Optimizing Tc-99m-DPD scintigraphy: adding value to the diagnosis and treatment of cardiac transthyretin amyloidosis

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Optimizing ^{99m}Tc-DPD scintigraphy: Adding value to the diagnosis and treatment of cardiac transthyretin amyloidosis

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Systemic transthyretin (ATTR) amyloidosis is an underdiagnosed disease in which cardiac involvement is the dominant clinical feature and the leading cause of morbidity and mortality.[1] ATTR can be the result of an inherited mutation (ATTRv) in the TTR gene, or from so-called ''wild-type'' ATTR (ATTRw), in which there is no genetic mutation. Once thought to be a rare disease, ATTR cardiac amyloidosis (ATTR-CA) is now increasingly recognized, and is a common comorbidity in calcific aortic stenosis (occurring in up to 16% of patients referred for interventional therapy[2]). ATTR-CA can also manifest as heart failure with preserved ejection fraction (HFpEF), atrial fibrillation, conduction disturbances, and sinus node dysfunction—especially in men over 60 years of age.[3,4] Up to 29% of patients with HFpEF have ATTR-CA, which has been considered as a reason for the failure of standard heart failure therapies in HFpEF trials.[5] Evidence is accruing for a number of paradigm-shifting therapies with the ability to change the natural course of this disease.[6] These drugs, e.g., tafamidis, are expected to demonstrate a greater benefit when administered early in the disease course.[6,7] The accurate and timely diagnosis and staging of ATTR-CA are therefore imperative. Although the reference standard for ATTR-CA diagnosis is histology, cardiac biopsy is invasive and not amenable to repetition. Technetium-99m (^{99m}Tc)-labeled scintigraphy has proven to be highly sensitive and fairly specific for the diagnosis of ATTR-CA, and various radiotracers have been employed, e.g., ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP).[8-10] Myocardial ^{99m}Tc uptake in ATTR is likely related to binding of the tracer to microcalcifications occurring within ATTR fibrils, and visualization involves planar and single-photon emission computed tomography/computed tomography (SPECT-CT) imaging after intravenous administration of the radiotracer. SPECT imaging is required to distinguish left ventricular blood pool uptake from myocardial uptake, and lowers the number of false-negative studies. Scintigraphy has shown promise not only for diagnosis of ATTR-CA, but also as a risk-stratification tool: the regional distribution of ^{99m}Tc-PYP has been linked to mortality in a population of patients with confirmed ATTR-CA.[11] Despite its proven ability to diagnose, stage, and risk-stratify ATTR-CA, the technique of ^{99m}Tc-labeled scintigraphy has not been rigorously standardized. A reproducible approach to ^{99m}Tc-labeled scintigraphy for ATTR-CA is of importance not only for patient-level diagnosis and follow-up, but also for the performance of multicenter studies.

In the current issue of the journal, Schatka et al.[12] compared various iterations of a planar and SPECT/CT scintigraphy protocol for ^{99m}Tc-DPD in the diagnosis of ATTR-CA. The authors compared the timing of planar imaging at 1 hour post infusion (p.i.) and at 3 hours p.i. and investigated whether H-mode or L-mode would perform better in SPECT/CT.[13] By calculating Perugini (visual) scores and heart to contralateral (H/CL) ratios from planar images 1 hour and 3 hours p.i. in 25 patients with and 38 without ATTR-CA, they could demonstrate that sensitivity and specificity were $\geq$ 95% for H/CL ratios at both time points. Visual scores at 1 hour p.i.

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were less specific for the diagnosis of ATTR-CA, and therefore the addition of earlier imaging (1 hour p.i.) added no real benefit. Accurate and reproducible quantification of myocardial ^{99m}Tc-DPD uptake could be achieved with both H-mode and L-mode SPECT/CT, but was superior when employing H-mode, especially with reference to extracardiac disease.

^{99m}Tc-scintigraphy has been thoroughly investigated and biopsy-proven as a diagnostic technique in ATTR-CA.[8,9] Although previous studies have examined the potential benefits of an optimized imaging protocol for ^{99m}Tc-PYP scintigraphy (mainly used in the USA),[14] similar data for ^{99m}Tc-DPD (which is more commonly used in Europe) are lacking. Castano et al.[14] found a lower sensitivity of ^{99m}Tc-PYP scintigraphy at 3 hours p.i., compared to 1 hour p.i., which is in contrast to the current study. While a different tracer (^{99m}Tc-PYP) was used, similar clearance to ^{99m}Tc-DPD in a preclinical rodent model argues against this as a reason for the discrepancy.[15]

Although ^{99m}Tc-DPD scintigraphy has an established role in the diagnosis of ATTR-CA, little attention has been paid to standardizing and optimizing the technique itself. With the advent of effective amyloid-specific therapies, it is reasonable to expect that ^{99m}Tc-DPD scintigraphy will be performed more frequently than what it currently is. Most data on its diagnostic performance originate from large centers of excellence, and proliferation of the technique will likely lead to ^{99m}Tc-scintigraphy being performed often in smaller centers. This trend mandates rigorous standardization in order to achieve the highest possible diagnostic efficacy, and to counter the potential effect of populations with a lower pretest probability. Optimization and standardization of the technical aspects of ^{99m}Tc-DPD scintigraphy may improve the diagnostic performance even further, and allow meaningful comparison when multicentric studies are performed. Many questions regarding ^{99m}Tc-scintigraphy remain: while its diagnostic performance is known in populations with a high pretest probability, little data exist on ^{99m}Tc-scintigraphy as a screening test. The Screening for Cardiac Amyloidosis Using Nuclear Imaging for Minority Populations (SCAN-MP; NCT03812172) study is expected to shed more light on scintigraphy in elderly African American and Hispanic populations with HFpEF. The timeous institution of pharmacotherapy for ATTR-CA will be predicated on early diagnosis, while currently early stages of the disease are considered a cause of false-negative scans. The utility of ^{99m}Tc-DPD scintigraphy as a biomarker for treatment response to the multitude of emerging therapies requires delineation. ATTR-CA's exact prognostic impact (and the effect of treatment) in calcific aortic stenosis still remains unknown. The realization that ATTR-CA underlies up to a third of HFpEF, carries the possibility of ^{99m}Tc-scintigraphy taking center stage in heart failure clinics; all the more reason to ensure that the test itself has been standardized and refined to a level commensurate with the challenge posed by the many clinical questions remaining around ATTR-CA.

Disclosures

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