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Slart, Riemer H J A; Glaudemans, Andor W J M; Noordzij, Walter; Nienhuis, Hans L A; Hazenberg, Bouke P C

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EDITORIAL

^{99m}Tc-aprotinin imaging in cardiac amyloidosis. Make an old tool new again?

Riemer H.J.A. Slart[1,2,5], Andor W.J.M. Glaudemans[1,5], Walter Noordzij[1,5], Hans L. A. Nienhuis[3,5], Bouke P.C. Hazenberg[4,5]

[1]Medical Imaging Center, Department of Nuclear Medicine and Molecular Imaging, [3]Department of Internal Medicine, [4]Department of Rheumatology & Clinical Immunology, [5]Amyloidosis Center of Expertise, University of Groningen, University Medical Center Groningen, The Netherlands, [2]TechMed Centre, Department of Biomedical Photonic Imaging, University of Twente, Enschede, The Netherlands.

Cardiac amyloidosis (CA) or amyloid cardiomyopathy (ACM), resulting from extracellular deposition of amyloid fibrils, is an underestimated cause of heart failure and cardiac arrhythmias [1,2]. Amyloid cardiomyopathy is a restrictive form of cardiomyopathy (CM) characterized by diastolic dysfunction and should be suspected in any patient presenting with heart failure with preserved ejection fraction (HFpEF). The two main types of cardiac amyloidosis are AL-type, derived from misfolded immunoglobulin light chains, and ATTR-type, derived from misfolded transthyretin (TTR) protein.

AL amyloidosis currently is the most common type of clinically significant cardiac amyloidosis, accounting for ~80% of all cases, invariably associated with an underlying clonal plasma cell dyscrasia and almost exclusively seen in individuals older than 40 years [3] Cardiac involvement is frequent (70%) in AL amyloidosis. It is usually associated with involvement of other organs and is rarely (<5%) limited as isolated cardiac amyloidosis. In early stages, ACM in AL amyloidosis is characterized by the presence of HFpEF. However, systolic dysfunction commonly follows in the course of the disease. [4].

ATTR amyloidosis is increasingly recognized as a cardiomyopathy in elderly people, especially in men [5]. Amyloid in these cases has been derived from non-mutated, so-called wild-type TTR. ATTR amyloidosis can also sometimes be found as hereditary disease, caused by a mutation in the *TTR* gene, often with a clinical picture dominated by polyneuropathy. However, cardiomyopathy is usually part of the clinical picture, sometimes at presentation, but frequently it evolves in the course of the disease.

Accurate and early diagnosis of heart failure as a result of CA has major implications on prognosis and treatment. Selective treatment is delayed in a substantial proportion of the affected individuals because of an often late recognition, thereby negatively affecting the quality of life as well as the survival of these individuals. Therefore, there is a definite clinical need for early and secure diagnosis of cardiac amyloidosis as well as for reliable typing of cardiac amyloid as AL or ATTR type. Molecular imaging with PET and SPECT nowadays plays a critical role in the diagnosis, identification and distinction between ATTR and AL type CA. Several SPECT and PET tracers are available for diagnosing CA [6]. Selective tracers with the potential of discriminating ATTR from AL type CA with confidence, are the most important ones.

Thioflavin-like agents (Pittsburgh Compound-B, florbetapir and florbetapen) bind directly to repetitive motifs on the exterior surface of the fibrils. Aprotinin has been used in the past to detect CA [7, 8] and it may also bind to repetitive motifs and/or electrostatically [9]. The accuracy of ^{99m}Tc-aprotinin scintigraphy has been reported previously for systemic amyloidosis, but not specifically for cardiac AL amyloidosis. A potential concern of the bovine lung tissue origin of aprotinin is the possible transfer of Bovine Spongiform Encephalopathy (BSE). The manufacturing process, however, contains a number of inactivation/removal steps to reduce the possibility of BSE in the order of 18 log 10, thereby leading to the conclusion that aprotinin is BSE safe [10].

The current study of Awaya and colleagues in this issue, evaluated the performance of ^{99m}Tc-aprotinin scintigraphy for diagnosing AL CA in a pilot study consisting of 10 patients suspected of suffering from amyloidosis [11]. Cardiac amyloidosis was histologically confirmed by endomyocardial biopsy in 5 of 10 patients. ^{99m}Tc-aprotinin (planar images) was positive in 4 out of 5 patients who had amyloid deposits in endomyocardial biopsy. On the other hand, all 5 patients without amyloid deposits were negative in planar image. ^{99m}Tc-aprotinin SPECT/CT imaging was positive in all 5 patients who had amyloid deposits, but also

showed subtle myocardial tracer uptake in 3 out of 5 patients (false positive) in whom an endomyocardial biopsy did not show amyloid. It was concluded that ^{99m}Tc-aprotinin scintigraphy including SPECT/CT may be valuable for the noninvasive diagnosis of AL cardiac amyloidosis. However, before this application can be implemented as a reliable non-invasive technique within the general work-up of patients with the suspicion of AL amyloidosis, further research is required in a substantial number of patients with cardiac amyloidosis and controls, especially aiming to reduce false-positive findings on SPECT/CT. Quantification of the heart-to-background ratio may be beneficial in this respect, by setting an upper reference limit to reduce false positive findings [8]

Although this pilot study consisted of a small, heterogeneous patient cohort, including treatment-naïve as well as pre-treated patients, it underlines the clinical value of applying new more specific imaging tracers in cardiac imaging, but the false positive findings with SPECT/CT should be kept in mind.

Selective radiopharmaceuticals are the benzothiazoles ^{11}C–Pittsburgh compound-B (^{11}C-PiB) and ^{18}F–florbetaben, while ^{18}F–florbetapir is a stilbene derivative with a very similar structure. A systematic review of the application of PET imaging with ^{11}C-PiB, ^{18}F-florbetapir and ^{18}F-florbetaben in 6 studies (n=98 subjects) demonstrated a sensitivity of 92% and a specificity of 83% for the detection of AL and ATTR CA [12].

^{11}C-PiB is however only available in centers with an on-site cyclotron. Further it is reported that ^{11}C-PIB and the ^{18}F-labeled thioflavin-like agents detect deposition of several types of amyloid (AL-kappa, AL-lambda, and TTR origin) in the heart, representing a less specific detection of amyloid [13,14].

Compared with control samples, mean ^{18}F-florbetapir-specific uptake is significantly higher in the amyloid samples, and higher in AL CA compared with the ATTR CA samples [14]

^{99m}Tc-aprotinin scintigraphy was directly compared with ^{11}C-PiB in AL CA, and ^{99m}Tc-aprotinin scintigraphy appears to offer a sensitive, specific diagnostic modality for patients with amyloidosis [15]. More specific targeted imaging may also result in more personalized therapy. However, this was based on small patient numbers and there is a need for studies comparing the different tracers mentioned above in substantial numbers of patients with well-defined types of cardiac amyloidosis and in well-defined cardiomyopathy controls who present themselves in a similar way.

It has been shown that chemotherapy including high-dose melphalan followed by peripheral blood stem cell transplantation can be effective if the load of AL amyloidosis has not progressed too far and cardiac involvement is subtle [16]. However, usually cardiac disease is detected too late and the risks are too high in these patients with AL CA to benefit from intensive chemotherapy. There is little time for patients with symptomatic cardiac AL amyloidosis to respond to treatment and therefore the prognosis of symptomatic cardiac AL amyloidosis is still grim, stressing the importance of early detection. Monitoring the load of cardiac amyloid will be a useful tool in patients receiving treatment. Manwani et al. evaluated cardiac uptake with ^{18}F-florbetapir PET in patients with systemic AL amyloidosis and cardiac involvement before and after treatment, as well as its serial utility in monitoring in 15 patients [17].

In summary, the role of molecular imaging in CA is significant in, (1) differentiating between AL and ATTR CA, (2) defining the extent of systemic amyloid manifestations, and (3) as a potential biomarker for treatment monitoring. Biphophonate scintigraphy is a strong tool for detecting ATTR CA, and will be negative in AL CA. At the other side the ^{18}F-labeled thioflavin-like agents are favorable in AL CA detection. Smart application or combination of these tracers is needed to optimally differentiate ATTR from AL CA. For diagnostic considerations, specific target imaging will play a role in the future. Several aspects have to be elucidated yet, but if aprotinin and other selective radiopharmaceuticals finally will break through as diagnostic and potential therapeutic possibilities in amyloidosis, molecular imaging might become an excellent tool to guide the clinician in diagnosing and treating the patient with cardiac amyloidosis. To overcome the spatial limitations of SPECT and to improve the accuracy of the imaging technique, radiolabeled-aprotinin with a PET isotope should be considered in future studies.

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