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Noninvasive Identification of ATTRwt Cardiac Amyloid: The Re-emergence of Nuclear Cardiology

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ABSTRACT

More than half of all subjects with chronic heart failure are older adults with preserved ejection fraction (HFpEF). Effective therapy for this condition is yet to be delineated by clinical trials, suggesting that a greater understanding of underlying biologic mechanisms is needed, especially for the purpose of clinical intervention and future clinical trials. Amyloid infiltration of the myocardium is an underappreciated contributing factor to HFpEF that is often caused by misfolded monomers or oligomers of the protein transthyretin. While previously called senile cardiac amyloidosis and traditionally requiring endomyocardial biopsy for diagnosis, advances in our pathophysiologic understanding of this condition, coupled with nuclear imaging techniques using bone isotopes that can diagnose this condition noninvasively and the development of potential therapies, have resulted in a renewed interest in this previously considered "rare" condition. This reviewer focuses on the re-emergence of nuclear cardiology using pyrophosphate agents that hold promise for early, noninvasive identification of affected individuals.
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KEYWORDS: Aging; Cardiac amyloid; Senile cardiac amyloid; Technetium pyrophosphate

Heart failure is among the most common causes of hospitalization among older adults in the US, with annual mortality rates of 15%-50%.[1] The incidence and prevalence of heart failure are strikingly age-dependent, with prevalence rates in adults >80 years approaching 10% and mortality rates increasing with advancing age. More than 50% of heart failure patients have heart failure with a preserved ejection fraction (HFpEF). The hospitalization rate continues to increase among subjects with HFpEF, as compared with a flattening in those with systolic heart failure.[2] Large-scale clinical trials,[3-7] unfortunately have not demonstrated efficacy of any specific therapy for the population with HFpEF. Identifying distinct subgroups of patients with HFpEF is vital, because the mechanism(s) of disease, prognosis, and optimal treatment can differ between groups. Thus, it is important to search for underlying mechanisms and prognostic factors in HFpEF, especially for the purpose of clinical intervention and future clinical trials. With an increasing burden of disease and the lack of efficacy observed in recently conducted clinical trials, a greater understanding of biologic mechanisms that contribute to diastolic dysfunction and the genesis of HFpEF is warranted.

Numerous biologic mechanisms have been implicated in the genesis of myocardial stiffness,[8-10] including intrinsic cardiomyocyte stiffness[9,11] related to abnormal calcium homeostasis,[12] the cytoskeleton (eg, microtubules and intermediate filaments[13,14] or titin[15,16]), as well as abnormalities in the extracellular matrix related to collagen and elastin.[17-20] Amyloid infiltration in the extracellular matrix markedly alters myocardial stiffness, resulting in upward and leftward shifts in the end-diastolic pressure volume

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relation[21]; it is associated with most severe forms of diastolic dysfunction by Doppler imaging,[22] and in vitro length-tension experiments demonstrate increased diastolic force compared with controls.[23] These data suggest that amyloid infiltration is a mechanism underlying HFpEF.

The diagnosis of transthyretin cardiac amyloidosis is difficult to make on clinical grounds alone, as congestive heart failure, atrial arrhythmia, and conduction abnormalities are all nonspecific disease manifestations and are otherwise common in older persons.[24] Classically, the gold standard for diagnosis is endomyocardial biopsy, which is not only costly (~$5400 including costs for pathologic interpretation), but also requires technical expertise for its performance and pathological evaluation. While a few presentations are more suggestive of the underlying restrictive physiology, including marked right-sided heart failure with increasing abdominal girth, early satiety, and lower-extremity edema, as well as the development of relative hypotension in a person with longstanding hypertension, none of these findings have sufficient sensitivity or specificity to establish the diagnosis. Thus, additional diagnostic testing is always required.

CLINICAL SIGNIFICANCE

- Amyloid infiltration of the heart is an under-appreciated cause of heart failure with preserved ejection fraction.
- Transthyretin (TTR) cardiac amyloid can be due to either mutations, called familial amyloid cardiomyopathy, inherited autosomal dominantly, or from wild-type TTR (formerly called senile cardiac amyloidosis).
- Cardiac imaging with bone scintigraphy has a high sensitivity and specificity for establishing the presence of TTR *not* light chain (AL) cardiac amyloidosis.

The most commonly ordered studies are the electrocardiogram and 2-dimensional transthoracic echocardiogram. Classic electrocardiographic findings in patients with cardiac amyloidosis include low QRS voltage, pseudo-infarction patterns, conduction abnormalities including bundle branch block and hemi-block, and rhythm disturbances such as atrial fibrillation. However, the classic finding of low voltage is a late-phase development in transthyretin cardiac amyloidosis, and a minority of subjects with biopsy-proven disease has low voltage based on typical definitions involving standard 12-lead electrocardiograms.[25] Indeed, up to 15% of patients have electrocardiographic evidence of left ventricular hypertrophy.[25] More useful is to calculate the voltage-to-mass ratio from the electrocardiogram and echocardiogram, though in practice this is rarely performed. In reality, however, electrocardiographic findings lack both sensitivity and specificity for subjects with biopsy-proven cardiac amyloidosis. The combination of low voltage and pseudo-infarct patterns are seen in only a minority of patients, and low voltage can be seen in many other conditions, including obesity, chronic obstructive pulmonary disease, pericardial effusion, and hypothyroidism.

As with the electrocardiogram, classic echocardiographic patterns of cardiac amyloidosis do exist, but are neither sensitive nor specific. Patients with cardiac amyloidosis are more likely to have thickened ventricular walls and refractile myocardium. However, in the early phases of the disease, many patients with amyloid will have normal or just slightly elevated echocardiographic wall thickness, and only a minority will have characteristic granular echogenicity. Data using bone isotopes (discussed below) have demonstrated that myocardial tracer uptake occurs before manifest echocardiographic findings indicative of transthyretin cardiac amyloid, demonstrating the enhanced sensitivity of this approach in comparison with echocardiography.[26-29]

Additional modalities can be used to further increase diagnostic accuracy. Sub-endocardial myocytes are oriented longitudinally and are particularly susceptible to damage in amyloidosis, resulting in early impairment in longitudinal contraction not appreciated on standard 2-dimensional echocardiography when evaluating global indices such as ejection fraction. More advanced echocardiographic techniques such as tissue Doppler imaging, as well as strain and strain rate measurements, which assess cardiac systolic function predominantly by assessing contraction of the heart along its short axis, can be useful. Both strain and strain rate techniques can show characteristic impairments—the pattern of apical sparring, especially, can enhance the suspicion for cardiac amyloidosis[30]—but their utility in early diagnosis has not been carefully studied.

Cardiac magnetic resonance imaging can also be used to identify cardiac amyloid. Intravenous gadolinium contrast accumulates within amyloid infiltrated myocardium. As a result, the combination of myocardial late gadolinium enhancement and altered gadolinium blood pool kinetics can suggest the presence of amyloid and localize it within the heart. Reports from small single-center studies suggest that sensitivity is reasonably high (~85%)[31-34] and that, while specific patterns are more suggestive of cardiac amyloid (eg, sub-endocardial enhancement), the patterns in cardiac amyloid can be quite heterogeneous,[35,36] thus, the specificity for identifying cardiac amyloid is reduced. Additionally, neither of the commonly employed imaging techniques (echocardiography or magnetic resonance imaging) can distinguish primary light chain from transthyretin cardiac amyloid.

Literature shows transthyretin cardiac amyloid is underdiagnosed and much more common than previously thought.[24,25,37,38] Transthyretin cardiac amyloidosis predominately afflicts older adults in their seventh and eighth decade of life. One form of the disease, previously called senile cardiac amyloidosis, is caused by deposits of monomer, oligomers of wild-type transthyretin (ATTRwt), and