T he systemic amyloidoses are disorders of protein folding that are characterized by the deposition of insoluble protein aggregates in soft tissue, nervous system, and solid organs. Amyloidosis is categorized by precursor protein, the most common entities involving the heart being light chain (AL) and transthyretin (TTR). Although the diagnosis of amyloidosis requires a tissue biopsy that demonstrates characteristic staining (typically Congo red), cardiac amyloidosis can be inferred in the context of suggestive noninvasive testing and concurrent identification of amyloid, histologically in another organ or site.1

Article see p 195

Cardiac amyloidosis is widely held to be a rare entity, and indeed, AL disease is rare, with an estimated incidence of ≈1 in 100,000, with cardiac involvement seen in ≈50% of cases.2,3 TTR amyloidosis (ATTR), subclassified as genetically normal (wild-type or senile systemic amyloidosis) or genetically abnormal (mutant/variant or familial amyloid cardiomyopathy), may be much more prevalent than is presently appreciated. Senile systemic amyloidosis disease is almost uniformly seen in men >60 years of age.4 Autopsy studies have demonstrated the presence of wild-type TTR amyloid aggregates in up to 25% of the elderly (>85 years of age), with ≈5% to 15% having extensive deposition.5,6 Furthermore, the most common inherited mutation in TTR, a valine-to-isoleucine substitution at position 122 (V122I or Ile122), has an accepted prevalence of 3% to 4% among US blacks and seems to be associated with the development of heart failure in elderly black patients.7 Thus, as the population ages and longevity increases, the incidence of TTR cardiac amyloidosis, both wild type and variant, will likely increase.

Amyloid infiltration results in progressive ventricular wall thickening, diastolic dysfunction, and heart failure with preserved ejection fraction, findings common in the general aged population and typically attributed to coexistent hypertension or other causes of diastolic heart failure. For this reason, diagnosis of cardiac amyloidosis is infrequently entertained by clinicians.8 Furthermore, serum tests in cardiac amyloidosis such as B-type natriuretic peptides and cardiac troponins, as well as echocardiographic findings, are relatively nonspecific. Although cardiac magnetic resonance imaging can identify patterns that might better separate cardiac amyloidosis from other processes, substantial overlap remains in imaging characteristics between AL and ATTR.9,10 Cardiac biopsy can clarify the diagnosis by identifying the precursor protein through histological or mass spectrometry techniques but is not feasible for all patients with suspected disease because of the risks associated with the procedure.

Many clinicians continue to falsely believe that cardiac amyloidosis has no effective treatments, but data now suggest the contrary. Contemporary chemotherapeutic strategies for AL can extend survival >12 years.11,12 Conventional treatment of TTR disease requires liver transplantation; however, new medical treatments for TTR disease that can halt TTR protein misfolding are now clinically available. Additionally, innovative new pharmacological strategies that involve suppression of TTR expression with antisense oligodeoxynucleotides or RNA interference are approaching human clinical trials.4

In this context, the work of Bokhari et al13 in this issue of Circulation: Cardiovascular Imaging has great potential. Using a Food and Drug Administration–approved, long-established, technetium-based tracer (99mTc-PYP) that is approved for bone scans and historically used for myocardial infarct–avid imaging, the authors report that a simple nuclear scan can provide a means to selectively distinguish TTR cardiac amyloidosis from AL. Although simple in design, the findings of the study are nuanced and, once verified in a larger cohort, represent great potential for immediate clinical impact. The authors enrolled 45 subjects, all with cardiac amyloidosis (cardiac biopsy proven in 82%), and obtained planar and single-photon emission computed tomography studies using 99mTc-PYP. Subjects included those with AL disease (n=12), ATTR wild type (n=16), and mutant ATTR (n=17, 70% of whom had V122I). Scans were then interpreted by blinded nuclear cardiologists and analyzed semiquantitatively by visual inspection (assigned a score of 0–3 on the basis of the intensity of myocardial tracer uptake relative to bone) and quantitatively by determining the number of counts, corresponding to a region of interest over the heart normalized to an identically sized area localized over the contralateral chest (defined as the heart:contralateral ratio [H/CL]). The authors found that tracer uptake was significantly greater among ATTR patients, regardless of wild type or variant, compared with AL patients by both visual semiquantitative and quantitative analysis methods. Using receiver-operating

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characteristic analysis, they concluded that an H/CL ratio ≥1.5 conferred a sensitivity and specificity for the differentiation of ATTR from AL that approached 100%. Markers of disease severity, including biomarkers and modified body mass index, were similar among AL and ATTR patients, supporting the commonly held perception that such measures are inadequate to differentiate disease type. The authors report that in multivariable analysis, the only independent variable associated with H/CL ratio was AL versus ATTR status.

Closer inspection of the data reveals some interesting observations. First, patients with wild-type ATTR (senile systemic amyloidosis) tended to be older and had significantly greater wall thickness and left ventricular mass, as predicted, whereas patients with mutant ATTR and AL were similar in these measures. Although tracer uptake (H/CL) correlated with both wall thickness and mass index for the entire cohort, it is important to note that tracer uptake among mutant ATTR was still significantly greater than AL, despite similar wall thickness. Second, review of the visual semiquantitative analysis indicates that there was minimal overlap between the groups, with only 2 AL patients with uptake graded as ≥2 (corresponding to uptake greater than or equal to bone) and only 1 ATTR subject with uptake <2 (absent uptake or less than bone). The semiquantitative analysis findings relative to bone uptake are critical to the widespread applicability of this test such that acquisition and analysis can be performed in the context of normal clinical workflow. Its weakness, however, is its inherent subjectivity, rendering the equally straightforward region-of-interest quantitative count analysis method proposed by the authors very appealing.

This study is by no means the first report of 99mTc-PYP or other technetium-based tracers for the identification of cardiac amyloidosis.14 Well summarized in the Discussion, prior studies over the past 3 decades using 99mTc-PYP have been limited by technique and incomplete characterization of amyloid type, diminishing enthusiasm. Importantly, data using 99mTc-PYP to differentiate amyloid from other forms of heart failure are limited. Other reported tracers that have efficacy in TTR cardiac amyloidosis include 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) and 99mTc-methylene diphosphonate (99mTc-MDP). 99mTc-DPD, widely used in Europe but unavailable in the United States, has had similarly excellent reported efficacy, showing >100% discrimination between amyloid type in small studies, whereas larger studies showed greater overlap.15–17 That being said, 99mTc-DPD uptake is considered strongly suggestive of TTR.

The major imaging and interpretive advance in the present report is the authors’ use of quantitative analysis of myocardial 99mTc-PYP uptake. This approach uses the inherently quantitative nature of nuclear imaging to complement semiquantitative subjective interpretation, which likely limited the power of previous use of this imaging technique in cardiac amyloidosis. In fact, although the authors describe that single-photon emission computed tomographic imaging was performed in patients who demonstrated 99mTc-PYP uptake on planar imaging, the H/CL data can easily be obtained from a rapidly acquired anterior planar image. It is notable that the contralateral chest region of interest using this anterior projection had consistent count data in all groups, validating the fact that an increased H/CL ratio came from increased myocardial 99mTc-PYP uptake.

Why 99mTc-PYP and other bone-avid compounds bind TTR amyloid in the heart is not clear. The authors hypothesize that calcium-dependent binding is a critical feature of uptake but acknowledge that the underlying mechanisms remain unknown. Importantly, they show that normalized calcium levels and renal function are similar among their 3 subject groups and that none is associated with H/CL ratio in the multivariate model. The study has some notable limitations that the authors acknowledge. Besides the small cohort size (which is an important caveat affecting interpretation of these data), there are no nonamyloid subjects such as those with left ventricular hypertrophy from hypertension or hypertrophic cardiomyopathy. Furthermore, one would expect that patients with prior myocardial infarction and calcification of scar would also uptake this bone-avid tracer, a particularly important point given the advanced age of TTR patients and the higher likelihood of comorbid coronary atherosclerosis. Interestingly, 1 of the 2 AL patients with uptake ≥2 had a history of myocardial infarction and a focal rather than diffuse pattern of tracer uptake. This suggests that concomitant perfusion imaging, for example, with thallium-201, may further enhance the specificity of this method in patients with a history of coronary artery disease.18

Finally, there are many intriguing questions raised that must be answered before widespread adaptation of 99mTc-PYP can be recommended. First, is there a threshold level of wall thickness in TTR disease wherein 99mTc-PYP uptake is seen? Second, will uptake be seen in the elderly with sub-clinical amyloid disease attributable to the high prevalence of TTR amyloid observed (25% aged >85 years)? Third, will the sensitivity and specificity be favorable so that 99mTc-PYP might be used as a noninvasive screening test for TTR disease, not simply as a discriminator from AL? In addition, will uptake reduce after treatment with new medicines for TTR disease, and thus can 99mTc-PYP be used to follow end-organ response to anti-TTR treatment (as is the case in AL with 123I-SAP for noncardiac amyloid burden)? These questions, as well as the concerns about previous myocardial infarction and differentiation of cardiac amyloidosis from hypertensive and hypertrophic cardiomyopathy, require further study.

99mTc-PYP has great potential to have substantial clinical impact in the recognition of TTR cardiac amyloid disease because of widespread availability, low cost, and ease of image analysis. Bokhari et al are to be commended for rejuvenating an old, disregarded radiopharmaceutical and subjecting it to appropriate scrutiny. Further vetting is required, however, with larger, more diverse cohorts before widespread adaptation.

Disclosures

None.

References


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