Myocardial hypoperfusion in severe aortic stenosis is reversed early after aortic valve replacement.

Brief Title: Myocardial Perfusion Reverses After AVR

George D Thornton[1,2,*], Jonathan B Bennett[1,2,*], Christian Nitsche[1,2], Francisco Gama[1], Nikoo Aziminia[1,2], Kristopher Knott[2], Rhodri H Davies[1,2], James C Moon[1,2], Peter Kellman[4], Thomas A Treibel[1,2]

Author affiliations:

[1] Barts Heart Centre, Barts Health NHS Trust, London, UK

[2] Institute of Cardiovascular Science, University College London, UK

[3] William Harvey Research Institute, Queen Mary University, London, UK

[4] National Heart, Lung, and Blood Institute, National Institute of Health, Bethesda, Maryland, USA

*contributed equally

Word count: 1000 words including references and figure legends.

Disclosures: All authors report no conflict of interest.

Address for correspondence:
Dr Thomas A Treibel
Barts Heart Centre,
St. Bartholomew's Hospital,
West Smithfield, London EC1A 7BE
Email: Thomas.Treibel@nhs.net
Twitter: @ThomasTreibel

Twitter: Myocardial ischemia in severe aortic stenosis is likely caused by raised intramyocardial pressure; stress myocardial hypoperfusion by #WhyCMR reverses early after valve replacement. @GD_Thornton @ThomasTreibel

Key Words: Cardiovascular magnetic resonance, Perfusion, Aortic stenosis, Aortic Valve Replacement

Funding: This study was in part supported by the British Heart Foundation, Treibel [FS/19/35/34374] and Thornton [FS/CRTF/21/24128] and a European Commission Horizon 2020 grant, Treibel and Bennett 848109.

Acknowledgements: We are extremely grateful to the study participants and their families for their participation and to our funding partners for making this study possible.

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 can also quantify myocardial blood flow (MBF) (3). We hypothesized that myocardial hypoperfusion in severe AS would be mainly due to 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 Mechanisms of Excess Risk in Aortic Stenosis (MASTER) study (NCT04627987) at a single tertiary centre. The study was approved by the UK National Research Ethics Service. Exclusion criteria included >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, Germany) including adenosine stress and rest perfusion (0.05mmol/kg gadolinium [gadoterate meglumine] bolus) and late gadolinium

enhancement (LGE) imaging. Perfusion maps were generated automatically with each pixel of the myocardium encoding myocardial blood flow (MBF). Automated segmentation of the LV using artificial intelligence (AI) techniques was used to calculate global, subendocardial and subepicardial segmental MBF. Image analysis was performed using CVI42 (version 5.14.2, Circle CVI, Canada). Controls were drawn from people referred for clinical adenosine stress CMR who were proven by contemporaneous invasive or CT coronary angiography not to have obstructive coronary disease (>30% coronary stenosis excluded). Propensity score matching (1:1) was used to reduce imbalance (age, sex, hypertension, diabetes, history of smoking) in confounders between the cohorts. Statistical analysis was performed using R version 4.0.2 (RStudio_2022.07.1).

46 patients were included; 23 with severe AS (median [IQR] age 71[66-75], 73% male) and 23 age, sex and co-morbidity matched controls. In AS, peak velocity (Vmax) was 4.3m/s [4.1-4.5] and AVA 0.8cm^2 [0.6-0.9], 21/26 had coronary atheroma, but all lesions were <70% (none required revascularization). AS patients had greater LV mass and LGE. The post-operative aortic valve Vmax was 2.5 [2.3-2.7]m/s. AS patients had lower stress MBF than controls (1.63ml/g/min [1.38-2.08] vs 1.96 [1.75- 2.46], p=0.009) which increased to 1.97ml/g/min after AVR (p=0.9 post-AVR vs. Controls). The improvement in flow was greatest in the subendocardium (1.26ml/g/min[1.18-1.78] to 1.77[1.62-2.32]), p<0.001) though subepicardial flow also improved (1.93ml/g/min[1.56-2.31] to 2.12[1.69-2.78], p=0.01). Rest MBF was higher in AS than controls but this was not statistically significant (0.88ml/g/min [0.74- 1.07] vs 0.76[0.68-0.99], p=0.4) and did not change significantly after AVR (p=0.2). Myocardial

perfusion reserve was reduced in AS vs controls (1.86[1.65-2.4] vs 2.72 [2.14-2.93], p=0.003) and improved post-op to be similar to controls (p>0.9 post-AVR vs. controls).

The main findings of the study are that stress MBF was reduced in severe AS, most in the subendocardium and that stress MBF increased to levels of matched control subjects early (median 8 weeks) post-AVR (40% increase in subendocardial MBF). The time course of improved transmural and especially subendocardial perfusion suggests that raised intramyocardial pressure, alleviated by AVR, is the most likely mechanism of myocardial hypoperfusion. This is supportive of the existing literature (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 AI-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 non-invasive clinical biomarker in severe AS to prompt intervention prior to scar formation, however further studies are required across the spectrum of AS severity and with longer-term follow-up.

FIGURE LEGENDS

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 AS and post-AVR. B. Per patient data of improvement in subendocardial flow after AVR.

References

1. Musa TA, Treibel TA, Vassiliou VS et al. Myocardial Scar and Mortality in Severe Aortic Stenosis. Circulation 2018;138:1935-1947.

2. Cheitlin MD, Robinowitz M, Mcallister H, Hoffman JI, Bharati S, Lev M. The distribution of fibrosis in the left ventricle in congenital aortic stenosis and coarctation of the aorta. Circulation 1980;62:823-830.

3. Kellman P, Hansen MS, Nielles-Vallespin S et al. Myocardial perfusion cardiovascular magnetic resonance: optimized dual sequence and reconstruction for quantification. Journal of Cardiovascular Magnetic Resonance 2017;19:43.

4. Rajappan K, Rimoldi OE, Camici PG, Bellenger NG, Pennell DJ, Sheridan DJ. Functional Changes in Coronary Microcirculation After Valve Replacement in Patients With Aortic Stenosis. Circulation 2003;107:3170-3175.

5. Mcconkey HZR, Marber M, Chiribiri A, Pibarot P, Redwood SR, Prendergast BD. Coronary Microcirculation in Aortic Stenosis. Circulation: Cardiovascular Interventions 2019;12.