Radiology

REVIEWS AND COMMENTARY • EDITORIAL

Four-dimensional Cardiac CT Depicts Coexistent Amyloidosis in Older Adults with Severe Aortic Stenosis

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Aortic stenosis (AS) is the most frequent valvular heart disease in older adults. It frequently coexists with cardiac amyloidosis. This is true particularly for the transthyretin amyloidosis subtype, which occurs in about 10%–15% of patients with AS (1). Concomitant cardiac amyloidosis worsens the prognosis of AS owing to several factors. Valvular amyloid infiltration can exacerbate AS progression, atrial wall infiltration can induce arrhythmias and related thromboembolic complications, and microvascular infiltration may lead to myocardial ischemia and dysfunction (1). Therefore, identifying this subgroup is important for risk stratification and patient management. However, this can be a formidable task, as AS and cardiac amyloidosis exhibit similarities in clinical presentation and fundamental phenotypic features. These similarities include concentric left ventricular (LV) remodeling, LV diastolic dysfunction, and abnormal LV global longitudinal strain (1). Therefore, a major challenge lies in the potential misattribution of clinical and imaging findings to solely AS. This misattribution may lead to the underdiagnosis of concomitant cardiac amyloidosis.

Confirmation of transthyretin cardiac amyloidosis typically involves evaluation with technetium 99m (^{99m}Tc) pyrophosphate, ^{99m}Tc hydroxymethylene diphosphonate, or ^{99m}Tc 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scintigraphy or SPECT (1). Additional investigation for monoclonal free light chain proteins in serum and urine is recommended to exclude systemic immunoglobulin light chain amyloidosis. This is another subtype rarely observed in the AS population and primarily associated with plasma cell dyscrasias. When uncertainty remains, endomyocardial biopsy may provide a definitive diagnosis (1,2). Despite well-defined confirmation steps, to our knowledge, a universally accepted consensus on screening for cardiac amyloidosis in patients with AS has yet to be established (1). A stepwise diagnostic approach is necessary because obtaining nuclear myocardial scans for all patients is not efficient due to cost considerations. Therefore, various clinical, biochemical, and radiologic red flags have been identified to evaluate potential concomitant amyloidosis and AS. Clinically suggestive findings include carpal tunnel syndrome, lumbar spinal stenosis, deafness, early pacemaker requirement, heart failure disproportionate to AS severity, intolerance to antihypertensive drugs, and signs of right ventricular failure. Additionally, elevated cardiac biomarkers and certain electrocardiographic changes serve as potential red flags (1).

Echocardiography is the primary imaging modality and a screening tool. Well-known echocardiographic red flags for amyloidosis include low-flow low-gradient AS, restrictive filling pattern, biatrial enlargement, right ventricular hypertrophy, atrial septal thickening, myocardial granular sparkling, decreased systolic mitral annular velocity, apical sparing pattern, and decreased global longitudinal strain (2). Cardiac MRI is generally used as a problem-solving tool in indeterminate cases. It can be used to detect myocardial tissue characteristics suggestive of cardiac amyloidosis, such as elevated native T1 values, expanded extracellular volume, and suggestive patterns of late gadolinium enhancement (1,2). However, myocardial tissue characterization with MRI may appear normal in up to 15% of patients with cardiac amyloidosis (1). Although CT is a suggested adjunct imaging modality for indeterminate cases, the limited validation data hinder its extensive incorporation into the diagnostic algorithm for concomitant cardiac amyloidosis and AS (2). Overall, the integration of echocardiography, cardiac MRI, and CT into clinical practice for diagnosing concomitant cardiac amyloidosis and AS remains an evolving process.

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See also the article by Bernhard et al in this issue.

Is there room for improvement in the diagnostic algorithm of concomitant cardiac amyloidosis and AS? It seems that the answer is "yes." In this issue of *Radiology*, Bernhard et al (3) found that, compared with reference standard scintigraphy, routine four-dimensional (4D) cardiac CT performed as part of preoperative transcatheter aortic valve implantation (TAVI) workup helped detect concomitant transthyretin cardiac amyloidosis with high diagnostic performance in older adults with severe AS (3). In their prospective study on 263 older adults aged 74–95 years, ^{99m}Tc-DPD scintigraphy helped detect concomitant amyloidosis in 10.3% of patients (27 of 263). This finding aligns with the reported prevalence in the literature (1,3). Their CT protocol consisted of a retrospective electrocardiography-gated acquisition with 20 cine reconstructions per cardiac cycle. After extensive postprocessing, the investigators obtained various CT-derived parameters and evaluated their performance in detecting concomitant amyloidosis. They selected four statistically significant CT-derived parameters (all with an area under the curve [AUC] of ≥0.70 for detecting concomitant cardiac amyloidosis): LV mass index, LV global longitudinal strain, left atrial global longitudinal strain, and relative apical longitudinal strain. They then calculated potential cutoff values for each parameter to develop a scoring system for amyloidosis detection. Subsequently, they formulated a four-item score by dichotomizing these four parameters according to predetermined cutoff values, with each parameter being one or zero point. The scoring system yielded high diagnostic performance, with the AUC of 0.89 ($P < .001$). The study also assessed the scoring system's performance at various threshold values. According to the reported metrics, the use of a two-point threshold value provided a high sensitivity and considerable specificity. When at least two points were accepted as positive for cardiac amyloidosis, the sensitivity and specificity were 96.3% and 58.9%, respectively (3).

These results are notable because 4D cardiac CT is routinely used for preoperative TAVI evaluation (4). In addition to demonstrating the structure and movement of the aortic valve and enabling the measurement of the aortic annulus dimensions, 4D CT provides information about myocardial mass, focal and global wall motion, and myocardial strain with a high reproducibility (3,5). Apart from the widespread use and availability of 4D CT, obtaining these data routinely without performing additional diagnostic workup is an important benefit. This relatively simple four-item scoring system enables the detection of occult amyloidosis through a practical and objective assessment based on quantitative cutoff values. It can also spare many patients from unnecessary testing due to its high sensitivity for cardiac amyloidosis. In the current study, not conducting cardiac scintigraphy for 140 patients below the threshold of two points would eliminate the need for further testing in 53% of patients, with the trade-off of potentially missing only one case of cardiac amyloidosis (3).

Various scoring systems have been developed to distinguish cases of concomitant cardiac amyloidosis from lone AS cases. Among them, the clinical RAISE (remodeling, age, injury, system, and electrical) score stands out as a current and comprehensive clinical scoring system (6). Its parameters include carpal tunnel syndrome, disproportionate electrical remodeling (electrocardiographic abnormalities), disproportionate myocardial remodeling (echocardiography findings), chronic myocardial injury (troponin levels), and age. The RAISE system demonstrated good diagnostic performance following external validation, with an AUC of 0.83 (6). Nonetheless, there is a risk of clinical findings being overlooked or ignored, especially with such diversity, potentially resulting in underdiagnosis or delayed diagnosis. In contrast, using 4D cardiac CT–derived data as a part of routine diagnostic workup in patients with AS may be an efficient way to reduce the possibility of missing concomitant cardiac amyloidosis. Moreover, the four-item scoring system in the study by Bernhard et al shows a similar or better result than the RAISE score (3).

Meanwhile, the literature on the use of CT-derived findings is steadily growing. Four-dimensional cardiac CT has demonstrated a good correlation with two-dimensional echocardiography for left atrium and LV strain assessment and a moderate to good correlation with cardiac MRI. CT strain predicted mortality and composite outcomes after TAVI in patients with normal LV ejection fraction (5). These findings suggest promise for the validity of CT-derived parameters and the new potential diagnostic role of CT as a cardiac amyloidosis screening tool.

What can be done to further enhance the diagnostic contribution of CT? Particularly in the older adult population, where there is relatively less concern about radiation dosage, adding a delayed phase to the pre-TAVI CT protocol, and possibly dual-energy CT acquisition, could be employed to generate an iodine map. These additional strategies may allow for a more detailed assessment of cardiac amyloidosis by obtaining late iodine enhancement images and calculating extracellular volume (2,7). Furthermore, artificial intelligence–based models combining clinical and radiologic data could provide earlier and more accurate diagnosis. These advancements would enable the early initiation of treatment with novel medications (eg, tafamidis). These medications may improve the quality of life and reduce mortality, cardiovascular-related hospitalizations, and functional capacity decline (8). In addition, in concomitant cardiac amyloidosis and AS, choosing the less-invasive TAVI approach over surgical valve replacement and extended postprocedural monitoring may mitigate the risk of amyloidosis-related complications (1,9).

In the single-center study by Bernhard et al (3), the use of an extensive postprocessing algorithm, examination of a selected patient sample, and the absence of external validation may limit the applicability of the reported approach to general clinical practice. Additionally, myocardial strain values used as a parameter in the scoring system can be influenced by variables such as age and sex, and specific cutoffs tailored to these factors have not been established (10). Finally, the relatively low specificity of the scoring system (if at least two criteria are filled) is suggestive of potential false positivity, highlighting an aspect that requires improvement (3).

In summary, routine 4D cardiac CT is a promising tool with a potential gatekeeping role for the diagnostic workup of transthyretin cardiac amyloidosis in older adults with AS, considering the high sensitivity (96.3%) of the four-item scoring system (3). Further research involving a broader range of

parameters in a larger study sample, along with external validation, is required to ensure standardization and demonstrate the applicability of the findings to general clinical practice.

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