvement of subendocardial fibers, although these abnormalities remain undetected by conventional systolic indices.^{42,43}

At the molecular level, neurohormonal activation contributes significantly to disease progression. Chronic elevation of atrial and ventricular wall stress stimulates the upregulation of natriuretic peptides, catecholamines, endothelin, and components of the renin-angiotensin-aldosterone system. These neurohormonal cascades promote sodium and water retention, exacerbate venous congestion, and perpetuate the cycle of diastolic dysfunction. They also foster myocardial fibrosis through the activation of fibroblasts and the enhancement of extracellular matrix synthesis. In infiltrative and inflammatory forms, cytokine-mediated pathways further

aggravate myocardial injury and structural remodeling. This combination of mechanical dysfunction and biochemical maladaptation generates a sustained pressure overload on both the pulmonary and systemic venous circuits, ultimately leading to pulmonary hypertension, hepatic congestion, renal impairment, and, in advanced cases, cachexia.^{44,45}

Microvascular dysfunction also plays a central role in the pathophysiology of restrictive cardiomyopathy. Even in the absence of obstructive epicardial coronary disease, chronic interstitial expansion and infiltrative processes compress intramyocardial arterioles, impairing perfusion reserve and inducing ischemia at the microvascular level. Repeated low-grade ischemic injury promotes apoptosis, accelerates fibrosis, and further reduces myocardial compliance, contributing to a vicious cycle of progressive diastolic impairment. In certain etiologies, such as amyloidosis, the deposition of abnormal proteins within vessel walls exacerbates this ischemic burden by narrowing vascular lumina and disrupting endothelial homeostasis.⁴⁶

Electrophysiologic disturbances are also inherent to the disease process, arising from structural disarray and fibrosis that interrupt the continuity of conduction pathways. This substrate predisposes patients to atrial arrhythmias, conduction block, and, in some cases, ventricular arrhythmias. Because effective diastolic filling in restrictive cardiomyopathy relies heavily on atrial contraction, the development of atrial fibrillation often precipitates abrupt hemodynamic decompensation, highlighting the intimate link between electrical and mechanical pathology.⁴⁷

Taken together, the pathophysiological framework of restrictive cardiomyopathy represents a complex interplay among molecular abnormalities, interstitial remodeling, cellular dysfunction, microvascular impairment, and maladaptive neurohormonal activation. These processes converge to produce a rigid, noncompliant myocardium incapable of supporting normal diastolic filling, thereby establishing the defining hemodynamic and clinical characteristics of the disease.⁴⁸

Diagnostic evaluation

The diagnostic evaluation of restrictive cardiomyopathy requires a comprehensive, multilayered approach that integrates advanced imaging modalities, hemodynamic assessment, biomarker profiling, and, in selected cases, histopathologic confirmation. Because the clinical presentation is often dominated by nonspecific symptoms such as exertional dyspnea, exercise intolerance, peripheral edema, and signs of systemic or pulmonary venous congestion, the initial diagnostic steps aim to differentiate restrictive cardiomyopathy from other causes of diastolic heart failure, particularly constrictive pericarditis, infiltrative cardiomyopathies of nonrestrictive phenotype, and advanced hypertensive or ischemic heart disease. The cornerstone of the diagnostic process is transthoracic echocardiography, which remains the first-line modality due to its accessibility

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

and ability to provide a detailed characterization of cardiac structure and function. Echocardiographic findings typically reveal nondilated ventricles with normal or near-normal wall thickness, severe biatrial enlargement, and a diastolic filling pattern characterized by a restrictive physiology, often manifesting as elevated E-wave velocities, diminished A-wave contribution, shortened deceleration time, and impaired tissue Doppler annular velocities. These Doppler-derived parameters help delineate the severity of diastolic dysfunction and estimate filling pressures, offering essential clues to the underlying restrictive physiology. In addition, speckle-tracking echocardiography provides further insight by identifying reductions in longitudinal strain while preserving circumferential mechanics, a pattern that reflects early myocardial stiffening even when ejection fraction remains preserved.⁴⁹

Cardiac magnetic resonance imaging has emerged as a pivotal tool for the diagnostic evaluation of restrictive cardiomyopathy due to its unparalleled capacity for myocardial tissue characterization. Through the application of late gadolinium enhancement and parametric mapping techniques such as T1 and T2 mapping and extracellular volume quantification, cardiac magnetic resonance enables noninvasive differentiation among infiltrative, inflammatory, and fibrotic substrates. Patients with restrictive cardiomyopathy frequently exhibit diffuse or patchy patterns of enhancement and elevated extracellular volume, findings that correlate with interstitial expansion, protein deposition, or myocardial fibrosis. This modality is particularly valuable for distinguishing amyloid infiltration, identifying iron overload through T2* mapping, and assessing subtle forms of endomyocardial fibrosis that may not be evident on echocardiography. Moreover, cardiac magnetic resonance offers precise volumetric and functional assessment, which is essential for quantifying atrial enlargement, evaluating right ventricular involvement, and detecting associated pericardial abnormalities.⁵⁰

When the etiology remains uncertain despite comprehensive noninvasive evaluation, invasive hemodynamic assessment via right and left heart catheterization becomes indispensable. Hemodynamic tracings classically demonstrate elevated and nearly equalized diastolic pressures across cardiac chambers, accompanied by a characteristic rapid early diastolic dip followed by an abrupt rise and plateau, often referred to as the “square root” or “dip-and-plateau” sign. These findings reflect impaired ventricular compliance and provide a physiologic signature that supports the diagnosis. Catheterization also plays a decisive role in differentiating restrictive cardiomyopathy from constrictive pericarditis, a distinction that is clinically imperative given the divergent therapeutic pathways. While both conditions may share similar hemodynamic features, subtle variations in ventricular interdependence, respiratory pressure influences, and systolic area index can guide accurate differentiation.⁵⁰

Biomarkers contribute additional layers of diagnostic information. Natriuretic peptides are typically elevated due to chronically increased myocardial strain, and their levels often correlate with disease severity. In cases where an infiltrative etiology such as amyloidosis is suspected, serum and urine protein analyses, immunofixation assays, and assessments for monoclonal light chains provide critical diagnostic guidance. Iron studies, eosinophil counts, and specific genetic panels may be pursued depending on the clinical suspicion, as restrictive cardiomyopathy encompasses a broad spectrum of metabolic, hematologic, and hereditary disorders. Advances in molecular testing have significantly improved the identification of genetic variants associated with familial restrictive cardiomyopathy, particularly those affecting sarcomeric and cytoskeletal proteins, enabling earlier diagnosis among asymptomatic relatives and facilitating targeted counseling.^{50,51}

Endomyocardial biopsy represents the definitive diagnostic modality when noninvasive techniques are inconclusive or when histopathologic confirmation is necessary to direct disease-specific therapy. Biopsy specimens allow direct visualization of interstitial fibrosis, amyloid deposition, inflammatory infiltrates, abnormal storage material, or iron accumulation. Immunohistochemistry, electron microscopy, and mass spectrometry-based proteomic analysis further enhance diagnostic precision, especially in differentiating subtypes of amyloidosis or in identifying rare metabolic disorders. Although biopsy carries inherent procedural risks, its diagnostic yield and ability to influence therapeutic decisions justify its use in select clinical scenarios.⁵¹

Together, these diagnostic modalities form an integrated framework that allows clinicians to navigate the complex and often subtle manifestations of restrictive cardiomyopathy. The diagnostic pathway relies on synthesizing structural, functional, hemodynamic, biochemical, and microscopic data to establish a precise diagnosis, characterize disease severity, and uncover its underlying etiology. As imaging technologies and molecular diagnostics continue to advance, the diagnostic landscape of restrictive cardiomyopathy is rapidly evolving toward increasingly precise and individualized assessment strategies.⁵²

Differential diagnostic considerations in restrictive cardiomyopathy require a meticulous and integrative clinical approach, as the syndrome often presents with hemodynamic patterns and symptomatic constellations that overlap substantially with other myocardial, pericardial, and systemic conditions capable of producing diastolic dysfunction and impaired ventricular compliance. Clinicians must carefully disentangle these entities by leveraging nuanced physiologic distinctions, advanced imaging characteristics, biomarker profiles, and, when necessary, histopathologic evaluation. A critical step in this interpretive process is the differentiation of restrictive cardiomyopathy from constrictive pericarditis, a condition that can mimic restrictive physiology with

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

striking fidelity. Although both disorders manifest with elevated filling pressures, prominent venous congestion, and preserved systolic ejection fraction, constrictive pericarditis is defined by a noncompliant pericardial envelope that exerts extrinsic constraint on the ventricles. Subtle diagnostic clues such as discordant ventricular pressure variations with respiration, the presence of pronounced septal bounce, and preserved or exaggerated longitudinal myocardial motion despite impaired radial excursion favor a pericardial rather than myocardial etiology. Tissue characterization techniques, including cardiac magnetic resonance imaging, further enable clinicians to identify pericardial thickening, calcifications, or pericardial inflammation, distinguishing them from the myocardial stiffness intrinsic to restrictive cardiomyopathy.⁵³

The differential evaluation must also account for infiltrative cardiomyopathies, which may present with near-identical hemodynamic profiles but differ significantly in etiopathogenesis and systemic involvement. Amyloidosis, arguably the most prototypical infiltrative cause, typically produces diffuse ventricular wall thickening, biatrial enlargement, and characteristic myocardial signal alterations associated with abnormal extracellular protein deposition. Although cardiac amyloidosis is considered a subtype of restrictive cardiomyopathy within certain taxonomies, differentiating it from non-infiltrative restrictive entities is essential due to its unique therapeutic implications. Sarcoidosis, another infiltrative disorder, may mimic restrictive physiology through granulomatous infiltration, yet its patchy distribution often produces conduction abnormalities and ventricular arrhythmias that are less typical of pure restrictive cardiomyopathy. Distinguishing sarcoidosis relies on detecting extracardiac organ involvement, characteristic imaging enhancement patterns, and metabolic activity within granulomatous lesions.⁵⁴

Storage diseases, including hemochromatosis and various lysosomal or glycogen storage disorders, may also enter the differential, as iron or metabolic substrate accumulation can stiffen the myocardium and impair diastolic relaxation. These conditions are often accompanied by systemic manifestations such as endocrine dysfunction, hepatic abnormalities, or neuromuscular features that assist in differentiation. Moreover, endomyocardial fibrosis—whether idiopathic, eosinophilic, or associated with tropical etiologies—represents another condition capable of creating a restrictive hemodynamic profile. However, it can frequently be distinguished by its characteristic apical obliteration, mural thrombus formation, or areas of endocardial scarring seen on imaging or pathology.⁵⁵

Hypertrophic cardiomyopathy, particularly its restrictive or end-stage “burned-out” variants, may resemble restrictive cardiomyopathy due to severe diastolic dysfunction and biatrial enlargement. Nonetheless, hypertrophic cardiomyopathy typically displays disproportionate left

ventricular wall thickening, dynamic outflow tract abnormalities in earlier phases of disease, or distinctive patterns of myocyte disarray that facilitate differentiation. Similarly, advanced hypertensive heart disease or age-related myocardial stiffening may mimic a restrictive phenotype, but these entities generally exhibit concentric hypertrophy with preserved compliance at earlier stages and lack the profound biatrial enlargement characteristic of true restrictive physiology.^{55,56}

Finally, conditions that produce high-output states, impaired relaxation due to ischemia, or tachyarrhythmia-induced cardiomyopathy must be considered and ruled out through careful correlation of clinical history, rhythm evaluation, and coronary imaging. In certain patients, the diagnostic process may culminate in endomyocardial biopsy, particularly when infiltrative, inflammatory, or storage disorders remain probable but unconfirmed based on noninvasive modalities.^{55,56,57}

Thus, differential diagnosis in restrictive cardiomyopathy represents a complex evaluative endeavor that hinges on interpreting a mosaic of subtle clinical features, hemodynamic signatures, tissue-specific imaging findings, systemic manifestations, and, when appropriate, histopathologic markers. The objective is to delineate restrictive cardiomyopathy from a host of mimicking conditions whose management strategies and prognostic implications differ substantially, ensuring that the underlying pathology is accurately identified and appropriately targeted in the therapeutic plan.⁵⁷

Therapeutic management

Therapeutic management of restrictive cardiomyopathy remains one of the most challenging domains within cardiovascular medicine, largely due to the heterogeneous etiologic spectrum, the predominance of irreversible myocardial stiffness, and the limited availability of interventions capable of modifying the underlying structural pathology. The overarching therapeutic philosophy centers on alleviating symptoms related to elevated filling pressures, optimizing hemodynamic stability, preventing arrhythmic and thromboembolic complications, and, whenever possible, implementing etiology-directed strategies aimed at halting or reversing disease progression. Because systolic function is often preserved during the early stages of the disease, conventional heart failure therapies that target left ventricular ejection fraction have limited utility, necessitating a tailored approach grounded in the specific pathophysiologic mechanisms at play.⁵⁸

The mainstay of symptomatic management is meticulous control of volume overload, primarily achieved through the judicious use of diuretics. Loop diuretics, often combined with thiazide-type agents in resistant cases, facilitate reductions in pulmonary and systemic venous pressures, thereby improving dyspnea, orthopnea, and peripheral edema. However, excessive diuresis must be avoided, as

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

patients with restrictive cardiomyopathy depend on adequate preload to maintain cardiac output, and aggressive volume depletion can precipitate hypotension or renal dysfunction. In this context, careful titration of diuretic therapy, coupled with close monitoring of renal parameters and electrolyte profiles, is essential. Vasodilators generally offer limited benefit because the fixed stroke volume limits their hemodynamic impact, and their use may provoke symptomatic hypotension. Beta-blockers and calcium channel blockers may be cautiously employed to modulate heart rate and promote diastolic filling in select patients, although their efficacy is variable and often constrained by the advanced diastolic dysfunction intrinsic to the disease.⁵⁹

Arrhythmia management represents another critical therapeutic domain, as atrial fibrillation and other supraventricular arrhythmias frequently exacerbate symptoms by eliminating atrial contribution to ventricular filling, which is disproportionately important in the setting of restrictive physiology. Rate control strategies may be pursued, but rhythm control is often preferred to preserve atrial mechanical function whenever feasible. Pharmacologic rhythm maintenance, catheter ablation, and device-based interventions may all contribute to arrhythmia management, tailored to the individual patient's clinical stability, atrial anatomy, and comorbid conditions. The heightened risk of thromboembolic events, particularly in the presence of atrial enlargement and atrial fibrillation, necessitates long-term anticoagulation in most patients, guided by an individualized assessment of bleeding risk. In those with advanced conduction disease or chronotropic incompetence, permanent pacemaker implantation may be required, while patients with significant ventricular arrhythmias may benefit from implantable cardioverter-defibrillator therapy.⁵⁹

A pivotal component of modern therapeutic strategy lies in the identification and treatment of specific etiologies underlying restrictive cardiomyopathy. For example, in amyloidosis, the advent of transthyretin stabilizers, monoclonal antibodies targeting amyloid fibrils, and gene-silencing therapies using RNA-interference or antisense oligonucleotides has transformed the therapeutic landscape, offering the possibility of slowing or halting disease progression. In light-chain amyloidosis, early initiation of therapies targeting the plasma cell clone, including proteasome inhibitors and immunomodulatory agents, is essential for improving cardiac outcomes. Patients with iron overload cardiomyopathy can experience substantial improvement in myocardial function through aggressive iron chelation therapy, while those with hypereosinophilic syndromes or endomyocardial fibrosis may benefit from immunosuppressive agents, corticosteroids, or antiparasitic treatments depending on the underlying cause. Genetic forms of restrictive cardiomyopathy increasingly invite the possibility of precision medicine approaches, including

targeted therapies aimed at correcting or mitigating the effects of specific molecular defects.⁵⁹

In advanced cases, where restrictive cardiomyopathy leads to refractory heart failure despite optimal medical therapy, consideration of advanced heart failure interventions becomes necessary. Although mechanical circulatory support is less commonly utilized in restrictive cardiomyopathy due to small ventricular cavity sizes and impaired diastolic filling, select patients may benefit from individualized device strategies. Ultimately, orthotopic heart transplantation remains the definitive therapy for end-stage restrictive cardiomyopathy, offering substantial survival benefit and symptomatic improvement when carefully selected candidates undergo timely referral and evaluation. Pre-transplant assessment must account for the severity of pulmonary hypertension, which may be exacerbated by chronic diastolic dysfunction and could influence eligibility for transplantation. For patients with systemic diseases such as amyloidosis, the feasibility and outcomes of transplantation depend on the degree of extramyocardial involvement and the availability of concomitant disease-modifying therapies.⁶⁰

Palliative care integration also plays an important role in the therapeutic continuum, particularly for patients with progressive disease in whom curative or disease-modifying options are limited. Symptom-focused management, optimization of quality of life, and thoughtful discussions about goals of care ensure that patients receive holistic and patient-centered treatment throughout the disease trajectory.⁶⁰

Together, the therapeutic strategies for restrictive cardiomyopathy reflect a complex interplay between symptomatic relief, arrhythmia control, thromboembolic prevention, and targeted treatment of underlying etiologies. As the understanding of molecular mechanisms continues to expand and novel therapeutic agents are developed, the management of restrictive cardiomyopathy is evolving toward increasingly personalized approaches that hold promise for improving long-term outcomes in this historically challenging condition.⁶¹

CONCLUSION

Restrictive cardiomyopathy stands as a uniquely complex and multifaceted entity within the broader spectrum of myocardial diseases, embodying the convergence of diverse etiologic pathways that culminate in a shared hemodynamic phenotype characterized by profound diastolic dysfunction and preserved or near-preserved systolic performance. The clinical trajectory of this disorder is shaped by the interplay between progressive myocardial stiffness, biatrial dilation, neurohormonal activation, arrhythmogenic vulnerability, and the systemic repercussions of chronically elevated filling pressures. Despite its relative rarity, restrictive cardiomyopathy imposes a significant clinical burden due to

Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

its insidious onset, high morbidity, and the intricate diagnostic challenges that often delay recognition until advanced stages. Contemporary advances in multimodal imaging, biomarker science, molecular genetics, and tissue characterization have markedly improved the ability to detect and characterize this disease, enabling more refined differentiation from phenotypically similar conditions such as constrictive pericarditis, infiltrative cardiomyopathies of alternative presentations, and advanced hypertensive or ischemic heart disease.

The therapeutic landscape of restrictive cardiomyopathy, historically dominated by supportive and symptom-directed interventions, is undergoing a gradual transformation driven by expanding insights into disease-specific mechanisms and the advent of targeted therapies. Novel pharmacologic agents for amyloidosis, improved iron chelation strategies for siderotic cardiomyopathy, and the increasing feasibility of immunomodulatory or antiproliferative therapies for inflammatory or infiltrative etiologies illustrate a shift toward precision-based approaches that address the root cause rather than the downstream hemodynamic consequences. Nevertheless, for many patients, management continues to rely heavily on careful volume regulation, rhythm stabilization, and thromboembolic risk mitigation, underscoring the need for individualized care plans that incorporate meticulous hemodynamic monitoring and close longitudinal follow-up. In advanced or refractory cases, heart transplantation remains the definitive therapeutic option, though its applicability is frequently constrained by extracardiac involvement, comorbidity profiles, and the hemodynamic consequences of long-standing pulmonary hypertension.

As the field progresses, it is increasingly evident that the future of restrictive cardiomyopathy management lies in the integration of high-resolution imaging modalities, molecular diagnostics, and emerging therapeutics within a comprehensive multidisciplinary framework. Continued research into the cellular, structural, and genetic underpinnings of myocardial rigidity promises to refine diagnostic algorithms, identify novel therapeutic targets, and facilitate earlier intervention before irreversible myocardial remodeling ensues. Ultimately, improving outcomes for patients with restrictive cardiomyopathy will depend on the ongoing alignment of clinical vigilance, technological innovation, and translational research, fostering a more nuanced understanding of this complex disorder and guiding the evolution of individualized treatment strategies that address both the physiologic and systemic dimensions of the disease.

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Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

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Restrictive Cardiomyopathy: Contemporary Insights into Pathophysiology, Diagnostic Complexity, and Evolving Therapeutic Perspectives

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