Significance of ^{11}C-PIB PET/CT in cardiac amyloidosis compared with ^{99m}Tc-aprotinin scintigraphy: A pilot study

Ryogo Minamimoto, MD, PhD,[a] Toru Awaya, MD,[b] Kentaro Iwama, MD,[b] Masatoshi Hotta, MD,[a] Kazuhiko Nakajima,[a] Risen Hirai, MD,[c] Osamu Okazaki, MD, PhD,[b] and Yukio Hiroi, MD, PhD[b]

[a] Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, Tokyo, Japan
[b] Department of Cardiovascular Medicine, National Center for Global Health and Medicine, Tokyo, Japan
[c] Division of Hematology, Internal medicine, Tokyo Kita Medical Center, Tokyo, Japan

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Background. **This study was to investigate the significance of ^{11}C-Pittsburgh B (PIB) PET/CT in patients with suspected cardiac amyloidosis compared with ^{99m}Tc-aprotinin scintigraphy.**

Methods. **Thirteen consecutive patients with suspected cardiac amyloidosis were considered for enrolment in this prospective pilot study. Participants were scheduled to undergo a series of ^{11}C-PIB PET/CT and ^{99m}Tc-aprotinin within a 2-month period. Finally, we evaluated nine cases who underwent both imaging modalities, and compared imaging results with clinical and pathological results and prognosis.**

Results. **Six of the 9 patients who underwent both imaging modalities were diagnosed with amyloidosis, of whom 3 patients were diagnosed with cardiac amyloidosis from endomyocardial biopsy. These 3 patients with positive ^{11}C-PIB uptake at the left ventricle wall showed worsening of cardiac function progressing in the short term or death caused by acute exacerbation of chronic heart failure. Six of 8 patients with positive uptake on ^{99m}Tc-aprotinin presented with amyloid deposition in the left ventricle wall, but symptoms remained stable if results of ^{11}C-PIB were not positive.**

Conclusion. **In a small sample of subjects, the present study showed that ^{11}C-PIB accumulation in myocardium indicated cardiac amyloidosis with poor prognosis. Uptake of ^{11}C-PIB may be related to progressive amyloid deposition to the heart and can predict patient prognosis. (J Nucl Cardiol 2020;27:202–9.)**

Key Words: Amyloidosis • Pittsburgh compound B • Aprotinin

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Reprint requests: Ryogo Minamimoto, MD, PhD, Division of Nuclear Medicine, Department of Radiology, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjyuku-ku, Tokyo 162-8655, Japan; *ryogominamimoto@yahoo.co.jp*

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Abbreviations	
PIB	Pittsburgh B
PET/CT	Positron emission tomography/ computed tomography
SPECT/CT	Single-photon emission computed tomography/computed tomography
VOIs	Volume of interests
SUV	Standardized uptake value
ATTR	TTR-related amyloidosis

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BACKGROUND

Cardiac amyloidosis is a myocardial disease characterized by extracellular amyloid infiltration in the heart, resulting in cardiomyopathy, heart failure, and atrial and ventricular arrhythmias, and tends to present a poor prognosis with a short median survival in the absence of treatment.[1] Histopathological diagnosis with Congo Red stain in a biopsy of tissue has been conducted for the final diagnosis of amyloidosis.[2] Although endomyocardial biopsy is the standard for diagnosis, early diagnosis with non-invasive imaging has been expected to improve the care of patients with cardiac amyloidosis.

Aprotinin (Trasylol; Bayer Pharmaceuticals, Müllerstr, Berlin) is a small bovine protein that acts as a basic pancreatic trypsin inhibitor. Aprotinin is used as an anti-coagulant drug and has been available for the prophylaxis and treatment of major blood loss during complex surgery.[3] Proteinase inhibitors have been detected within amyloid deposits, allowing binding of amyloid to aprotinin. Aprile, et al. described the first evaluation of ^{99m}Tc-aprotinin for the imaging of amyloid deposit in patients with AL amyloidosis, and as a potential tracer for detecting cardiac amyloid.[4] Pittsburgh B (PIB) compound, a derivative of thioflavin T, has been used for imaging β-amyloid in Alzheimer's disease [5] and is believed to bind to amyloid fibrils of any type.[6] A few recent studies have shown that ^{11}C-PIB positron emission tomography/ computed tomography (PET/CT) could visualize cardiac amyloidosis in several types of amyloid (AL k, AL l, and transthyretin origin). [7,8] However, we reported a mismatch between results of ^{11}C-PIB and ^{99m}Tc-aprotinin in the myocardium in patient with amyloidosis, and whether ^{11}C-PIB uptake is relevant to amyloid deposition remains unclear.[9] The aim of this pilot study was to evaluate the significance of ^{11}C-PIB-positive findings in patients with cardiac amyloidosis, compared to positive findings for ^{99m}Tc-aprotinin, which binds specifically to amyloid.

MATERIALS AND METHOD

Patients Selection

All patients provided written informed consent to participate in this prospective study, and the study was approved by the institutional review board at our hospital in accordance with the Declaration of Helsinki. Each patient was referred to our hospital with suspected cardiac amyloidosis by US and/or MRI or systematic amyloidosis related to multiple myeloma. A total of 13 consecutive patients were assessed for eligibility for this prospective study from August 2010 to August 2016, which consisted of a series of ^{11}C-PIB PET/CT and ^{99m}Tc-aprotinin scintigraphy. Four of the 13 patients did not undergo ^{99m}Tc-aprotinin, because treatment was initiated for multiple myeloma in three patients, and the purity of ^{99m}Tc-aprotinin was lower than 90% in one case, which did not fulfill the quality standards for the tracer. Finally, we analyzed nine patients (3 women, 6 men; mean age ± standard deviation (SD), 64 ± 14 years) who underwent both ^{11}C-PIB PET/CT and ^{99m}Tc-aprotinin scintigraphy. The difference in time between ^{11}C-PIB PET/CT and ^{99m}Tc-aprotinin scintigraphy was mean age ± standard deviation 33.4 ± 32.8 days (range 4 to 117 days). Amyloid deposition was histopathologically diagnosed by biopsy specimens stained with Congo red dye. Enrolled patients were followed up for maximum 21 months (mean ± SD: 264 ± 189 days, range 32 to 633 days) in terms of progressing of cardiac function and/or cardiac symptom.

Imaging Protocol

^{99m}Tc-Aprotinin scintigraphy. Planar and tomographic imaging were performed 90 min after a 2-mL injection containing 740 MBq of ^{99m}Tc-aprotinin (mean radiochemical purity, 98.6%; range 95.7% to 99.8%). Acquisition included anterior and posterior whole-body scans (11 to 13 cm/min) and regional static imaging (acquisition time, 5 to 7 min per image) obtained with a single-photon emission computed tomography/computed tomography (SPECT/CT) system (Infinia Hawkeye4; GE Health Care, Milwaukee, WI). The camera was equipped with a low-energy, high-resolution parallel-hole collimator. SPECT tomograms of the chest were also obtained for all patients. Images were taken on a 512 × 512 matrix for static views and on a 128 × 128 matrix for SPECT images.

^{11}C-PIB PET/CT. Injection of ^{11}C-PIB (620 ± 168 MBq; range 366 to 746 MBq) was performed after an emission scan, 40 min after tracer injection using a PET/CT scanner (Discovery 600M; GE Health Care). After low-dose CT, PET scan was performed in 3-dimensional mode for 20 min. PET images were reconstructed on 192 × 192 matrices using an ordered-subset expectation maximization method (4 iterations, 8 subsets) with application of a 4-mm Gaussian filter.

Image Interpretation and Analysis

Images were reviewed by two board-certified nuclear medicine specialists. Accumulation of each tracer in

Table 1. Patients' characteristics

Patient no	Age	Sex	Clinical background	Primary disease and/or clinical symptom	Myocardial biopsy (positive / negative, tissue type)	Non-myocardial biopsy (positive / negative, tissue type)	^{11}C-PIB PET findings	^{99m}Tc-Aprotinin findings	Clinical outcome
1	60	F	US (Granular sparking sign at interventricular septum)	Multiple myeloma: IgA type	Negative	-	Negative	Positive (interventricular septum)	Stable EF 69.5% → 62.4% (21 months)
2	72	F	Myocardial biopsy	Atrial fibrillation	Positive AL	Subcutaneous adipose tissue biopsy positive, stomach biopsy positive, type unknown	Positive (entire myocardium)	Positive (entire myocardium)	Worsen EF 54.2% → 39.1% (2 months)
3	45	M	Cardiac MRI (LGE at interventricular septum and lateral wall)	Primary systematic amyloidosis/left ventricular hypertrophy	Negative	Subcutaneous adipose tissue biopsy negative, stomach and colon biopsy negative	Negative	Positive (interventricular septum and lateral wall)	Improved EF 25.6% → 53.3% (11 months)
4	82	M	Subcutaneous adipose tissue biopsy	Atrial fibrillation	-	Subcutaneous adipose tissue biopsy positive, AL	Negative	Positive (entire myocardium)	Stable cardiac symptom
5	78	F	Subcutaneous adipose tissue biopsy	Hypertrophic cardiomyopathy	-	Subcutaneous adipose tissue biopsy positive, AL	Negative	Positive (apex)	Stable cardiac symptom
6	58	M	Myocardial biopsy	Left ventricular hypertrophy	Positive AL	Stomach and colon biopsy positive, type unknown	Positive (entire myocardium)	Positive (entire myocardium)	Worsen EF 65.4% → 31.4% (1 months)

Table 1. continued

Patient no	Age	Sex	Clinical background	Primary disease and/or clinical symptom	Myocardial biopsy (positive / negative, tissue type)	Non-myocardial biopsy (positive / negative, tissue type)	^{11}C-PIB PET findings	^{99m}Tc-Aprotinin findings	Clinical outcome
7	75	M	Stomach biopsy gastric amyloidosis	Anemia, Shortness of breath on exertion, Myocardium failure	-	Stomach biopsy positive, AL	Negative	Negative	Stable cardiac symptom
8	43	M	Cardiac MRI (LGE at interventricular septum)	Atrioventricular block	Negative	-	Negative	Positive (apex to lateral wall)	Clinically suspected sarcoidosis
9	67	M	Myocardial biopsy	Primary macrocryglob-ulinemia	Positive AL	-	Positive (entire myocardium)	Positive (interventricular septum)	EF 72.1% → death due to heart failure (6 months)

US, ultrasonography; *LGE*, late gadolinium enhancement; *EF*, ejection fraction; '+', positive findings; '−', negative findings

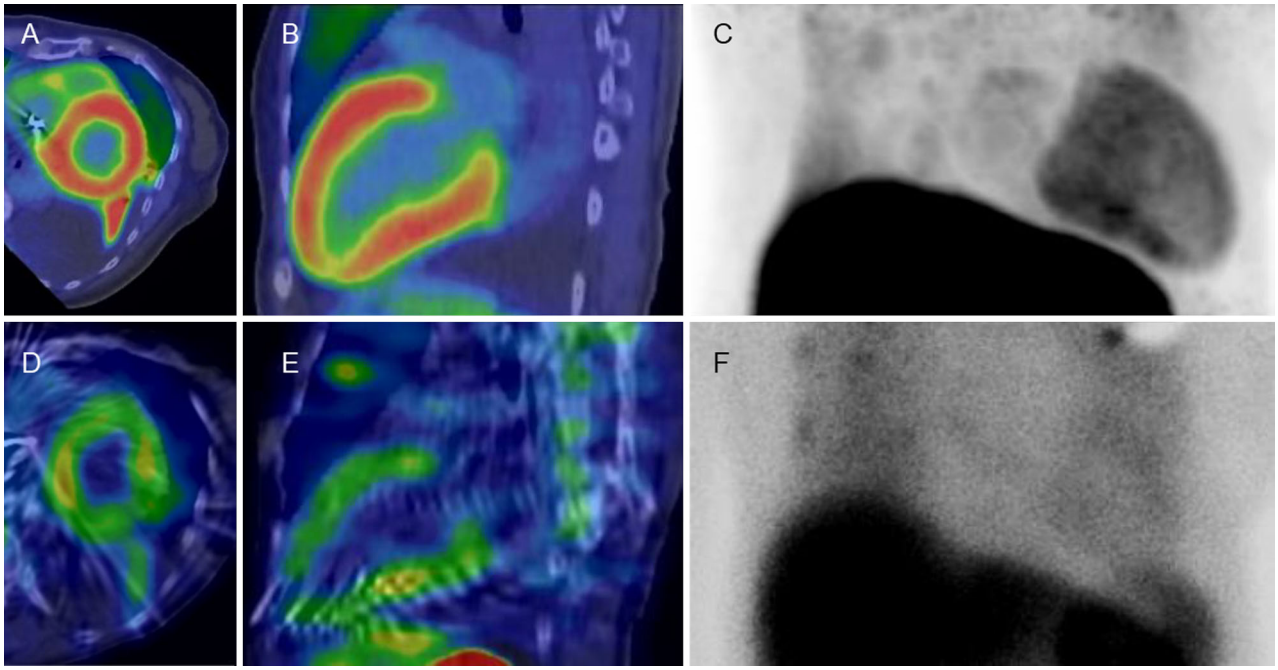

Figure 1. Patient No. 2. ^{11}C-PIB PET/CT; **A** short, **B** vertical long, **C** MIP image, ^{99m}Tc-aprotinin scintigraphy; **D** short, **E** vertical long, **F** Planer image. Both ^{11}C-PIB and ^{99m}Tc-Aprotinin imaging showed intense uptake at the entire left ventricle wall. AL-type amyloid deposition was proved by cardiac biopsy. Patient had a poor prognosis with progressing serious heart failure within 2 months.

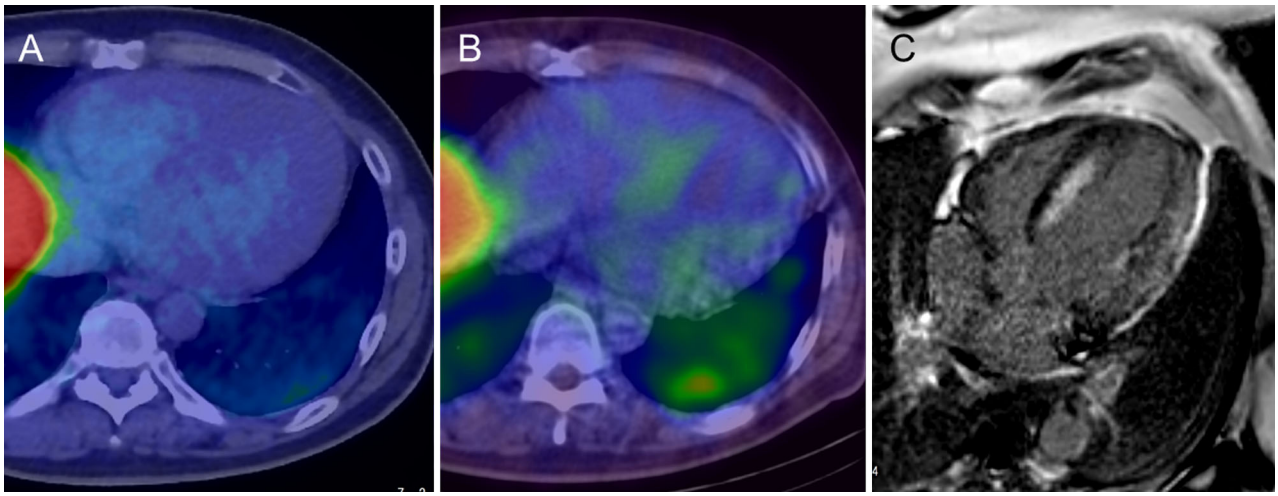

Figure 2. Patient No. 3. **A** ^{11}C-PIB PET/CT, **B** ^{99m}Tc-aprotinin scintigraphy, **C** Delayed enhanced cardiac MRI image (phase-sensitive inversion recovery) ^{99m}Tc-aprotinin uptake was identified in septal and lateral myocardial wall, which correspond to the delayed enhanced area in cardiac MRI. However, ^{11}C-PIB PET/CT showed negative findings in entire myocardial wall. Amyloid deposition in patients was not confirmed by cardiac biopsy, and ejection fraction of heart was improved in 11 months.

myocardium was determined by visual interpretation. The reference ^{99m}Tc-aprotinin image for visual interpretation referred to the image of a control subject is presented in the article by Han et al.[10] If the obtained image showed intense focal uptake that was not confirmed in the reference image, the result was regarded as positive ^{99m}Tc-aprotinin uptake. A positive ^{11}C-PIB result was defined as ^{11}C-PIB uptake by myocardium higher than that in the blood pool. These findings

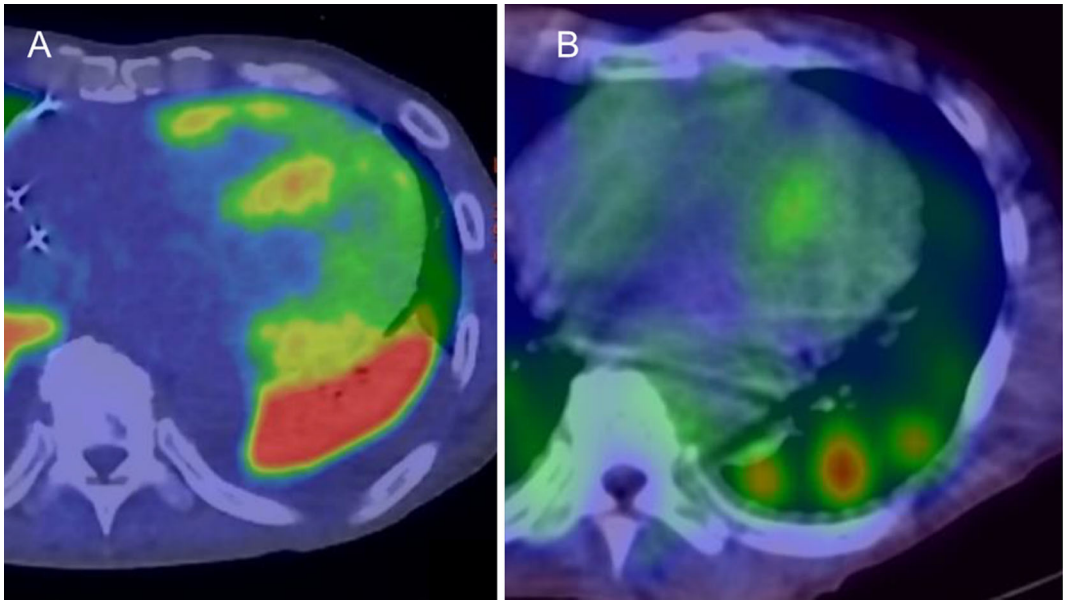

Figure 3. Patient No. 9. **A** ^{11}C-PIB PET/CT, **B** ^{99m}Tc-aprotinin scintigraphy. The patient was referred our hospital with cardiac failure caused by cardiac amyloidosis proved by cardiac biopsy. ^{11}C-PIB showed positive uptake at left and right ventricle wall, whereas ^{99m}Tc-Aprotinin was weak positive only at interventricular septum. In spite of treatment of heart failure, patient died with progressive cardiac failure after 6 months of ^{11}C-PIB PET/CT scan.

were compared with the final clinical and histopathological diagnoses. Images were displayed on trans-axial, coronal, and sagittal planes with 5-mm slice thickness.

Volume of interests (VOIs) with 10 mm diameter were carefully positioned on the highest uptake points in myocardium as identified visually on trans-axial ^{11}C-PIB images, and the standardized uptake value (SUV) was measured. As for the measurement of uptake in the blood pool, a 10-mm diameter VOI was placed centrally within the ascending aorta.

Statistical Analysis

The Mann-Whitney U test was used to evaluate differences in ^{11}C-PIB uptake between ^{11}C-PIB-positive and ^{11}C-PIB-negative case, and between amyloid-positive and amyloid-negative cases. A two-sided value of $P < 0.05$ was considered significant.

RESULTS

Patient characteristics are shown in Table 1. Three patients with positive ^{11}C-PIB uptake in the left ventricle wall showed worsening of cardiac function progressing in the short term or death caused by acute exacerbation of chronic cardiac failure. Six of the 8 patients with positive uptake on ^{99m}Tc-aprotinin suspected amyloid deposition in the left ventricular wall, but myocardial symptoms consistently remained stable if results of ^{11}C-PIB were not positive. One case showing negative findings on both ^{11}C-PIB and ^{99m}Tc-aprotinin at the cardiac wall had no evidence of amyloid deposition on pathological diagnosis or according to clinical status. Representative images are shown in Figures 1, 2, and 3.

All four cases that underwent ^{11}C-PIB alone showed negative findings on ^{11}C-PIB PET/CT, and cardiac function was stable for at least 6 months according to clinical diagnosis.

The SUVmax and SUVmean of ^{11}C-PIB uptake in the myocardium were 5.1 ± 1.7 and 4.1 ± 0.9, respectively ($P = 0.02$), in ^{11}C-PIB-positive cases, significantly higher than the 1.2 ± 0.6 and 0.8 ± 0.2, respectively ($P = 0.02$) in ^{11}C-PIB-negative cases. Uptake in the ascending aorta showed no significant difference between ^{11}C-PIB-positive and ^{11}C-PIB-negative cases (SUVmax: 1.2 ± 0.2 vs 1.2 ± 0.6, $P = 1.00$; SUVmean: 0.8 ± 0.3 and 0.9 ± 0.1, $P = 1.00$). Myocardium-to-background (blood pool) ratios with SUVmax and SUVmean of ^{11}C-PIB uptake were 2.7 ± 2.0 and 2.0 ± 1.3, respectively, in ^{11}C-PIB-positive cases, tending to be higher than the 1.1 ± 0.4 and 0.9 ± 0.3, respectively, in ^{11}C-PIB-negative cases, but these differences were not significant ($P = 0.22$ and $P = 0.39$, respectively).

DISCUSSION

In a small sample of subjects, this preliminary study showed that ^{11}C-PIB accumulation in the myocardium indicated cardiac amyloidosis with poor prognosis. Uptake of ^{11}C-PIB may relate to progressive amyloid deposition in the myocardium and can predict patient prognosis. Theoretically, ^{11}C-PIB can bind with conformational dependence to amyloid fibrils of any type.[5] Antoni et al. first reported that ^{11}C-PIB could detect deposition of several types of amyloid (AL k, AL l, and transthyretin origin) in the heart, representing a usage of ^{11}C-PIB beyond detection of brain amyloid.[7] Lee et al. reported a value of ^{11}C PIB for the diagnosis of cardiac amyloidosis and the possibility of using this tracer as a surrogate for active light chain deposition in the myocardium.[11] A recent study reported that ^{11}C-PIB could bind to TTR-related amyloidosis (ATTR) amyloid and seems to bind much more strongly to type B than to type A fibrils of ATTR.[12] The quantitative aspects of ^{11}C-PIB binding to ATTR amyloid might depend on fibril type, rather than amyloid burden.

A significant increase in ^{11}C-PIB uptake was found in patients with amyloidosis, whereas myocardial blood flow was significantly reduced. The author concluded that increased ^{11}C-PIB is associated with decreased myocardial blood flow.[7] As a result, ^{11}C-PIB accumulation is independent of cardiac blood flow. In our study, positive ^{11}C-PIB uptake could be seen in three of the 8 cases with ^{99m}Tc-aprotinin-positive results in myocardium, and prognosis of all three cases was quite poor.

Given the ability of ^{99m}Tc-aprotinin to detect amyloid deposits in myocardium,[13,14] this tracer appears valuable for the imaging of myocardial amyloid. In a study by Han, all 5 patients (out of 35 examined) who had histologically confirmed heart amyloidosis showed positive uptake of ^{99m}Tc-aprotinin in the myocardium.[10] In our study, ^{99m}Tc-aprotinin scintigraphy showed positive findings in all 5 patients with histologically confirmed amyloid deposit.

Based on such findings, ^{99m}Tc-aprotinin scintigraphy appears to offer a sensitive, specific diagnostic modality for patients with amyloidosis. However, this tracer is not widely used in cardiac surgery due to concerns over safety.[15,16] Our results showed that ^{99m}Tc-aprotinin might yield false-positive findings or amyloid deposition unrelated to patient prognosis.

All patients in our study showed AL-type amyloidosis. Median survival from onset of heart failure has been reported as approximately 6 months,[17] but recent therapies can prolong remission and extend life.[18] Early diagnosis using ^{11}C-PIB PET/CT may be critical for achieving better outcomes in patients with cardiac amyloidosis.

Limitations

The key limitation was that this study was performed on a small number of patients. The ^{11}C-PiB myocardial retention index advocated by the Uppsala University group[7] and a full compartmental analysis of ^{11}C-PIB PET data could not be performed in this study. Cardiac MRI is not performed routinely due to the prevalence of pacemaker carriers. Not all patients were investigated for concomitant amyloid deposition, even though AL cardiac amyloidosis is part of a systemic disease that most commonly affects the kidney.

CONCLUSIONS

This present study evaluated the significance of ^{11}C-Pittsburgh B (PIB) positron emission tomography in patients with suspected cardiac amyloidosis compared with ^{99m}Tc-aprotinin scintigraphy. Our result showed that ^{11}C-PIB accumulation in myocardium indicated cardiac amyloidosis with poor prognosis. Uptake of ^{11}C-PIB may be related to progressive amyloid deposition to the heart and can predict patient prognosis.

NEW KNOWLEDGE GAINED

^{11}C-PIB accumulation in myocardium indicated cardiac amyloidosis with poor prognosis. Uptake of ^{11}C-PIB may be related to progressive amyloid deposition to the heart and can predict patient prognosis.

Disclosure

None of the authors have any conflicts of interest to disclose.

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