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Progress in the Application of Positron Emission Tomography Amyloid Radiotracers in Cardiac Amyloidosis

Tao Zhu, Hua Pang*

Department of Nuclear Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: zhutao176@126.com, *phua1973@163.com

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Abstract

Cardiac amyloidosis (CA) is a progressive and life-threatening manifestation of systemic amyloidosis characterized by extracellular deposition of insoluble amyloid fibrils in the myocardium. The two most common subtypes of CA are immunoglobulin light-chain (AL) and transthyretin (ATTR) amyloidosis, with ATTR further classified into hereditary (ATTRv) and wild-type (ATTRwt) forms. Early and accurate diagnosis of CA remains challenging, as the current gold standard, endomyocardial biopsy, is invasive and subject to sampling heterogeneity. In recent years, the rapid development of positron emission tomography (PET) molecular imaging has offered new possibilities for noninvasive detection, quantification, and monitoring of cardiac amyloid deposition. This review summarizes recent advances in PET imaging applied to CA, focusing on the performance and clinical potential of several emerging amyloid-targeting radiotracers. ^{11}C-PiB demonstrates excellent sensitivity for detecting AL-CA but is limited by its short half-life (20 minutes) and high production costs. ^{18}F-florbetapir, with a longer half-life of approximately 2 hours, shows promise for identifying CA and monitoring disease progression, although its ability to distinguish AL from ATTR subtypes remains suboptimal. Similarly, ^{18}F-florbetaben and ^{18}F-flutemetamol have been employed for cardiac amyloid imaging, with encouraging results in detecting myocardial amyloid burden, yet their specificity for amyloid subtyping requires further validation. The novel radiotracer ^{124}I-evuzamitide (^{124}I-p5+14) has demonstrated broad-spectrum targeting of systemic amyloid deposits and superior performance in imaging multiorgan involvement, although its prolonged half-life and associated radiation exposure may limit widespread clinical use. Future directions include the development of subtype-specific PET tracers, optimization of quantitative imaging techniques, and the integration of artificial intelligence for automated burden assessment and prognostication. Further-

more, PET imaging has the potential to serve as a biomarker for treatment response, facilitating individualized therapeutic strategies. Advances in amyloid PET imaging will undoubtedly play a crucial role in improving the diagnosis, management, and long-term prognosis of patients with cardiac amyloidosis.

Keywords

Positron Emission Tomography, Cardiac Amyloidosis, Amyloid Radiotracers

1. Introduction

Systemic amyloidosis comprises a heterogeneous group of protein misfolding disorders characterized by the extracellular deposition of insoluble amyloid fibrils, leading to progressive organ dysfunction and structural damage [1] [2]. Although amyloid deposits can involve multiple organs, cardiac involvement has been recognized as the leading cause of morbidity and mortality in systemic amyloidosis [3]. Cardiac amyloidosis (CA) is most commonly associated with two major subtypes: immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). Based on the presence or absence of transthyretin gene mutations, ATTR is further classified into hereditary (variant, ATTRv) and wild-type (ATTRwt) forms [4] [5]. ATTR-CA is primarily age-related [6], whereas AL-CA is typically characterized by a more aggressive clinical course and poorer prognosis [7]. Although rare, other forms of amyloidosis, such as AA amyloidosis, may also affect the heart [8].

Traditionally, endomyocardial biopsy combined with Congo red staining for the detection of amyloid fibril deposition has been considered the gold standard for the diagnosis of cardiac amyloidosis (CA) [9]. However, the invasive nature of biopsy, coupled with its associated risks—including bleeding, cardiac tamponade, arrhythmias, and even procedure-related mortality—has limited its widespread application in routine clinical practice [10]. Moreover, sampling heterogeneity may result in incomplete or unrepresentative diagnostic information. Therefore, the development of noninvasive imaging techniques capable of accurately assessing the burden, distribution, and progression of cardiac amyloid deposition has emerged as a critical need.

In recent years, the rapid advancement of molecular imaging has opened new avenues for the diagnosis and management of cardiac amyloidosis. Among these modalities, positron emission tomography (PET) has demonstrated unique advantages in the early detection and quantification of disease burden. PET radiotracers, including compounds targeting amyloid proteins, have been successfully employed to visualize amyloid fibril deposition in the heart. In addition, these tracers enable the assessment of disease progression and therapeutic response, supporting the development of more personalized treatment strategies. Importantly, PET imaging results have direct implications for clinical decision-making. By quantifying

myocardial amyloid burden and identifying extracardiac involvement, PET imaging helps stratify patients according to disease severity and organ involvement. Furthermore, by enabling early detection of cardiac involvement before overt clinical manifestations, PET imaging opens a therapeutic window for earlier intervention, potentially altering the natural history of the disease and improving long-term prognosis. Thus, PET imaging is poised not only as a diagnostic tool but also as a cornerstone for risk stratification, treatment planning, and prognosis prediction in cardiac amyloidosis.

This review focuses on emerging PET radiotracers targeting cardiac amyloid deposition and their applications in diagnosis, prognostic assessment, and therapy monitoring. By summarizing recent studies and advances in the field, we aim to provide valuable insights into the precise diagnosis and comprehensive management of cardiac amyloidosis.

2. ^{11}C-PiB

^{11}C-PiB is one of the most widely used PET radiotracers for amyloid imaging. Derived from the modification of thioflavin-T, ^{11}C-PiB enables direct visualization and quantitative assessment of β-amyloid deposition, particularly in the context of Alzheimer's disease (AD) research. Klunk *et al.* first applied ^{11}C-PiB PET imaging in 16 patients with mild AD and reported the feasibility of detecting amyloid deposition *in vivo* [11]. Subsequently, Antoni *et al.* explored the potential utility of ^{11}C-PiB for imaging cardiac amyloid deposition. In this study, cardiac amyloid uptake was compared between 10 patients with either AL or ATTR cardiac amyloidosis and 5 healthy controls. Cardiac amyloid burden was assessed using ^{11}C-PiB PET, while myocardial blood flow was measured using ^{11}C-acetate PET, allowing for the analysis of the correlation between tracer retention and perfusion. The results demonstrated significantly increased ^{11}C-PiB uptake in all patients with cardiac amyloidosis, whereas no uptake was observed in the control group [12]. These findings suggested that ^{11}C-PiB PET may serve as a promising noninvasive diagnostic tool for cardiac amyloidosis. Further evidence was provided by a prospective study conducted by Lee *et al.*, which included 22 patients with monoclonal gammopathy and suspected CA. Within one month, all participants underwent ^{11}C-PiB PET/CT, echocardiography, cardiac magnetic resonance imaging (CMR), and endomyocardial biopsy. Among the 15 biopsy-confirmed CA cases, 13 showed positive ^{11}C-PiB PET/CT findings, while none of the patients without histological confirmation of CA demonstrated positive uptake. Moreover, the study revealed that CA patients who received chemotherapy exhibited lower standardized uptake values (SUVs) than those who were untreated [13]. These results further support the role of ^{11}C-PiB PET not only as a noninvasive diagnostic tool for CA but also as a potential imaging biomarker for monitoring disease burden and treatment response following chemotherapy.

Pilebro *et al.* further compared ^{11}C-PiB PET/CT and ^{99m}Tc-DPD scintigraphy in 10 biopsy-confirmed patients with variant transthyretin amyloidosis (ATTRv)

and 5 healthy controls. The results showed that all patients exhibited increased myocardial ^{11}C-PiB uptake, whereas no uptake was observed in the control group. Notably, the study revealed that patients with type B amyloid had significantly higher ^{11}C-PiB retention compared to those with type A amyloid, despite type B being typically associated with less severe cardiac involvement. In contrast, ^{99m}Tc-DPD uptake was markedly elevated in type A patients but absent in type B patients [14]. These findings suggest that ^{11}C-PiB PET may provide mechanistic insights into cardiac amyloidosis and hold promise as a specific imaging modality for detecting myocardial amyloid deposition, independent of amyloid fibril composition, which may complement or even outperform conventional DPD scintigraphy. Another study investigated the combined application of ^{11}C-PiB PET and ^{99m}Tc-PYP SPECT for the detection and differentiation of AL, ATTRv, and ATTRwt cardiac amyloidosis. A total of 17 patients with AL-CA, 22 with ATTRv-CA, and 8 with ATTRwt-CA were enrolled. The results demonstrated distinct imaging patterns: AL patients exhibited a PiB pattern (positive ^{11}C-PiB, negative ^{99m}Tc-PYP), whereas ATTRwt patients showed a PYP pattern (negative ^{11}C-PiB, positive ^{99m}Tc-PYP). Interestingly, ATTRv patients displayed age-dependent patterns: patients with early-onset V30M (p.V50M) mutation predominantly exhibited the PiB pattern, while those with late-onset V30M or non-V30M mutations showed the PYP pattern. These results indicate that ^{11}C-PiB may have lower sensitivity in certain ATTR subtypes and highlight the complementary roles of multimodal imaging and genetic testing in the diagnosis and classification of cardiac amyloidosis [15]. However, the clinical utility of ^{11}C-PiB remains limited due to its short physical half-life (20 minutes) and the high production cost associated with cyclotron synthesis, posing challenges for its routine use in clinical practice [16].

3. ^{18}F-Florbetapir

^{18}F-florbetapir is structurally distinct from ^{11}C-PiB, characterized by a styrylpyridine backbone, and possesses a longer physical half-life of approximately 2 hours [17]. Developed and approved by the U.S. Food and Drug Administration (FDA) in 2012, this tracer has been widely used for imaging β-amyloid plaques in the brains of patients with Alzheimer's disease (AD) [18] [19].

In 2014, Dorbala *et al.* first investigated the application of ^{18}F-florbetapir PET imaging in cardiac amyloidosis (CA) and evaluated its potential to differentiate between AL and ATTR subtypes. The study enrolled 14 participants, including 9 patients with biopsy-proven CA and 5 healthy controls. The results demonstrated diffuse uptake of ^{18}F-florbetapir in both the left and right ventricles of all CA patients, whereas no myocardial uptake was observed in the control group. Notably, AL patients exhibited higher tracer uptake compared to ATTR patients, suggesting a potential association with disease activity [20]. Subsequently, the same group further validated these findings using ^{18}F-florbetapir combined with digital autoradiography on postmortem myocardial biopsy specimens from patients with his-

tologically confirmed AL and ATTR cardiac amyloidosis. The results confirmed the specific binding of ^{18}F-florbetapir to myocardial amyloid fibrils, with significantly higher uptake observed in AL samples compared to ATTR samples [21].

Cuddy *et al.* investigated the retention index (RI) of ^{18}F-florbetapir in patients with different stages of AL cardiac amyloidosis (CA). The study included three groups: 25 patients with active AL-CA and cardiac involvement, 10 patients with active AL amyloidosis without cardiac involvement, and 10 patients in hematologic remission. The results showed that ^{18}F-florbetapir uptake was observed in all participants, with significantly higher retention in patients with cardiac involvement. Furthermore, when compared with cardiac magnetic resonance (CMR) imaging and echocardiography, ^{18}F-florbetapir PET detected tracer uptake even in patients with normal CMR and echocardiographic findings. These results suggest that PET imaging may detect subclinical disease and has potential value in the early diagnosis of CA [22]. In a subsequent prospective study, Ehman *et al.* performed ^{18}F-florbetapir PET/CT imaging in 40 biopsy-confirmed patients with systemic AL amyloidosis, including 30 with active disease and 10 in hematologic remission. Compared to the established international consensus criteria [23], ^{18}F-florbetapir PET/CT identified a greater number of organ systems with amyloid deposition, regardless of disease activity status. Importantly, the study also demonstrated that amyloid deposits could still be detected by PET imaging in patients who had achieved hematologic remission. These findings highlight the potential of PET imaging to facilitate early recognition of systemic organ involvement and to serve as a non-invasive tool for guiding individualized treatment and monitoring disease progression [24].

In a prospective study, Clerc *et al.* followed 81 newly diagnosed patients with systemic AL cardiac amyloidosis (CA) to investigate the relationship between left ventricular (LV) amyloid burden quantified by ^{18}F-florbetapir PET/CT and major adverse cardiovascular events (MACEs). The study demonstrated that LV amyloid burden, expressed as the percentage of injected dose (%ID) of ^{18}F-florbetapir retained in the myocardium, was a significant predictor of MACE. This association appeared to be largely mediated by elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, reflecting myocardial stretch and the development of heart failure. However, after adjustment for Mayo AL staging, the predictive value of LV amyloid burden was no longer statistically significant. This study was the first to establish a link between cardiac amyloid burden assessed by molecular imaging, Mayo AL staging, and clinical outcomes in patients with AL-CA [25].

4. ^{18}F-Florbetaben

^{18}F-florbetaben is a styryl benzene derivative structurally similar to PiB and was initially developed for imaging studies in patients with Alzheimer's disease (AD). Preclinical and clinical investigations demonstrated that this tracer selectively binds to β-sheet-rich-structures of β-amyloid fibrils [16].

In the context of cardiac amyloidosis (CA), Law *et al.* were the first to apply ^{18}F-

florbetaben PET imaging in a cohort of 10 patients with amyloidosis and 4 control subjects with hypertensive heart disease. The results demonstrated that both the target-to-background standardized uptake value (SUV) ratio and tracer retention percentage were significantly higher in CA patients than in controls. Using a cut-off value of 40% tracer retention, ^{18}F-florbetaben PET effectively discriminated between amyloidosis and hypertensive heart disease. Moreover, myocardial tracer retention was identified as an independent predictor of left and right ventricular longitudinal strain [26]. However, ^{18}F-florbetaben appeared to be limited in differentiating between AL and ATTR subtypes of cardiac amyloidosis. A subsequent small-scale study assessed whole-body organ involvement in 9 suspected CA patients using ^{18}F-florbetaben PET/MRI. Delayed imaging revealed tracer uptake in multiple extracardiac sites, including the bone marrow, stomach, brain, salivary glands, tongue, and spleen, suggesting the potential of this technique for systemic amyloidosis localization and its possible utility in guiding biopsy and assessing treatment response [27]. Another study evaluated cardiac amyloid burden using ^{18}F-florbetaben PET/CT in 22 patients with clinically diagnosed or suspected CA. The results showed that this technique could differentiate CA subtypes, with AL patients exhibiting the highest tracer uptake. Furthermore, myocardial tracer retention was correlated with cardiac magnetic resonance (CMR) and echocardiographic parameters but showed no significant association with cardiac biomarkers. In four patients who underwent follow-up PET/CT scans after therapy, changes in tracer retention were consistent with treatment response. These findings suggest that ^{18}F-florbetaben PET/CT holds promise for assessing CA subtypes, quantifying amyloid burden, and monitoring therapeutic response [28].

5. ^{18}F-Flutemetamol

^{18}F-flutemetamol is another thioflavin-derived PET radiotracer originally developed for the diagnosis of Alzheimer's disease (AD) and other dementias [29].

Dietemann *et al.* were the first to evaluate the application of ^{18}F-flutemetamol PET imaging for the diagnosis of cardiac amyloidosis (CA). The study included 9 patients with CA and 3 control subjects. Except for one case, all CA patients exhibited significant ^{18}F-flutemetamol uptake in the left ventricular myocardium, with a markedly elevated target-to-background ratio, suggesting the potential of this tracer not only for CA diagnosis but also for monitoring treatment response [30]. Papathanasiou *et al.* further investigated the diagnostic performance of ^{18}F-flutemetamol PET in CA. The study enrolled 12 patients with CA (10 with ATTR and 2 with AL) and 5 patients with non-amyloid heart failure. Only 2 CA patients demonstrated significantly increased tracer uptake, indicating relatively limited diagnostic accuracy of ^{18}F-flutemetamol in this cohort [31]. It is noteworthy that the administered tracer dose was relatively low, and the imaging acquisition protocol differed from that of other studies. Additionally, the limited number of AL patients (n = 2) restricts the generalizability of these findings to the AL-CA population, underscoring the need for further research. A complementary histological

study investigated the binding characteristics of fluorescent-labeled flutemetamol in CA. The study included myocardial specimens from 29 CA patients (including ATTRwt, ATTRv, and AL subtypes) and 10 control subjects without amyloid deposition. Fluorescence imaging showed that flutemetamol binding consistently colocalized with amyloid deposits. Further analysis revealed that the mean fluorescence intensity was significantly higher in ATTRwt samples compared to AL samples and was positively correlated with interventricular septal thickness, posterior wall thickness, and left ventricular mass. These findings support the potential role of ^{18}F-flutemetamol PET in the diagnosis of both ATTR and AL subtypes of CA [32].

6. ^{124}I-Evuzamitide

^{124}I-evuzamitide (^{124}I-p5+14) is a synthetic polypeptide specifically designed to bind to negatively charged glycosaminoglycans present within amyloid fibrils. It is a novel PET radiotracer derived from the broadly reactive amyloid-targeting peptide p5+14 [33] [34] and has recently been applied in imaging studies of cardiac amyloidosis.

In the first-in-human study, ^{124}I-evuzamitide was applied to three patients with systemic AL amyloidosis. The results demonstrated that the tracer rapidly distributed to anatomical sites known to harbor amyloid deposits, including the heart, kidneys, liver, and lungs. The pattern of tracer uptake showed excellent concordance with clinically documented organ involvement, indicating its high specificity for amyloid deposition. This study suggested that ^{124}I-evuzamitide PET/CT imaging enables noninvasive detection of multiorgan amyloid involvement [35]. Compared with thioflavin-derived tracers, ^{124}I-evuzamitide offers the additional advantage of quantifying hepatic and potentially renal amyloid deposition [36]. Notably, the unbound tracer undergoes deiodination in the kidneys, a property that may facilitate accurate imaging of renal amyloid deposits [34]. Moreover, the relatively long physical half-life of ^{124}I (4.2 days) allows for convenient long-distance transportation and flexible imaging schedules [37].

In a preliminary study involving 26 patients with ATTRwt, AL, and ATTRv amyloidosis, along with healthy controls, Clerc *et al.* compared the performance of ^{124}I-evuzamitide and ^{18}F-florbetapir for the detection of cardiac amyloidosis (CA). The results demonstrated that ^{124}I-evuzamitide uptake was significantly higher in both AL and ATTRwt patients compared to controls, enabling accurate discrimination between patients with cardiac amyloidosis and healthy individuals. Moreover, in ATTRwt-CA patients, ^{124}I-evuzamitide exhibited higher myocardial uptake than ^{18}F-florbetapir, suggesting its potential superiority in quantifying amyloid burden in ATTRwt cardiac amyloidosis [36].

In another study, ^{124}I-evuzamitide was utilized for imaging a variety of amyloidosis subtypes, including light-chain (ALκ and ALλ), transthyretin (ATTRv and ATTRwt), leukocyte chemotactic factor 2 (ALECT2), gelsolin (AGel), lysozyme (ALys), and apolipoprotein A1 (AApoA1) amyloidosis. The results demonstrated

tracer uptake across all clinically involved organs. Notably, radioactive accumulation was also observed in organs without clinically apparent involvement, suggesting that ^{124}I-evuzamitide may possess high sensitivity for detecting early or subclinical organ involvement [38].

7. Future Perspectives

Advances in amyloid PET imaging have provided essential tools for the diagnosis and management of amyloidosis. Compared to conventional imaging modalities, PET imaging offers significant advantages in the early detection, burden quantification, prognostic assessment, and therapeutic monitoring of amyloid deposits due to its unique molecular targeting mechanisms. However, current PET radiotracers still face several challenges, and improving the precision and clinical utility of imaging techniques remains a major focus for future research.

Existing amyloid PET tracers exhibit variable specificity and sensitivity in diagnosing different subtypes of cardiac amyloidosis. For instance, ^{11}C-PiB has shown excellent performance in detecting AL amyloidosis, yet its clinical application is limited by a short physical half-life of approximately 20 minutes. Although ^{18}F-florbetapir benefits from a longer half-life of around 2 hours, its ability to differentiate AL from ATTR amyloidosis remains suboptimal. Similarly, ^{18}F-florbetaben and ^{18}F-flutemetamol have demonstrated potential in detecting myocardial amyloid deposits, but their subtype-specific diagnostic accuracy requires further validation. On the other hand, ^{124}I-evuzamitide, as a broad-spectrum tracer, has shown excellent performance in assessing systemic multiorgan amyloid deposition. However, its prolonged half-life (4.2 days) may increase patient radiation exposure and impose higher production and logistical costs.

A key future direction is the development of novel PET tracers with improved specificity for different amyloid subtypes. Optimizing molecular structures and targeting mechanisms will be crucial to achieving more accurate diagnosis and amyloid typing. Furthermore, enhancing the quantitative capacity of PET imaging, especially when integrated with machine learning techniques, could allow for a more precise evaluation of amyloid burden and better prediction of disease progression. In therapeutic monitoring, the design of tracers capable of dynamically reflecting treatment response will be particularly valuable, facilitating real-time efficacy assessment and enabling individualized treatment strategies. The development of long half-life tracers that are cost-effective and easier to synthesize could also improve their feasibility and broader application in clinical practice.

In addition, the integration of multimodal imaging techniques may offer a more comprehensive and accurate assessment of amyloid deposition, particularly in the early detection and classification of cardiac amyloidosis. Although amyloid PET imaging has made significant progress in the diagnosis and management of cardiac amyloidosis, further efforts are needed to enhance its sensitivity and specificity, advance the development of novel tracers, and optimize imaging protocols. These advancements will not only improve diagnostic accuracy, but also promote

the implementation of precision medicine and long-term management of cardiac amyloidosis, ultimately providing patients with more effective and individualized therapeutic options.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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