Journal of the Postgraduate Institute of Medicine 2021; 8(1): E138 1-14

http://doi.org/10.4038/jpgim.8270

Original Article

Planar and SPECT/CT 99m Tc-DPD scintigraphy in cardiac amyloidosis: a single centre experience

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Key words: cardiac amyloidosis, 99m Tc DPD scan, cardiac magnetic resonance imaging, echocardiography in amyloidosis, transthyretin amyloidosis

Abstract

Background and Objectives

Cardiac amyloid is an increasingly recognised disorder leading to premature death and severe symptoms. Amyloid transthyretin (ATTR) is known to benefit from specific anti-inflammatory and RNA-modulating treatments. Non-invasive assessment for cardiac ATTR would facilitate targeted treatments. Typically, ATTR is assessed with planar images using Technetium (Tc)-99m-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scans. This study aims to assess whether single photon emission computed tomography (SPECT) / computed tomography (CT) has additive diagnostic value.

Methods

A retrospective, cross-sectional study assessed 53 patients who had undergone DPD scans between 19/10/2018 and 13/09/2019 at the Westmead Hospital Nuclear Medicine Department. Data collection was from electronic patient record. Data analysis was performed using an Excel worksheet.

Results

Fifty-three scans were performed on, 41(77.36%) males (age range 35-90 years) and 12(22.64%) females (age range 37-88 years). Of 17 patients with cardiac amyloidosis 94.1% had ATTR cardiac amyloidosis and 5.9% apolipoprotein (Apo) 2 cardiac amyloidosis with no AL cardiac amyloidosis. The sensitivity, specificity and diagnostic accuracy of the planar and SPECT/CT DPD scans were 88.2%, 100% and 96.2%, respectively. Five equivocal studies in the Planar and SPECT/CT scan were positive by other imaging methods or biopsy. Better anatomical assessment was possible by SPECT/CT Cardiac MRI or echocardiography had lower sensitivity in detecting cardiac amyloidosis. Good cardiac function with a New York Heart Association (NYHA) assessment of 1 and 2 and good ejection fraction (EF) was noted in 73% of patients with DPD planar positive cardiac amyloidosis.

Conclusions

Our data suggests that SPECT/CT imaging does not add significant value to planar images and should not be adopted in routine clinical practice. Further research is required with outcome data for the subgroup of equivocal DPD studies.

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Received: 23 Jul 2020, Accepted revised version: 22 Jan 2021, Published: 30 Jun 2021

Competing Interests: Authors have declared that no competing interests exist

Introduction

Cardiac amyloidosis is an uncommon cause of heart disease resulting in restrictive cardiomyopathy [1-,2,3]. It is a recognized cause of increased morbidity and mortality in the restrictive cardiomyopathy group due to difficulties in treatment [1,4,5]. Recent developments in the drug treatment of amyloidosis may improve the outcome of patients [3,4,6]. Therefore, there is greater emphasis on early diagnosis by imaging modalities and histopathology [3].

Amyloidosis is described as the deposition of abnormal protein "amyloid" in various body tissues, which leads to organ dysfunction [3,4,7,8,9]. Amyloid deposition in the heart muscles results in cardiac dysfunction leading to heart failure [1,2]. Amyloidosis can be familial, due to various gene mutations, or acquired. Cardiac involvement in amyloidosis can be as a sequel of systemic amyloidosis or as isolated cardiac involvement [1,2,9]. Amyloidosis is classified according to the type of protein that is deposited [1,7].

The majority of amyloidosis occurs in the systemic form and localized amyloidosis accounts for approximately 15% [7]. Amyloid light chains (AL), which are synthesized by plasma cells, are seen in conditions with monoclonal proliferation of plasma cells. Amyloid transthyretin (ATTR) is seen in senile systemic amyloidosis/neuropathic cerebral angiopathy and is the most common form of familial amyloidosis [1,7]. It is further divided into wild type (ATTRwt), which is seen in elderly patients and hereditary or mutated (ATTRv) type [1,4,6]. AL and ATTR amyloidosis are the most common forms to affect the heart [1,2,6,9,10,11].

The gold standard for diagnosis is endomyocardial biopsy [1,3,4,6,8,9,12]. However, due to the high risk associated with this, various imaging modalities are used to assess disease burden [3,4,6,8].

Echocardiography findings include a characteristic granular appearance of the left ventricular (LV) myocardium, increased LV wall thickness, decreased LV end-diastolic volume, typically preserved or mildly reduced LV ejection fraction, restrictive filling pattern, bi or uni atrial enlargement with atrial septal thickening, significantly reduced atrial strain, impaired longitudinal strain (LS) in the left ventricle with impairment more pronounced at base and mid ventricular regions compared to the apex [1,2,3,4,10].

MRI features include diffuse reduction in the T1 and T2 signal intensity of myocardium, diffuse left ventricular wall thickening, restriction of diastolic filling, disproportionate atrial enlargement, pericardial and pleural effusions and diffuse sub-endocardial heterogeneous increased signal on delayed contrast-enhanced inversion recovery T1-weighted images which is a characteristic feature [1,2,3,4,8,10]. A diagnostic framework for suspected cardiac amyloidosis s given in figure 1.

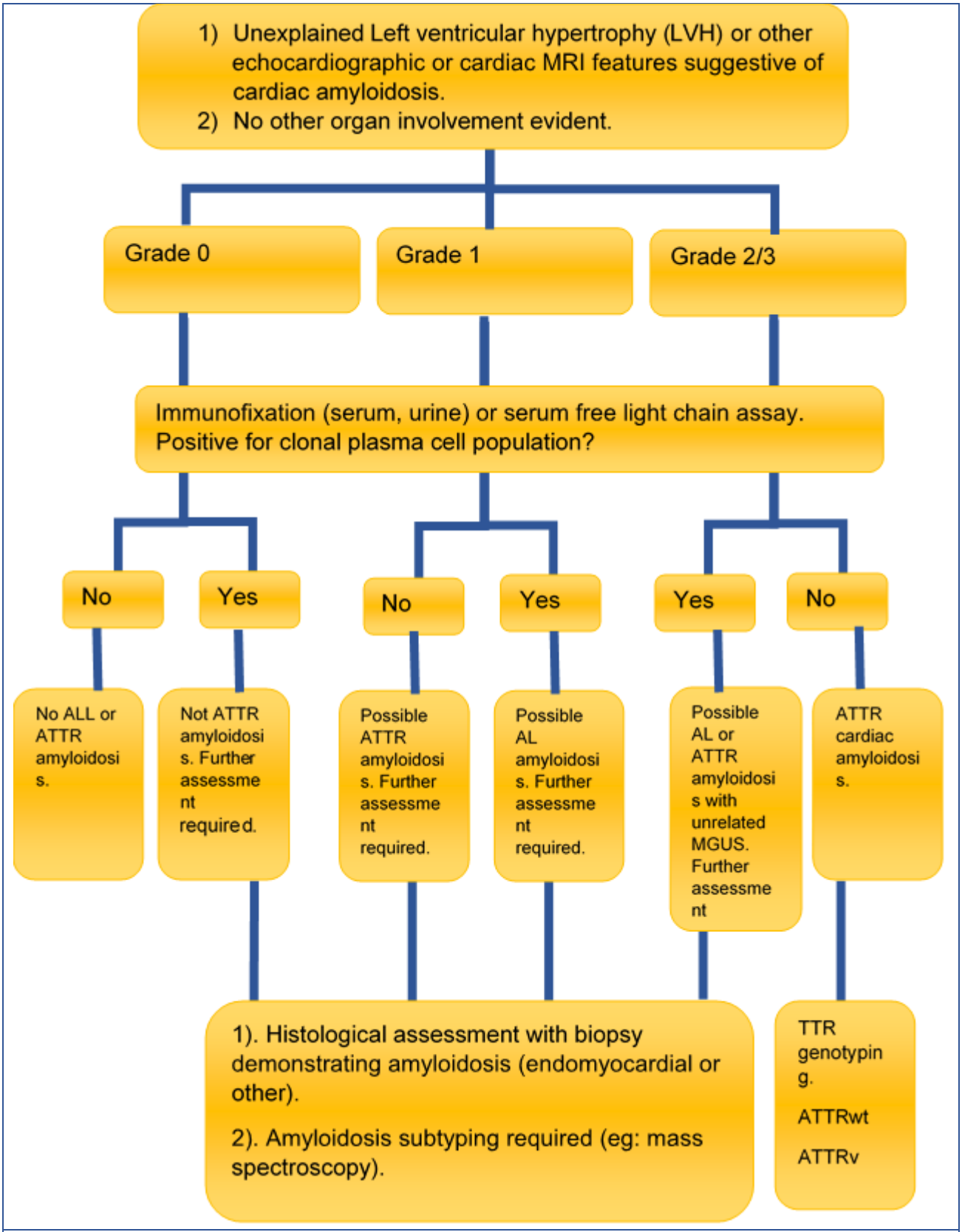

Figure 1: Diagnostic framework for suspected cardiac amyloidosis. [9]

Visual scoring of cardiac 99mTc-DPD retention in planar DPD imaging is given in figure 2.

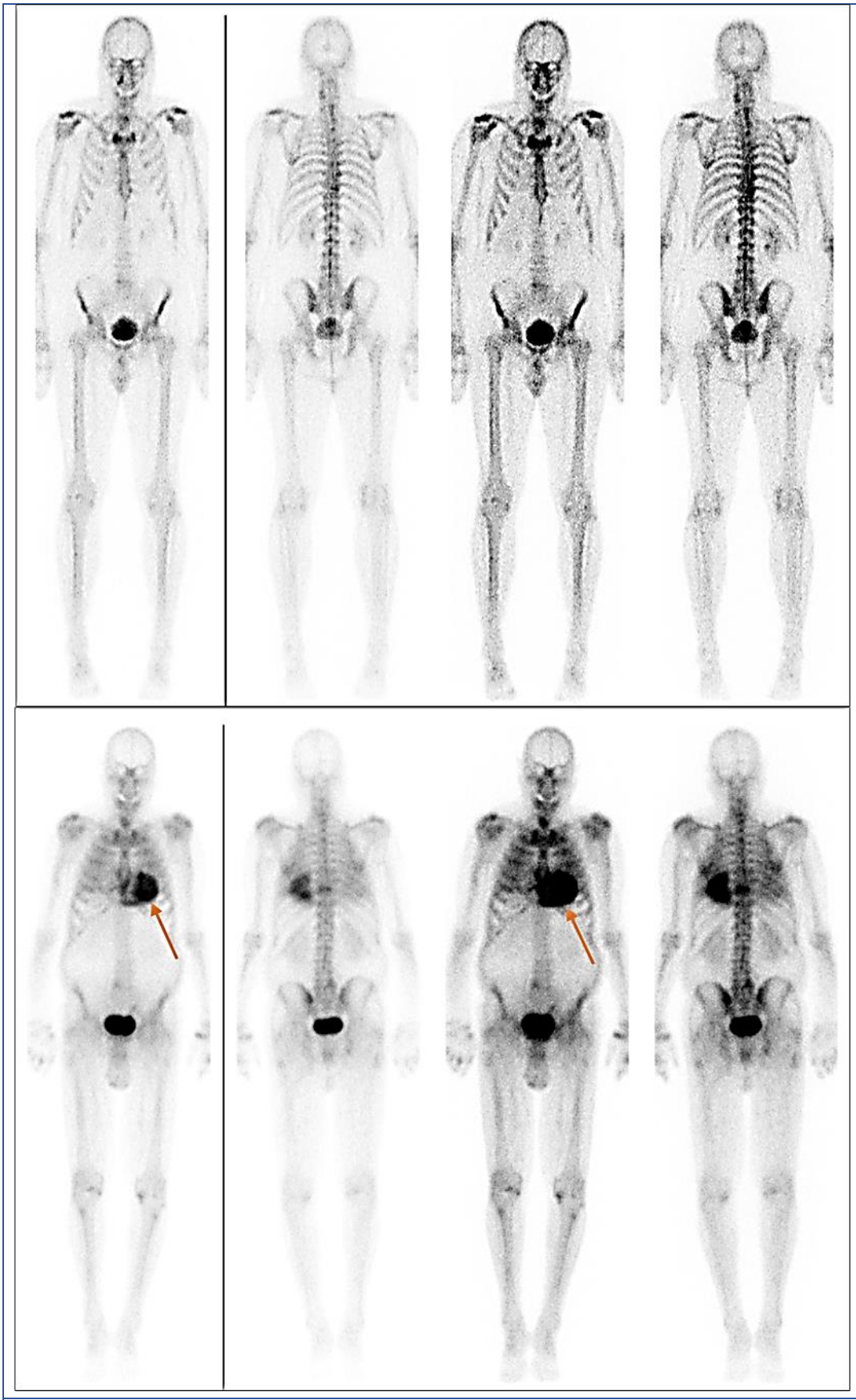

Figure 2: Visual scoring of cardiac 99mTc-DPD retention in planar DPD imaging: absent cardiac uptake and normal bone uptake (Upper); Intense cardiac uptake (Lower). Arrows indicate cardiac 99m Tc-DPD uptake.

DPD scan is a well-known method for diagnosing ATTR-type cardiac amyloidosis. It has a distinct advantage over the other diagnostic methods such as echocardiography and magnetic resonance imaging (MRI), both of which are non-specific and not useful in differentiating the type of amyloidosis. The goal of non-invasive diagnosis with DPD scans is to avoid the risk of myocardial biopsy to diagnose amyloidosis in the setting of known familial amyloidosis in asymptomatic relatives or diagnosing amyloidosis in patients with newly diagnosed restrictive cardiomyopathy [4,11,12].

The current method for amyloidosis diagnosis on DPD scans is to conduct an anterior planar (2 dimensional) scan 3 hours after injection of tracer [3,11,12]. Diagnosis depends on the relative uptake of tracer in myocardium relative to the soft tissues and bone [3,11,12]. The limitation of planar scans is obscuration of myocardial uptake by overlying structures. SPECT images in conjunction with CT are used for better anatomical localization [13]. It is also helpful in differentiating myocardial uptake from blood pool or overlying bone activity [3].

SPECT-CT images illustrating cardiac uptake of 99mTc-DPD is given in figure 3.

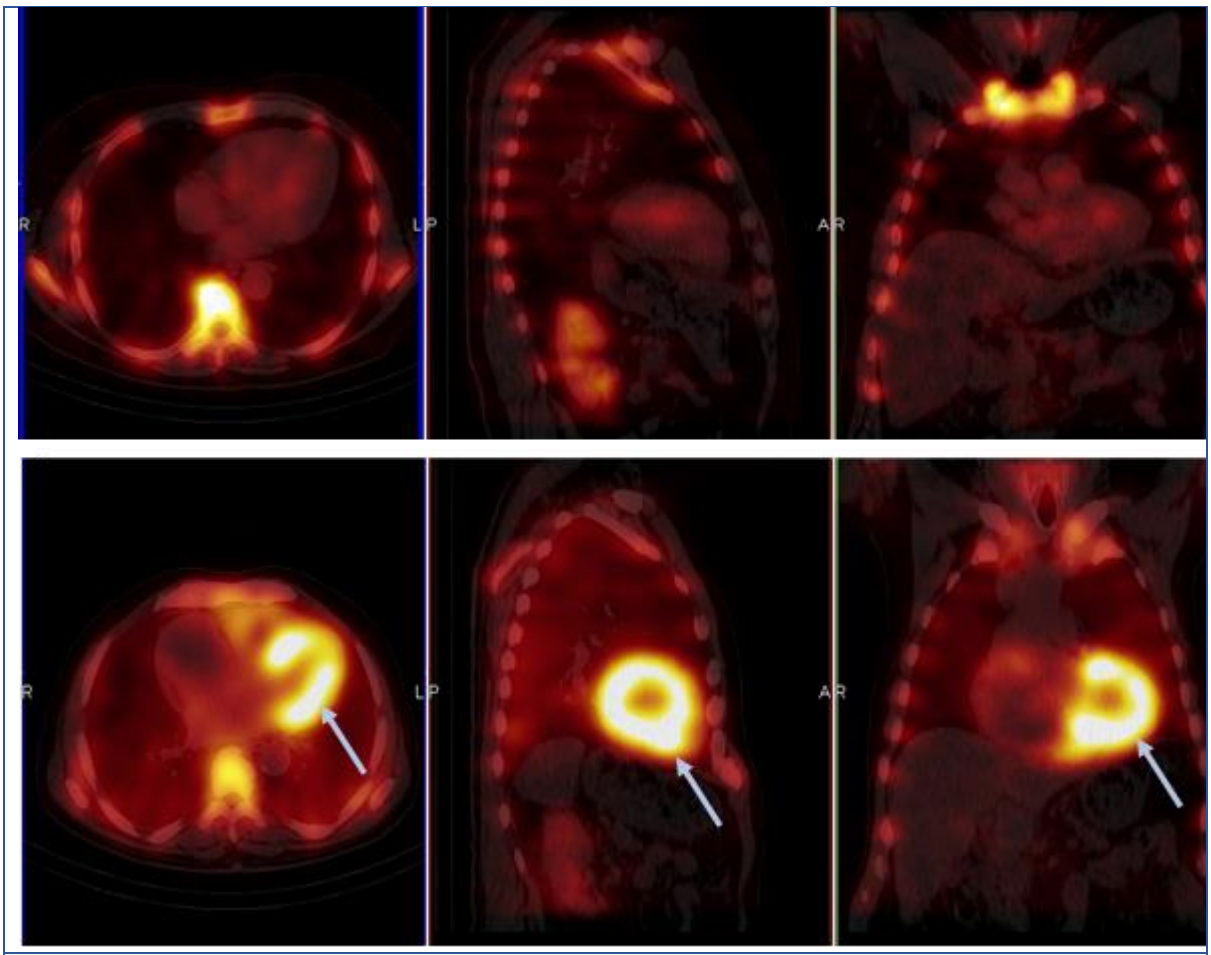

Figure 3: SPECT-CT images in a patient with no cardiac uptake of 99mTc-DPD (upper); and in a patient with intense 99m Tc-DPD uptake (lower). Arrows indicates cardiac 99m Tc-DPD uptake.

The Westmead Hospital Nuclear Medicine Department has been utilizing SPECT/CT DPD (3 dimensional) scans to characterize myocardial uptake 1 and 3hrs after radiopharmaceutical injection.

Planar DPD scan with Perugini score is a good method for assessing cardiac amyloidosis. Few studies have compared planar DPD imaging to SPECT/CT. The aim of this study was to analyse the efficacy of SPECT/CT vs planar imaging in cardiac amyloidosis.

Primary objective was to compare the sensitivity, specificity, predictive value and accuracy of SPECT/CT vs planar DPD scans. Other objectives were to describe the demographic features of patients with cardiac amyloidosis, evaluate the sensitivity, specificity, predictive value and accuracy of other diagnostic modalities, such as echocardiography and cardiac MRI, in the diagnosis of cardiac amyloidosis.

Methods

A descriptive, cross-sectional study was performed analysing DPD scans done at Westmead Hospital, Nuclear Medicine Department between 19/10/2018 and 13/09/2019 (n=53). Basic demographic data were obtained such as age, gender, date of scan, indication for scan, previous relevant scan findings (DPD, echocardiography and MRI), administered activity and timing of scan, working diagnosis, renal function, New York Heart Association (NYHA) assessment, pacemaker status and genetic assessment. The administered radiopharmaceutical dose varied between 804-921Mbq with a mean value of 843.98 Mbq. Quantitative evaluations of the imaging data were done. For each scan, planar and SPECT/CT data with interpretation were collected. Myocardial uptake was classified as absent or present in the form of either focal or diffuse. The data were evaluated according to a published standard for planar scans (Perugini scale) and SPECT/CT imaging which visually demonstrated any cardiac uptake in the 1 hour or 3 hour scans were taken into account. In planar and SPECT/CT imaging a Perugini score of 2 or above were taken as positive for cardiac amyloidosis and a Perugini score of 1 was taken as equivocal [3,10]. Cardiac uptake visualized in SPECT/CT but not on planar imaging was classified as Grade 1[9].

The Perugini score was applied as follows [3,9,10,11,12]:

0 - Absent cardiac uptake.
1 - Mild uptake less than bone.
2 - Moderate uptake equal to bone.
3 - Higher uptake than bone.

Renal function was evaluated according to the estimated glomerular filtration rate (EGFR).

Normal or Stage1 renal failure- EGFR >90 ml/min.
Stage 2 renal failure – EGFR 60-89 ml/min.
Stage 3 renal failure- EGFR 30-59 ml/min.
Stage 4 renal failure – EGFR 15-29 ml/min.
Stage 5 renal failure – EGFR <15ml/min.

The NYHA cardiac functional assessment was classified as follows:

1- No symptoms and no limitation of ordinary physical activity.
2- Mild symptoms (mild shortness of breath and/ or angina) and slight limitation during ordinary activity.
3- Marked limitation in activity due to symptoms, even during less than ordinary activity. e.g., walking short distance (20-100mm). Comfortable only at rest.
4- Severe limitation. Experience symptoms even while at rest. Mostly bed bound.

The ejection fraction (EF) was classified using the standard method:

Normal-55-70%
Mild impairment-40-55%
Moderate impairment-30-40%
Severe impairment<30%

Data on the interpretation of previous echocardiography or cardiac MRI imaging in the last one year prior to the DPD scan were collected. The previous scans were analysed to identify concordance with the DPD scans. Cardiac amyloidosis was diagnosed based on the working diagnosis of the amyloid clinic (n=16), histology (n=3) MRI (n=4) echocardiograms (n=11) and cardiac functional status (n=4).

Echocardiogram positivity for cardiac amyloidosis was defined as the presence of either left ventricular hypertrophy (LVH), Increased LV mass, LV longitudinal strain pattern or restrictive filling pattern [3,10]. MRI positivity for cardiac amyloidosis was defined as the presence of late Gadolinium enhancement or increased LV mass [3]. Normal LV mass for males were taken as 116g with a SD value of 20. For females it was taken as 85g with a SD value of 14 [14]. Furthermore, the LV mass measurement was correlated with the age group of relevant sex as documented in the literature [14].

Statistical analysis was performed to determine the diagnostic efficacy of planar and SPECT/CT scans compared to planar scans only, the clinical impression, histology and other scans. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for planar scans and SPECT/CT compared to clinical impression or histology and the magnitude or significance of the difference was calculated. Clinical information was obtained from the electronic medical records. Data collection and analysis done using the Microsoft Excel platform. The research study was approved by the NSW Health Western Sydney Local Health District Human Research Ethics committee as a quality assurance (QA) project.

Results

Fifteen out of 20 patients who were DPD SPECT/CT positive had positive cardiac amyloidosis and 5 patients were not proven to have cardiac amyloidosis. Positivity for cardiac amyloidosis was assumed from the amyloid clinic working diagnosis, other imaging findings, cardiac assessment, and available cardiac biopsy histology results.

Thirty-three patients had negative SPECT/CT studies, but one was positive for Apo 2 cardiac amyloidosis and one had biopsy proven ATTR amyloidosis with the site of biopsy unknown.

All 15 patients with a positive DPD planar scan had cardiac amyloidosis. One of 38 patients with a negative DPD planar scan had APO 2 cardiac amyloidosis and one had biopsy proven ATTR amyloidosis. Sensitivity of both DPD Planar and SPECT/CT studies for detection of cardiac amyloidosis was 88.2%. The specificity and diagnostic accuracy were 100% and 96.2% respectively. Positive and negative predictive values were 100% and 94.7% respectively. The sensitivity of planar and SPECT/CT DPD scan to detect ATTR cardiac amyloidosis was 93.75%. The specificity of planar and SPECT/CT to diagnose ATTR cardiac amyloidosis was 100%. Five equivocal studies, with a Perugini score of 1, were detected on DPD Planar and SPECT/CT imaging.

Forty-one of 53 patients in the study, were males (77.36%). Among the males, 18 scans were positive or equivocal for DPD and 23 were negative. In the females 2 scans were DPD positive and 10 scans were negative. No equivocal studies were detected in the females (Table 1).

Table 1: Distribution of DPD scan results according to gender and age groups

	Females		Males	
Age (years)	**DPD Negative**	**DPD Positive/Equivocal**	**DPD Negative**	**DPD Positive/Equivocal**
<39	1	0	0	1
40-49	0	0	2	1
50-59	1	0	6	1
60-69	1	1	5	2
70-79	2	0	8	4
80-89	5	1	2	8
>90	0	0	0	1
Total	10	2	23	18

Fifteen of the 20 patients with positive or equivocal DPD SPECT studies had positive planar scans with a Perugini score of 3. Five patients had cardiac to background ratio of <1.5 in the 3 hours planar DPD scan with discordance. Mild cardiac uptake in the 1- and 3-hour SPECT/CT DPD scan (less than skeletal uptake) was noted in this group. Two patients in the discordant equivocal DPD SPECT group had a positive biopsy for amyloidosis at a non-cardiac site. Biopsy was not done in 3 patients. In this group, 3 patients had hereditary TTR, one patient had wild type TTR and genetic testing was not done in one patient. One of five in this group had a negative cardiac MRI study and MRI was not performed in 4 patients. In one patient no cardiac involvement was seen in the echocardiogram while one patient had right ventricular hypertrophy and three patients had not undergone echocardiograms. Figure 4 describes the flow chart of discordant equivocal DPD SPECT group.

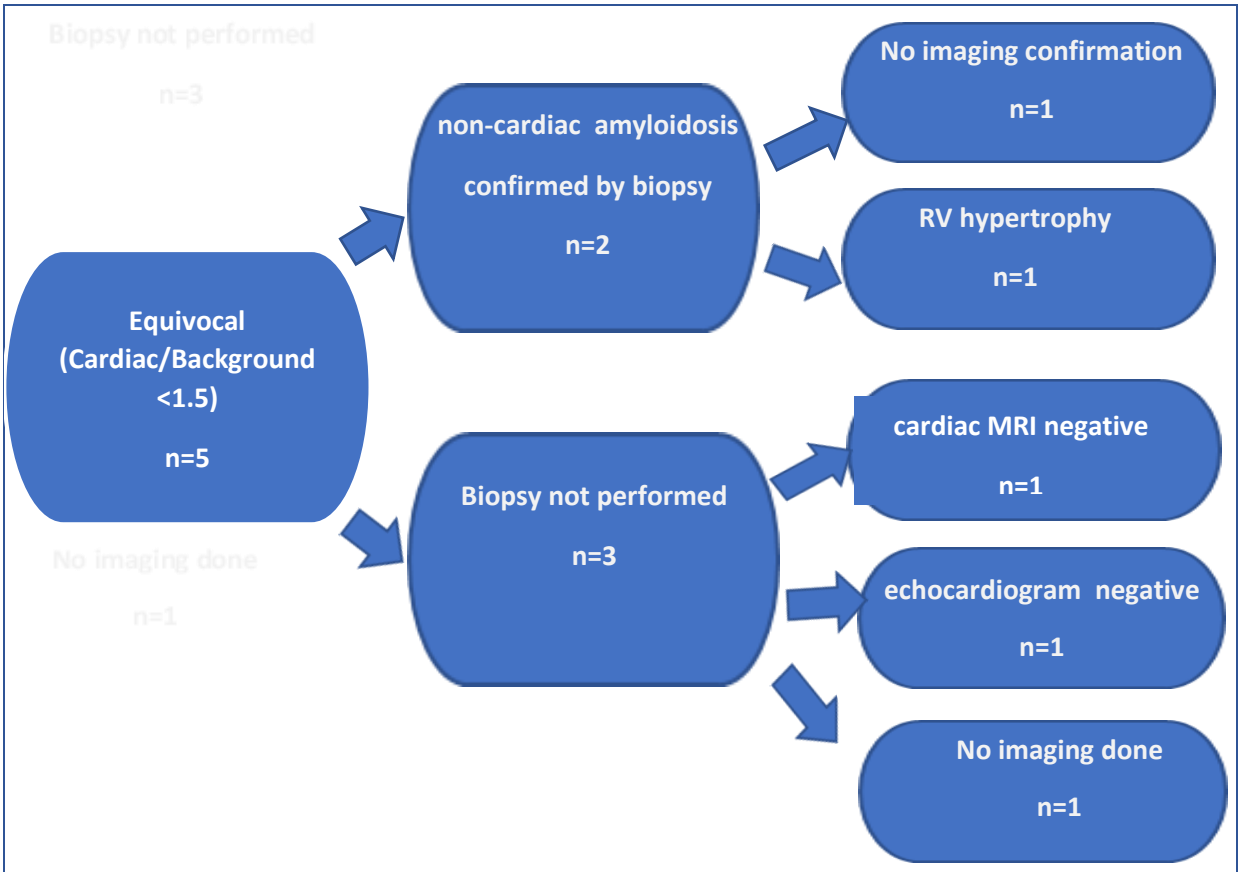

Figure 4: Description of the discordant equivocal DPD SPECT group

Sixteen of the 20 patients who had positive DPD SPECT scan studies had undergone echocardiogram to evaluate cardiac amyloidosis and 10 echocardiograms were positive and 6 were negative for cardiac amyloidosis. Out of positive echocardiogram scans 6 patients had normal EF, 6 patients had mildly impaired EF and 1 patient had moderately impaired EF and none had severely impaired EF while EF was not documented in two patients. Ten of 15 DPD planar scan positive patients had positive echocardiogram results, while 4 were negative and one patient had not undergone echocardiogram.

A restrictive pattern was described in 9 patients. Increased LV mass was documented in 3 patients (Table 2).

Table 2: Echocardiogram findings in cardiac amyloidosis

Echocardiogram study	Cardiac Amyloidosis		Total
	Positive	Negative	
Positive	11	9	20
Negative	4	11	15
Total	15	20	35

Eleven of 35 patients who underwent echocardiogram were true positives for cardiac amyloidosis. Eleven patients were true negatives (sarcoidosis n=1, heart failure n=3, non-cardiac amyloidosis n=3, ATTR gene mutation carrier n=1, cardiomyopathy n=3) and nine false positives (non-cardiac amyloidosis n=2, ATTR gene mutation carrier n=1, heart failure n=4, ischaemic heart disease n=1 and arrhythmia n=1). Four patients who had ATTR cardiac amyloidosis had negative echocardiograms. Sensitivity of echocardiogram in detecting cardiac amyloidosis was 73.3%%. Specificity and diagnostic accuracy were 55% and 62.86% respectively. Positive predictive value was 55% and negative predictive value was 73.3%.

MRI scans were performed in 6 patients who were DPD SPECT scan positive. Fourteen patients had not undergone cardiac MRI though the DPD SPECT scan was positive. Four patients who underwent MRI studies demonstrated late enhancement suggestive of cardiac amyloidosis. Two patients had negative MRI scan. Four of 15 patients positive for planar DPD scan had positive cardiac MRI studies while one had negative study. Ten patients in this group had not undergone cardiac MRI (Table 3).

Table 3: MRI findings in cardiac amyloidosis

Cardiac MRI study	Cardiac Amyloidosis		Total
	Positive	Negative	
Positive	4	3	7
Negative	1	2	3
Total	5	5	10

Out of 10 patients who underwent cardiac MRI 4 were true positives and 3 were false positives (cardiac sarcoidosis n=1, heart failure n=2). One false negative in a patient having hereditary ATTR cardiac amyloidosis was noted and there were two true negatives (cardiac fibrosis with septal scar n=1, ATTR gene mutation carrier n=1). Sensitivity of cardiac MRI in detection of cardiac amyloidosis was 80%. The specificity was 40% with a diagnostic accuracy of 60%. Positive and negative predictive values were 57.1% and 66.6%respectively.

Table 4: DPD scan results characterization according to common indications

DPD	suspected amyloidosis	cardiomyopathy	Heart failure & LVH	Total
Negative	20	5	8	33
Positive/Equivocal	16	2	2	20
Total	36	7	10	53

The commonest indication for DPD scans was suspected cardiac amyloidosis 36(67.9%), followed by heart failure, LVH 10(18.9%) and cardiomyopathy 7(13.2%). Highest number of positive DPD scans were in the group imaged due to suspected cardiac amyloidosis (Table 4).

Table 5: Histology finding analysis in DPD scans.

Biopsy	DPD Positive/Equivocal	DPD Negative	Total
Positive	6	5	11
Negative	2	2	4
Not done	12	26	38
Total	20	33	53

Of the 20 patients who were DPD positive or equivocal 6 patients had a tissue diagnosis of amyloidosis, which included either myocardial or other regions like gastrointestinal, salivary, and subcutaneous tissues. Two patients had negative biopsy which did not include myocardial tissues. Twelve patients had not undergone biopsy. In 33 DPD negative patients, 7 patients underwent biopsy for amyloidosis. Five were positive by tissue diagnosis. Twenty-six patients did not undergo biopsy for tissue diagnosis of amyloidosis (Table 5).

Table 6: NYHA cardiac functional assessment in relation to DPD scan results.

DPD	Stage 1	Stage 2	Stage 3	Stage 4	Total
Positive/Equivocal	7	9	4	0	20
Negative	17	5	5	0	27
Total	24	14	9	0	47

In the population who had a positive or equivocal study, cardiac functional assessment according to NYHA revealed seven patients in stage 1, nine patients in stage 2 and four patients in stage 3. No patients were in stage 4. Three of the patients had a pacemaker in situ. Three patients in DPD negative group had pacemakers. NYHA staging was not done in 6 patients (Table 6).

Table 7: Genetic findings according to DPD scan results

DPD	Wild type TTR	Hereditary TTR	Other Amyloid	Not assessed	Total
Positive/Equivocal	8	6	0	6	20
Negative	3	4	1	25	33

Out of 20 patients with positive or equivocal DPD scans, 8 had wild type TTR, 6 patients had hereditary TTR and in 6 patients' genetic sequences were not checked or results were pending. Out of 33 patients who had negative DPD scans 3 had wild type TTR, 4 had hereditary TTR and one had Apo A2 amyloidosis. In 25 patients genetic testing was not done or not available.

Discussion

In the study population males were more affected and with higher incidence with advanced age, which in par with general population's behaviour described in the literature [10].

In all the positive DPD scans, SPECT/CT images were helpful in better localization of the involved segments of the heart than the planar images. For the planar and SPECT/CT images, sensitivity, specificity, and diagnostic accuracy for the detection of cardiac amyloidosis were 88.2%, 100% and 96.2% respectively. Previously published studies reported the sensitivity and specificity of DPD scans in TTR cardiac amyloidosis as 100% [11]. The reduction of sensitivity and specificity was likely due to non TTR type cardiac amyloidosis, which is negative or non-avid on DPD scans. The false negative scan could be due to low level of cardiac amyloid infiltration at the time of the scan, and further DPD scanning is recommended due to positive genetic testing.

None of the five equivocal studies detected in the planar and SPECT/CT studies were confirmed as cardiac amyloidosis by cardiac biopsy or other imaging modalities. There were no further investigations in this group at the time of this review to compare the efficacy of SPECT/CT over planar imaging in diagnostic accuracy.

73% of the patients who were positive for cardiac amyloidosis in planar DPD scan had good cardiac function with a normal EF and NYHA assessment of 1 (n=3) and 2 (n=8), indicating that early treatment may improve outcome and survival rates.

Echocardiogram and cardiac MRI had low sensitivity and specificity in diagnosing cardiac amyloidosis, which is likely to be due to other cardiac diseases demonstrating similar appearance as cardiac amyloidosis in these imaging modalities (e.g.: cardiac sarcoidosis and other cardiac infiltrative diseases).

Limitations

1. There was under documentation of echocardiogram, MRI findings and clinical data in some of the patients, which lead to difficulty in correlating other imaging modalities with DPD scans.
2. The definite diagnosis for cardiac amyloidosis is the cardiac biopsy, which was not performed in majority in our population which caused diagnostic difficulty in the group with equivocal studies. Due to unavailability of cardiac biopsy in this group confirmation of possible low volume disease was not possible.

Conclusion

In our study DPD SPECT/CT scan was not superior to planar DPD scans in diagnosing cardiac amyloidosis The DPD SPECT/CT scan was more useful for accurately localizing the involved regions of the heart in ATTR cardiac amyloidosis. DPD scans are sensitive for early diagnosis of transthyretin cardiac amyloidosis in asymptomatic patients and may have clinical impact and survival benefit if effective therapy is available.

Recommendations

Further research with outcome data is required for the subgroup of equivocal DPD/SPECT studies. Our data suggests that SPECT/CT imaging does not add significant diagnostic value to planar DPD images in cardiac amyloidosis and should not be adopted in routine clinical practice.

Acknowledgments

We sincerely thank Dr. Shahroz Khan for obtaining the ethics clearance and Dr George Larcos for manuscript review and Scott Evans for assistance with images.

Abbreviations

AL-Amyloid light chain
APO-Apo lipoprotein
CT-Computed tomography
EF-Ejection fraction
EGFR-Estimated glomerular filtration rate
LF-Left ventricle
LVH-Left ventricular hypertrophy
MRI-Magnetic resonance imaging
NYHA-New York Heart Association
SPECT-Single photon emission computed tomography
DPD Scan-Tc-99m-3,3-diphosphono-1,2-propanodicarboxylic acid scan
Tc-Technetium
ATTR-Transthyretin

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