A comparison of ^{99m}Tc-DPD scintigraphy, cardiac magnetic resonance imaging and echocardiography in patients with V30M-associated hereditary transthyretin amyloidosis

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Variant transthyretin amyloid cardiomyopathy (ATTRv-CM) is most frequently associated with three TTR variants; V122I (p.(Val142Ile)), T60A (p.(Thr80Ala)) and V30M (p.(Val50Met)), the latter typically accompanied by ATTR amyloid polyneuropathy (ATTRv-PN). ATTR-CM was, until recently, diagnosed histologically, usually via an endomyocardial biopsy (EMB). More recently, non-biopsy diagnosis of ATTR-CM was established, enabling ~99% patients with ATTR-CM who do not have a confounding incidental monoclonal gammopathy to be diagnosed without recourse to EMB.(1) Non-biopsy diagnosis relies heavily on technetium-99m labelled radionuclide bone scintigraphy using the bone tracers 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), hydroxymethylene diphosphonate (^{99m}Tc-HMDP) or pyrophosphate (^{99m}Tc-PYP), which is known to be extremely sensitive for detecting ATTR-CM. However, according to some authors, V30M-ATTRv-CM is associated with less intense cardiac uptake on ^{99m}Tc-DPD scintigraphy than would be expected for the degree of myocardial amyloid infiltration or with complete absence of cardiac uptake despite presence of cardiac amyloidosis, thus risking misdiagnosis.(2)

We sought to establish the diagnostic performance of radionuclide scintigraphy in V30M-ATTRv-CM by analysing a cohort of 64 patients with histologically proven V30M-ATTRv who had undergone ^{99m}Tc-DPD scintigraphy and echocardiography within 3 months of one another, including 23 cases in whom cardiac magnetic resonance (CMR) imaging was also performed. Whole body planar and SPECT-CT images were acquired 3hrs after intravenous administration of ~700 MBq of ^{99m}Tc-DPD and categorized according to Perugini grade.(3). Echocardiograms were performed and categorized according to the validated IWT score as 'characteristic of' (IWT score ≥8), 'inconclusive for' (IWT score 2-7), or 'no evidence of' (IWT score<2 points) cardiac amyloidosis.(4). CMR with LGE imaging and T1 measurement were performed as previously described(5) and graded as

follows; Negative CMR – CMR normal or indicating non-amyloid diagnosis (e.g., hypertensive heart disease); Positive CMR – diffuse subendocardial or transmural late gadolinium enhancement (LGE), altered gadolinium kinetics, and/or diffusely elevated extra-cellular volume (ECV); Inconclusive CMR – not meeting criteria for positive or negative. All imaging was interpreted by two independent readers who were blinded to all other imaging modalities; a single discrepant read was resolved by in-person review. Study approval was from Royal Free Hospital ethics committee (ref: 06/Q0501/42).

A negative ^{99m}Tc-DPD scan (Perugini grade 0) in 34 patients was accompanied in all cases by absence of a characteristic amyloid echocardiogram, although 12/34 (35%) echocardiograms were categorized as 'inconclusive' for amyloid. Among 30 patients in whom there was abnormal cardiac uptake of ^{99m}Tc-DPD (i.e. Perugini score of 1, 2 or 3), the echocardiogram was characteristic in 10 (33%), inconclusive in 12 (40%), and showed no evidence of cardiac amyloidosis in 8 (27%). There was complete concordance between ^{99m}Tc-DPD scintigraphy and CMR findings in all 23 patients who underwent CMR. Among 5 patients in whom there was an absolute discrepancy between ^{99m}Tc-DPD scintigraphy (positive) and echocardiography (negative) and in whom CMR was also performed, the CMR findings corroborated ^{99m}Tc-DPD scintigraphy findings in 5/5 (100%) cases (Table). Among 18 patients with evidence of cardiac amyloid by both ^{99m}Tc-DPD scintigraphy and CMR, only 5/18 (28%) had a characteristic amyloid echocardiogram with echocardiograms categorized as inconclusive in 8 (44%) and no amyloid in 5 (28%) cases. Results of ^{99m}Tc-DPD scintigraphy were consistent with the expected phenotypes in V30M-ATTRv with absence and presence of cardiac uptake respectively in early-onset Portuguese and late-onset British patients.

This study indicates complete concordance between the diagnostic performance of ^{99m}Tc-DPD scintigraphy and CMR, albeit in a subset of 23 patients from the cohort. Our

findings suggests that a negative ^{99m}Tc-DPD scan (with CT-SPECT imaging) or CMR in patients with V30M-ATTRv all but rules out amyloid cardiomyopathy and a positive ^{99m}Tc-DPD scan (Perugini grade 1, 2 or 3) or CMR indicates cardiac amyloid infiltration. Our data also appear to corroborate the previously reported limitations of echocardiography for diagnosing cardiac amyloid infiltration.

References

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Table. Comparison of ^{99m}Tc-DPD scintigraphy, echocardiography and CMR in V30M-ATTRv

^{99m}Tc-DPD scintigraphy	**Echocardiogram (all patients)**			**Total**	**Contrast CMR Findings**			**Total**
Perugini Grade	No evidence of cardiac amyloidosis	Inconclusive	Characteristic of cardiac amyloidosis		No cardiac amyloidosis	Inconclusive	Cardiac amyloidosis	
0	22	12	0	**34**				
1	4	1	0	**5**				
2	4	9	9	**22**				
3	0	2	1	**3**				
Total	**30**	**24**	**10**	**64**				
^{99m}Tc-DPD scintigraphy	**Echocardiogram (subset of patients with CMR imaging)**				**Contrast CMR Findings**			
0	4	1[§]	0	**5**	5	0	0	**5**
1	3[#]	0	0	**3**	0	0	3	**3**
2	2[#]†	6†	5	**13**	0	0	13	**13**
3	0	2†	0	**2**	0	0	2	**2**
Total	**9**	**9**	**5**	**23**	**5**	**0**	**18**	**23**

There was 100% concordance between presence of cardiac amyloid by ^{99m}Tc-DPD scintigraphy and CMR. One patient with a Perugini grade 0 ^{99m}Tc-DPD scan and no cardiac amyloidosis by CMR had an echocardiogram that was inconclusive for presence of amyloid (denoted by [§]). Five patients with a Perugini grade 1 or 2 ^{99m}Tc-DPD scan and evidence of cardiac amyloid by CMR, did not have echocardiographic evidence of cardiac amyloidosis (denoted by [#]). Ten patients with a Perugini grade 2 or 3 ^{99m}Tc-DPD scan and evidence of cardiac amyloid by CMR, did not have conclusive echocardiographic evidence of cardiac amyloidosis (denoted by †).