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Letters

RESEARCH LETTER

Myocardial Hypoperfusion in Severe Aortic Stenosis Is Reversed Early After Aortic Valve Replacement

Myocardial hypoperfusion resulting in ischemia is common in severe aortic stenosis (AS), precedes symptoms, and has been hypothesized to drive irreversible myocardial scarring which is associated with a doubling in mortality after aortic valve replacement (AVR).[1,2] AS increases impedance to left ventricular (LV) blood ejection and increases compressive forces (greatest at the endocardial border) from increased intramyocardial pressure. Concentric LV hypertrophy compensates for increased systolic wall stress with increased myocardial oxygen demand. Whether it is the hemodynamic effect of the AS itself that results in impaired perfusion or structural alterations of the myocardium and coronary circulation remains incompletely understood. A better understanding is required of what treatment options may mitigate myocardial scarring and increased postoperative risk. Cardiac magnetic resonance (CMR) can determine myocardial function, remodeling, and scar burden, but it can also quantify myocardial blood flow (MBF).[3] We hypothesized that myocardial hypoperfusion in severe AS would be mainly caused by the load imposed by the AS and would therefore be reversible and occur early after AVR.

Patients with severe symptomatic AS were enrolled to the MASTER (Mechanisms of Excess Risk in Aortic Stenosis; NCT04627987) study at a single tertiary center. The study was approved by the UK National Research Ethics Service. Exclusion criteria included greater than moderate other valve disease, contraindications to CMR, primary cardiomyopathy, or obstructive coronary disease (>70% stenosis in any coronary vessel). Patients underwent clinical assessment, echocardiography, and CMR; this was repeated early at 8 weeks post-AVR. CMR was performed at 1.5 Tesla (Aera, Siemens Healthineers) including adenosine stress and rest perfusion (0.05 mmol/kg gadolinium [gadoterate meglumine] bolus) and late gadolinium enhancement imaging. Perfusion maps were generated automatically with each pixel of the myocardium measuring MBF. Automated segmentation of the LV using artificial intelligence techniques was used to calculate global, subendocardial, and subepicardial segmental MBF. Image analysis was performed using CVI42 (version 5.14.2, Circle CVI). Controls were drawn from people referred for clinical adenosine stress CMR who were proven by contemporaneous invasive or computed tomography coronary angiography not to have obstructive coronary disease (>30% coronary stenosis excluded). Propensity score matching (1:1) was used to reduce imbalance (ie, age, sex, hypertension, diabetes, and history of smoking) in confounders between the cohorts. Statistical analysis was performed using R version 4.0.2 (RStudio_2022.07.1).

Forty-six patients were included; 23 with severe AS (median age 71 years[Q1-Q3: 66-75 years], 73% male) and 23 age-, sex-, and comorbidity-matched controls. In AS, peak velocity (Vmax) was 4.3 m/s (Q1-Q3: 4.1-4.5 m/s) and aortic valve area was 0.8 cm^2 (Q1-Q3: 0.6-0.9 cm^2); 21 of 26 had coronary atheroma, but all lesions were <70% (none required revascularization). AS patients had greater LV mass and late gadolinium enhancement. The postoperative aortic valve Vmax was 2.5 m/s (Q1-Q3: 2.3-2.7 m/s). AS patients had lower stress MBF than controls (1.63 mL/g/min [Q1-Q3: 1.38-2.08 mL/g/min] vs 1.96 mL/g/min [Q1-Q3: 1.75-2.46 mL/g/min]; $P = 0.009$) which increased to 1.97 mL/g/min after AVR ($P = 0.90$ post-AVR vs controls; **Figure 1**). The improvement in flow was greatest in the subendocardium (1.26 mL/g/min [Q1-Q3: 1.18-1.78 mL/g/min] to 1.77 mL/g/min [Q1-Q3: 1.62-2.32 mL/g/min]; $P < 0.001$) though subepicardial flow also improved (1.93 mL/g/min [Q1-Q3: 1.56-2.31 mL/g/min] to 2.12 mL/g/min [Q1-Q3: 1.69-2.78 mL/g/min]; $P = 0.01$). Rest MBF was higher in AS than in the control group but this was not statistically significant (0.88 mL/g/min [Q1-Q3: 0.74-1.07 mL/g/min] vs 0.76 mL/g/min [Q1-Q3: 0.68-0.99 mL/g/min]; $P = 0.40$) and did not change significantly after AVR ($P = 0.20$). Myocardial perfusion reserve was reduced in AS vs controls (1.86 mL/g/min [Q1-Q3: 1.65-2.4 mL/g/min] vs 2.72 mL/g/min [Q1-Q3: 2.14-2.93 mL/g/min]; $P = 0.003$) and improved postoperative to be similar to controls ($P > 0.90$ post-AVR vs controls).

The main findings of the study are that stress MBF was reduced in severe AS, mostly in the subendocardium, and that stress MBF increased to levels of matched control subjects early (median 8 weeks)

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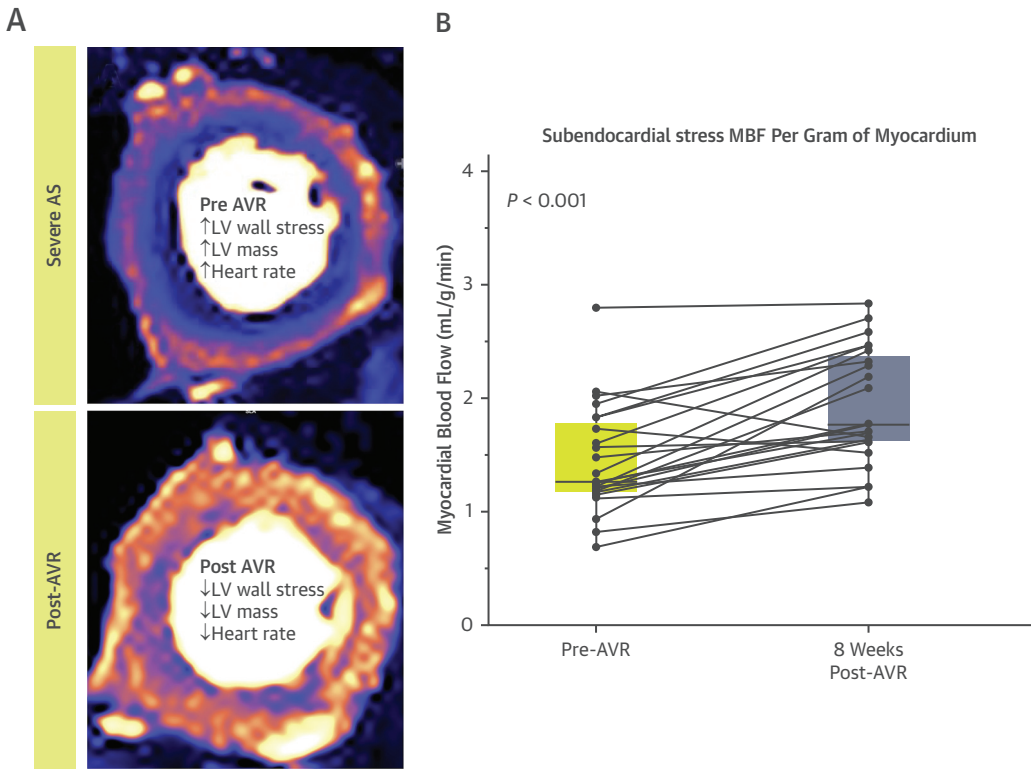
FIGURE 1 Stress MBF in Severe AS Before and Early (Median, 8 Weeks) After AVR



(A) Stress MBF per gram of myocardium at stress in severe aortic stenosis (AS) and post-aortic valve replacement (AVR). (B) Per patient data of improvement in subendocardial flow after AVR. LV = left ventricle; MBF = myocardial blood flow.

post-AVR (40% increase in subendocardial MBF). The time course of improved transmural and especially subendocardial perfusion suggest that increased intramyocardial pressure alleviated by AVR is the most likely mechanism of myocardial hypoperfusion. This is supportive of the existing published reports.[4,5] Irreversible myocardial fibrosis in frequently observed in severe AS and associated with increased mortality despite AVR.[1] This scar is more prevalent in the subendocardium, which may suggest an association between the development of scar and myocardial ischemia. The use of artificial intelligence-generated and segmented myocardial perfusion maps combined with the superior in plane resolution of CMR compared with positron emission tomography adds strength to the findings.

This is an observational study performed at a single tertiary center, which may limit its generalizability; the sample was small which reduces the power of some comparisons. The patients included in the study were a subgroup of a larger patient cohort who were able to return early after AVR; therefore, there is a risk of selection bias. Image acquisition of perfusion sequences begins in systole; variation in perfusion across the cardiac cycle was not evaluated. End-diastolic pressure was not measured; therefore, the data cannot evaluate the effect of diastolic compressive forces.

Severe AS results in subendocardial hypoperfusion under adenosine stress which is reversible after AVR. These findings advance our understanding of the mechanisms underpinning myocardial hypoperfusion in severe AS. Quantitative perfusion mapping may be an important early noninvasive clinical biomarker in severe AS to prompt intervention before scar formation; however, further studies are required across the spectrum of AS severity and with longer follow-up.

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