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EDITORIAL

Nuclear medicine practice for the assessment of cardiac sarcoidosis and amyloidosis. A survey endorsed by the EANM and EACVI.

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Introduction

Cardiac amyloidosis (CA) is an infiltrative and restrictive cardiomyopathy that might rapidly lead to heart failure if left untreated. The prognosis is variable and depends on the type of cardiac amyloidosis, but the end stages are associated with poor outcomes and the disease is often associated with important morbidity and reduced quality of life.

Sarcoidosis is a systemic chronic granulomatous disease of unknown aetiology characterized by multi-organ involvement. Cardiac sarcoidosis (CS) is observed clinically in 5–10% of patients, but is a common cause of death in these patients and often goes unrecognized. Granulomatous inflammation in the myocardium, if left untreated, can lead to scarring, cardiac rhythm problems and the development of heart failure.

Both CA and CS are significantly underdiagnosed [1, 2]. Endomyocardial biopsy has been the reference standard for diagnosing CA and CS [3–5]. Due to the invasive nature of such procedures and the accompanied risks, biopsy was generally performed only in patients with significant suspicion. Moreover, biopsy is associated with sampling bias,

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particularly in cardiac sarcoidosis which is a focal patchy condition. In contrast, imaging offers the advantages of being widely available and noninvasive, with the ability to assess the entire myocardium as we all as the extra-cardiac structures that may also be involved in these systemic conditions. Moreover, imaging techniques can be easily and successfully repeated to assess therapy response. With recent advances in nuclear imaging, these techniques are changing the diagnostic workup of these diseases and frequently replacing the role of biopsies.

The current diagnostic approach for CA and CS involves the use of one or more imaging modalities. Echocardiography usually represents first-line imaging and has the advantage of being widespread, easily and rapidly performable even at the bedside. Cardiovascular magnetic resonance (CMR) additionally provides high-definition structural imaging and tissue characterization based on the contrast-enhanced patterns of myocardial infiltration and quantification of cardiac chamber volumes and ventricular mass. In nuclear medicine imaging, myocardial uptake of Tc-99m–labeled bone-avid radiotracer imaging has long been recognized to represent CA [6, 7]. Technetium-labeled cardiac scintigraphy with (^{99m}Tc-pyrophosphate [^{99m}Tc-PYP], ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid [^{99m}Tc-DPD], and ^{99m}Tc-hydroxymethylene diphosphonate [^{99m}Tc-HMDP]) has been proved to have high sensitivity, specificity, and positive predictive value in the diagnosis of transthyretin (ATTR)-CA, providing incremental value to echocardiography and CMR [8]. Moreover, ^{99m}Tc-PYP/DPD/HMDP cardiac uptake has been shown to have a prognostic role, positively correlating with overall mortality and survival free from major adverse cardiac events [9, 10].

Targeted amyloid binding positron emission tomography (PET) tracers allow direct detection of amyloid fibrils and appear to bind to both AL and ATTR [11]. 123I-metaiodobenzylguanidine (^{123}I-mIBG), an established tracer for imaging myocardial denervation, has been utilized to image myocardial denervation in familial ATTR cardiac amyloidosis [12].

In the absence of histological evidence of CA on endomyocardial biopsy, current guidelines recommend the use of a combination of extracardiac biopsy, ^{99m}Tc-PYP/DPD/HMDP scintigraphy, myocardial uptake of targeted PET amyloid tracers, echocardiographic and CMR findings [13, 14]. Uptake of ^{99m}Tc-methylene diphosphonate [^{99m}Tc MDP], on the other hand, was found not be useful in ATTR, providing very low sensibility [15].

In CS, radionuclide imaging with ^{67}Ga-citrate SPECT and $^{[18F]}$FDG-PET has been widely used to diagnose myocardial inflammation. Importantly, the additional benefit of radionuclide evaluation is that these tracers provide the ability to image cardiac and systemic amyloid and sarcoidosis deposits concurrently, allowing evaluation of multi-organ systemic involvement. Although ^{67}Ga-citrate is specific for inflammation, it has relatively low sensitivity and poor spatial resolution compared with $^{[18F]}$FDG-PET, particularly in detecting extra-pulmonary sarcoidosis involvement. $^{[18F]}$FDG-PET has emerged as a leading modality and powerful technique, not only to assess the extent of systemic sarcoidosis but also to assess the extent and activity of myocardial involvement, as it is highly sensitive in detecting granulomatous inflammation [16, 17]. In addition, studies have demonstrated that CS may lead to myocardial perfusion defects, which are associated with a higher risk of ventricular arrhythmias due to scar formation and sometimes followed by death [18, 19]. The combined assessment of perfusion and inflammation would thus provide additional information about the status of CS (scar or inflammation) and risk from cardiac involvement [20]. Current guidelines for the diagnosis of CS recommend combining both $^{[18F]}$FDG-PET in conjunction with myocardial perfusion imaging (MPI) to differentiate the patterns of disease [21]. It has to be noted that notwithstanding the guidelines, $^{[18F]}$FDG-PET without MPI is still the actual protocol for the diagnosis of CS in many centers. Moreover, a careful preparation with a fat-enriched diet lacking carbohydrates for 12–24 h before the scan is recommended to optimize the target to background ratio of $^{[18F]}$FDG-PET and to minimize background physiological myocardial glucose uptake, which can lead to false positive scan results.

Despite nuclear imaging techniques having the potential to provide unique information in cardiac sarcoidosis/amyloidosis, an overview of current clinical practice in Europe is lacking. To evaluate the use of the current guidelines/recommendations in clinical practice, a survey was launched. We sought to evaluate how CA and CS imaging are currently assessed in routine clinical practice with nuclear imaging and to assess whether current clinical guidelines are being followed in the real world.

Methods

The online survey was constructed by the working groups of the EANM and EACVI and was distributed electronically through the organizations' websites between the beginning of 2021 and the end of 2023. It was freely accessible to Nuclear Medicine (NM) physicians without specific prerequisites or restrictions. Information was collected using an electronic questionnaire, consisting of 15 questions in English on both amyloidosis and sarcoidosis. Questions were a mixture of multiple-choice, rating scale, and closed

questions (see Appendix). All responses were collected and analyzed anonymously to identify trends.

These questions covered both technical and non-technical aspects of nuclear medicine practice: responders were asked to provide technical information on the type of nuclear imaging (i.e. PET, SPECT, or scintigraphy), the camera system and radiopharmaceuticals used most commonly in their practice. Participants were also requested to provide information on the number of patients evaluated every year, the main indications to perform NM imaging, the reasons to be referred to NM, as well as reasons why NM imaging might not be performed. Additionally, the survey also collected information on the role of a multi-modality imaging team for both amyloidosis and sarcoidosis patients and on the actual interest of NM physicians in these pathologies, as well as on their career stage. Finally, we aimed to provide insights into best practices for integrating NM imaging into clinical workflows, and evaluate the presence of a collaborative and multidisciplinary approach.

Results

Responses were obtained from 258 professionals, equally distributed in their career stage, with 27% having practiced in the field for more than 20 years, 20% between 10 and 20 years, 24% between 5 and 10 years and 29% for less that 5 years. The majority of the participants worked in centers where between 10 and 40 patients with cardiac amyloidosis and < 10 patients with cardiac sarcoidosis are imaged each year. Of note, a fifth of sites (21%) assessed > 40 patients with cardiac amyloidosis per year. Although the vast majority of the responders were involved in the management of patients with cardiac amyloidosis, only 34% described the regular use of nuclear imaging in these patients whilst on 17% of respondents described the regular use of nuclear imaging in patients with cardiac sarcoidosis (17%).

The most common reasons for performing nuclear imaging in cardiac amyloidosis were: at first as imaging tests to establish a diagnosis (36%) or secondly as to establish the diagnosis in uncertain cases (33%). Scintigraphy with bone-seeking radiopharmaceuticals was the most used imaging modality (Fig. 1) with ^{99m}Tc-DPD, ^{99m}Tc-HDP, and ^{99m}Tc-PYP being almost equally used (32%, 28% and 27%, respectively), followed by ^{99m}Tc-MDP (12%) (Fig. 2). Cardiac ^{123}I-MIBG was the second most used nuclear technique in a minority of patients to evaluate the autonomic cardiac dysfunction due to amyloidosis.

In the case of cardiac sarcoidosis, nuclear imaging was more often requested as a 2nd line imaging to establish the diagnosis in uncertain cases (34%), for the staging of extracardiac disease (9%), and for monitoring treatment response (3%). $^{[18F]}$FDG PET/CT, either whole body or cardiac, followed by MPI PET or SPECT and ^{67}Ga-citrate- SPECT were the most frequently used techniques (Fig. 3).

The main reasons why NM imaging was not performed for diagnosis in patients with suspected cardiac amyloidosis or sarcoidosis were (i) lack of proper equipment (82% and 75% respectively); (ii) not being in charge for the evaluation of those patients (35% and 55%), and (iii) lack of reimbursement (6% and 5%) (Fig. 4).

Half of the participating centers (53%) used a multimodality imaging team to help manage patients with cardiac

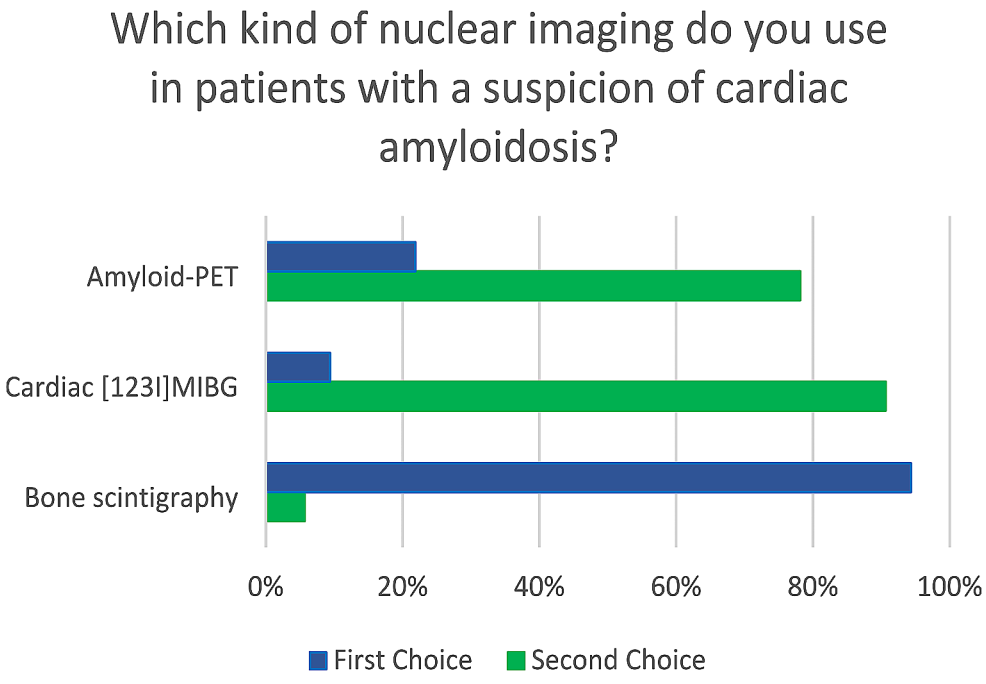

Fig. 1 Column bar graph showing the first and second choice NM imaging technique used in case of suspected CA

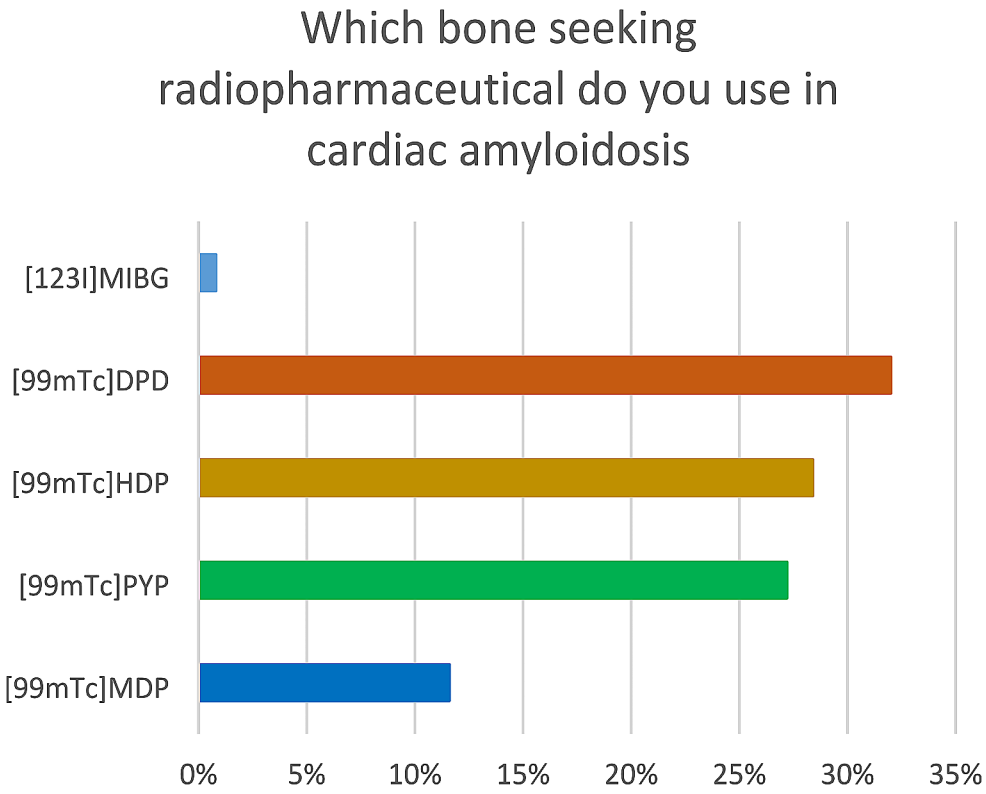

Fig. 2 Column bar graph showing the preferred bone-seeking radiopharmaceutical used when scintigraphy for CA is performed

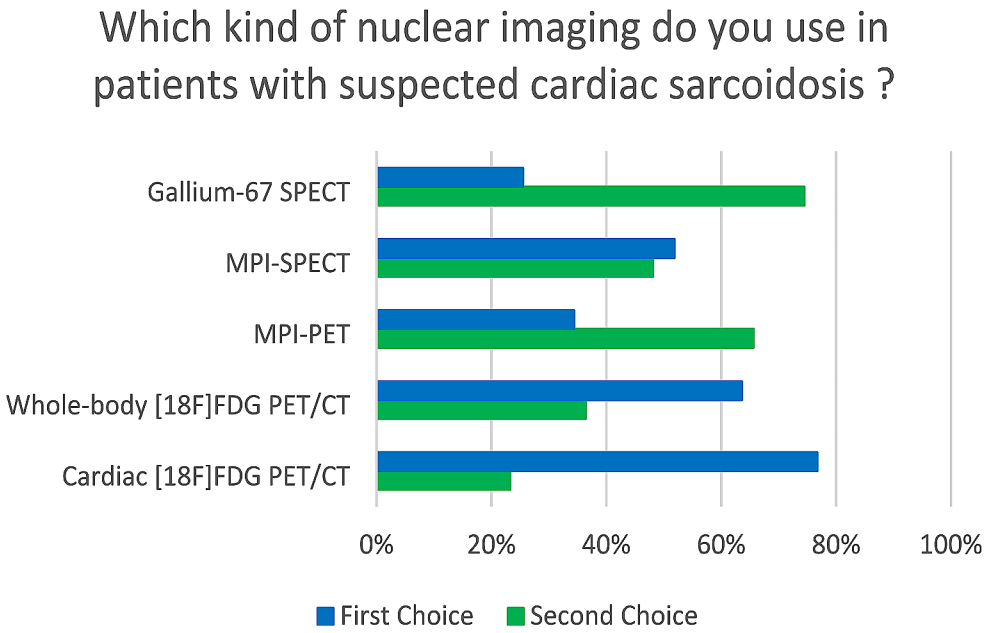

Fig. 3 Column bar graph showing the first and second choice NM imaging technique used in case of suspected CS

amyloidosis whilst these teams were involved for the management of patients with cardiac sarcoidosis in 38% of centers.

The vast majority of responders (82%) indicated willingness to be involved in a European network registry/study for cardiac amyloidosis, whilst two thirds of centres (66%) were interested in a similar endeavor for cardiac sarcoidosis.

Discussion

This survey on cardiac amyloidosis and sarcoidosis provides valuable insights into the perspectives and experiences of participants regarding the use of nuclear medicine imaging systems in these conditions. The findings highlight both the advantages and challenges associated with NM imaging in everyday clinical practice.

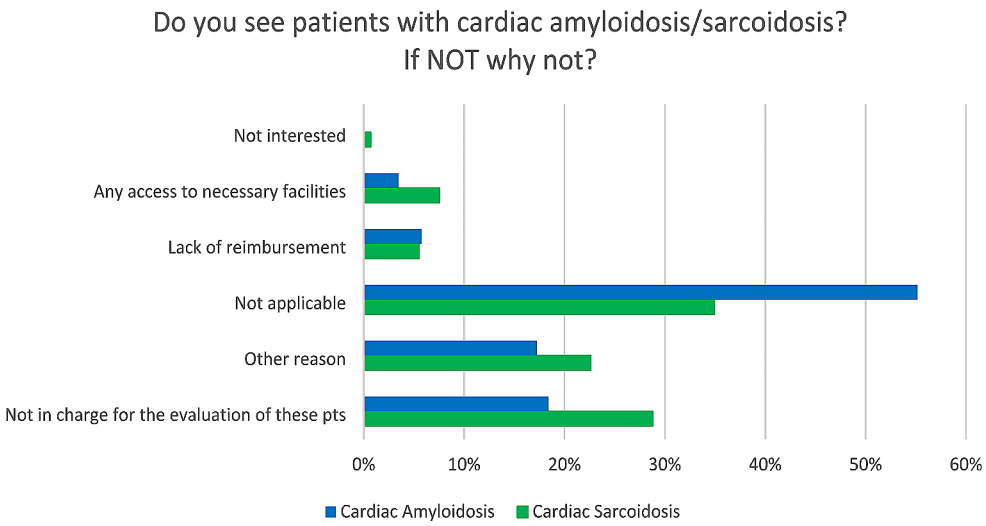

Fig. 4 Column bar graph showing the reasons by which NM imaging was not performed for diagnosis of both CA and CS

Nuclear imaging in CA and CS is highly recommended (Ib) in the recently published ESC Cardiomyopathy Guideline [22]. Most participants are involved in the management of a considerable number of patients with these diseases, mostly CA. However, extensive use of NM imaging (34% in CA and 17% in CS) is still lacking in the majority of centers. This appears mainly due to the lack of the proper equipment to assess the patients and to the alternative use of alternative imaging techniques such as echocardiography and MRI.

As far as CA is concerned, scintigraphy with bone-seeking radiopharmaceuticals is mainly performed as a 1st line imaging test to establish a diagnosis; although ^{99m}Tc-MDP is still used by a higher than expected number of participants despite current evidence and guidelines [13, 15].

In the case of CS, NM imaging remains largely a 2nd line imaging test used to establish a diagnosis in uncertain cases; with MPI imaging still not employed in the majority of centres. Multimodality imaging teams were not involved in decision making for both cardiac sarcoidosis and amyloidosis in a higher proportion of centres than expected.

NM protocols showed large heterogeneity across the different centres, in particular the use of different radiotracers for cardiac amyloidosis imaging. This highlights that standardization in the nuclear imaging of patients with cardiac sarcoidosis and amyloidosis is still lacking.

Since CA is a relatively rare disease, clinical and diagnostic expertise in the diagnosis and follow-up of these patients is mostly limited to a few expert centers. Despite the development of different imaging options for noninvasive evaluation of the disease, only a limited number of studies based on multicenter experiences have been published. This is becoming of primary importance as an accurate diagnosis at earlier stages of the disease could lead to a better application of emerging therapeutic options.

In 2021, the ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis established the diagnostic criteria, clinical indications, and appropriate utilization of echocardiography, CMR, and radionuclide imaging for the assessment of cardiac amyloidosis, to encourage the development of prospective clinical trials that would validate the suggested diagnostic criteria and pave the way for the development of dedicated guidelines.

Another effort towards the use of standardized protocols was made with the creation of the European Increasing Awareness of Nuclear Scintigraphy in Cardiac Amyloidosis (EURO-LEARN), an initiative supported by the European School of Multimodality Imaging & Therapy (ESMIT), the European Association of Nuclear Medicine (EANM), and the European Association of Cardiovascular Imaging (EACVI). It aims to provide clinicians involved in the management of patients with CA with a training platform to increase their awareness and to improve their practice on the use of multimodality imaging techniques in the diagnostic work-up and nuclear scintigraphy with bone-seeking radiopharmaceuticals, focusing mainly on ATTR-CA. This could help spread the knowledge on the correct radiopharmaceuticals to be applied for scintigraphy (i.e. ^{99m}Tc-PYP/DPD/HMDP), as our results show that ^{99m}Tc-MDP is still used in many centers, despite evidence against its routine employment.

The same holds true for CS, which is a rare systemic disease that often requires a multi-imaging approach for the diagnosis and long-term follow-up. It is therefore of paramount importance to obtain imaging based on standardized evidence-based procedural guidelines for both acquisition and interpretation. However, despite several criteria that have been proposed, there is still limited supporting data and a lack of large studies and prospective validation.

In 2017, the Joint SNMMI–ASNC Expert Consensus Document on the Role of $^{[18F]}$FDG PET/CT in Cardiac

Sarcoid Detection and Therapy Monitoring and the joint procedural position statement on imaging in cardiac sarcoidosis from the Cardiovascular and Inflammation & Infection Committees of the EANM/EACVI and ASNC were published, again aiming towards a consensus in guiding clinical practice and research [20, 21].

The diagnostic process of both CA and CS involves many disciplines, which may cause a delay in diagnosis. Moreover, the patient's condition is complex and may change at any time during therapeutic management, requiring a close follow-up by multiple departments. Given the lack of appropriate guidelines, a multidisciplinary team (MDT) approach in which experts in different fields discuss the case and formulate the optimal personalized diagnostic and treatment scheme based on the integration of opinions of various disciplines is thus highly needed in the management of these diseases. Moreover, most responders indicated a willingness to be involved in a network registry/study, further underlining their interest in the topic.

Conclusions

In conclusion, the survey underlines the complexity of implementing NM imaging in clinical practice and management of CA and CS patients. Despite physicians being familiar with CA diagnosis mainly by scintigraphy, its diagnostic potential and recommended radiotracers are still not standardized. The same holds for CS, where NM is less employed and still not used routinely.

A multidisciplinary and multicenter collaborative approach is essential for implementing and optimizing NM imaging in the clinical practice for both CA and CS.

There is an additional need to enhance knowledge through continuing medical education programs and the creation of coordinated European efforts to promote clinical practice and research, leading to the standardization of protocols and diagnostic algorithms throughout Europe.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-024-06727-5.

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Declarations

Ethics approval All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent to anonymously collect and publish personal and opinion data of this survey was obtained on the presentation page of the web questionnaire.

Conflict of interest The authors declare no competing interests.

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