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Aortic valve calcium scoring on cardiac computed tomography: Ready for clinical use?

Calcific aortic stenosis (AS) is the most common valvular heart disease in developed countries,[1] characterized by progressive fibrocalcific changes within the valve leaflets leading to eventual outflow tract obstruction. Severe symptomatic stenosis is an indication for aortic valve replacement, and timely referral is essential to prevent adverse clinical events. The evaluation of AS severity is routinely performed using echocardiography and commonly graded using the peak aortic jet velocity, mean gradient, and aortic valve area.[2] For the majority of patients this assessment provides concordant assessments, and the severity of AS is clear. However, in around a quarter of cases, these measures are discordant, creating confusion as to the true severity of AS and difficulties in clinical decision making.[3] An independent, complementary test that could be used to arbitrate the true severity of AS would, therefore, have major clinical utility and potentially improve patient care.[4] What then to do in that common situation?

Although extensive work has been dedicated to the mechanisms underlying coronary artery disease, and this knowledge has led to numerous targeted preventive therapies, the complex cellular interplay contributing to AS remains less well understood. Aortic stenosis was traditionally thought of as a passive process of aging and calcific degeneration, but it is now increasingly recognized that valve calcification results from two phases: 1) initiation – which has similar underlying mechanism to coronary artery disease via accumulation of lipids and free cholesterol within the fibrosa, followed by infiltration of inflammatory cells, e.g. macrophages and T lymphocytes and 2) progression – which is dissimilar to coronary artery disease and more similar to bone formation via valve interstitial cells entering an osteogenic program, initiating calcium nodule formation, and valve calcification.[5–7]

Major interest now surrounds computed tomography aortic valve calcium scoring (CT-AVC) as a method to assess AS severity in cases where echocardiographic measurements are conflicting.[4] Progressive calcification is the predominant driver of aortic valve obstruction[8] and can be easily quantified using the same acquisition protocol and Agatston scoring method as used for a coronary artery calcium scan. CT-AVC is also of particular appeal because it provides an assessment of AS severity that is independent of geometric assumptions and left ventricular ejection fraction.[8] The last few years have witnessed rapid advances in this field and CT-AVC has demonstrated a close association with hemodynamic measures of moderate to severe AS on doppler echocardiography. However, until recently, the significant overlap in AVC between patients with hemodynamically severe and those with non-severe AS made its implementation difficult in clinical practice. This conundrum has been resolved with the demonstration that women have a lower AVC load than men for the same hemodynamic AS severity.[9] This finding led to the derivation of sex-specific thresholds of AVC for the identification of severe AS. These thresholds of AVC and AVC density were initially proposed by Clavel et al.[3] and have been recently confirmed in a multicenter study.[10]

This development has led to great interest in using CT-AVC as an alternative and complimentary assessment of AS severity, especially in patients with discordant echocardiographic findings.[11] Indeed: 1) AVC is strongly but nonlinearly associated with hemodynamic measures of moderate to severe AS severity,[12] 2) AVC can help to discriminate severe from non-severe AS in patients with discordant echocardiographic findings and 3) in patients with moderate to severe disease AVC is also likely associated with more rapid progression of aortic valve stenosis and survival although this analysis did not adjust for the individual patients' coronary artery calcium scores.[13]

Although AVC scoring has recently been recommended in the latest European Society of Cardiology guidelines to confirm AS severity in 1) patients with low left ventricular ejection fraction (LVEF), low flow, low gradient in whom dobutamine stress echocardiography remains inconclusive and 2) patients with low-gradient AS and preserved LVEF - it is not yet part of American Heart Association/American College of Cardiology guidelines.[14] Certainly, before it enters routine clinical use, its widespread clinical applicability must be established. So, what are the next steps?

While the reproducibility of coronary calcium quantification by multidetector CT has been tested for various workstation platforms before,[15,16] the same has not been performed so far for AVC quantification. Variation in AVC scoring across workstation platforms in patients with paradoxical low-flow, low-gradient aortic stenosis, however, would have implications for patient treatment.[14,17]

In this issue of the Journal, Eberhard et al.[18] investigated the inter-individual variance and the variability of AVC scoring performed with different workstation platforms in patients with symptomatic aortic stenosis undergoing CT prior to transcatheter aortic valve implantation. Between September 2016 and April 2017, they screened 104 consecutive patients with symptomatic aortic stenosis planned to undergo transcatheter aortic valve replacement and who underwent CT as part of the pre-procedural protocol. Patients with previous aortic valve replacement (n = 4) were excluded, resulting in the inclusion of 100 patients (median age 81 years, inter-quartile range 77–85 years, 56 females) into this study. In brief, on the basis of these CT data, they demonstrated for both independent observers, that each workstation platform produced very similar numeric AVC Agatston scores, without statistical significance (p = 0.96 and p = 0.98) produced similar results

Abbreviations: AS, Aortic stenosis; AVC, Aortic valve calcification; CT, Computed tomography; CT-AVC, Computed tomography aortic valve calcium scoring; LVEF, Left ventricular ejection fraction

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for classification of aortic stenosis according to the AVC burden. Comparing Agatston score results of all four workstation platforms, they found an excellent correlation between platforms with r = 0.991–0.996 for observer 1 and 2. Regression analysis revealed a strong relationship between measurements of all platforms with r^2 = 0.981–0.992 for observer 1 and r^2 = 0.981–0.989 for observer 2. Furthermore, they found low inter-observer (mean differences 1 ± 43 to 12 ± 70) and intra-observer variability (mean differences 9 ± 42 to 20 ± 96) for AVC Agatston scores using the same software-platform with substantial agreement regarding likelihood classification. Observer 1 assigned 11 (kappa 0.85–0.97) and observer 2 assigned 10 patients (kappa 0.88–0.95) to different likelihood groups of severe aortic stenosis with at least one platform. Overall, there was no significant difference of likelihood assignment between platforms (p = 0.98 and p = 1.0, respectively). While absolute values differed slightly, common commercially available software platforms produced comparable results for AVC scoring, which indicated software independency of the method.

This study has several limitations including a small sample size and lack of generalizability to patients without severe symptomatic aortic stenosis. In addition, all of the measurements were performed using data acquired from one CT scanner. Thus, it remains to be elucidated whether their results are generalizable to other CT scanners as well. Further, they did not assess inter-platform variability of volume, mass, or density score as current recommendations on CT assessment of aortic stenosis are based on the Agatston score. Finally, they included four commonly used software platforms for calcium quantification, however, there exist further products from other vendors on the market. There are various workstation platforms dedicated to calcium scoring. Each calcium scoring software has individual calculation algorithms and innate region of interest placement options (volume based versus slice based). It was previously shown that results from coronary calcium quantification might differ depending on the software platforms used, but results were overall comparable with minor inconsistencies in risk group assignments.[16]

Eberhard et al. are the first to describe the inter-platform reproducibility of AVC Agatston scores on the basis of identical CT data sets. Precise, reproducible and vendor-independent assessment of AVC scores represents a prerequisite for the clinical application of the technique, having an impact on patient management and treatment. This finding indicates a software and observer independency of AVC scoring regarding the CT assessment of patients with severe aortic stenosis. Moreover, the use of different scanners for image acquisition and different software for image analysis is reported not to have any significant effect on thresholds levels or accuracy of AVC (area under the curve ≥0.89) to identify severe AS.[3,10] The thresholds of AVC have also been validated by outcome studies demonstrating that patients with severe AVC experience an excess mortality under medical management.[10,19] In addition, AVC load has prognostic value over clinical and echocardiographic assessment to predict both AS progression rates and need for aortic valve replacement, which may help in determining the optimal timing for intervention.[19,20]

Eberhard et al. are to be congratulated on their innovative study that provides important information to support the clinical use of CT-AVC as a complementary imaging test in patients with symptomatic AS and discordant echocardiography findings. However, before AVC scoring can be adopted for widespread clinical use, further AVC research is needed to describe the clinical utility of AVC for patients earlier in the aortic stenosis disease process. In particular, data is needed to describe the age, sex, and race population percentiles, which is a core tool for interpreting coronary artery calcium scoring. In addition, future studies should also focus on the relationship between minimal subclinical AVC and the long-term risk for severe aortic stenosis.

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