Sex and regional differences in myocardial plasticity in Aortic Stenosis are revealed by 3D model machine learning

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Abstract

Aims Left ventricular hypertrophy (LVH) in aortic stenosis (AS) varies widely before and after aortic valve replacement (AVR), and deeper phenotyping beyond traditional global measures may improve risk stratification. We hypothesized that machine learning derived 3D LV models may provide a more sensitive assessment of remodeling and sex-related differences in AS than conventional measurements.

Methods and results 116 patients with severe, symptomatic AS (54% male,70±10 years) underwent cardiovascular magnetic resonance pre and one year post-AVR. Computational analysis produced co-registered 3D models of wall thickness (WT), which were compared with 40 propensity-matched healthy controls. Pre-operative regional WT and post-operative percentage WT regression were analyzed, stratified by sex.

AS hypertrophy and regression post-AVR was non-uniform – greatest in the septum with more pronounced changes in males than females (WT regression: -13±3.6 vs -6±1.9% respectively, $p<0.05$). Even patients without LVH (16% with normal indexed LV mass, 79% female) had greater septal and inferior WT compared with controls (8.8±1.6 vs 6.6±1.2mm,$p<0.05$), which regressed post-AVR. These differences were not detectable by global measures of remodeling.

Changes to clinical parameters post-AVR were also greater in males: NT-proBNP (-37[IQR -88,-2] vs -1[-24,11]ng/L,$p=0.008$), and systolic blood pressure (12.9±23 vs 2.1±17mmHg,$p=0.009$), with changes in NT-proBNP correlating with percentage LV mass regression in males only (ß 0.32,$p=0.02$).

Conclusion In patients with severe AS, including those without overt LVH, LV remodeling is most plastic in the septum, and greater in males, both pre and post-AVR. 3D machine learning is more sensitive than conventional analysis to these changes, potentially enhancing risk stratification.

Abbreviations

3D	Three-dimensional
AS	Aortic stenosis
AVR	Aortic valve replacement
BSA	Body surface area
CMR	Cardiovascular magnetic resonance
LVH	Left ventricular hypertrophy
LVM(i)	Left ventricular mass (indexed to body surface area)
MVR	Mass to end-diastolic volume ratio
NT-proBNP	N-terminal pro-brain natriuretic peptide

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the developed world and is associated with high mortality once symptoms develop.(1) Aortic valve replacement (AVR) improves survival but risk stratification and timing is difficult because symptoms are hard to elucidate and current grading criteria focus largely on echocardiographic valvular parameters which may be discordant.(2) Outcome is however also known to be determined by left ventricular (LV) remodeling, encompassing changes to geometry and hypertrophy (LVH), which may be asymmetrical and varies in extent between individuals.(3–5) In response to pre-coronary pressure overload, ventricular remodeling may be initially adaptive but later maladaptive and associated with adverse consequences of diastolic dysfunction, ischemia, fibrosis, heart failure and eventually death.(4,6) Following intervention, reverse remodeling is also variable,(7) and linked to re-hospitalization rates.(8) These changes appear to be at macro- and microscopic levels and have sex specific features,(9–13) and impact.(14) Conventional metrics of remodeling using left ventricular mass indexed (LVMi) to body surface area (BSA) and concentricity (global LV mass to end-diastolic volume ratio [MVR]) provide broad insight into the myocardial response to AS,(15) however may mask early changes or regional differences. By capturing asymmetry in LV remodeling, it is possible to add incremental value for identification of early disease, different disease pathways and outcome prediction.(16) Advances in atlas approaches utilizing machine learning for robust automated segmentation and co-registration now permit unbiased appreciation of three-dimensional (3D) ventricular architecture (local myocardial wall thickness and shape) and comparison with health and change over time, *Cover illustration*.(17) 3D phenotyping delivers deeper insights into the complex structural patterns in cardiac imaging data, moving closer towards personalized imaging biomarkers for risk assessment.(18) But before 3D machine learning can be incorporated into predictive models, it should demonstrably deliver

a more sensitive marker of LV remodeling than conventional metrics. We hypothesized that such a 3D machine learning approach would provide new insights into AS remodeling, including sex dimorphism and reverse remodeling one year post-AVR.

Methods

Study population

A prospective observational cohort study was conducted in patients with severe, symptomatic AS who underwent AVR between January 2012 and January 2015 in a single tertiary referral cardiac center, University College London Hospital NHS Trust, London, UK. The study was approved by the ethical committee of the UK National Research Ethics Service (07/H0715/101). The study conformed to the principles of the Helsinki Declaration, and all subjects gave written informed consent.

Full details of study design and methodology have been previously published.(9,19) Pre-AVR and one year post-AVR, comprehensive assessment included functional status (New York Heart Association, NYHA), blood pressure, 6 minute walk test (6MWT), blood sampling for N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT), electrocardiography, trans-thoracic echocardiography, and cardiovascular magnetic resonance (CMR). Adult patients with severe AS (two or more of: aortic valve area $<1cm^2$, peak pressure gradient >64mmHg, mean pressure gradient >40mmHg, aortic valve velocity ratio <0.25) who were undergoing AVR with or without coronary artery bypass grafting were recruited before pre-operative evaluation. Exclusion criteria were pregnancy or breastfeeding, estimated glomerular filtration rate $<30ml/min/1.73m^2$, non MRI-conditional implanted devices, inability to complete the scanning protocol, previous valve surgery, or greater then moderate valve disease other than AS.

Controls were matched to balance for age, sex, BSA and African Caribbean ethnicity covariate distributions from a prospective observational study of 1,968 healthy adult volunteers free of cardiovascular disease for the United Kingdom Digital Heart Project (www.digital-heart.org), *Table S1*.

CMR

CMR was performed at 1.5 T (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany), using a standard clinical scan protocol.(19) Short axis cine imaging was acquired using a standard balanced steady-state free precession pulse sequence with the following parameters: 7mm slice thickness, 3mm slice gap, 25 phases, typical field of view 270x 360cm, echo time 1.35ms, repetition time 2.7ms, flip angle 88º. LV remodeling pattern categorization and extracellular volume fraction (ECV) calculation for matrix and cell volumes were performed as previously described, *Supplementary Methods*.(19)

Global and regional (3D) assessment of LV structure

3D analysis was performed as previously described using an atlas-based machine learning approach for image segmentation to produce global LV metrics and 3D models of wall thickness and geometry, co-registered in the same space.(17,20) Image processing was performed using Matlab R2013a (The MathWorks, Inc., Natick, Mass, USA) and ITK-SNAP (US National Institutes of Health). Each voxel was segmented based on a reference atlas of over one thousand individuals.(17) In brief, this was initialized by manually placing six anatomical landmarks (left ventricular apex, mitral valve annulus, left and right ventricular free walls, superior and inferior right ventricular insertion points). This produced a patient-specific mesh of ~40,000 vertices aligned within a common reference space. At each vertex, wall thickness was calculated by measuring the distance between the endocardium and epicardium perpendicular to the midwall plane. Changes in end-diastolic chamber and epicardial volume were measured as a positive or negative displacement from an average healthy volunteer template shape. By 3D geometric analysis, regional concentric remodeling was defined as chamber volume reduction due to inward displacement of the endocardium; and conversely, regional eccentric remodeling was defined as cavity dilatation due to outward

endocardial expansion. If either of these processes was associated with outward epicardial expansion, this resulted in concentric hypertrophy and eccentric hypertrophy respectively (*Fig. 1a*). For a 3D assessment of function, fractional wall thickening (FWT) was calculated as the percentage change between end-diastolic and end-systolic wall thickness. For baseline comparison to matched controls, all 116 patients with AS were analyzed.(19) At follow-up, two patients (one male, one female) were excluded due to significant slice misregistration precluding 3D model construction.

For global parameters, inter-observer agreement was performed between manual and atlas-based measures of LV metrics using intraclass correlation coefficient (ICC, mixed model). The ICCs for LV EDV, end-systolic volume (ESV), ejection fraction (EF) and mass were between 0.93 and 0.96, *Table S2*. Previous work using this technique has shown that 72 (interquartile range [IQR]: 49-104) subjects are needed to detect a 1mm difference in wall thickness.(21)

Statistical analysis

Data were analyzed in R (R foundation, Vienna, Austria) using RStudio Server version 0.98 (Boston, Mass, USA). All continuous variables are expressed as mean±SD or median(IQR) for skewed data. Normality was checked using the Shapiro-Wilk test. Categorical variables are expressed as percentages. Groups were compared using independent-samples Student's t-tests for normally distributed continuous variables or Mann-Whitney U test and the Chi-square tests for non-normally distributed and categorical variables respectively. A regression sensitivity analysis was performed using an allometric adjustment of height^1.7 instead of BSA, which did not alter interpretation of results. Beta coefficients from regression models were standardized. Changes between pre-AVR and post-AVR visits were compared using paired Student's t-tests for continuous variables and using Wilcoxon signed rank test for

ordinal variables. As previously described in 3D datasets, group comparisons applied threshold-free cluster enhancement to optimize sensitivity to significant signal in ‘clusters’ of adjacent LV vertices. P values were derived from permutation testing at each vertex after control for false discovery rate (FDR).(21,22) To describe the changes in 3D parameters, the summary variables reported are the mean and standard deviation across the percentage area of ventricular surface that achieved statistical significance (p values are therefore not reported given that all reported comparisons and associations are $p<0.05$ after correction for FDR).

Results

Patients

One hundred and sixteen patients (54% male) with severe, symptomatic AS were assessed at baseline. There were no sex differences in patient age or echocardiographic severity of aortic stenosis, but males had lower systolic blood pressure (129±17 vs 137±16mmHg,p=0.004) and had greater functional capacity (6MWT: 533±163 vs 399±183m,p<0.001). Demographic, clinical, and imaging characteristics are shown in *Table 1*.

Global and regional (3D) LV shape: AS versus matched controls

Patients had increased LVM compared to matched controls (161±43 vs 120±27g,p<0.001) with similar EDV (154±61 vs 155±34mls,p=0.92), *Table S1*. By 3D analysis, patients had significantly greater wall thickness across 83% of the ventricular surface (wall thickness averaged across the whole myocardium: 9.1±2.3 vs 6.9±1.3mm). This was most pronounced in the septum, *Fig. 1*, with a maximal wall thickness of 16±2.5mm in patients versus 12±1.8mm in matched controls. There was inward displacement of the septal endocardium, whilst in the lateral wall there was outward expansion of the endocardium, compared to controls. The epicardium expanded outwards globally, meaning that there was overall septal concentric hypertrophy and lateral eccentric LV hypertrophy, *Fig. 1*.

Sex differences in regional shape: AS versus matched controls

Males demonstrated greater outward expansion of the lateral endocardium (ß 0.53, 33% ventricular surface), whilst females had greater inward displacement of the septal endocardium (ß -0.77, 4% ventricular surface) compared to sex-matched controls. Both males and females demonstrated circumferential outward expansion of the epicardium (males: ß 0.88, 76% ventricular surface, females: ß 0.74, 33% ventricular surface). Overall this

represents septal concentric hypertrophy in both males and females and lateral eccentric hypertrophy in males.

Sex differences in wall thickness and function in AS

Male sex was positively associated with LVM when adjusting for age, BSA, hypertension and aortic valve area (ß 0.22; 95% CI: 0.05, 0.38), *Tables S3 and S4.* By 3D analysis, male sex was positively associated with wall thickness across 56% of the ventricular surface - most pronounced in the septum, *Fig. 2*. Males had lower FWT both in the septum and lateral walls when compared to females (58±20 versus 77±23%, 18% ventricular surface).

Sex differences in reverse remodeling and clinical measures one year post-AVR

One year post-AVR, LVMi was lower (-12.2±16g/m^2,p<0.001, *Table 2* and *Fig. 3*) with a significant reduction in wall thickness across 77% of the ventricular surface by 3D analysis (average over this region: -1.0±0.6mm, most pronounced in the septum). Males had similar percentage LVM reduction to females (-15.4±13.8 vs -9.6±18.2%,p=0.07), but a greater reduction in 3D percentage wall thickness (-13±3.6 vs -6±1.9%, 8% ventricular surface), with significant differences between sexes confined to the septum, *Fig. 4*. In the septum, males increased contractility, and females showed a reduction from more hyperdynamic contractility (FWT: +10±5 vs -4±10% respectively, 11% of the ventricular surface), with no sex differences at follow-up (FWT males: 68±59%, females: 70±44%, p=0.47).

One year post-AVR, NT-proBNP reduced only in males (-37[-88,-2] vs -1[-24,11]ng/L, p=0.008), with no sex differences at follow-up (38[17-130] vs 38[26-79]ng/L, p=0.96). Males also had a greater increase than females in systolic blood pressure (SBP) (12.9±23 vs 2.1±17mmHg respectively, p=0.009) and diastolic blood pressure (DBP) (5±14 vs -1±14mmHg respectively, p=0.04) post-AVR, with no sex differences at follow-up (SBP:

140±16 vs 139±19mmHg,p=0.69; DBP: 79±11 vs 76±11mmHg,p=0.12). Changes in other clinical measures are summarized in *Table S5*.

In men, percentage change in 3D septal wall thickness correlated more strongly than global LVM with the change in hs-TnT (β 0.37,p=0.006 versus 0.3,p=0.03 respectively). Conversely, percentage change in LVM correlated more strongly than percentage change in 3D septal wall thickness with the change in NT-proBNP (β 0.32,p=0.02 versus 0.23,p=0.08 respectively). There was no correlation in females, with only 4 (8%) having elevated NT-proBNP at baseline. For either sex, there was no correlation with the change in NYHA class, 6MWT or SBP.

Wall thickness in patients with severe AS and normal geometry versus matched controls

There were 19 patients with normal LVM and geometry at baseline (n=19, 79% female, mass:end-diastolic volume<1.15). Echocardiographic severity of AS was similar to patients with abnormal LV geometry, but NT-proBNP was lower and hypertension less frequent, *Table S6*.

Although global measures of LVM were similar in this group to matched controls (122±27 vs 107±22g,p=0.11), *Table S1*, by 3D analysis patients had greater inferior and septal wall thickness (8.8±1.6 vs 6.6±1.2mm, 46% ventricular surface), *Fig. 5*.

One year post-AVR, these patients had a trend to a reduction in LVMi (-5±11g/m^2, p=0.054 and no change in LVEDVi (-0.5±15mls/m^2, p=0.59). 3D analysis however revealed a reduction in wall thickness in the inferior and septal walls (-1.6±0.3mm, 0.8% ventricular surface) that remained hypertrophied compared to matched controls (7.8±1.9 vs 6.5±1.4mm, 29% ventricular surface).

Discussion

This study shows that in patients with severe symptomatic AS the septum is the most adaptive myocardium compared to other regions- it hypertrophies to a greater extent and regresses the most one year post-AVR. Men had twice the percentage wall thickness regression in this region than women, correlating with improvements in serum biomarkers, suggesting functionally significant, sex-specific responses to aortic stenosis. Even in patients without overt LVH by global parameters, inferior and septal hypertrophy is present compared to controls. Whilst males did not recover normal LV geometry by conventional measures following AVR as often as females, even females with normal geometry at baseline showed wall thickness regression, but not normalization, post-AVR. The 3D machine learning approach highlights regional reverse remodeling and sex differences in patients with AS that are not detectable using global measures. These findings show that cardiac remodeling is an asymmetric continuous spectrum challenging conventional categorization. Because 3D machine learning provides a more sensitive measure of LV remodeling, this may permit enhanced risk stratification in patients with AS.

Asymmetric remodeling in aortic stenosis

3D machine learning enables co-registration, shape changes and unbiased whole-heart coverage that are not possible with conventional wall thickness analysis. Our findings are consistent with previous data showing that asymmetric septal hypertrophy is a common structural variant in 22-27% of patients with AS.(15) In addition we demonstrate that there is a septal preponderance to remodeling across all patients with severe AS, rather than a characteristic specific to predisposed patients.(9,15) 3D analysis also shows that patients with normal conventional global measures of LVM and volume display relative inferior and septal

hypertrophy compared to matched controls. This may represent a region of early adaptation to pressure overload providing functional advantages.

Regional sex differences before and after AVR

We observed the greatest sex difference in hypertrophy in the basal to mid septum, independent of other drivers of asymmetric remodeling, including hypertension and AS severity. The regions are similar to where Dobson et al. found males had more focal fibrosis, measured regionally using late gadolinium enhancement.(12) This suggests males have greater hypertrophy and matched fibrosis in response to AS, highlighting the complex regional interplay. The association between change in hs-TnT and change in septal wall thickness was stronger than with the change in global LVM, potentially related to regional variations in wall stress. Recently we have shown that fibrosis is also plastic, and a regional comparison of fibrosis regression between sexes may also contribute to our understanding of remodeling post-AVR.(19)

We previously described that CMR detects more concentric remodeling in women compared to echocardiography.(9) We build on this by using a more detailed phenotype to show that the female concentric remodeling response is predominantly septal, and the eccentric hypertrophy observed in males is predominantly lateral.

We additionally observed small but significant sex differences in percentage wall thickness regression in the septum. Greater relative regression of hypertrophy in males has not been previously reported, but greater absolute LVM regression was observed in one other CMR study.(12)

Greater sensitivity to AS remodeling using machine learning imaging biomarkers

Current decision-making regarding intervention in AS includes an assessment of myocardial structure and function, however this relies on waiting for a reduction in global EF – an

insensitive and downstream marker of myocardial remodeling. These data show that a 3D atlas-based approach for assessment of remodeling provides a visually and clinically intuitive insight into the complex changes in response to AS over time. These data support the notion that that there are sex-specific biological pathways that may require separate intervention thresholds.(10,12) Importantly, this was only detectable using a 3D machine learning approach, as were myocardial changes in patients classified with overall normal geometry by reference standard global measures. Because 3D approaches are able to maximize information from a dataset, these may offer scope to identify additional biomechanical risk components, moving closer to more personalized decision-making.

Sex differences: what constitutes adaptive remodeling?

The LV remodeling phenotype described in males is associated with a depressed contractile state, higher levels of NT-proBNP and lower blood pressure, which may indicate a maladaptive response. Consistent with this, we have previously reported that males have more focal fibrosis.(9) Following AVR however there appears to be greater septal reverse remodeling in males, an improvement in contractility, with a greater reduction in NT-proBNP, and increases in blood pressure. Both inappropriately high LVM in response to AS, and the extent of reverse remodeling response post-AVR, particularly in women, have been associated with worse prognosis.(4,14,23) The observation of greater myocardial plasticity in males therefore supports a less favorable remodeling response to AS but one which is more modifiable with AVR. Conversely, remodeling in women, whilst less pronounced, is less likely to be reversed with AVR. This suggests that rather than a transition from concentric remodeling to a decompensated eccentric hypertrophic phenotype, there are different biological pathways between sexes.(11)

Mechanisms of sex differences in reverse remodeling

Greater hypertrophy, interstitial and focal fibrosis in males with AS(6,9,24) may be attributed to a different cardio-metabolic environment modulated by deregulation of muscle contraction genes,(25) less favorable cardiac metabolism,(24) background atherosclerosis, and the effect of sex hormones, itself modulated by ACE I/D polymorphism.(26) Given the females in our cohort were post-menopause, androgens may have a more important effect than estrogen. Testosterone is considered to have deleterious effects on cardiac remodeling resulting in excessive hypertrophy and increased fibrosis.(9,24) We however describe greater, potentially beneficial, ventricular plasticity in men than women post-AVR. This suggests that remodeling in men may be a more adaptive response to a more unfavorable cardio-metabolic environment. There are several genetic, animal and cell culture models that describe such beneficial hypertrophy to pressure overload,(27) and whilst testosterone promotes LV hypertrophy(28) it exerts a protective effect against apoptosis and necrosis.(29) Consistent with this, it has been reported that men are less likely to develop symptoms in AS but display a greater remodeling response.(13,30)

Differences in remodeling post-AVR have also been explained by aortic regurgitation,(12) patient prosthesis mismatch, and ACE I/D polymorphism. In our cohort, aortic regurgitation was similar between sexes and both mean and peak forward pressure gradients at baseline and follow-up were similar. There was a greater increase in indexed effective orifice area at follow-up in men, however area change is not linearly associated with LVM regression, and significant hemodynamic relief resulted in improved pressure gradients at follow-up in both sexes.

Why do we observe regional shape differences in aortic stenosis?

In all patients with AS compared to matched controls, concentric septal hypertrophy and eccentric lateral hypertrophy were noted, contributing to visually greater sphericity. Greater sphericity may increase wall stress and has been associated with mortality after myocardial infarction. Asymmetric septal hypertrophy has been observed for over forty years yet adequate explanations have still not been provided. In part this is because historically it has been difficult to quantify regional geometry accurately. Advanced 3D phenotyping of CMR data has shown that the septum appears to be particularly plastic in response to obesity and SBP.(20,31) The regional pattern of remodeling of concentric septal hypertrophy and eccentric lateral dilatation in AS has also been observed in response to pressure overload associated with rising SBP.(20) Sex differences in regional remodeling have also been observed in association with increased body fat, with women demonstrating more lateral eccentric hypertrophy.(31) This suggests either that the mechanical influences on LV remodeling are more complex than envisaged, or that there are non-mechanical mechanisms which modulate the myocardial response to mechanical load.(32) This work supports that of Becker in 1982 who noted that "the part of the septum underneath the aortic valve shows a very different fiber orientation",(33) namely a greater proportion of mid-wall circumferential fibers may contribute to a greater mechanical transduction of LV pressure, compounded by late electrical activation (which itself may be exaggerated in conduction disease present in AS). Adequate myocardial perfusion may also be necessary for hypertrophy,(34) and this also appears to show regional differences in AS and changes differentially in association with LV regression post-AVR.(35)

Study limitations

The differences we observed are in patients with severe symptomatic aortic stenosis and so do not reflect mild or moderate AS, where females have been noted to demonstrate greater plasticity.(6) Given that all patients recruited had severe AS and were awaiting AVR, further work validating the prognostic power of this approach will require expanding the population to include mild or moderate AS and incorporating motion analysis. Genetic, downstream metabolic variants, and medication were not accounted for and may contribute to the differences. Whilst aortic regurgitation was similar between sexes, aortic root morphology is different between sexes and subsequent variation in regurgitant flow pattern and direction may influence septal remodeling. Controls were healthy volunteers free of cardiovascular disease and prescription medication which may introduce bias. Whilst our approach is adequately powered,(21) short axis stack cine imaging requires base to apical smoothing to represent 3D geometry. We did not look at the association of 3D LV remodeling and clinical outcomes because permutation testing was limited to 3D LV metrics as the dependent variable.

Conclusion

In severe symptomatic AS, the septum is the most adaptive myocardium with greatest hypertrophy and regression one year post-AVR, even when global LV mass is normal. LV remodeling is greater in males than females and tracks clinical parameters, suggesting sex-specific responses to AVR. Changes are only detectable using a 3D phenotyping approach with machine learning, and may offer a more sensitive risk assessment in severe AS.

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Figure legends

Cover illustration Machine learning 3D phenotype assessment to identify sex differences in regional LV remodeling in aortic stenosis. Top: Imaging data is used to construct 3D ventricular models which are co-registered with follow-up studies. This approach permits regional analysis of shape and wall thickness. **Bottom:** Male patients have a greater hemodynamic, biochemical and remodeling response to aortic stenosis which is more modifiable with valve replacement.

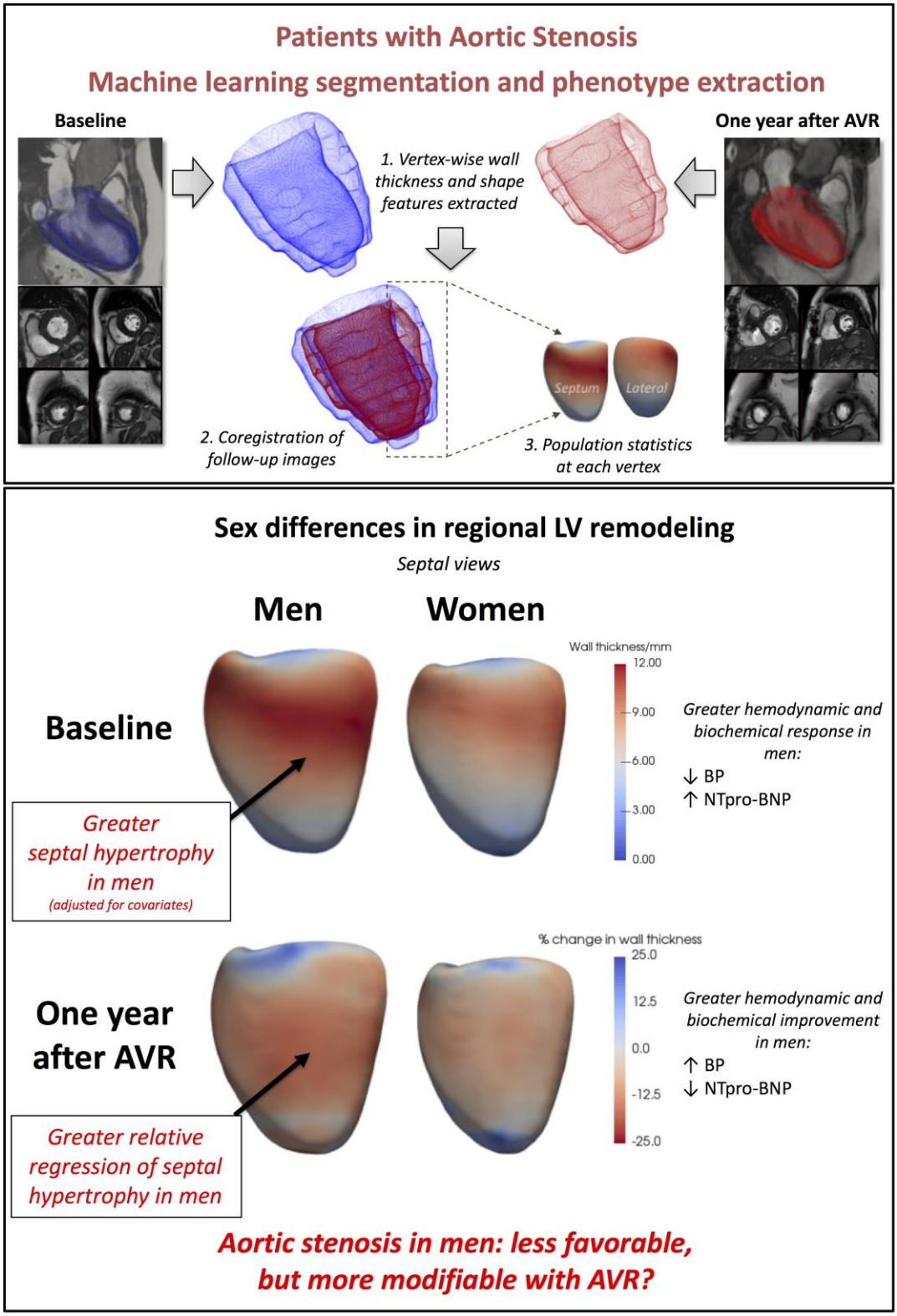
Figure 1 Left ventricular end-diastolic shape (1a) and wall thickness (1b) in patients with aortic stenosis versus matched controls. 1a Ventricular four chamber cross-cut showing a regional response of septal concentric and lateral eccentric hypertrophy (black contour = AS; red= matched controls). **1b** Mean shape and wall thickness are represented in en-face septal (top row) and lateral (bottom row) views for patients with aortic stenosis (left) and matched controls (right). Red= thicker wall (mostly septal). Yellow contour encloses 83% of the ventricular surface with $p<0.05$ after correction for multiple testing.

Figure 2 Sex difference in regional wall thickness in patients with aortic stenosis, septal (left) and lateral (right) en-face views. More positive standardized beta coefficients (red) demonstrate a more extensive remodeling response in males compared to females in the septum (ß 0.55, 56% ventricular surface). Yellow contour encloses 56% of the ventricular surface (positive beta coefficients, red region), $p<0.05$. Models adjusted for covariates.

Figure 3 Changes in remodeling categories at one year after aortic valve replacement (AVR), stratified by sex. All male versus female comparisons both before and post-AVR are statistically significant, $p<0.05$.

Figure 4 Percentage change in wall thickness at one year after aortic valve replacement in males (left) and females (right). The greatest percentage regression in wall thickness is in the mid septum for both sexes and it is more pronounced in males. Yellow contour encloses 8% of the ventricular surface with statistically significant greater wall thickness regression in males than females, $p<0.05$.

Figure 5 Left ventricular wall thickness in patients with aortic stenosis and normal baseline geometry, septal (left) and lateral (right) en-face views. There is relative inferior and septal hypertrophy compared to controls (red= thicker wall). Yellow contour encloses 46% of the ventricular surface, $p<0.05$.



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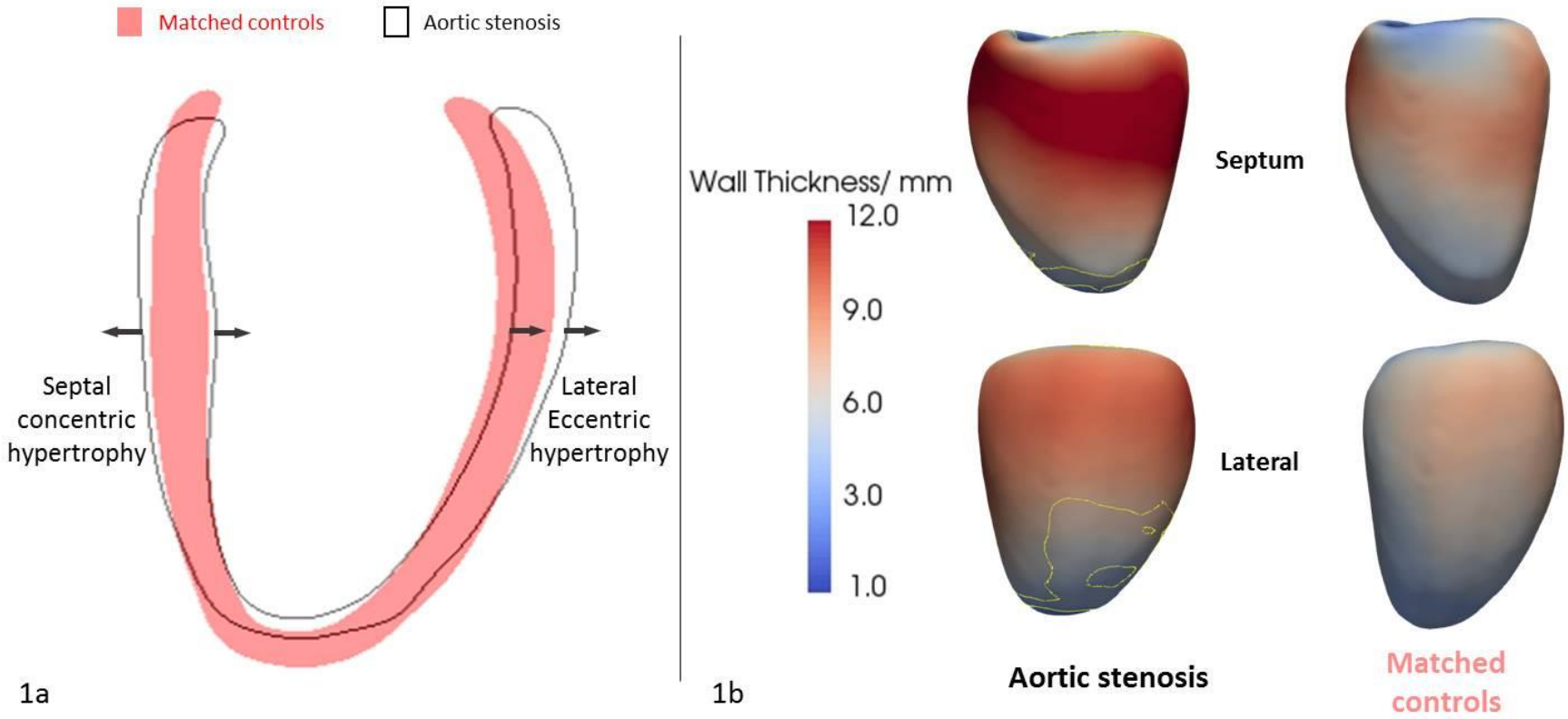

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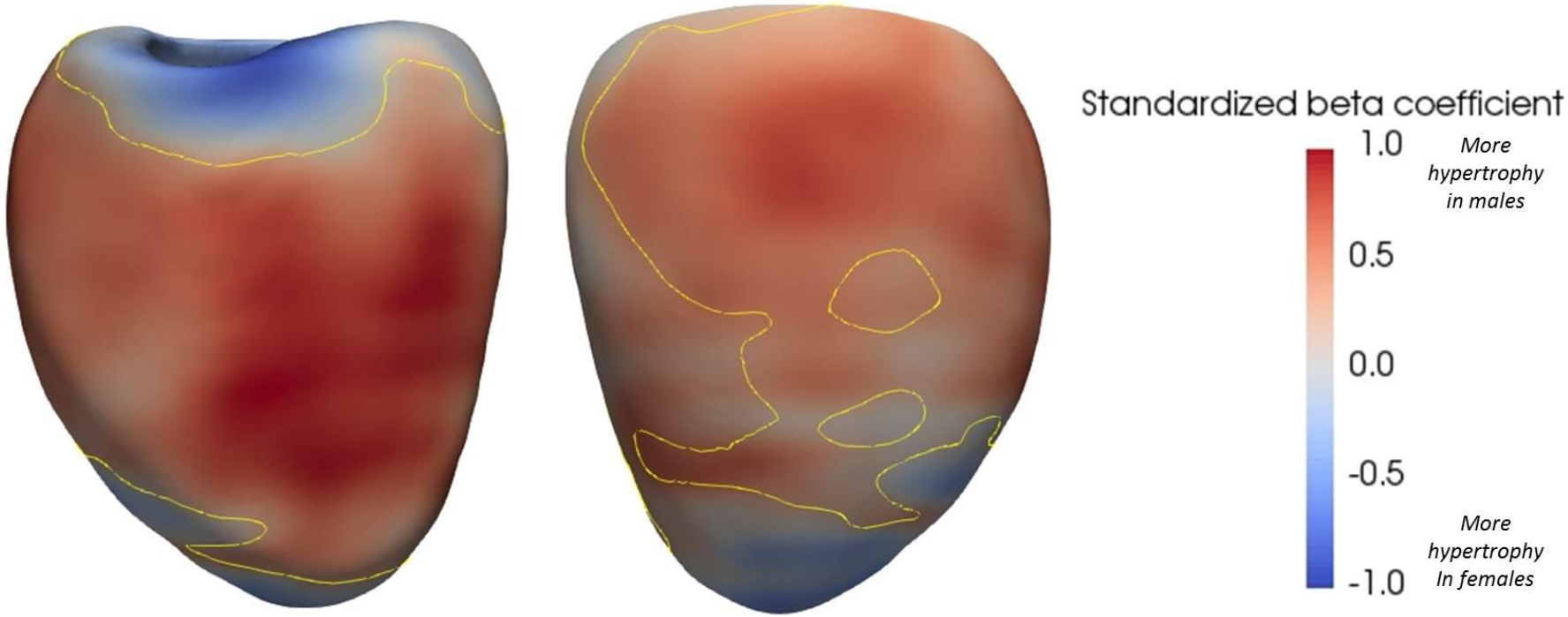

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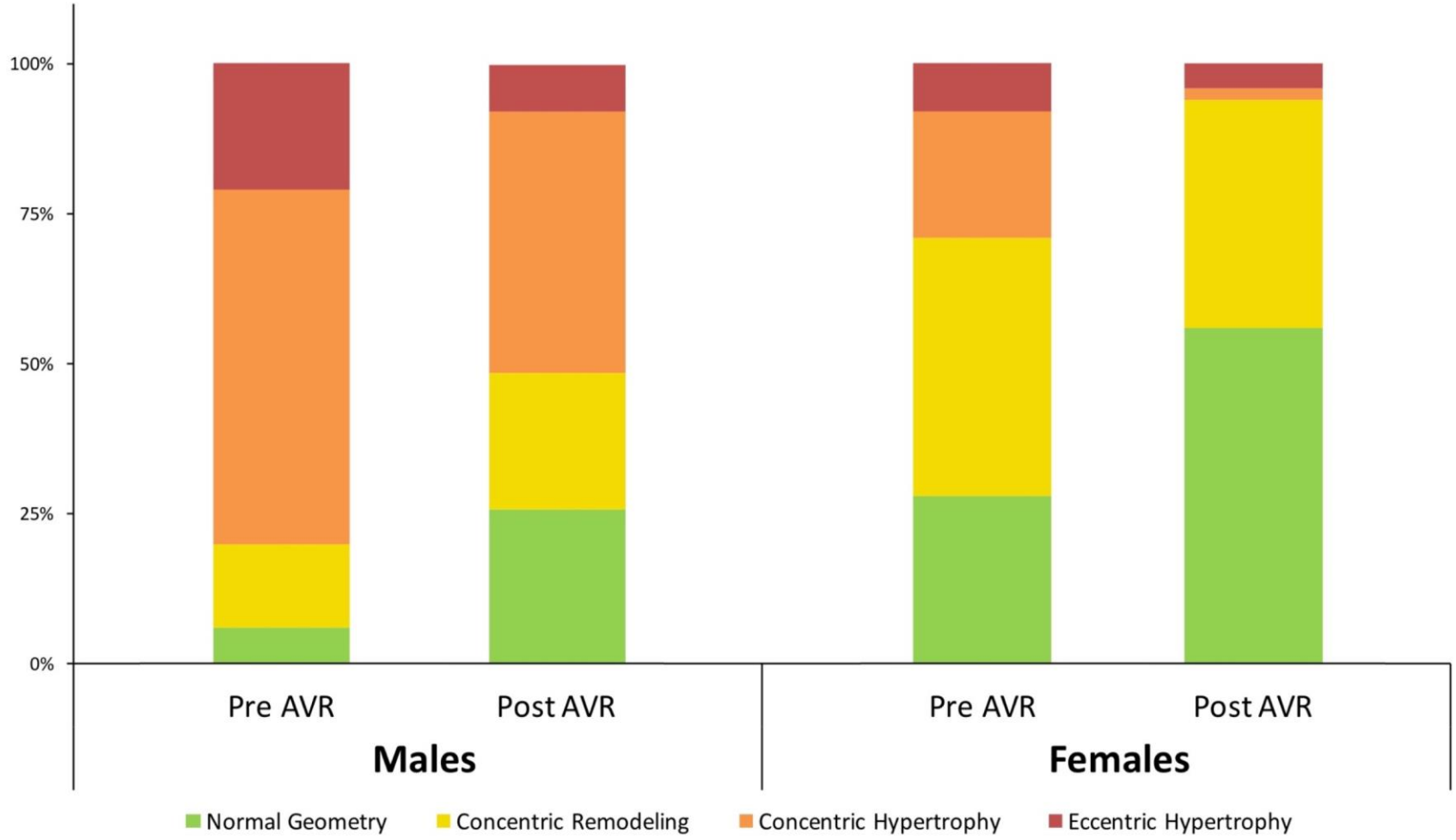

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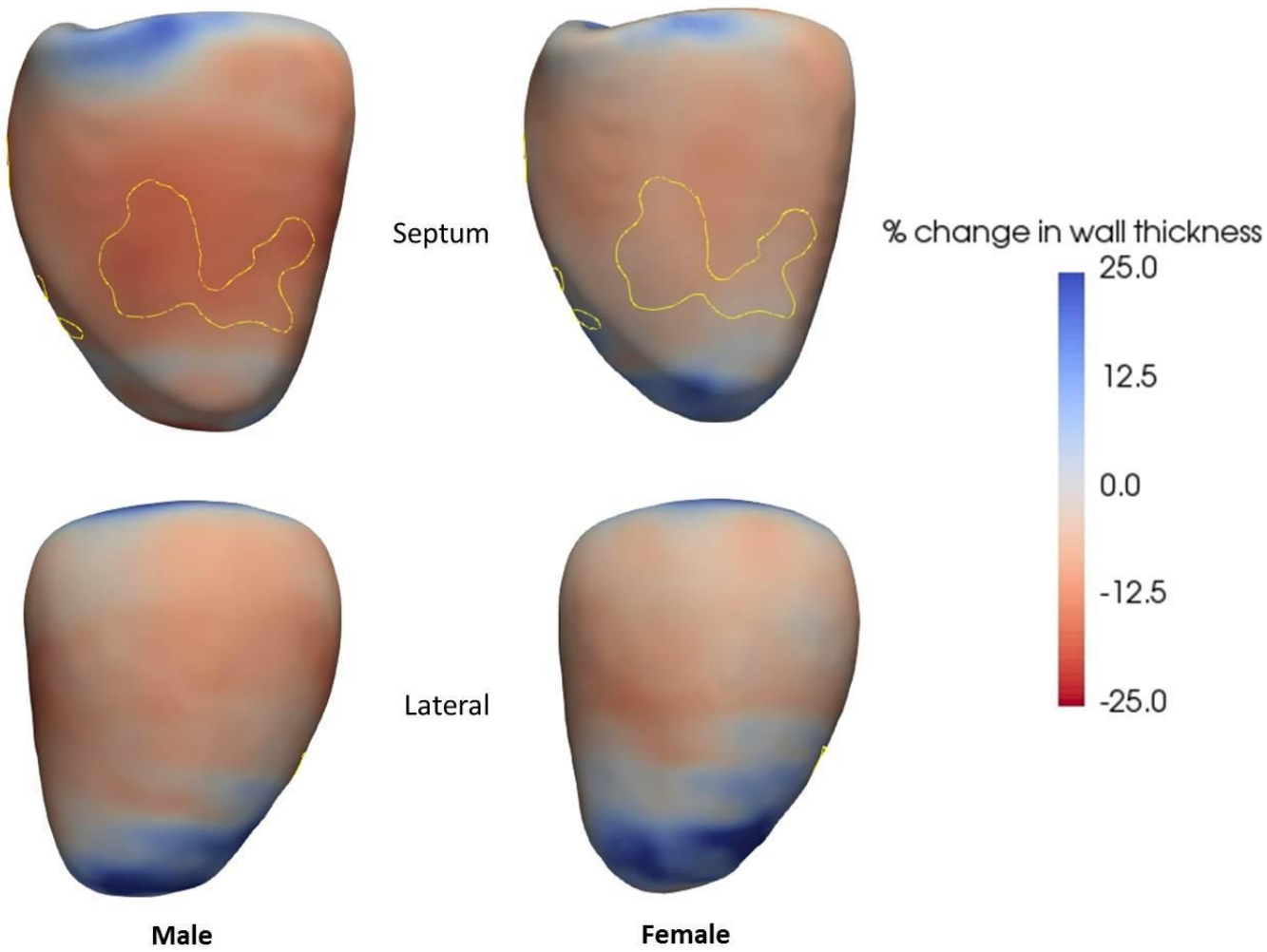

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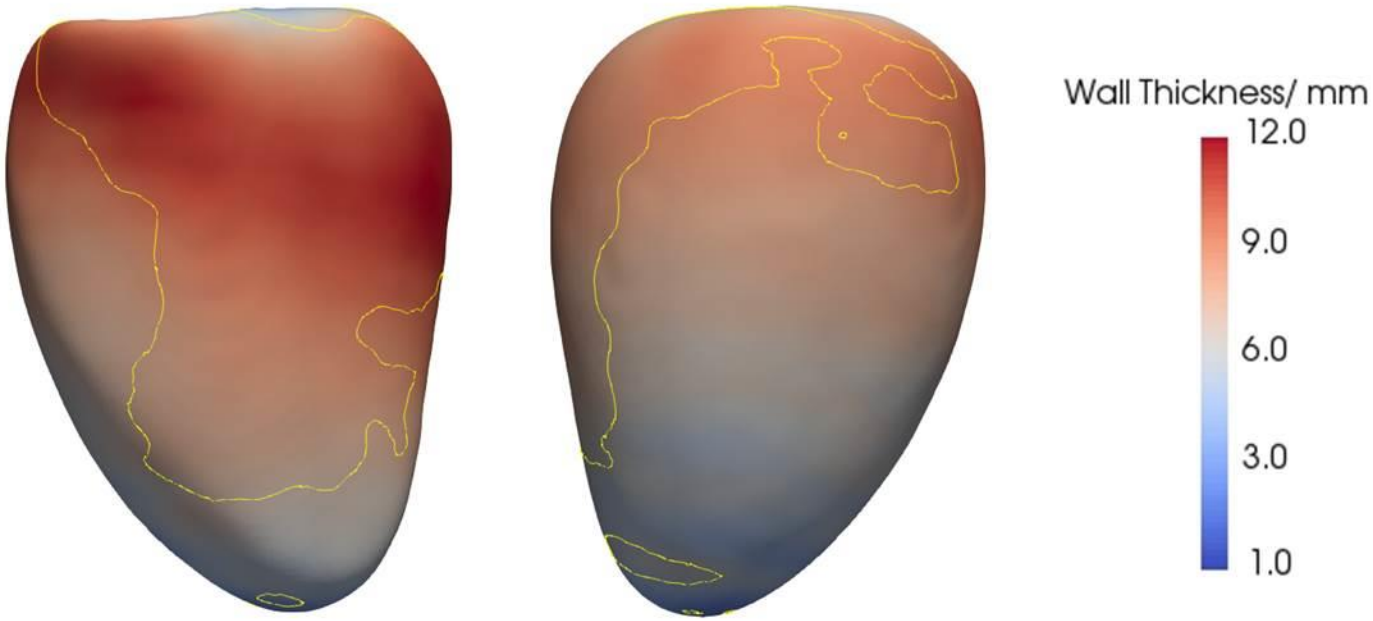

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Tables

Baseline characteristics					
	AS cohort	**Males**	**Females**	***p***	**Matched controls**
N	**116**	**63 (54%)**	**53 (46%)**		**40**
Male sex	63 (54%)				23 (58%)*
Age	70 ±9	68 ±11	71 ±8	*0.13*	65 ±7
BSA (m^2)	1.90 ±0.22	2.00 ±0.20	1.77 ±0.16	***<0.001***	1.86 ±0.20*
African Caribbean	1 1%	0 0%	1 2%		1 (3%) †
Bicuspid	33 (28%)	23 (37%)	10 (17%)	*0.06*	-
Hemodynamics					
SBP (mmHg)	133 ±17	129 ±17	137 ±16	***0.004***	126 ±17
DBP (mmHg)	76 ±10	74 ±9	77 ±12	*0.17*	80 ±8
Heart rate (bpm)	73 ±13	71 ±12	75 ±12	*0.08*	-
Comorbidities					
Hypertension (%)	75%	79%	71%	*0.45*	0%
Hypercholesterolemia (%)	64%	65%	64%	*0.99*	0%
Diabetes (%)	20%	21%	19%	*0.98*	0%
Coronary artery disease	29%	35%	21%	*0.14*	0%
Clinical status					
NYHA Functional Class	2.3 ±0.7	2.1 ±0.6	2.4 ±0.7	*0.07*	-
Six minute walk test (m)	472 ±184	533 ±163	399 ±183	***<0.001***	-
NT-proBNP (ng/L)	50 (26-173)	91 (31-286)	40 (25-105)	*0.059*	-
hs-TnT (pmol/L)	13 (9-20)	15 (11-24)	11 (7-16)	***<0.001***	-
Echocardiography					
AVA (cm^2)	0.75 ±0.26	0.77 ±0.29	0.72 ±0.22	*0.24*	-
AVAi (cm/m^2)	0.4 ±0.13	0.39 ±0.13	0.41 ±0.13	*0.36*	-
MPG (mmHg)	47.9 ±14.2	48.6 ±15.3	46.9 ±13	*0.92*	-
Vmax (m/s)	4.4 ±0.58	4.4 ±0.56	4.3 ±0.59	*0.51*	-
Mean E/E’ ratio	13.2 ±5.8	12.8 ±5.8	13.8 ±5.7	*0.41*	-
E/A ratio	0.94 ±0.49	1.00 ±0.61	0.87 ±0.29	*0.17*	-
Cardiovascular magnetic resonance					
LA volume indexed (mls)	54 ±19	56 ±21	51 ±17	*0.14*	-
Aortic Regurgitation (%)	10 (3-29)	13.5 (4-46)	9 (2-23)	*0.21*	-

Table 1 Baseline clinical characteristics. * no significant difference (p>0.05) between matched controls and patients with aortic stenosis. † No statistical comparison between controls and patients due to low frequencies. p values are for sex differences in patients with aortic stenosis, in **bold** are less than 0.05. Abbreviations: *AVA(i)= Aortic valve area (indexed to BSA); BSA = Body surface area; DBP = diastolic blood pressure; hs-TnT = high-sensitivity troponin T; LA = Left atrium volume indexed to BSA; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; MPG = mean pressure gradient; SBP = systolic blood pressure; Vmax = peak velocity through the aortic valve*

Changes in global LV metrics one year after aortic valve replacement							
	Total AS cohort	***p***	**Males**	***p***	**Females**	***p***	***p (sex difference)***
LVM (g)	-24.0 ±31.9	***<0.001***	-31.8 ±34.6	***<0.001***	-14.7 ±25.7	***<0.001***	***0.003***
LVMi (g/m^2)	-12.2 ±16.0	***<0.001***	-15.7 ±16.2	***<0.001***	-8.1 ±14.9	***<0.001***	***0.01***
% LVM	-12.7 ±16.2		-15.4 ±13.8		-9.6 ±18.2		*0.07*
LVEDV (ml)	-12.9 ±37.4	***<0.001***	-19.3 ±41.0	***0.001***	-5.3 ±31.2	*0.22*	***0.04***
LVEDVi (ml/m^2)	-6.2 ±19.1	***<0.001***	-9.4 ±19.2	***<0.001***	-2.4 ±18.3	*0.39*	*0.05*
% LVEDV	-4.1 ±21.6		-7.6 ±18.5		0.2 ±24.2		*0.06*
LVESV (ml)	-9.9 ±29.6	***<0.001***	-15.0 ±34.9	***0.001***	-3.8 ±20.3	*0.38*	***0.04***
LVESVi (ml/m^2)	-4.9 ±14.9	***<0.001***	-7.2 ±16.5	***0.002***	-2.0 ±12.2	*0.25*	*0.06*
% LVESV	-3.1 ±39.6		-8.8 ±36.2		3.7 ±42.7		*0.10*
LVEF (%)	2.0 ±10.0	***0.03***	3.2 ±11.2	***0.03***	0.7 ±8.4	*0.37*	*0.17*
MVR	-0.22 (-0.4,-0.05)	***<0.001***	-0.22 (-0.4,-0.04)	***<0.001***	-0.21 (-0.3,-0.07)	***<0.001***	*0.90*
ECV (%)	1.4 (-0.5,3.1)	***<0.001***	1.5 (-0.5,3.3)	***0.002***	1.1 (-0.7,3.0)	***0.003***	*0.34*
% ECV	4.8 (-1.9,11.9)		5.5 (-1.9,12.5)		4.1 (-2.6,11.1)		*0.41*
Matrix volume (g/m^2)	-3.3 (-0.6,-6.1)	***<0.001***	-4.0 (-1.5,-7.5)	***<0.001***	-1.9 (0.2,-4.8)	***<0.001***	***0.04***
% Matrix volume	-15.5 (-4.8,-24.3)		-16.6 (-6.6,-24.5)		-14.4 (-3.3,-23.9)		*0.41*
Cell volume (g/m^2)	-11.9 (-7.2,-19.2)	***<0.001***	-14.9 (-9.8,-22.2)	***<0.001***	-10.0 (-5.5,-15.1)	***<0.001***	***0.001***
% Cell volume	-19.8 (-13,-26.8)		-20.8 (-14,-29.6)		-18.6 (-12,-24.8)		*0.12*

Table 2 Changes in global left ventricular metrics one year after aortic valve replacement, stratified by sex. Changes in CMR parameters derived from atlas analysis, represented as mean±standard deviation or median (IQR). Abbreviations: ECV = extracellular volume fraction; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LVM(i)= Left ventricular mass (indexed to body surface area); MVR = mass to volume ratio; SV = stroke volume.