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Opinion Article

Cardiac Amyloidosis: Emerging Diagnostic Strategies and Therapeutic Innovations

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DESCRIPTION

Cardiac amyloidosis, once considered a rare and invariably fatal condition with limited therapeutic options, has emerged as an increasingly recognized cause of heart failure with substantial advances in both diagnosis and treatment over the past decade. The evolving aspect of cardiac amyloidosis has been driven by increased disease awareness, improved non-invasive diagnostic techniques, and breakthrough targeted therapies that have fundamentally altered the natural history of this previously devastating condition.

Amyloidosis encompasses a group of disorders characterized by extracellular deposition of misfolded proteins that aggregate into insoluble fibrils with a characteristic β-pleated sheet conformation. While over 30 proteins have been identified as potential precursors of amyloid fibrils, two types account for the vast majority of cardiac involvement: Immunoglobulin light chain Amyloidosis and Transthyretin (ATTR) amyloidosis, the latter comprising both hereditary and wild-type forms. The clinical presentation of cardiac amyloidosis typically includes heart failure with preserved ejection fraction, ventricular wall thickening, restrictive filling patterns, and various electrical disturbances, often accompanied by systemic manifestations that reflect the multiorgan nature of the disease.

The diagnosis of cardiac amyloidosis has historically been challenging, with significant delays between symptom onset and definitive diagnosis frequently exceeding one year. The non-specific nature of early symptoms, the heterogeneity of clinical presentations, and the requirement for specialized testing have contributed to this diagnostic challenge. However, increased disease awareness and the development of non-invasive diagnostic algorithms have substantially improved early detection rates. Contemporary approaches often begin with recognition that suggest amyloid infiltration, including disproportionate left ventricular hypertrophy relative to electrocardiographic voltage, intolerance to standard heart failure medications, discordance between degree of diastolic dysfunction and age, and characteristic echocardiographic findings such as speckled myocardial appearance and relative apical sparing on strain imaging.

Cardiac Magnetic Resonance imaging (CMR) has emerged as a powerful diagnostic tool, with characteristic late gadolinium enhancement patterns and abnormal myocardial and blood pool kinetics demonstrating high sensitivity and specificity for cardiac amyloidosis. The development of more widely available nuclear scintigraphy techniques using bone avid tracers has revolutionized the diagnosis of ATTR cardiac amyloidosis specifically. The high sensitivity and specificity of these nuclear techniques, when combined with appropriate serum and urine testing to exclude AL amyloidosis, allow for non-invasive diagnosis of ATTR cardiac amyloidosis without the need for endomyocardial biopsy in many cases. This simplified diagnostic pathway has contributed significantly to increased detection rates, particularly of ATTRwt, which is now recognized as a common cause of heart failure with preserved ejection fraction in older adults, especially men.

The therapeutic landscape for cardiac amyloidosis has undergone a parallel transformation, with novel targeted therapies addressing the underlying disease processes rather than merely managing symptoms. For AL amyloidosis, the introduction of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies has dramatically improved hematologic response rates and survival. The goal of therapy in AL amyloidosis is rapid suppression of the clonal plasma cell population producing the amyloidogenic light chains, ideally achieving complete hematologic response. Autologous stem cell transplantation remains an option for selected patients without advanced cardiac involvement, while those with significant cardiac disease typically receive less intensive chemotherapy regimens.

For ATTR amyloidosis, three distinct therapeutic approaches have emerged: Stabilization of the transthyretin tetramer to prevent dissociation into monomers that can misfold and aggregate; suppression of transthyretin production through gene silencing; and removal of existing amyloid deposits. Transthyretin stabilizers include tafamidis, which received Food

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and Drug Administration (FDA) approval for ATTR cardiomyopathy based on the landmark ATTR-act trial demonstrating reduced all-cause mortality and cardiovascular hospitalizations. Non-selective stabilizers like diflunisal (a non-steroidal anti-inflammatory drug) have shown benefit in ATTRv polyneuropathy but must be used cautiously in patients with cardiac involvement due to potential nephrotoxicity and fluid retention.

CONCLUSION

Despite these advances, several challenges remain in the management of cardiac amyloidosis. Diagnosis often occurs at advanced stages when significant irreversible organ damage has already occurred, highlighting the importance of early detection strategies. Screening high-risk populations, such as patients with unexplained left ventricular hypertrophy, heart failure with preserved ejection fraction, specific ethnic groups with high prevalence of amyloidogenic transthyretin variants, and individuals with bilateral carpal tunnel syndrome or spinal stenosis (conditions associated with systemic ATTR amyloidosis), may identify patients at earlier, more treatable stages. Additionally, the optimal timing and sequencing of available therapies, particularly for ATTR amyloidosis with multiple mechanistic approaches now available, requires further investigation.