

A pilot study demonstrating cardiac uptake with 18F-florbetapir PET in AL amyloidosis patients with cardiac involvement

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Abstract

¹⁸F-florbetapir is a promising tracer in amyloidosis. This study evaluates its use in patients with systemic AL amyloidosis (AL) before and after treatment, as well as its serial utility in monitoring. Fifteen AL patients with cardiac involvement underwent ¹⁸F-florbetapir PET imaging, and ~~three~~ three underwent repeat imaging post-chemotherapy. ~~three patients underwent repeat imaging after chemotherapy.~~ All ~~patients~~ patients had demonstrable cardiac uptake with ¹⁸F-florbetapir. Cardiac uptake appeared greater in chemotherapy-naïve vs chemotherapy-established AL patients ~~median~~ (mean left ventricular retention index 0.21 vs 0.14 min⁻¹, respectively) and greater in patients that had not achieved at least a partial haematological response (mean left ventricular retention index 0.2 vs 0.14 min⁻¹, respectively). There was no interval difference in cardiac uptake, and no correlation in cardiac uptake with cardiac biomarkers or serum free light chains. This is the largest study of ¹⁸F-florbetapir in ~~patients with AL amyloidosis~~. It is the first ~~study~~ to include patients ~~prior to starting before~~ chemotherapy and uniquely includes patients who underwent repeat imaging ~~after post~~-chemotherapy. All patients had cardiac uptake with ¹⁸F-florbetapir, regardless of haematological or NT-proBNP response to chemotherapy. There was a suggestion that treatment-naïve patients may have higher cardiac uptake. Larger studies are required to establish the role of this tracer in screening patients with amyloidosis for cardiac involvement, discriminating between ATTR and AL amyloidosis, and in disease monitoring.

Keywords: Amyloidosis; Florbetapir; PET; AL; imaging

Abbreviations

¹²³I-SAP: ¹²³I-labeled serum amyloid P component

AL: systemic immunoglobulin light chain amyloidosis

ATTR: transthyretin amyloidosis

CR: complete haematological response

ECV: extracellular volume

MRI: magnetic resonance imaging

PET: positron emission tomography

NT-proBNP: N-terminal pro b-type natriuretic peptide

PR: partial haematological response

RI: retention index

SUV: standardised uptake value

VGPR: very good partial haematological response

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Introduction

The amyloidoses are a group of disorders characterised by extracellular deposition of amyloid fibrils, derived from pathological misfolding of precursor proteins. Cardiac involvement is a feature of both systemic immunoglobulin light chain (AL) and transthyretin (ATTR) amyloidosis, whereby the extracellular space of the heart is expanded by an amorphous fibrillary material, causing a restrictive cardiomyopathy. [1] Cardiac involvement is the critical determinant of outcomes in AL amyloidosis. Early diagnosis is key, as treatment delay in AL can lead to stark outcomes. Histological diagnosis is the gold standard but the risks of endomyocardial biopsy are not insignificant – especially in elderly, frail patients with other comorbidities.

Imaging has been a cornerstone of diagnosing cardiac amyloidosis. Echocardiography is the most widely used method but continues to lack specificity and sensitivity. [2] Cardiac magnetic resonance imaging (MRI) overcomes some of these limitations but is contraindicated in a substantial proportion of patients, and is only available in specialist centres with interpretation often dependent on the use of specific protocols. [3] ^{123}I -labeled serum amyloid P component (^{123}I -SAP) scintigraphy binds specifically to amyloid deposits in viscera and is helpful to quantify and localise amyloid deposition, but is only available in two centres in the world and does not demonstrate cardiac amyloid deposits. [4] Bone seeking tracers such as $^{99\text{m}}\text{Tc}$ -DPD or $^{99\text{m}}\text{Tc}$ -PyP have a very high sensitivity for imaging cardiac ATTR amyloidosis but are less sensitive in detecting other types of cardiac amyloidosis. [5]

PET modalities have emerged in cardiac amyloidosis. Antoni et al reported increased cardiac uptake with ¹¹Carbon-Pittsburgh compound B (¹¹C-PIB) in patients with ATTR and AL cardiac amyloidosis. [6] Lee et al reported a significant increase in ¹¹C-PIB myocardial uptake in chemotherapy-naïve AL patients compared to already treated patients, but this tracer is only available in centres with a cyclotron. [7]

Dorbala's group performed a pilot study of PET imaging with ¹⁸F-florbetapir, a tracer with a high affinity for beta amyloid in the brain, in patients with ATTR and AL cardiac amyloidosis. [8] They found that left ventricular retention index (RI), target-to-background ratio, left ventricular myocardial standardised uptake values (SUV) and left ventricular myocardial to liver SUV were higher in patients with cardiac amyloidosis compared to controls. They also reported higher cardiac retention indices in patients with cardiac AL amyloidosis compared to patients with ATTR cardiac amyloidosis, although sample sizes were small and this finding was not statistically significant. Autoradiography studies have demonstrated ¹⁸F-florbetapir uptake in autopsy cases of cardiac AL and ATTR amyloidosis, but no uptake in control samples. [9] Osborne et al reported delayed myocardial washout with ¹⁸F-florbetapir imaging in 8 subjects with cardiac amyloidosis compared to 3 control subjects. [10] ¹⁸F-florbetaben PET has shown similar promise in another study, differentiating between cardiac amyloidosis and hypertensive heart disease. [11] **Uptake with 18F-florbetapir PET at extra-cardiac sites of amyloid deposition (spleen, tongue, parotids, fat, lungs and kidneys) has also been recently described. [12]**

Currently, clinical cardiac response to chemotherapy in patients with systemic AL amyloidosis is defined by an improvement in NT-proBNP after chemotherapy. [13] This biomarker response has been found to predict long term survival, but other factors such as renal insufficiency, causes of heart failure independent of AL amyloidosis, immunomodulatory agents and acute heart failure can also lead to elevation of NT-proBNP and may not necessarily reflect true organ response. Echocardiographic and cardiac MRI imaging, whilst useful after treatment, are not used in routine evaluation of organ response.

In this pilot study, we evaluated cardiac uptake with ¹⁸F-florbetapir PET in patients with systemic AL amyloidosis with cardiac involvement before and after treatment, as well as its serial utility in monitoring.

Materials and methods

All patients were recruited to a prospective study of ¹⁸F-florbetapir in cardiac amyloidosis from September 2016 to June 2017. The inclusion criteria were: confirmed diagnosis of AL amyloidosis defined by amyloid deposition confirmed on a tissue biopsy and documented AL amyloid fibril typing, and evidence of cardiac involvement as defined by international amyloidosis consensus criteria. [14] The exclusion criteria were: inability to lie flat, NYHA Class IV heart failure, pregnancy or unwilling to undergo pregnancy test prior to study (in women of child bearing potential), the presence of any contraindication to undergoing PET imaging, and a known allergy to Amyvid. All patients were aged 40 years or over.

The primary outcome was ^{18}F -florbetapir uptake in the heart. The variables of the study were left ventricular retention index (RI), mean and maximum left ventricular myocardial standardised uptake variable (SUV_{mean} and SUV_{max}). ^{18}F -florbetapir RI was calculated by the method described by Dorbala et al, as the mean LV myocardial tissue radiotracer concentration between 10 and 30 minutes after injection of ^{18}F -florbetapir, divided by the integral of the blood pool ^{18}F -florbetapir time activity curve from 0 to 20 minutes. [8] A volume of interest in the left ventricular cavity was used by Dorbala's group. However, our group felt that counts in the left ventricular wall were spilling over into the blood pool volume of interest, potentially giving falsely low results in some patients. An approach was therefore taken using a volume of interest in the aorta for the blood pool instead, as this was less likely to include counts from other areas of uptake.

All patients underwent serial protocolized assessment at the UK National Amyloidosis Centre including full biochemical tests for organ function, serum free light chain measurement as well as serum and urine protein electrophoresis and immunofixation, cardiac biomarker measurement, echocardiography, cardiac MRI (unless contraindicated), and ^{123}I -SAP scintigraphy. Organ involvement was defined as per international amyloidosis consensus criteria. [14]

Imaging Protocol:

Patients underwent list mode dynamic PET imaging for 60 minutes using a Siemens Biograph PET/CT machine following a mean intravenous administration of 331 MBq (range 294-

370MBq) of ^{18}F -florbetapir. The heart was placed in the centre of the field of view. CT imaging was performed over this area using automatic exposure control (CARE Dose 4D, CARE kV – Siemens Healthcare) with exposure parameters of 65mAs and 120kV. After dynamic imaging, the patient was asked to void. A half body acquisition PET-CT was then performed. Images underwent iterative reconstruction (2 iterations, 21 subsets) using time of flight information and point spread function modelling, with 2mm Gaussian post filtering. The 60 minute list mode data was reconstructed into 37 frames (12 frames of 5 s each, 6 frames of 10 s each, 4 frames of 30 s each, 6 frames of 60 s each, 8 frames of 300 s each, and 1 frame of 600 s).

Images were assessed by a nuclear medicine physician using HERMES workstation (HERMES Medical Solutions). The dynamic images (0-60 minutes) were assessed visually for cardiac uptake. The delayed half body images were visually analysed for uptake in the heart and other organs. All acquired data for all time frames was analysed and interpreted. For the dynamic images of the heart, the nuclear medicine physician assessed the presence of uptake in the myocardium and its localisation. For delayed half body images, cardiac uptake was assessed in the same manner. For extra-cardiac uptake, comparison was made with normal tracer distribution as described in the literature and as inferred from this study's patient population.

The study had approval from the institutional review board, and written consent was obtained from all patients in accordance with the Declaration of Helsinki. Statistical analysis was conducted using SPSS Version 24 software.

Results

Baseline characteristics are found in Table 1. **Fifteen patients with systemic AL amyloidosis were included. Two patients underwent repeat imaging – before starting chemotherapy and after completion of treatment.** All had cardiac involvement. Median age was 58 years (range 46-73 years). All patients had an ECOG score of 0-2 and the majority had NYHA class I-II symptoms. Median NT-proBNP was 2287 ng/L (range 114 – 6739 ng/L). All patients had Mayo Stage III cardiac involvement at presentation. [15] Median ventricular wall thickness and left ventricular ejection fraction on echocardiography were 16mm (range 13 - 18mm) and 54% (range 29-63%), respectively.

Two patients were treatment-naïve at the time of the study, and two were early in their first cycle of chemotherapy (although one of the latter had achieved a haematological partial response at the time of imaging). At the time of imaging, the haematological response status was: patients in a complete haematological response (CR) - 9/12 (75%), very good partial response (VGPR) - 2/12 (16.7%), partial response (PR) - 1/12 (8.3%). Of the three remaining patients, two were treatment-naïve and one was too early into chemotherapy for response assessment. Six patients had achieved a cardiac response as per international amyloidosis consensus criteria at the time of imaging. [14]

All patients had cardiac uptake with ¹⁸F-florbetapir (Figure 1). There were no false negative scans. Primary outcome variables are presented in Table 2. **The median LV retention index**

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was 0.16 min^{-1} ($0.05 - 0.29 \text{ min}^{-1}$). Median myocardial SUV_{max} and SUV_{mean} was 7.2 (range 0.8 – 15.7) and 3.6 (range 0.8 - 7.1), respectively. The pattern of uptake was diffuse. Uptake in the liver was seen in all cases as this tracer is excreted by the liver into the biliary system.

Previous reports suggested a lack of uptake in patients not “actively depositing” amyloid protein i.e. those in a haematological response. In this cohort, all patients in a clonal response still showed cardiac uptake. **There was a suggestion that there was greater cardiac uptake in the treatment-naïve patients, although the number of treatment-naïve patients was too small for meaningful statistical analysis of difference in cardiac uptake between the two groups (Table 3).** Patients that had not achieved at least a partial haematological response appeared to have higher LV retention indices, myocardial SUV_{mean} and myocardial SUV_{max} , although these findings were not statistically significant (Table 3). There was no statistically significant correlation with primary outcome variables and achievement of a cardiac response by NT-proBNP criteria. [13]

There was no statistically significant correlation between the retention indices of ^{18}F -florbetapir with global longitudinal strain rate, left ventricular ejection fraction, mean ventricular thickness, myocardial extracellular volume fraction (ECV) on cardiac MRI, serum troponin-T, serum NT-proBNP, difference in involved and uninvolved light chains (dFLC), and kappa:lambda ratio.

Comparison between initial and repeated ¹⁸F-florbetapir imaging

Three patients with AL had repeated ¹⁸F-florbetapir imaging. At the time of initial imaging: one patient was treatment-naïve; one was early into first cycle of chemotherapy (but had achieved a haematological PR); one was on chemotherapy and in a haematological CR. All three patients were in a haematological CR at the time of repeat imaging and two had achieved an NT-proBNP response. There was no significant difference in primary outcome variables between initial and repeated imaging (Table 4).

Discussion

This is the largest study to date reporting on the use of ¹⁸F-florbetapir PET imaging in AL patients with cardiac involvement. It is the first study to include patients that underwent ¹⁸F-florbetapir imaging prior to starting chemotherapy, and the first to include repeat ¹⁸F-florbetapir PET imaging at later timepoints. Crucially, this study also captures patients in differing haematological responses. It has previously been suggested that patients with normal light chains may have “inactive” amyloid deposits, which may not be associated with cardiac uptake with ¹⁸F-florbetapir. There was a suggestion of greater cardiac uptake in patients with higher light chains than those in a good light chain response. However, all patients in this cohort had demonstrable cardiac uptake, irrespective of serum free light chain burden or NT-proBNP response. This is an important novel observation that offers new insight into the argument of ‘active vs. ‘inactive’ amyloid hearts.

Two patients in this study underwent ¹⁸F-florbetapir imaging before starting chemotherapy. These patients appeared to have increased cardiac uptake compared to the rest of the cohort. Similarly, the three patients in this cohort who had not achieved at least a partial haematological response (two treatment-naïve patients and one in the first week of chemotherapy) appeared to have increased cardiac uptake, compared to those who did not. It must be emphasised that the latter two findings were not statistically significant. There remains a distinct possibility, however, that patients with particularly active clonal disease may have a higher cardiac disease burden, manifesting in increased cardiac uptake – but this relationship needs to be explored further in a study with larger patient numbers. Differing cardiac uptake in ‘active’ and ‘inactive’ amyloid deposits would have a potential role in monitoring treatment response as currently cardiac organ response after chemotherapy is defined as a 30% fall in NT-proBNP [13], but there are drawbacks of solely using a biomarker in assessment of cardiac response, when this biomarker is confounded by many other factors (e.g. renal insufficiency, immunomodulatory agents, acute fluid status and other causes of heart failure).

Three patients underwent follow-up imaging. At the time of initial imaging, one of these patients was treatment-naïve and subsequently went on to have chemotherapy, one patient had recently started chemotherapy and one had achieved a complete haematological response with chemotherapy. All patients were in a complete haematological response at the time of repeat imaging. There was no significant difference in cardiac uptake on initial and repeated imaging. **However, the interval between imaging was short (range 2-8**

months) and future studies need to include greater numbers of patients and assess further the optimal timing of repeat ^{18}F -florbetapir imaging post-treatment.

No correlation was identified between primary outcome variables and cardiac biomarkers, LV ejection fraction, ventricular strain, ventricular wall thickness and ECV on cardiac MRI. **The reasons for this are uncertain, but possibilities include a “saturation” effect due to a very high tracer affinity for amyloid, the heterogeneity of patients included in this cohort, or the relatively small sample size.** Whilst the uptake in all cases suggests a role for this tracer in diagnosis of cardiac amyloidosis, the lack of correlation with other markers may limit the utility of this tracer as a marker of prognosis in patients with more advanced cardiac amyloidosis.

The pattern of cardiac uptake in this study was diffuse and not restricted to the ventricular base as seen in $^{99\text{m}}\text{Tc}$ -DPD or $^{99\text{m}}\text{Tc}$ -PyP imaging. The exact reason for this discrepancy is unclear but is likely to be due to the different mechanisms of tracer binding to amyloid deposits. $^{99\text{m}}\text{Tc}$ -DPD or $^{99\text{m}}\text{Tc}$ -PyP probably bind to calcium in amyloid deposits, whereas ^{18}F -florbetapir is fibril-specific. On endomyocardial biopsies, amyloid deposition can be seen throughout the myocardium and hence, we believe that diffuse cardiac uptake with ^{18}F -florbetapir reflects total amyloid deposition at the time of imaging.

The findings of this study need to be interpreted within its limitations. The overall number of patients in this study is small. As there were no control subjects included in the cohort, it was not possible to evaluate specificity of this tracer for cardiac amyloidosis. Interval imaging was only performed in three AL patients and was carried out at differing timepoints in patients - further studies are needed to assess cardiac uptake at standardised timepoints before and after chemotherapy. Additionally, the utility of this tracer in early cardiac amyloidosis has yet to be defined as all patients in this study had clearly identifiable cardiac involvement.

¹⁸F-florbetapir is licensed for detecting brain beta amyloid deposits in Alzheimer's disease. During the numerous studies of patients with Alzheimer's disease, imaging was limited to the head only and no systemic imaging details are available. Dorbala et al reported the first use of ¹⁸F-florbetapir in 9 patients with cardiac amyloidosis (5 AL, 4 ATTR) and 5 control subjects. [8] Increased myocardial tracer uptake was seen in all amyloid subjects and none of the controls.

The small number of total subjects in studies thus far limits definitive conclusions on sensitivity and specificity, but both appear promising and make ¹⁸F-florbetapir potentially attractive in distinguishing cases of true cardiac amyloid from non-amyloid pathologies which can share some echocardiographic and cardiac MRI appearances with amyloidotic infiltration. This is the first tracer to consistently demonstrate myocardial uptake in cardiac AL amyloidosis. This, if confirmed in larger studies, will be a step change in our approach to the diagnosis of cardiac AL amyloidosis.

The striking appeal of ^{18}F -florbetapir is in its seemingly high affinity for cardiac amyloid deposits, as demonstrated by our study and previous literature. [8, 9, 16] **The exact place for this tracer in the amyloid diagnostic paradigm remains unclear. Larger studies are needed to clarify if this tracer will complement or, indeed, supplant the current methods of imaging cardiac amyloidosis.**

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Conflict of interest disclosures

No author declares disclosures relevant for the manuscript or any conflict of interest or potential conflict of interest.

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Table 1: Baseline characteristics.

Overall cohort (n=15)	Median (range) / n(%)
Age	58 (46-73)
Male	11 (73%)
Female	4 (24%)
ECOG:	
0-2	15 (100%)
3-4	0
NYHA:	
I-II	15 (87%)
III-IV	2 (13%)
Median NT-proBNP (ng/L)	2287 (114-6739)
Median troponin T (ng/L)	59 (35-259)
Median LV wall thickness (mm)	16 (13-18)
Median LV ejection fraction (%)	54 (29-63)
Median 6 minute walk test (metres)	472 (138-662)
Median serum creatinine (umol/L)	114 (66-203)
Median 24 hour urinary protein (g/24h)	0.3 (0.1-7.2)

Median serum albumin (g/L)	42 (22-49)
Median bilirubin (umol/L)	8 (5-38)
Median ALP (ULN 129 units/L)	106 (45-1702)
Organ involvement:	
Cardiac	15 (100%)
Renal	8 (53%)
Liver	4 (24%)
Autonomic nerve	2 (12%)
Peripheral nerve	1 (6%)
Soft tissue	4 (24%)
Gastrointestinal	0
Cardiac Mayo stage at presentation :	
I	0
II	0
III	15 (100%)
Haematological response at time of imaging:	
CR	9 (60%)
VGPR	2 (13%)
PR	1 (7%)
No haematological response	3 (20%)
NT-proBNP response at time of imaging	6 (40%)
No NT-proBNP response at time of imaging	9 (60%)

LV: left ventricular
NT-proBNP: N-terminal prohormone of brain natriuretic peptide
CR: complete response
VGPR: very good partial response
PR: partial response

Table 2: Primary outcome variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Diagnosis	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL	AL
LV retention index (min ⁻¹)	0.05	0.22	0.29	0.05	0.11	0.06	0.23	No data	0.11	0.19	0.17	0.25	0.22	0.14	0.13
Myocardial SUV max	1.6	6.5	12.4	0.8	2.1	5.8	15.7	5.4	7.2	7.2	9.9	9	9.4	7.2	7.9
Myocardial SUV mean	1.1	3.6	7.1	0.8	1.2	3.6	6.8	2.2	3.2	2.7	5.3	4.8	4.5	2.7	4.6

Table 3: Relationship between primary outcome variables and clinical parameters.

	LV retention index (min ⁻¹)	LV myocardial SUV _{max}	LV myocardial SUV _{mean}
AL patients that were treatment-naïve (n=2), mean	0.21 (range 0.17-0.25)	9.45 (range 9 – 9.9)	5.05 (range 4.8-5.3)
AL patients established on treatment (n=13), mean	0.14 (0.05-0.29)	7.2 (range 0.8-15.7)	3.6 (range 0.8-7.1)
NT-proBNP response (n=6), mean	0.19 (range 0.11-0.29)	7.3 (range 2.1-12.4)	3.9 (range 1.2-5.2)
No NT-proBNP response (n=9), mean	0.16 (range 0.05-0.25)	8.7 (range 1.6-15.7)	4.3 (range 1.1-6.8)
	p=0.68	p=0.52	p=0.73
Haematological partial response (PR) or better (n=12), mean	0.14 (range 0.05-0.29)	6.38 (range 0.8-12.4)	3.38 (range 0.8-7.1)
No haematological PR or better (n=3), mean	0.21 (range 0.17-0.25)	11.5 (range 9-15.7)	5.63 (range 4.8-6.8)
	p=0.11	p=0.07	p=0.07

Table 4: Repeated ¹⁸F-florbetapir imaging in three cardiac AL patients.

Patient	Initial ¹⁸ F-florbetapir imaging						Repeat ¹⁸ F-florbetapir imaging						
	Treatment	Haematologic response	NT-proBNP response	LV RI (min ⁻¹)	SUV max	SUV mean	Treatment	Interval (months)	Haematologic response	NT-proBNP response	LV RI (min ⁻¹)	SUV max	SUV mean
1	Day 15, cycle 1 bortezomib, cyclophosphamide, dexamethasone	Partial response	No	0.05	1.6	1.1	7 months post chemotherapy	2	Complete response	Yes	0.06	1.4	1.0
3	Carfilzomib, pomalidomide, dexamethasone cycle 11	Complete response	Yes	0.29	12.4	7.1	Carfilzomib, pomalidomide, dexamethasone Cycle 14	8	Complete response	Yes	0.19	11.8	4.7
12	Pre-chemotherapy	Not applicable	No	0.25	9	4.8	Completed 2 cycles of chemotherapy	8	Complete response	No	0.21	10.7	5.2
Difference in primary outcome variables between initial and repeat imaging											p=0.3	p=0.71	p=0.5

LV RI: left ventricular retention index

Figure 1. Myocardial uptake with ^{18}F -florbetapir was demonstrated in all patients in the study.

a) Diffuse, intense myocardial uptake is seen in a patient with cardiac AL amyloidosis undergoing first cycle of chemotherapy. b) Markedly intense myocardial uptake with ^{18}F -florbetapir in a patient with cardiac AL amyloidosis, prior to chemotherapy initiation. c) Diffuse, low grade myocardial uptake in a patient with cardiac AL amyloidosis in a complete clonal response three months after completion of chemotherapy.

Supplemental data: Clinical characteristics of entire cohort at the time of initial ¹⁸F-florbetapir imaging