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Original Article

Cardiac Amyloidosis in 2023: Transformative Advances inDiagnosis and Therapy

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Abstract

Cardiac amyloidosis, characterized by amyloid fibril deposition in the myocardium, has seen significant advancements in diagnosis and treatment over the past two decades. This paper reviews the current understanding of cardiac amyloidosis, emphasizing developments up to 2023, including novel diagnostic modalities, therapeutic strategies, and future research directions.JRCD 2023; 4(7): 145–150

key words: Cardiac amyloidosis, amyloid fibril deposition, myocardium, diagnosis, treatment, advancements, 2023, diagnostic modalities, therapeutic strategies, future research directions

Introduction

Cardiac amyloidosis, an increasingly recognized infiltrative cardiomyopathy, is caused by the deposition of amyloid fibrils in the heart, leading to progressive heart failure and arrhythmias [1], [2]. The disease, once considered rare and often misdiagnosed, has come into sharper focus over the past two decades due to advancements in diagnostic and therapeutic strategies [3]. In particular, the differentiation of light-chain (AL) amyloidosis from transthyretin (ATTR) amyloidosis—comprising hereditary (ATTRv) and wild-type (ATTRwt) forms—has been pivotal in understanding the underlying pathophysiology and tailoring treatment. These strides have redefined cardiac amyloidosis from a grim diagnosis with limited options to a manageable chronic condition for many patients [4].

Amyloidosis is a systemic disorder characterized by the extracellular deposition of misfolded proteins in the form of insoluble fibrils. In cardiac amyloidosis, these fibrils infiltrate the myocardium, resulting in thickened ventricular walls, diastolic dysfunction, and restrictive physiology [5]. The pathogenesis varies significantly between AL and ATTR amyloidosis, necessitating a nuanced approach to diagnosis and treatment. AL amyloidosis arises from the overproduction of monoclonal immunoglobulin light chains, typically associated with plasma cell dyscrasias such as multiple myeloma. These light chains not only form amyloid fibrils but also exhibit direct cardiotoxic effects. In contrast, ATTR amyloidosis results from the deposition of transthyretin, a protein primarily synthesized in the liver. While ATTRwt is related to age-associated conformational changes in transthyretin, ATTRv stems from mutations in the transthyretin gene, making it an inherited condition [6].

Historically, the diagnosis of cardiac amyloidosis was challenging, as clinical presentations often mimicked other forms of cardiomyopathy or heart failure with preserved ejection fraction (HFpEF). Symptoms such as fatigue, dyspnea, and peripheral edema are nonspecific, frequently leading to delayed or missed diagnoses. However, the advent of advanced imaging techniques, refined biomarker assays, and genetic testing has transformed diagnostic accuracy. Tools such as cardiac magnetic resonance imaging (CMR) with late gadolinium enhancement, technetium-99m-labeled bone scintigraphy, and serum free light-chain assays now allow for earlier detection and precise characterization of amyloid deposits. These advancements are particularly significant for differentiating between AL and ATTR amyloidosis, a distinction that is critical due to differences in treatment protocols and prognoses [7].

In parallel with diagnostic improvements, therapeutic strategies have also evolved. The management of cardiac amyloidosis now extends beyond symptomatic relief to include disease-modifying treatments that target the underlying amyloidogenic process. For AL amyloidosis, chemotherapy regimens aimed at plasma cell suppression remain the mainstay of treatment, with autologous stem cell transplantation being an option for select patients [8]. Novel agents, such as daratu-

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mumab, have emerged as effective therapies by targeting the clonal plasma cells responsible for light-chain production. ATTR amyloidosis, on the other hand, has benefited from groundbreaking advancements in molecular medicine. Transthyretin stabilizers such as tafamidis have demonstrated significant benefits in reducing mortality and hospitalization rates. Additionally, gene-silencing therapies like patisiran and vutrisiran, which utilize RNA interference to reduce transthyretin production, represent a paradigm shift in the treatment of hereditary forms of the disease [9].

Despite these advancements, challenges remain in the management of cardiac amyloidosis. Many patients are diagnosed at advanced stages of the disease, where therapeutic interventions are less effective. Furthermore, the economic burden of novel treatments such as tafamidis poses significant barriers to accessibility. In AL amyloidosis, the risk of treatment-related complications remains high, particularly in patients with severe cardiac involvement. These challenges highlight the need for continued research and innovation, particularly in early detection methods and affordable treatment options [10].

The clinical landscape of cardiac amyloidosis is further complicated by its systemic nature and association with other organ dysfunctions. AL amyloidosis frequently involves the kidneys, liver, and peripheral nerves, complicating the management of cardiac symptoms. ATTR amyloidosis, particularly the hereditary form, often presents with polyneuropathy, which can overshadow cardiac manifestations and delay diagnosis. Multidisciplinary care involving cardiologists, hematologists, neurologists, and other specialists has thus become essential in optimizing patient outcomes.

Emerging research is shedding light on the molecular mechanisms underlying amyloidogenesis, paving the way for novel therapeutic targets. Efforts to stabilize amyloid precursors, promote fibril clearance, and mitigate downstream organ damage are at the forefront of ongoing clinical trials. Additionally, advancements in genetic screening and molecular diagnostics hold promise for earlier identification of at-risk individuals, particularly in families with hereditary ATTR mutations. Such approaches could enable proactive intervention, potentially preventing the onset of clinical disease.

In this review, we explore the transformative advances in the diagnosis and management of cardiac amyloidosis, with an emphasis on the developments that have shaped the field up to 2023. We discuss the latest diagnostic tools and biomarkers, evaluate the efficacy of emerging treatments, and highlight the challenges that remain in optimizing care for affected patients. By synthesizing the most recent evidence, we aim to provide a comprehensive overview of the current state of cardiac amyloidosis and offer insights into the future directions of research and clinical practice. Through these efforts, we hope to contribute to a broader understanding of this complex and often underdiagnosed condition, ultimately improving outcomes for patients worldwide.

Diagnostic Advancements in Cardiac Amyloidosis

The diagnosis of cardiac amyloidosis, once reliant on invasive procedures and frequently delayed due to nonspecific clinical presentations, has seen remarkable advancements over the past two decades. In 2023, diagnostic tools now allow earlier detection, precise differentiation between types of amyloidosis, and improved risk stratification. These developments have been instrumental in enabling timely treatment, improving outcomes, and tailoring therapeutic approaches to individual patients.

Imaging Modalities

Echocardiography

Echocardiography remains the initial diagnostic modality for suspected cardiac amyloidosis, with specific advancements enhancing its sensitivity and diagnostic power. Traditional echocardiography identifies characteristic features such as ventricular wall thickening, diastolic dysfunction, and biatrial enlargement. Recent advancements in strain imaging, particularly two-dimensional speckle-tracking echocardiography, have significantly improved the ability to detect early myocardial involvement [11]. Global longitudinal strain (GLS) has emerged as a sensitive marker, revealing impaired longitudinal contraction that is often disproportionate to radial and circumferential strain. This pattern, termed “apical sparing,” is highly suggestive of cardiac amyloidosis, particularly ATTR amyloidosis.

Cardiac Magnetic Resonance Imaging (CMR)

Cardiac MRI has become a cornerstone of advanced cardiac amyloidosis diagnosis, offering unparalleled detail in tissue characterization. The hallmark finding on CMR is late gadolinium enhancement (LGE), typically demonstrating a diffuse subendocardial pattern. The unique imaging signature, combined with quantitative assessments of extracellular volume (ECV), allows for the differentiation of amyloidosis from other hypertrophic cardiomyopathies [12]. Moreover, CMR provides critical prognostic information by quantifying amyloid burden, which correlates with disease severity and patient outcomes.

Nuclear Imaging

Nuclear imaging has revolutionized the non-invasive diagnosis of ATTR amyloidosis. Technetium-99m-labeled tracers, such as pyrophosphate (PYP) and 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), selectively bind to transthyretin amyloid deposits. A positive scan with these tracers, in the absence of monoclonal protein evidence, confirms ATTR amyloidosis without the need for endomyocardial biopsy. This approach has

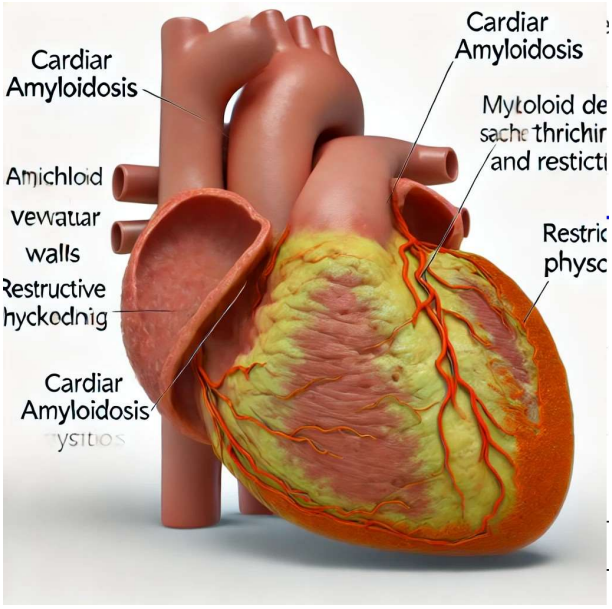

Figure 1: Anatomical illustration of a human heart showcasing amyloid deposits, ventricular thickening, and other pathological changes associated with cardiac amyloidosis

significantly simplified and accelerated the diagnostic process, particularly in elderly patients where ATTRwt amyloidosis is common. In 2023, nuclear imaging is considered the gold standard for differentiating ATTR from AL amyloidosis when combined with serological testing.

Biomarker Developments

Natriuretic Peptides and Troponins

Biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponins are integral to the diagnostic and prognostic evaluation of cardiac amyloidosis. Elevated NT-proBNP reflects increased myocardial stress and filling pressures, while troponin elevation indicates ongoing myocyte injury. The combination of these biomarkers has been incorporated into staging systems for AL amyloidosis, aiding in risk stratification and treatment planning [13].

Free Light Chain Assays

In AL amyloidosis, circulating monoclonal light chains serve as the pathogenic precursor to amyloid fibrils. The serum free light chain (FLC) assay, which quantifies κ and λ light chains and calculates their ratio, is highly sensitive in detecting plasma cell dyscrasias. An abnormal κ/λ ratio strongly suggests clonal production of light chains, guiding further hematologic evaluation. In conjunction with immunofixation electrophoresis of serum and urine, FLC assays provide a comprehensive diagnostic framework for AL amyloidosis [14].

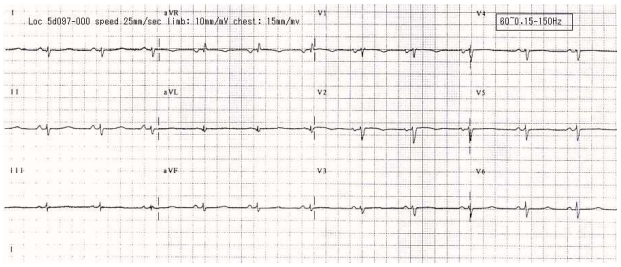

Figure 2: ECG in AL amyloidosis of the heart

Advanced Mass Spectrometry

Mass spectrometry has emerged as a transformative tool for the precise characterization of amyloid fibrils. By analyzing biopsy specimens, this technique can determine the specific amyloidogenic protein, allowing differentiation between AL, ATTR, and rarer forms such as apolipoprotein or fibrinogen amyloidosis. This precision is particularly valuable in cases with atypical presentations or ambiguous imaging results [15].

Tissue Diagnosis

While non-invasive techniques have reduced the need for biopsy in many cases, tissue diagnosis remains the gold standard in challenging or ambiguous scenarios. Endomyocardial biopsy provides definitive evidence of amyloid deposition, with Congo red staining revealing apple-green birefringence under polarized light. Immunohistochemistry or mass spectrometry can then be employed to identify the amyloid subtype [16].

In cases where cardiac biopsy is not feasible, alternative tissue sources such as abdominal fat pad aspirates or minor salivary gland biopsies can confirm systemic amyloidosis. These minimally invasive procedures are positive in approximately 70% of AL amyloidosis cases, reducing the need for more invasive diagnostics.

Genetic Testing

Genetic testing has become a critical component in the evaluation of suspected hereditary ATTR amyloidosis. Mutations in the transthyretin (*TTR*) gene confirm ATTRv amyloidosis, facilitating family screening and genetic counseling. The Ile122Val mutation, common in African American populations, and the Val30Met mutation, prevalent in certain endemic regions, are among the most frequently identified variants. Genetic testing not only aids in diagnosis but also informs therapeutic decisions, particularly in assessing eligibility for targeted RNA interference therapies.

Integration of Multimodal Diagnostics

A key advancement in the diagnosis of cardiac amyloidosis is the integration of multiple diagnostic modalities into streamlined clinical workflows. For example, combining nuclear imaging with FLC assays can rapidly dif-

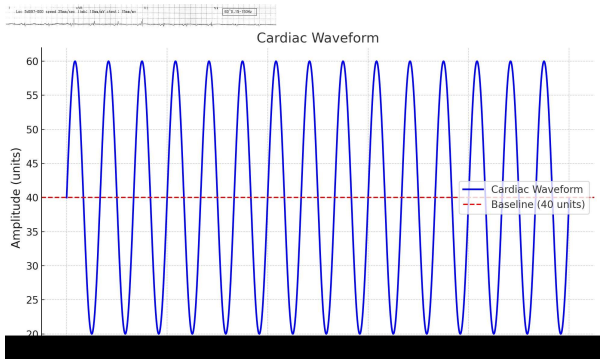

Figure 3: Simultaneous right and left ventricular pressure tracings in a patient with AL amyloidosis and atrial fibrillation

ferentiate ATTR from AL amyloidosis, avoiding delays and unnecessary biopsies. Multidisciplinary amyloidosis centers now leverage these tools to provide comprehensive diagnostic evaluations, improving both accuracy and efficiency.

Therapeutic Developments in Cardiac Amyloidosis

The management of cardiac amyloidosis has undergone remarkable transformation over the past decade, particularly with the advent of disease-modifying therapies targeting the underlying pathophysiology. Historically, treatment options focused primarily on symptom management, leaving patients with limited survival and poor quality of life. By 2023, novel pharmacological approaches, genetic interventions, and advanced supportive therapies have redefined the therapeutic landscape, offering hope for improved outcomes in both light-chain (AL) and transthyretin (ATTR) amyloidosis.

Treatment Approaches for AL Amyloidosis

AL amyloidosis, caused by clonal production of amyloidogenic light chains, is primarily treated with therapies aimed at reducing the production of these misfolded proteins. Early intervention is crucial, as untreated cardiac involvement in AL amyloidosis is associated with a median survival of less than a year.

Chemotherapy and Plasma Cell-Directed Therapies

The cornerstone of AL amyloidosis treatment remains chemotherapy, which targets the underlying plasma cell dyscrasia. Regimens such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD) are widely used, with bortezomib-based therapies showing rapid and deep hematologic responses. These proteasome inhibitors reduce light-chain production, helping to stabilize or improve cardiac function.

Immunotherapy with Monoclonal Antibodies

Recent developments in monoclonal antibody therapy, particularly daratumumab, have expanded treatment options for AL amyloidosis. Daratumumab targets CD38 on plasma cells, promoting their destruction and reducing amyloidogenic light-chain production. Clinical trials have demonstrated improved hematologic responses and survival rates, particularly in patients who are ineligible for high-dose chemotherapy.

Autologous Stem Cell Transplantation (ASCT)

ASCT remains a potentially curative option for highly selected patients with AL amyloidosis. Patients with good performance status and limited cardiac involvement are candidates for this aggressive approach, which uses high-dose melphalan to ablate plasma cells before stem cell rescue. Advances in patient selection and supportive care have reduced treatment-related mortality, making ASCT a viable option for a subset of patients.

Emerging Therapeutics

Ongoing research aims to develop therapies that directly target and clear light-chain deposits from tissues, addressing the toxic effects of amyloid fibrils. Experimental drugs such as CAEL-101, an amyloid-targeting monoclonal antibody, are showing promise in early-phase clinical trials for reversing organ damage, including cardiac involvement.

Treatment Approaches for ATTR Amyloidosis

ATTR amyloidosis, caused by the misfolding and deposition of transthyretin (TTR), has seen significant advancements in both hereditary (ATTRv) and wild-type (ATTRwt) forms. While symptom management was previously the primary strategy, novel disease-modifying therapies have shifted the focus to addressing the underlying molecular defects.

Transthyretin Stabilizers

The development of TTR stabilizers marked a major breakthrough in the treatment of ATTR amyloidosis. These drugs bind to the TTR tetramer, preventing its dissociation into amyloidogenic monomers.

- Tafamidis: Approved for both ATTRv and ATTRwt amyloidosis, tafamidis reduces mortality and cardiovascular hospitalizations in patients with symptomatic cardiac involvement. Clinical trials have demonstrated its ability to slow disease progression, with better outcomes observed in earlier stages of the disease.
- Acoramidis: A next-generation TTR stabilizer currently in clinical trials, acoramidis offers enhanced stabilization of the TTR tetramer and may further improve outcomes compared to existing therapies.

Gene Silencing Therapies

RNA-based therapies targeting TTR production have revolutionized the management of ATTRv amyloidosis. These therapies significantly reduce circulating TTR levels, slowing or halting amyloid deposition.

- Patisiran: An RNA interference (RNAi) therapy, patisiran has been approved for hereditary ATTR amyloidosis with polyneuropathy. By silencing TTR mRNA in the liver, it reduces amyloidogenic protein production and has shown promising results in cardiac endpoints.
- Vutrisiran: A next-generation RNAi therapy, vutrisiran is administered subcutaneously every three months, offering a more convenient dosing regimen with sustained efficacy.
- Inotersen: An antisense oligonucleotide therapy, inotersen also reduces TTR synthesis, offering another therapeutic option for patients with hereditary ATTR amyloidosis.

Amyloid Clearance Strategies

Amyloid fibril clearance represents a novel frontier in the treatment of cardiac amyloidosis. Monoclonal antibodies targeting amyloid deposits, such as PRX004, are under investigation for their potential to promote fibril clearance and reverse organ dysfunction. Although in early phases, these therapies offer hope for reducing the amyloid burden in affected tissues.

Supportive Therapies for Cardiac Amyloidosis

Diuretics and Heart Failure Management

Diuretics remain the mainstay of symptomatic management for heart failure in cardiac amyloidosis. Their judicious use helps alleviate congestion and reduce preload, but care is needed to avoid hypotension, particularly in patients with autonomic dysfunction.

Anticoagulation and Rhythm Management

Atrial fibrillation is common in cardiac amyloidosis and carries a high risk of thromboembolism. Anticoagulation is strongly recommended, even in sinus rhythm if there is evidence of atrial dysfunction. Rhythm management strategies, including the use of amiodarone, may be employed, though the efficacy is often limited due to extensive atrial involvement.

Pacemakers and Implantable Defibrillators

Advanced conduction system disease in amyloidosis may necessitate pacemaker implantation. However, the role of implantable cardioverter-defibrillators (ICDs) remains controversial, as sudden death in amyloidosis is often due to electromechanical dissociation rather than ventricular arrhythmias.

Multidisciplinary Care and Future Directions

The complexity of cardiac amyloidosis underscores the importance of a multidisciplinary approach to management. Cardiologists, hematologists, neurologists, and genetic counselors work together to provide comprehensive care, optimizing outcomes for this multifaceted condition.

Future research is focused on developing therapies that combine fibril clearance with the prevention of amyloid formation. Advances in genetic screening and early intervention hold promise for preventing disease progression in at-risk individuals. Additionally, efforts to improve the affordability and accessibility of novel therapies are critical to ensuring equitable care for all patients.

Conclusion

The diagnostic landscape of cardiac amyloidosis in 2023 reflects a paradigm shift from invasive, delayed diagnoses to precise, non-invasive, and early detection. Innovations in imaging, biomarkers, and genetic testing have not only improved diagnostic accuracy but also enhanced the ability to stratify risk and tailor treatment. As these tools become more accessible, the prospects for early intervention and better patient outcomes continue to improve, marking a new era in the management of this complex condition.

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