Quantifying the burden of cardiac amyloid: The future is about numbers!

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Cardiac transthyretin (ATTR) amyloidosis is caused by the accumulation of amyloid fibrils of misfolded TTR proteins in the heart and leads to restrictive cardiomyopathy. Until recently, treatment has been limited to supportive care, and median survival for wild-type ATTR amyloidosis was 3.6 years.[1] However, in 2018, a randomized trial revealed that morbidity and mortality of these patients is reduced by tafamidis, a medical therapy that inhibits the dissociation of TTR tetramers into amyloid fibrils.[2] In view of the lower treatment response in patients at more advanced stages of the disease,[2] early diagnosis has been deemed critical to maximize treatment response and improve patients' outcome. However, in everyday clinical practice ATTR amyloidosis is often overlooked. Recent data suggests a prevalence of 13% among elderly patients with heart failure with preserved ejection fraction[3] and 16% among patients undergoing transcatheter aortic valve replacement for severe aortic stenosis.[4] The underestimated prevalence and the opportunity to alter the course of the disease is currently transforming the diagnostic work-up of these patients. In men after the age of 65 years and in women after 70 years, an increased wall thickness of $\geq$ 14 mm as well as the presence of heart failure or clinical ''red flags'' (e.g., bilateral carpal tunnel syndrome, discrepancy between left ventricular wall thickness and QRS voltage, or reduction in longitudinal strain with 'apical sparing' pattern in echocardiography) should trigger screening for ATTR amyloidosis by radionuclide imaging.[5] More importantly, ATTR amyloidosis can be diagnosed without the need of invasive endomyocardial biopsy. In the absence of a monoclonal protein in serum or urine, and grade 2 or 3 myocardial radiotracer uptake on ^{99m}Tc-labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), pyrophosphate (PYP), or hydroxymethylene diphosphonate (HMDP) scintigraphy the specificity and positive predictive value for cardiac ATTR amyloidosis is 100%.[6]

In the presence of cardiac amyloid fibrils, there is myocardial uptake of the aforementioned bone avid tracers (i.e., DPD, HMDP, or PYP) on single-photon emission computed tomography (SPECT) and planar images. The myocardial uptake is compared to the surrounding bone uptake and assessed by visual grading from zero to three (Perugini score).[7] Grade 0 indicates no radiotracer uptake, grade 1 shows myocardial uptake but it is lower than bone uptake; in grade 2, myocardial uptake is similar to bone uptake; and in grade 3, myocardial uptake is higher than bone uptake. Grade 2 and 3 confirm ATTR amyloidosis while grade 0 excludes it. Grade 1 is associated with other forms of

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amyloidosis, may suggest early disease, or could even be normal. To reduce interrater reliability and improve diagnostic accuracy, especially in separating grade 1 from grade 2, the heart to contralateral lung (H:CL) ratio has been introduced.[8] In an initial study of patients with biopsy proven amyloidosis, a H:CL ratio of $\geq$ 1.5 has a sensitivity of 97% and a specificity of 100% for differentiating ATTR from AL amyloidosis. In addition to its diagnostic value, this semiquantitative approach improves risk stratification: a ratio of $\geq$ 1.6 results in an 8-fold increase of mortality after multivariate adjustment.[9] These qualitative and semi-quantitative methods of image assessment have advanced the field of ATTR amyloidosis tremendously. However, to maximize treatment benefit in cardiac amyloidosis, the field is moving from highly symptomatic patients at advanced disease stages to screen oligo- or even asymptomatic patients. Absolute quantification of the amyloid burden is therefore critical: (1) to detect a mild burden of cardiac as well as extracardiac amyloid, (2) to risk stratify patients early in the disease process, (3) to monitor disease progression, and (4) to assess treatment response.

Thus, how should radiotracer uptake be quantified? Absolute quantification of myocardial radiotracer uptake requires accurate attenuation correction (AC) with radionuclide or CT-based transmission imaging. Defining a region/volume of interest can be easier in positive cases. But, defining a region or volume of interest (VOI) can be challenging in cases of early amyloidosis and in negative cases. If a CT-based AC is used, an epicardial contour can be defined on the CT to place a VOI on the radionuclide images. This way, myocardial uptake of the radiotracer can be quantified in visually negative cases too. The decay-corrected radiotracer activity within the VOI is divided by the injected activity per unit body weight and represents the standardized uptake value (SUV). Based on this framework, multiple metrics have been described[10]: (1) SUV_{max} is a single voxel value of the maximal activity within the VOI; although most commonly reported, it may be contaminated by spillover from overlapping bone activity. (2) SUV_{mean} is the mean activity of all voxels in the VOI and, in theory, may be a good reflection of amyloid burden. However, as the metric depends on VOI definition, repeatability is low. (3) Multiplying SUV_{mean} with the VOI volume results in the integrated cardiac amyloid activity (CAA) which is a volumetric metric that accounts for the myocardial volume. (4) Similarly, when the absolute radiotracer activity within the VOI is multiplied by the VOI volume and divided by the injected dose, the percentage injected dose (%ID) results, which had high correlation with extracellular volume in cardiac magnetic resonance and may emerge as a key metric to quantify cardiac amyloid burden.[11]

In the current issue of the Journal, Kessler and colleagues[12] have revisited whole-heart quantification in a large sample of 136 patients with suspected cardiac amyloidosis that underwent ^{99m}Tc-DPD SPECT/CT bone avid tracer cardiac scintigraphy. By visual grading, 62% of patients did not have myocardial radiotracer uptake. In 15% of patients, there was borderline uptake (Perugini grade 1). Significant uptake was present in 24% of patients (7% with Perugini grade 2, 17% with Perugini grade 3). Myocardial SUV_{max} values showed a good linear relationship with Perugini scores. The area under the curve of SUV_{max} to diagnose ATTR amyloidosis was 0.96, and a threshold of 6.1 had a sensitivity of 99% and specificity of 87%. In other words, only 1% of patients suffering from cardiac ATTR amyloidosis have an SUVmax < 6.1 (i.e., a false negative finding). In contrast, the false positive findings were mostly explained by patients with light chain (AL) amyloidosis, and if plasma cell dyscrasia was excluded, the specificity of an SUVmax > 6.1 could be increased to 99%. Therefore, the authors conclude that whole-heart quantification of myocardial ^{99m}Tc-DPD uptake and an SUVmax > 6.1 have high diagnostic performance to predict ATTR amyloidosis.

The authors should be congratulated for their well-designed and nicely illustrated study in the largest patient sample so far. By highlighting the excellent accuracy of quantitative ^{99m}Tc-DPD uptake to diagnose cardiac ATTR amyloidosis, they hit the nail on the head and advance the field into the right direction. Integrating their findings with previous publications (Table 1), the distinct step-up of SUV_{max} from Perugini grade 0/1 to grade 2/3 displays the clinical utility of the metric. Indeed, a threshold of SUV_{max} around 6 crystallizes as a sensitive marker to diagnose cardiac ATTR amyloidosis quantitatively. However, the reference standard for diagnosing cardiac amyloidosis was likely visual grading in most of these studies. Comparing SUV_{max} to visual grading should be evaluated carefully as it may inflate accuracy. Specifically for this study, there are some weaknesses and limitations that need to be mentioned. The authors did not include SUVmean or volumetric parameters like CAA or %ID which—at least in theory—may have superior utility to quantify total amyloid burden and monitor changes over time.[10] Although a phantom study was used to determine the scaling factor to accurately estimate SUV values for SPECT/CT, it is unclear if this calibration was repeated at periodic intervals (e.g., quarterly) over the course of the 3-year study period to maintain accurate SUV measures. Finally, the authors did neither test interrater

Table 1. Systematic review of quantitative SPECT studies in cardiac amyloidosis

Publication	Study group	Year	Tracer	Method	n	Cutoff for sensitivity ≥ 99%	Normal	Abnormal	Grade 0	Grade 1	Grade 2	Grade 3
Caobelli et al[13]	Basel	2019	DPD	SUVmax	13				2.2 ± 1.1	3.3 ± 0	17.5 ± 7.0	14.8 ± 4.0
Ren et al[14]	Beijing	2020	PYP	SUVmax	37				1.6 ± 0.4	1.9 ± 0.3	4.7 ± 0.2	9.0 ± 1.9
Scully et al[15]	London	2020	DPD	SUVpeak	100	1.7			1.0 ± 0.4	3.7 ± 1.5	11.9 ± 3.8	10.6 ± 1.5
Wollenweberet al[16]	Vienna	2020	DPD	SUVpeak	32	3.1			1.4 ± 0.4	2.0 ± 0.7	16.5 ± 4.7	11.1 ± 4.4
Ben-Haim et al[17]	Jerusalem	2021	DPD	SUVmax	28	6.0			1.9 ± 0.3	2.8 ± 0.5	14.1 ± 3.1	15.3 ± 4.3
Dorbala et al[10]	Boston	2021	PYP	SUVmax	72		2.3 ± 0.6	4.7 ± 1.1				
Kessler et al[12]	Essen	2022	DPD	SUVmax	136	6.1			2.5 ± 0.9	4.0 ± 1.8	15.2 ± 3.4	14.8 ± 4.2

reliability nor re-test repeatability of their methods. This is instrumental for its future clinical applications.

In summary, quantifying myocardial uptake of bone avid radiotracers using SPECT/CT has emerged as a promising and highly specific tool to non-invasively diagnose cardiac ATTR amyloidosis. However, there is a lot of work to do: (1) Our focus should shift from the fact that we can quantify radiotracer uptake to establishing the most robust techniques and identifying the most reliable metrics. For that, accessible and user-friendly software solutions are needed. (2) Quantification may allow the detection of very low levels of amyloid accumulation in the left atrium, the right ventricle or even extracardiac uptake in the lungs. We should not miss this opportunity to enhance our understanding of ATTR amyloidosis. (3) Future studies should investigate the added clinical value of quantifying myocardial radionuclide uptake—most importantly to risk stratify patients, but also to monitor disease progression and to evaluate treatment response.

The future of bone avid tracer cardiac scintigraphy for transthyretin cardiac amyloidosis has never been brighter. And the future is about numbers.

Disclosure

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