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Letters

RESEARCH LETTER

Severe Aortic Stenosis With High Noncalcific Aortic Valve Volume

A Novel Marker of Myocardial Fibrosis

Progressive aortic valve (AV) leaflet calcification is the pathological hallmark of significant aortic stenosis (AS). AV calcium scoring allows for the quantification of calcific remodeling and has become an important diagnostic and prognostic imaging biomarker in the evaluation and management of patients with AS,[1] However, this technique does not account for noncalcific fibrotic remodeling of the AV, which is particularly important in women and younger patients. Recent cardiac computed tomography angiogram (CTA) techniques allow quantification of both fibrotic and calcific aortic valve thickening, providing predictive information on AS progression, and short-term outcomes following AV intervention.[2] These can be combined with assessments of myocardial fibrosis on cardiac CTA scans performed clinically for pre-transcatheter aortic valve replacement (TAVR) planning, which therefore has the potential to provide a comprehensive anatomical assessment of the AV and myocardium that might be helpful in clinical decision making.[3]

In this study, we wanted to investigate whether noncalcific fibrotic remodeling of the AV associates with specific characteristics of myocardial disease in patients with severe AS evaluated through comprehensive cardiac CTA analysis, in particular myocardial fibrosis assessed by myocardial extracellular volume (M-ECV).

Between November 2020 and June 2022, 280 patients were included in our comprehensive database focused on pre-TAVR imaging assessment with measurable CT-ECV and comprehensive clinical and imaging data. For this proof-of-concept study, we randomly selected 91 patients with equal distribution within the 19-month study period (roughly 4.8 patients/mo). This study was approved by the Allina Institutional Review Board and conducted following the Declaration of Helsinki. Patients underwent clinical evaluation, transthoracic echocardiography, and pre-TAVR cardiac CTA using a third-generation dual-source CT system (Somatom Force, Siemens Healthineers). TAVR cardiac CTA followed our institution acquisition protocol encompassing assessment of septal M-ECV as previously described.[3] Calcific and noncalcific AV volumes were quantified using the FibrocalcificPlaque software (3Mensio Structural Heart v10.4 research edition, Pie Medical Imaging BV) on a systolic phase, defining specific tissue type according to the different pixel intensity. For calcific AV volume, the lower threshold was set as the 99.7 percentile of blood pool attenuation, and all tissue above this threshold was considered to be calcium. To quantify noncalcific AV volume, a lower threshold of 100 HU was used to exclude artefacts, with an upper threshold at 250 HU; in addition, precontrast AV calcium score was measured using the Agatston method.

Median age was 83 years (Q1-Q3: 77-87 years), 48% female, 55% had atrial fibrillation, and 64% were in NYHA functional class III or IV. Median left ventricular (LV) ejection fraction was 57% (Q1-Q3: 50%-63%), median AV area (AVA) was 0.76 cm^2 (Q1-Q3: 0.61-0.89 cm^2), and 37% had low-flow low-gradient AS. Median AV calcium volume was 344 mm^3 (Q1-Q3: 183-507 mm^3), noncalcific volume was 340 mm^3 (Q1-Q3: 234-502 mm^3), with a median noncalcific to calcific volume ratio (NC/C) of 0.96 (Q1-Q3: 0.68-1.54). Median AV calcium score was 1,770 AU (Q1-Q3: 1267-2,502 AU), and with excellent correlation with AV calcium volume (Spearman's rho = 0.837; $P < 0.001$).

When dividing the cohort according to the median value of the NC/C ratio, age, coronary artery disease prevalence and Society of Thoracic Surgeons Predicted Risk of Mortality score were similar between the 2 groups ($P = 0.619$; $P = 0.357$; and $P = 0.540$, respectively), whereas patients with a high NC/C ratio were more often female (33 [73%] vs 11 [24%]; $P < 0.001$). Echocardiographically, although no differences were noted in LV ejection fraction ($P = 0.799$) or AV mean gradient ($P = 0.662$), patients with a high NC/C ratio had higher LV filling pressures (E/e′ ratio 20 [Q1-Q3: 18-28] vs 14 [Q1-Q3: 12-20]; $P < 0.001$), increased relative wall thickness (0.50 [Q1-Q3: 0.44-0.60] vs 0.45 [Q1-Q3: 0.40-0.53]; $P = 0.018$), smaller AVA (0.70 cm^2 [Q1-Q3: 0.60-0.85 cm^2] vs 0.80 cm^2 [Q1-Q3: 0.69-0.90 cm^2]; $P = 0.029$), and larger left atrium indexed volumes (49 mL/m^2 [Q1-Q3: 42-55 mL/m^2] vs 43 mL/m^2 [Q1-Q3: 36-53 mL/m^2]; $P = 0.098$ due to type II error). Patients with high NC/C ratio had higher M-ECV (32% [Q1-Q3: 28%-35%] vs 28% [Q1-Q3:

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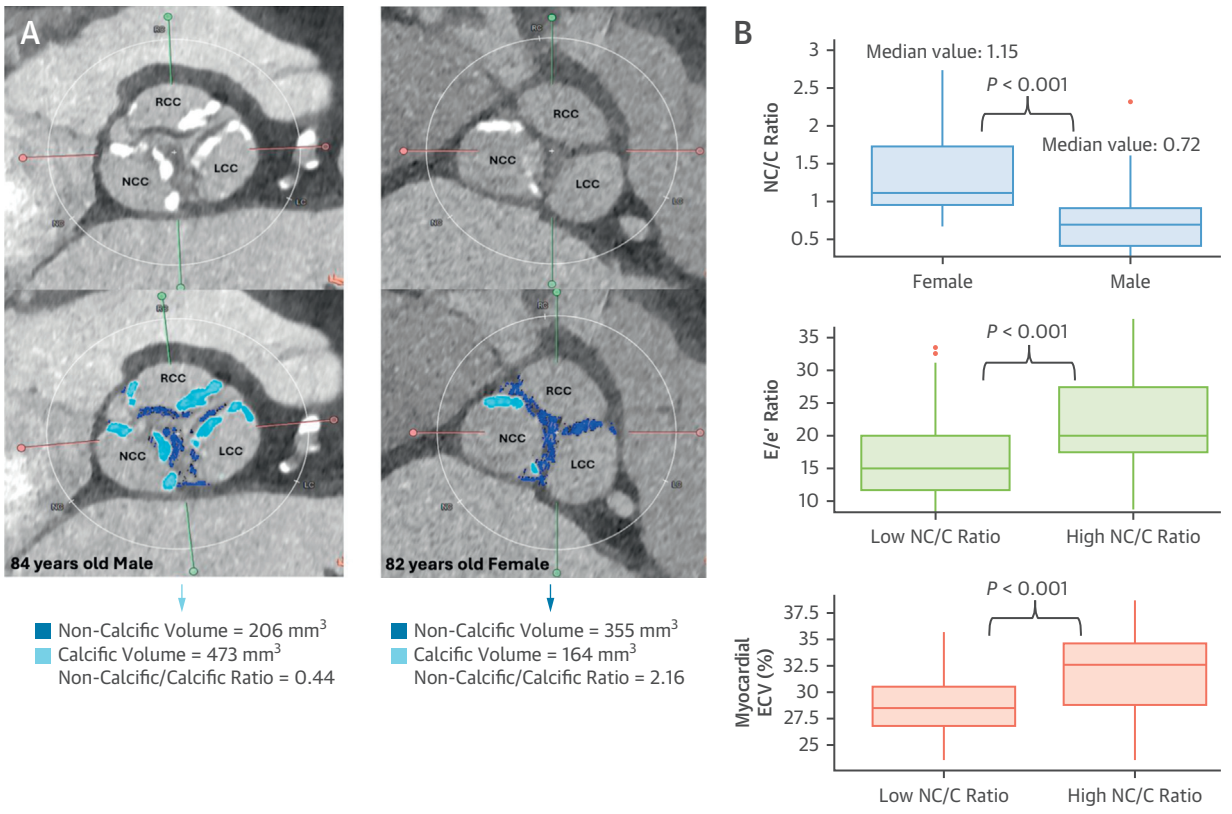
FIGURE 1 **Quantification of AV Calcific and Noncalcific Volumes by CTA and Associated Myocardial Remodeling**



(A) Two examples of aortic valve (AV) tissue quantification, one with higher calcific volume and the other with higher noncalcific volume. (B) The significance difference on AV noncalcific/calcific NC/C ratio according to gender (top), and on E/e′ ratio (middle) and myocardial extracellular volume (lower) according to AV NC/C ratio. ECV = extracellular volume; LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp.

26%-31%]; $P < 0.001$) (Figure 1) and lower global longitudinal LV strain (−16.5% [Q1-Q3: 19.4%-13.1%] vs −18.0% [Q1-Q3: 21.4%-15.8%]; $P = 0.132$). Results were unchanged when indexing M-ECV to LV mass by cardiac CTA. In multivariable analysis, NC/C ratio ≥ median was independently associated with elevated M-ECV, even after adjustment for age, gender, and AVA (OR: 3.69 [95% CI: 1.47-9.28]; $P = 0.005$).

This is the first study to examine the association between in vivo AV tissue composition characteristics by comprehensive cardiac CTA and myocardial functional and structural changes in patients with severe AS. Our findings confirm the importance of quantification of different AV tissue characteristics, and further provide novel mechanistic insights and explanation on the association of short-term adverse outcomes of noncalcific AV. That is, despite similar age, prevalence of coronary artery disease, and AV gradient, patients with a high NC/C ratio had worse LV structural remodeling with worse LV filling pressures and higher M-ECV. Whether a potential coexisting myocardial or a systemic pathological process, including but not limited to AS phenotype, its hemodynamic and clinical consequences require further research.

Important limitations are acknowledged. This is a single-center, single-vendor study with a limited number of patients. No ex vivo tissue validation is available to confirm our analysis, which will be important for future method standardization. Lastly, our results require validation by a larger cohort to evaluate the clinical and prognostic implications of our findings.

In conclusion, severe AS patients and predominant noncalcific AV remodeling presented with worse myocardial structural alterations. Such phenotype of AV remodeling appears to associate with increased

myocardial fibrosis and worse filling pressures. The clinical consequences of our findings are unknown after TAVR treatment.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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