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Can ^{99m}Tc-Pyrophosphate Aid in Early Detection of Cardiac Involvement in Asymptomatic Variant TTR Amyloidosis?

Amyloid transthyretin-related cardiac amyloidosis (ATTR-CA) is increasingly recognized as an important cause of heart failure with preserved ejection fraction (HFpEF) (1). Recent single-center studies in North America have established the high sensitivity and specificity of 99m-technetium pyrophosphate (^{99m}Tc-PYP) cardiac imaging in the noninvasive detection of ATTR-CA (2,3). ATTR-CA can result from genetically normal (wild-type) or mutant ATTR protein (ATTRm). Transthyretin (TTR) mutations exhibit autosomal dominant inheritance and affect individuals of all ages with variable penetrance and phenotype. The most common TTR mutation in the United States, the valine for isoleucine substitution at position 122 (V122I), is found in ~4% of African Americans (4). Although ^{99m}Tc-PYP imaging has shown utility in identification of ATTR-CA in patients with heart failure, the capacity of ^{99m}Tc-PYP to detect TTR deposition in asymptomatic carriers of TTR mutations remains undetermined. We therefore investigated whether ^{99m}Tc-PYP cardiac imaging can detect early uptake in patients with mutant TTR genopositivity but without heart failure in a single-center experience.

Forty patients who underwent clinical examinations, echocardiography, measurement of cardiac biomarkers, and ^{99m}Tc-PYP scintigraphy (planar imaging) were subsequently subdivided into 3 groups: group 1 included patients with nonamyloid HFpEF (n = 8); group 2 included asymptomatic TTR mutation carriers (n = 12); and group 3 included patients with TTR mutation and symptomatic heart failure (ATTRm) (n = 20). The cohort consisted of 13 mutations, including V122I, T60A, V30M, E42G/H90N, Y114C, D18G, T59K, S77Y, L58H, E89K, F64L, A97S, and F33L. Cardiac magnetic resonance and echocardiographic strain parameters were not acquired in this study. Cardiac biomarkers (brain-type natriuretic peptide and troponin I) were measured at the time of nuclear scanning. Cardiac uptake of ^{99m}Tc-PYP was assessed using both a semiquantitative visual score (range 0 [no uptake] to 3 [uptake greater than bone]) and a heart-to-contralateral (H/CL) ratio of uptake on planar images. Grade 0 is considered normal, grade 1 indeterminate, and grade 2 or 3 supports TTR deposition. Continuous and categorical variables were compared between the groups.

As shown in **Table 1**, asymptomatic TTR mutation carriers appeared echocardiographically, biochemically, and clinically normal when compared to patients with ATTRm cardiac amyloidosis as determined by left ventricular ejection fraction, interventricular septal thickness, E/e′, brain-type natriuretic peptide, and troponin I. In contrast, qualitative analysis of ^{99m}Tc-PYP uptake in the 12 asymptomatic TTR

TABLE 1 Clinical, Genetic, Echocardiographic, and Scintigraphic Characteristics of ATTR and HFpEF

	HFpEF (n = 8)	Asymptomatic TTRm Carriers (n = 12)	Symptomatic TTRm Carriers (ATTRm) (n = 20)	p Value
Age, yrs	72 ± 8	51 ± 15*†	68 ± 9	0.003
Male	6 (75)	8 (67)	17 (80)	0.477
NYHA functional class > II	2 (25)	0 (0)	5 (25)	
TTR mutation				
V122I	0	1 (8)	8 (40)	
T60A	0	4 (33)	5 (25)	
V30M	0	1 (8)	1 (5)	
B-type natriuretic peptide, pg/ml	1,042 (484–1,263)	15 (10–37)*†	234 (128–752)	0.001
Troponin, ng/ml	0.1 (0.02–0.21)	0.008 (0.006–0.01)*†	0.09 (0.03–0.19)	<0.001
Left ventricular ejection fraction, %	59 ± 14	61 ± 8†	51 ± 14	0.04
Interventricular septal thickness, cm	1.2 ± 0.2	0.9 ± 0.3†	1.5 ± 0.3	<0.001
E/e′	18.8 ± 8.2	8 .1 ± 1.5*†	18.1 ± 8.9	<0.001
Abnormal ^{99m}Tc-PYP visual grade	4 (50)	10 (83)	20 (100)	0.04
H/CL ratio	1.2 ± 0.1	1.5 ± 0.4*†	1.8 ± 0.4	<0.001

Values are mean ± SD, n (%), or median (interquartile range). *p < 0.05 in comparison to HFpEF. †p < 0.05 in comparison to ATTRm.

ATTR = amyloid transthyretin; ATTRm = amyloid transthyretin mutation; H/CL = heart-to-contralateral ratio; HFpEF = heart failure with preserved ejection fraction; NYHA = New York Heart Association; ^{99m}Tc-PYP = 99m-technetium pyrophosphate (abnormal uptake = grade 1, 2, or 3); TTRm = transthyretin mutation.

mutation carriers revealed at least some degree of myocardial uptake in 10 cases (84%) and diagnostic tracer avidity (grade 2 or 3) in 7 cases (58%). Quantitatively, ^{99m}Tc-PYP uptake was increased among asymptomatic carriers (H/CL ratio 1.5 ± 0.4) versus patients with nonamyloid HFpEF (1.2 ± 0.1; p = 0.02), but remained lower than patients with ATTRm and heart failure (1.8 ± 0.4; p = 0.02).

This observational study suggests that abnormal uptake of ^{99m}Tc-PYP by both qualitative and semiquantitative methods among asymptomatic carriers of TTR mutations may be the first measurable manifestation of amyloid heart involvement, preceding overt echocardiographic, cardiac biomarker, or clinical signs. This finding may permit early intervention and functional organ preservation for a disease that cannot be pathophysiologically reversed at present. Although our cohort consisted of mutations commonly associated with cardiac involvement, such as V122I (28%) and T60A (28%), neuropathic mutations such as D18G and F33L also exhibited ^{99m}Tc-PYP avidity, suggesting that these findings may be generalizable to all TTR mutations, even those not classically associated with clinically important heart involvement. We hope our findings will invite further investigation of the natural history of TTR mutation carriers and help elucidate how best to use ^{99m}Tc-PYP cardiac imaging in monitoring, risk assessment, and treatment of this population.

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