

Contribution of ^{99m}Tc -DPD Scintigraphy in the Diagnosis of Cardiac Amyloidosis in Black Africans

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Abstract

Cardiac amyloidosis presents a picture of hypertrophic cardiomyopathy with heart failure with preserved ejection fraction. It is largely underdiagnosed, especially in black Africans, and therefore falls under the category of heart disease classified as idiopathic. Light chain amyloidosis (AL) is mainly found in Caucasian subjects and the mutant variant of transthyretin (TTRm) in negroid subjects. Numerous studies have shown that ATTRm was found predominantly in black American and black British patients. In African countries the entity of idiopathic heart failure is quite important because of lack of diagnosis, ETT, MRI and immuno-histochemistry are expensive or not available. We can probably assume that the proportion of cardiac amyloidosis is quite important in black Africans. The question is if ^{99m}Tc -DPD really easy to perform, can probably help to investigate in the nuclear medicine department in Africa. No large-scale study has been able to demonstrate the prevalence or not of cardiac amyloidosis in black-African subjects and by extension reduce this nosological entity of idiopathic heart disease. The ^{99m}Tc -DPD scintigraphy using Perrugini's visual score allows localization and classification of amyloid damage. The mechanism of binding of ^{99m}Tc -DPD to amyloid fibril deposits is not well known, its binding to TTR-type (mutated or wild type) amyloidosis is greater than the AL variant. In the diagnostic algorithm, endomyocardial biopsy is the gold standard but remains invasive, ETT with the strain allows a presumptive diagnosis and remains an operative examination dependent and is not reproducible. Cardiac MRI allows some localization of amyloid deposits but still remains less sensitive than scintigraphy. In addition, performing the whole-body MRI is very restrictive (time, antenna change and cost). The aim of this literature review was to show the superiority of

^{99m}Tc -DPD scintigraphy compared to other diagnostic modalities and to consider its use given its simplicity when it comes to usage in Sub-Saharan Africa to diagnose the disease. cardiac amyloidosis and by extension reduce the number of cases of heart disease classified as idiopathic and thus allow early and appropriate management.

Keywords

Amyloidosis, TTRm, AL, ^{99m}Tc -DPD, Bone Scintigraphy

1. Introduction

Amyloidosis is a heterogeneous group of diseases linked to the extracellular accumulation of insoluble fibrillar proteins: amyloid fibrils [1]. These can be hereditary or acquired diseases. They can be localized or systemic, asymptomatic or, on the contrary, have a redoubted prognosis. The clinical manifestations result from the location and type of these amyloid deposits, as well as from the toxicity of certain soluble precursors (for example immunoglobulins). These are relatively rare (underdiagnosed) pathologies, which can pose diagnostic and therapeutic problems. About twenty proteins have already been identified as potential amyloid precursors, thus determining the type of amyloidosis. Two precursors are responsible for the three types of cardiac amyloidosis: immunoglobulin light chains, involved in AL amyloidosis; mutated transthyretin (TTRm) involved in hereditary amyloidosis and wild type or wild type TTR (TTRwt) involved in senile amyloidosis. The epidemiology of amyloidosis is poorly understood around the world. Amyloidosis is described to be rare in sub-Saharan Africa [2]. Amyloidosis is mimicking a heart failure with preserved ejection fraction (HFpEF). Indeed, if we exclude the African autopsy series [3] [4] [5], less than a hundred cases of amyloidosis have been reported. The prevalence and incidence of amyloidosis in sub-Saharan Africa are likely to be underestimated and probably can be added in the “idiopathic heart failure”. In addition, the specific characteristics of the black African subject are little studied [6].

The definitive diagnosis of amyloidosis is histological. However, the cardiac biopsy is not without risk of hemorrhage, increased by the fragility of the vessels due to the disease. Cardiac amyloidosis is an infiltrative cardiomyopathy mimicking hypertensive and hypertrophic cardiomyopathies. Raising awareness and advances in imaging over the past two decades have improved the diagnosis of cardiac amyloidosis, an increasingly recognized cause of heart failure for elderly people [7].

In addition, it has been reported that black subjects presented heart failure at a much younger age and for different causes compared to the Caucasian subjects [8]. Physical examination, ECG, echocardiography, and MRI can help in the diagnosis but cannot distinguish between the different types of cardiac amyloidosis. With good sensitivity, those examinations facilitate the diagnosis of amyloidosis with cardiac involvement and thus provide assistance in the differential

diagnosis of hypertrophic cardiomyopathies.

The objective of this systematic review of the literature was to show the place of nuclear imaging and more particularly of bone scintigraphy in the diagnosis of cardiac amyloidosis, which is a significant cause of idiopathic heart failure. Its diagnosis, facilitated by DPD bone scintigraphy, would allow a better assessment of the prevalence of cardiac amyloidosis in this heterogeneous group of idiopathic heart failure.

2. Methodology

A comprehensive literature search was performed using the Medline database to identify relevant articles. We used various search algorithms based on a combination of the following terms: amyloidosis, cardiac, MRI, ETT, bone scintigraphy, amyloidosis in black African. No language restrictions were applied. All articles reporting data on the diagnostic performance of ^{99m}Tc -DPD or ^{99m}Tc -PYP scintigraphy were considered relevant and studies reporting data about patient involve in cardiac amyloidosis and particularly in black population.

We have thus analyzed the scientific publications found to first show the real problem of diagnosis of cardiac amyloidosis, then to describe the scintigraphic aspects of cardiac amyloidosis and finally to better appreciate the place of bone scintigraphy with DPD compared to other modalities of imaging in diagnosis.

3. Results and Discussion

3.1. Problem of Diagnosis

In current practice, the diagnosis is made based on a series of arguments in favor of cardiac amyloidosis. These include the clinical history of the disease, additional tests such as ETT, MRI, and extracardiac biopsies. These investigations do not make it possible to distinguish AL amyloidosis from ATTR. This is why the key examination to make the diagnosis with certainty is based on the endo-myocardial biopsy. Given the cardiovascular comorbidities of patients with suspected cardiac amyloidosis, the biopsy is not systematic, and the amyloidosis typing done by immunohistochemistry or immunofluorescence has certain limitations. The positivity of an anti-light chain antibody labeling (κ or λ) will sign AL amyloidosis. The positive labeling of transthyretin (TTR) indicates cardiac transthyretin amyloidosis [9]. Despite these performances, this examination does not make it possible to distinguish ATTRm amyloidosis from ATTRwt. The sensitivity of detection in AL amyloidosis is reduced in the event of low affinity of the antibodies for certain free chains. Some anti-TTR antibodies also frequently lack specificity and can lead to false positives. Subtyping is difficult, even in experimental laboratories, due to the background noise associated with serum contamination and epitope loss correlated with crosslinking of proteins after formalin fixation. Mass spectrometry is the gold standard for amylose typing with an accuracy of 98%. It is performed after laser microdissection of the sample, followed by formalin fixation and paraffin embedding before spectrometric

analysis [9]. However, it is still not readily available and remains expensive. In developing countries, non-invasive examinations such as ^{99m}Tc -DPD or ^{99m}Tc -HMDP whole body scintigraphy may be an alternative.

The prevalence of cardiac amyloidosis is unknown and underestimated worldwide and particularly in Sub-Saharan Africa. Indeed, the causes of heart failure with preserved ejection fraction associated with myocardial hypertrophy are rarely investigated amongst black subjects.

Taking into account all the TTR mutations (~100), familial amyloidosis is disseminated in 30 countries including 15 countries where the identification of the Val30Met mutation (the valine in position 30 is replaced by methionine) has been reported, with the reservation that molecular biology techniques allowing the identification of mutations are not available in all countries. The average age of subjects with symptomatic TTR amyloidosis is 35.3 years (18 to 83 years) [10]. The most frequently identified mutation is the Val122Ile mutation (or isoleucine 122, substitution of isoleucine for valine at position 122) found in approximately 4% of African Americans regardless of location. This mutation is also common in people from West Africa. A study by Jacobson found 66 alleles of Val122Ile in DNA samples from 1688 patients [11]. However, it is likely that this mutation is a grossly underdiagnosed cause of heart failure in African and Caribbean populations, the evidence of which is based on a subgroup analysis performed on an African American population participating in the trial “Beta-Blocker Evaluation in Survival Trial (BEST)”. In addition, the prevalence and incidence of amyloidosis in sub-Saharan Africa are underestimated as the specific characteristics of the black African subject are little studied [6] and it has been reported that subjects of African origin present with heart failure at one level at younger age and for different reasons than Caucasians [7]. In fact, Cardiac amyloidosis is a significant cause of heart failure, studies have shown relatively high penetrance in African American and black British [12]. It has also been proven that mutated ATTR is more frequent in black subjects than in white subjects [13]. These facts could lead one to believe in a strong penetrance among the Negro-African subjects. All the more so since no study has assessed the prevalence of idiopathic heart disease in black Africa.

“Shah KB” and “al have” shown that cardiac amyloidosis with mutated transthyretin affects black subjects much more compared to white subjects who develop more senile cardiac amyloidosis [13]. Myocardial fixation on scintigraphy with diphosphonates (bone tracers) is more frequent and intense in transthyretin amyloidosis (senile or hereditary) than in AL amyloidosis. The place of scintigraphy therefore appears essential in the decision-making strategy for establishing the diagnosis.

3.2. Cardiac Amyloidosis Scintigraphic Aspects

The ^{99m}Tc -DPD scintigraphy using Perrugini’s visual score allows localization and classification of amyloid damage. In fact, myocardial fixation during whole body scintigraphy was found and made it possible to establish the Perugini score in favor of amyloidosis. This score uses a visual metric to establish 4 grades:

- Grade 0: absence of significant binding of the radio-tracer in projection of the cardiac area.
- Grade 1: discreet fixation of the radio-tracer of the cardiac area, inferior to the fixation of the rib grid.
- Grade 2: intense fixation of the cardiac area, superior to fixation of the rib grid.
- Grade 3: very intense fixation of the cardiac area with weak physiological fixation of the tracer by the rest of the skeleton.

Figure 1 illustrates the different grades of Perugini on scintigraphy [14].

Indeed, grade 0 does not demonstrate cardiac amyloidosis. On the other hand, a grade 1 of the Perugini score is positive and increases the sensitivity of the diagnosis of ATTR, but its specificity is poor. For other types of cardiac amyloidosis such as AL in particular, the authors found a grade 1 and more rarely a grade 2 or 3 [14].

In the etiological diagnosis, scintigraphy also has a role to play. Indeed, if its interpretation takes into account the biological results, the determination of the free light chains in the blood and in the urine, it undoubtedly makes it possible to differentiate AL amyloidosis from transthyretin amyloidosis. From the above, some authors concluded that cardiac amyloidosis scintigraphy is therefore used to confirm the diagnosis of cardiac transthyretin amyloidosis, which has a different prognosis from light chain amyloidosis. Claudio Rapezzi *et al.* compared the overall survival among three subtypes of cardiac amyloidosis AL, mutated ATTR and wild-type ATTR, the unadjusted two-year survival was 63% versus 98% and 100% in the mutated and wild type ATTRs, respectively [15]. The prognosis is generally more favorable in ATTR than in AL amyloidosis, although very significant differences are observed depending on the mutations. In a study by Connors & al. in patients with predominantly cardiac amyloidosis, survival was significantly better in the mutated ATTR group (n = 30) compared to the

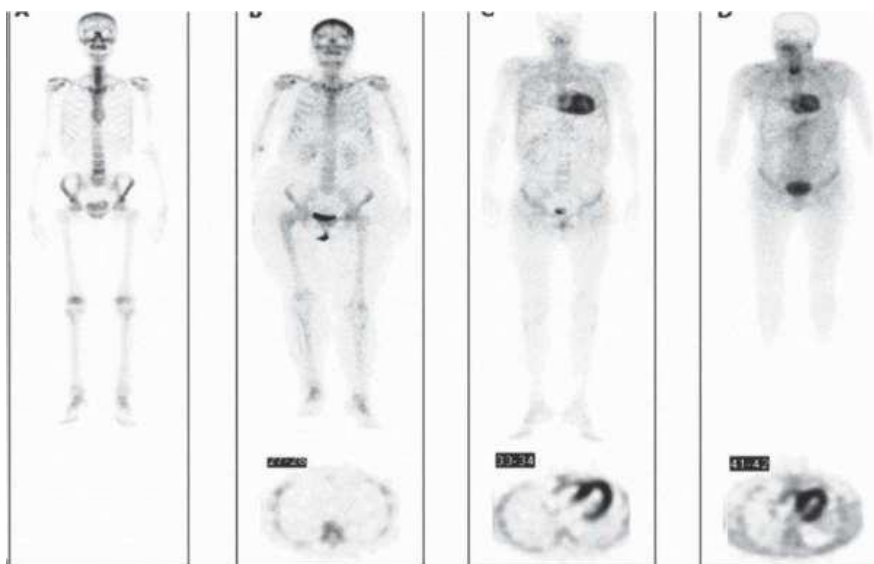


Figure 1. Illustration of the different grades of myocardial uptake according to the visual Perugini scale in ^{99m}Tc -DPD bone scintigraphy [14].

AL group (n = 31): 27 vs. 5 months. The group consisted of 156 African American patients with amyloidosis; the most frequent mutation, V122I, was present in 36 patients, *i.e.* 23.7% [16]. The clinical presentation of the mutated Val122Ile ATTR frequently mimics that of wild-type (senile) ATTR with often isolated cardiac involvement, preceding carpal tunnel syndrome in some cases. Very rarely, neurological damage is found [17].

3.3. Place of Bone Scintigraphy at DPD Compared to Other Imaging Modalities

- Quantitative comparison between ETT and ^{99m}Tc -DPD scintigraphy

In a rare study relating to the degree of cardiac amyloid deposition as assessed by ^{99m}Tc -DPD scintigraphies with BNP values and echocardiographic data in patients with familial amyloidosis linked to TTR, twenty-eight patients (9 men, 19 women) of mean age 50 ± 14 years underwent, on the same day, the following examinations: BNP assay, 2D Doppler echocardiography and a ^{99m}Tc -DPD scintigraphy. At the time of inclusion, all patients were Class I or II according to the New York Heart Association (NYHA) classification and without a clinical history of heart disease. In addition, 14 normal asymptomatic control subjects (5 men, 9 women), with a mean age of 48 ± 9 years also without a history of heart disease were recruited and had undergone 2D Doppler and stress echocardiography [18].

^{99m}Tc -DPD SPECT demonstrated uptake in 14 of 28 patients (50%). Cardiac uptake was mild in 5 patients (mild AC group) and severe in 9 patients (severe AC group). No patient showed moderate cardiac uptake.

At ^{99m}Tc -DPD, the study of the ratios shows the extent of cardiac amyloid deposit because it is well correlated with the values of BNP.

Morphologic echocardiography shows a decrease in longitudinal LV strain indicating an increase in amyloid deposition, while circumferential and radial deformities increase with severe cardiac deposition as a compensatory phenomenon. These results show that when the amyloid deposit increased, an aggravation of the longitudinal strain occurred. It has been observed that trans-thoracic cardiac ultrasound is more of an entry point into the process of looking for amyloidosis [18].

The usefulness of ETT in diagnostic and etiological confirmation remains less compared to that of ^{99m}Tc -DPD scintigraphy where the binding of ^{99m}Tc -DPD to the amyloid deposit seems more specific to the ATTR type than to the AL type [18] [19] [20] but this binding does not seem to be able to differentiate ATTRwt from ATTRm. The elevation of BNP values only in patients with severe amyloid deposition confirms that a slight amyloid deposition is detected earlier by ^{99m}Tc -DPD scintigraphy. From the above, it is clear that echocardiography makes it possible to detect cardiac amyloidosis but belatedly compared to the ^{99m}Tc -DPD scintigraphy, especially since the echocardiography remains a dependent operator examination and does not allow visualization of an extracardiac extension unlike bone scintigraphy.

- Quantitative comparison between MRI and ^{99m}Tc -DPD scintigraphy.

Other authors have also compared ^{99m}Tc -DPD scintigraphy and MRI in the

assessment of cardiac involvement in patients with familial amyloid transthyretin polyneuropathy. For this, a study was carried out in 18 patients who received ^{99m}Tc -DPD imaging and MRI with late enhancement with gadolinium [21].

Whole body scintigraphy and SPECT revealed cardiac hyperfixation to ^{99m}Tc -DPD in 10 of 18 patients (56%) and no hyperfixation in the others. Cardiac hyperfixation was inferior to bone fixation in 5 out of 10 patients and superior to bone fixation in the remainder. MRI with late enhancement with gadolinium was positive in 8 out of 18 patients (44%). These authors specified that all the patients with late myocardial enhancement with gadolinium also presented cardiac hyperfixation of ^{99m}Tc -DPD, whereas no late myocardial enhancement with gadolinium of positive areas was found in the 8 patients without cardiac uptake of ^{99m}Tc -DPD Fig 2. All patients with positive MRI results were symptomatic (four patients with polyneuropathy, three with carpal tunnel syndrome and one patient with heart failure), while all patients with negative MRI results were asymptomatic. The LV patterns of late enhancement with gadolinium were circumferential subendocardial in one patient (the only one with signs of heart failure), focal in six patients, and diffuse in one patient. **Figure 2** and **Figure 3**

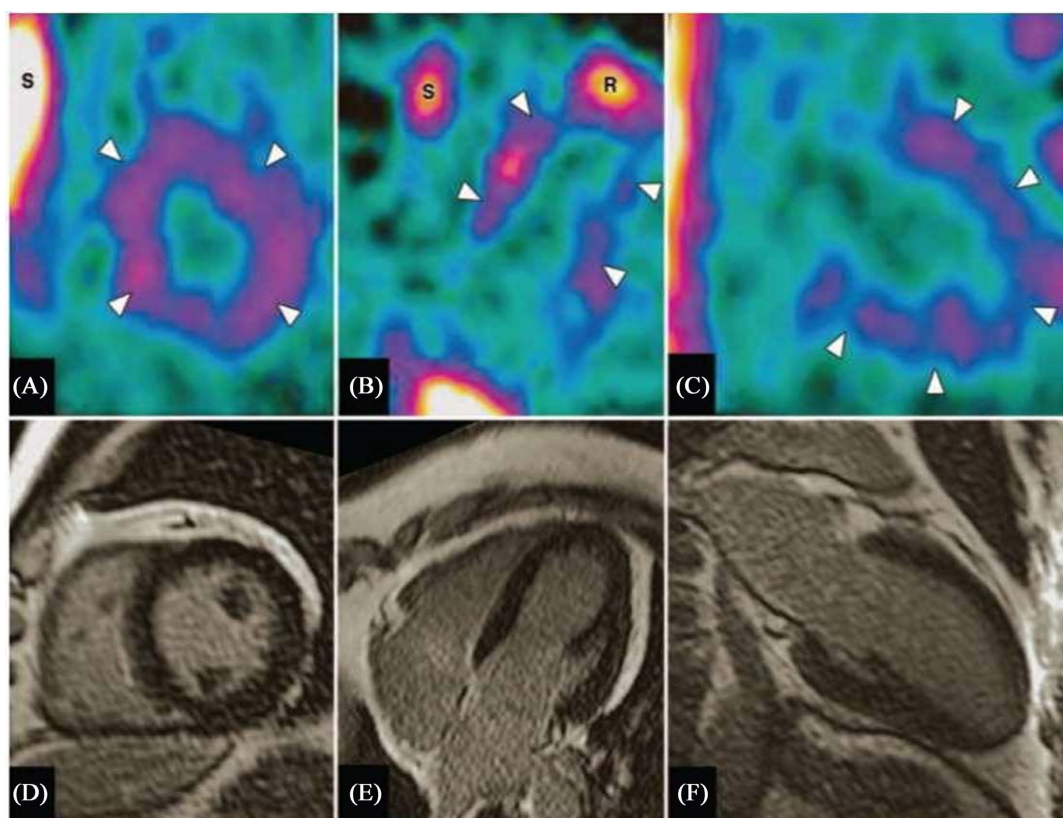


Figure 2. Asymptomatic 50-year-old man with positive results of genetic testing for transthyretin familial amyloid polyneuropathy (Glu89Gln). (A)-(C), Technetium-99m-diphosphonate SPECT images in short-axis (A), horizontal long-axis (B), and vertical long-axis (C) views show radiotracer uptake (*arrowheads*) involving entire left ventricle. Left ventricle uptake was lower than that in bone. R = rib, S = sternum. (D)-(F), MRI with late gadolinium enhancement in short-axis (D), horizontal long-axis (E), and vertical long-axis (F) views show no cardiac enhancement.

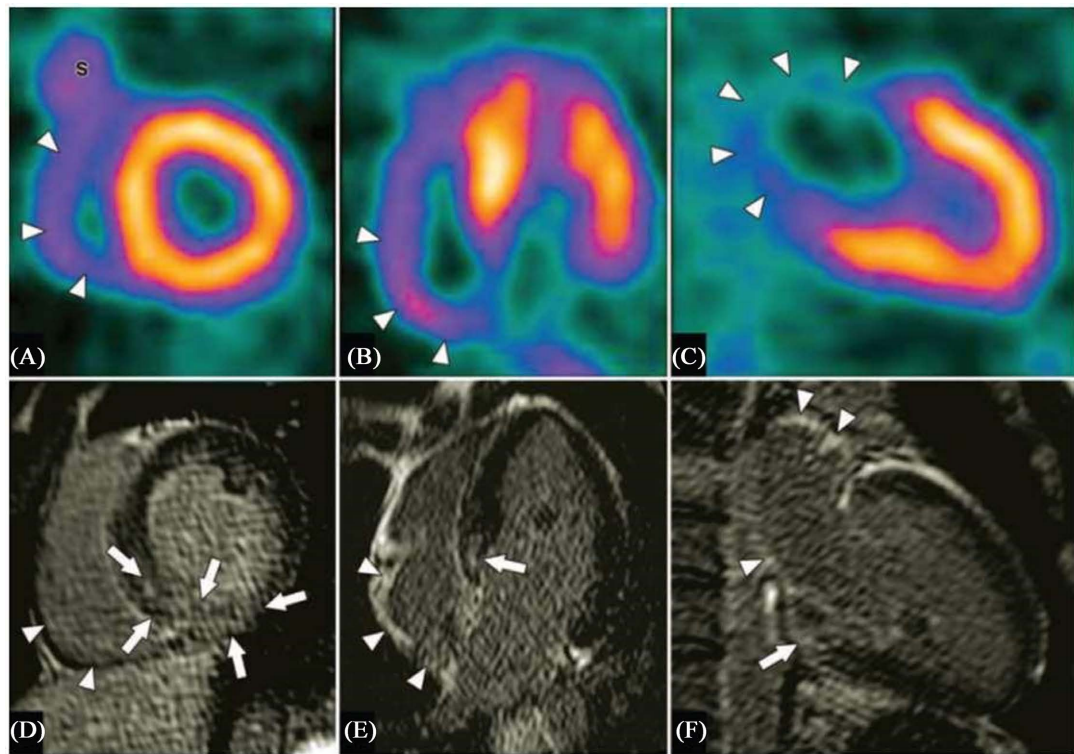


Figure 3. 35-year-old man with somatic polyneuropathy and positive results of genetic testing for transthyretin familial amyloid polyneuropathy (Thr49Ala). (A)-(C), Technetium-99m-diphosphonate SPECT images in short-axis (A), horizontal long-axis (B), and vertical long-axis (C) views show radiotracer uptake (*arrowheads*) involving entire left ventricle. Left ventricle uptake was higher than that in bone. Also right ventricle (A), right atrium (B), and left atrium (C) show radiotracer uptake. S = sternum. (D)-(F), MRI with late gadolinium enhancement in short-axis (D), horizontal long-axis (E), and vertical long-axis (F) views show focal enhancement of left ventricle only (*arrows*) involving basal inferoseptal and inferior segments. Also right ventricle (*arrowheads*, (D)), right atrium (*arrowheads*, (E)), and left atrium (*arrowheads*, (F)) show late gadolinium enhancement.

illustrate the results of the MRI [21].

Amongst nine patients, the hyperfixation of ^{99m}Tc -DPD affected the entire LV (17 segments in each patient). In only two out of these nine patients, the authors observed full LV involvement (one patient with a late gadolinium diffuse enhancement model and one patient with a subendocardial circumferential late gadolinium enhancement model). In the remaining seven patients, they noted less segment involvement than scintigraphy (Figure 3). Hyperfixation of ^{99m}Tc -DPD involved RV in 8 patients and both atria in 5 patients. The burden of cardiac amyloid infiltration is considerably underestimated by visual analysis of MRI with late enhancement with gadolinium compared to imaging with ^{99m}Tc -DPD. This is more emphasized since the ^{99m}Tc -DPD allows a complete mapping of extracardiac uptake where full-body MRI is difficult to perform [21].

Since ^{99m}Tc -DPD scintigraphy is superior to MRI and echo, it remains the reference imaging modality for the diagnosis of cardiac amyloidosis. It is reproducible, inexpensive, and is now widely available in black African countries. It uses a very accessible radiopharmaceutical protocol with the very practical Mo-

lybdenum generator. In fact, ^{99m}Tc -DPD is accessible in all nuclear medicine departments in the same way as the HMDP, which is most frequently used as a bone tracer in the assessment of the extension of osteolytic cancers. This scintigraphic indication is timely because the recognition of the amyloid nature of heart disease has a direct therapeutic impact. This is because symptomatic drug treatment cannot be strictly superimposed on that for usual heart failure. Some drug classes are used with caution according to Bodez *et al.* [22]. In cardiac amyloidosis, the decrease in myocardial compliance leads to a decrease in the telediastolic volume of the LV. Diuretics should therefore be used with caution as they reduce the preload. These two mechanisms combined can lead to symptomatic arterial hypotension or even true hemodynamic failures. For the same reason, ACE inhibitors and angiotensin II receptor antagonists (ARA2) may be hemodynamically poorly tolerated, particularly in AL amyloidosis. Tachycardia is the predominant mechanism of adaptation to reduce ejection volume in advanced forms. The use of negative chronotropic drugs such as β blockers should therefore be avoided. These are frequently used in other causes of altered ejection fraction heart failure to increase the diastolic filling phase and thereby improve LVEF.

In a single-center study on 20 patients with ATTR with a wild subtype (10), mutant (10), the authors found a positive scintigraphy (in the sense of Perugini) at ^{99m}Tc -PYP [23]. On average, a year and a half later, a new scintigraphy performed under the same conditions with a semi-quantitative analysis (H/CL ratio) [23] did not find any significant modification of the fixation despite the clinical progression of the disease, according to serum biomarkers, echocardiographic or NYHA score [23].

Admittedly, ^{99m}Tc -DPD cannot allow monitoring of the evolution of the pathology but will make it possible to have a first series on the incidence of cardiac amyloidosis in subjects with african origins.

4. Conclusion

This literature review has highlighted the problem of diagnosing cardiac amyloidosis in the world and more particularly in Sub-Saharan Africa. ^{99m}Tc -DPD can make a difference on all these heart failures so frequent in black African classified as idiopathic. DPD scintigraphy is a superior contribution to MRI and ultrasound, it remains a reproducible and inexpensive examination. In addition, it is widely available in black African countries and the supply of technetium for DPD labeling is relatively easy. Hence the interest in improving the awareness of practitioners on the contribution of scintigraphy to DPD for the diagnosis and adequate management of cardiac amyloidosis. ^{99m}Tc -DPD can be used to have an idea of the prevalence of Cardiac amyloidosis in black African people.

Conflicts of Interest

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

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