Comparison of different technetium-99m-labelled bone tracers for imaging cardiac amyloidosis

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Radionuclide bone scintigraphy is the cornerstone of an imaging-based algorithm for accurate non-invasive diagnosis of transthyretin cardiac amyloidosis (ATTR-CA).[1] In patients with heart failure and suggestive echocardiographic and/or cardiac magnetic resonance imaging findings, the positive predictive value of Perugini grade 2 or 3 myocardial uptake on a radionuclide bone scan approaches 100% for the diagnosis of ATTR-CA as long as there is no biochemical evidence of a clonal dyscrasia.[1–3] The technetium-labelled tracers that are currently validated for non-invasive diagnosis of ATTR-CA are pyrophosphate (^{99m}Tc-PYP), hydroxymethylene diphosphonate (^{99m}Tc-HMDP), and 3,3-diphosphono-1,2-propanodicarboxylate (^{99m}Tc-DPD).[4] Although they are considered to have similar diagnostic performance, no head-to-head comparison of these tracers has yet been undertaken and potentially clinically important differences in kinetics and distribution of these radiotracers have been reported.[4,5]

We sought here to compare the diagnostic performance of ^{99m}Tc-HMDP and ^{99m}Tc-DPD in a series of 11 patients with suspected cardiac amyloidosis (CA) who first had a bone scan with ^{99m}Tc-HMDP at their local hospital, mostly during the work-up of a known or suspected cancer, and a second bone scan with ^{99m}Tc-DPD at the UK National Amyloidosis Centre (NAC) as part of a comprehensive amyloidosis assessment. Characteristics of gamma camera and acquisition protocols used at the NAC have been published previously.[1,4] DICOM images of all scans were reviewed at the NAC by two expert nuclear medicine operators who assigned a Perugini grade and established the heart-to-contralateral (H/CL) ratio, as previously described.[5] Study approval was from the Royal Free Hospital ethics committee (ref: 06/Q0501/42).

Baseline patient characteristics are shown in the *Table 1*. CA was confirmed in 10 patients (9 ATTR-CA and 1 light chain (AL) CA [AL-CA]); a single case (ID #3) had no CA on comprehensive NAC evaluation, accompanied by absence of cardiac uptake of either

^{99m}Tc-HMDP or ^{99m}Tc-DPD. The median (25–75% CI) time interval between the first and second radionuclide scan was 4.9 (2.3–11.5) months. Perugini grade differed between ^{99m}Tc-HMDP and ^{99m}Tc-DPD in 3/9 (33%) patients, all of whom had wild-type ATTR-CA, with lower myocardial uptake on ^{99m}Tc-HMDP (grade 1) in all such cases compared with ^{99m}Tc-DPD (grade 2), suggesting a diagnosis other than ATTR-CA that would have required an unnecessary endomyocardial biopsy, with its attendant risks, to confirm the clinical suspicion of ATTR-CA. H/CL ratios were consistently lower with ^{99m}Tc-HMDP than ^{99m}Tc-DPD, including among patients with scans taken < 3 months apart. Locally, single photon emission computed tomography (SPECT) imaging was done in three of 10 patients and confirmed myocardial location of ^{99m}Tc-HMDP. SPECT imaging was systematically performed at the NAC and confirmed the myocardial location of ^{99m}Tc-DPD uptake in all patients with CA.

To the best of our knowledge, this is the first cohort of patients with CA in which cardiac uptake of two different bone tracers has been systematically compared in each patient. Our findings suggest that ^{99m}Tc-DPD is superior to ^{99m}Tc-HMDP for diagnosing ATTR-CA, as the latter failed to establish the diagnosis of ATTR-CA in 3 of 9 cases (33%). This observation may have important clinical implications given that most patients are now diagnosed non-invasively[6,7] enabling access to disease-modifying therapies or entry into clinical trials including: (i) patients with ATTR-CA might have a diagnostic scan (i.e. grade 2) with ^{99m}Tc-DPD before ^{99m}Tc-HMDP and (ii) the non-invasive diagnostic algorithm might be applied differently depending on which bone tracer is used. Understanding the characteristics and relative diagnostic performance in CA of each of the different bone tracers is therefore an urgent unmet clinical need.

In this small retrospective series, despite similar time from injection to image acquisition, 33% of patients had a higher Perugini grade with ^{99m}Tc-DPD thereby satisfying the non-biopsy imaging criteria for

Table 1 Baseline characteristics of patients with suspected cardiac amyloidosis undergoing scintigraphy with different bone tracers

ID	Age	Sex	Amyloid type	NAC Stage	MWT mm	LVEF %	GLS %	Months between scans	Indication for scan	Local Tracer	Delay after injection	Perugini grade	H/CL ratio	Injected dose (MBq)	NAC Tracer	Delay after injection	Perugini grade	H/CL ratio	Injected dose (MBq)	Change in H/CL ratio, %[a]
All	76 (71–86)	M	—	1 (1–3)	16.5 (14.5–17)	53 (50–57)	−12.7 (−16.2 to −11.4)	4.9 (2.3–11.5)	—	—	3 hr (2.35–3)	1 (1–2)	1.61 (1.41–1.83)	603 (529–609)	—	3 hr (3–3)	2 (2–2)	2.32 (1.80–3.00)	673 (665–683)	+44%
Scans < 3 months apart																				
1	71	M	ATTRwt	1	16	52	−13.3	1.1	Prostate cancer	HMDP	3 hr	2	1.79	649	DPD	3 hr	2	2.69	667	+50%
2	**74**	**M**	**ATTRwt**	**1**	**19**	**58**	**−23.6**	**2**	**Prostate cancer**	**HMDP**	**3hr**	**1**	**2.11**	**603**	**DPD**	**3 hr**	**2**	**3.36**	**657**	**+59%**
3	60	M	None	—	14	55	−21.3	2.1	Prostate cancer	HMDP	3.5 hr	0	—	605	DPD	3 hr	0	—	665	—
4	90	M	ATTRwt	1	17	56	−12.3	3	Prostate cancer	HMDP	2.5 hr	2	1.63	498.5	DPD	3 hr	2	3.06	698	+88%
Scans 3–6 months apart																				
5	**64**	**M**	**ATTRwt**	**1**	**17**	**61**	**−12.1**	**3.1**	**Lytic bone lesion**	**HMDP**	**2.5 hr**	**1**	**1.60**	**1120**	**DPD**	**3 hr**	**2**	**2.42**	**668**	**+51%**
6	87	M	ATTRwt	1	12	56	−18.3	4.1	Prostate cancer	HMDP	3 hr	1	1.38	529	DPD	3 hr	1	1.79	684	+30%
7	82	M	ATTRwt	3	17	53	−15.5	5.7	Paget's disease	HMDP	2.36	2	1.88	586	DPD	3 hr	2	3.02	685	+61%
8	85	M	ATTRwt	2	18	53	−7.9	5.7	Paget's disease	HMDP	2 hr	2	1.84	609	DPD	3 hr	2	2.93	673	+59%
Scans 6–12 months apart																				
9	72	F	ATTRv (V122I)	1	13	48	−11.6	7.9	Breast cancer	HMDP	3.15 hr	2	1.72	608	DPD	3 hr	2	2.22	678	+28%
Scans > 12 months apart																				
10	**76**	**M**	**ATTRwt**	**1**	**15**	**50**	**−13.1**	**12.8**	**Prostate cancer**	**HMDP**	**3 hr**	**1**	**1.36**	**800**	**DPD**	**3 hr**	**2**	**1.82**	**674**	**+33%**
11	76	M	AL	—	14	45	−8.3	17.3	Colorectal cancer	HMDP	3 hr	2	1.56	500	DPD	3 hr	2	1.74	665	+12%

AL, light chain; ATTRv, variant transthyretin; ATTRwt, wild-type transthyretin; F, female; GLS, global longitudinal strain; H/CL, heart-to-contralateral ratio; LVEF, left ventricular ejection fraction; M, male; NAC, national amyloidosis centre; 99mTc-DPD, 99mTc-3,3-diphospho-1,2-propanodicarboxylate; 99mTc-HMDP, 99mTc-hydroxymethylene diphosphonate; –, not applicable. Patients with different Perugini grade on 99mTc-HMDP and 99mTc-DPD shown in bold.

[a]Percentage change in cardiac uptake measured by H/CL ratio between 99mTc-DPD and 99mTc-HMDP.

ATTR-CA that were otherwise unsatisfied with ^{99m}Tc-HMDP. In a single patient, the difference in Perugini grade may have been attributable to disease progression since there was a time interval of >12 months between scans. However, in the two remaining patients the scans were performed within 3 months of one another which, coupled with the lower H/CL ratio with ^{99m}Tc-HMDP across the whole cohort, suggests a difference in biological behaviour of the different radiotracers. Interestingly, two patients (#2 and #5 in the *Table 1*) had Perugini grade 1 myocardial uptake on ^{99m}Tc-HMDP scan that was less than that expected for the degree of wall thickening which suggested a significant amyloid burden in their hearts. In both such patients, ^{99m}Tc-DPD scintigraphy demonstrated Perugini grade 2 cardiac uptake. Of note, a single patient in the cohort had AL-CA and had Perugini grade 2 myocardial uptake and similar H/CL ratio with both radiotracers. Whilst cardiac uptake has been described in 40% of patients with AL-CA undergoing ^{99m}Tc-DPD scintigraphy,[1] ^{99m}Tc-HMDP scintigraphy has been proposed to be specific for ATTR-CA which is evidently not the case. The requirement for biochemical exclusion of a monoclonal protein in order to diagnose ATTR-CA non-invasively is therefore independent of the specific radiotracer.[8] The absence of cardiac uptake with ^{99m}Tc-HMDP and ^{99m}Tc-DPD in patient #3 of the study cohort who did not have CA confirmed further the diagnostic specificity of these bone tracers in ATTR-CA after biochemical exclusion of cardiac AL amyloidosis. Routine implementation of SPECT/CT imaging following acquisition of planar images is recommended to provide more accurate localization of bone tracer retention, thus differentiating myocardial uptake from blood pooling artefact.[5,6]

We believe that a prospective head-to-head comparison of the characteristics and diagnostic performance of the three approved radiotracers which comprises the 'imaging' component of non-biopsy diagnosis of ATTR-CA is urgently required.

Author's contributions

Authorship: A.P., D.F.H., P.N.H., and J.D.G. contributed to the conception or design of the work. S.G., A.M.N., Y.R., R.P., A.I., M.U.R., and L.V. contributed to the acquisition, analysis, or interpretation of data for the work. A.P. and J.D.G. drafted the manuscript. M.F., A.M.Q., J.G., and D.R. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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