Sex-related differences in left ventricular remodeling in severe aortic stenosis and reverse remodeling following aortic valve replacement; a cardiovascular magnetic resonance study

Short title: Sex-related differences in aortic stenosis

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ABSTRACT

Background: Cardiac adaptation to aortic stenosis (AS) appears to differ according to sex but reverse remodeling following aortic valve replacement has not been extensively described. The aim of the study was to determine using cardiac magnetic resonance (CMR) imaging, whether any sex-related differences exist in AS in terms of left ventricular (LV) remodeling, myocardial fibrosis and reverse remodeling after valve replacement.

Methods: One hundred patients (men, n=60) with severe AS undergoing either trans-catheter or surgical aortic valve replacement underwent CMR scans at baseline and 6m following valve replacement.

Results: Despite similar baseline co-morbidity and severity of AS, women had a lower indexed LV mass than men (65.3± 18.4 vs. 81.5±21.3g/m^2, p<0.001) and a smaller indexed LV end diastolic volume (87.3±17.5 vs. 101.2±28.6ml/m^2, p=0.002) with a similar LV ejection fraction (LVEF) (58.6±10.2 vs. 54.8±12.9%, p=0.178). Total myocardial fibrosis mass was similar between sexes (2.3±4.1 vs. 1.3±1.1g, p=0.714) albeit with a differing distribution according to sex. Following aortic valve replacement, men had more absolute LV mass regression than females (18.3±10.6 vs. 12.7±8.8g/m^2, p=0.007). When expressed as a percentage reduction of baseline indexed LV mass, mass regression was similar between the sexes (men 21.7±10.1 vs. women 18.4±11.0%, p=0.121). There was no sex-related difference in post-procedural LVEF or aortic regurgitation. Sex was not found to a predictor of LV reverse remodelling on multiple regression analysis.

Conclusions: There are significant differences in the way that male and female hearts adapt to AS. 6m following aortic valve replacement, there are no sex-related differences in reverse remodeling, but superior reverse remodeling in men as a result of their more adverse remodeling profile at baseline.

Key words: Aortic Valve Stenosis, Sex, Hypertrophy, Heart Valve Prosthesis Implantation, Aortic Valve Disease, Gender

ABBREVIATIONS

AR	Aortic regurgitation
AS	Aortic stenosis
AVAi	Indexed aortic valve area
AVR	Aortic valve replacement
BSA	Body surface area
CABG	Coronary artery bypass grafting
CMR	Cardiac magnetic resonance
COPD	Chronic obstructive pulmonary disease
EuroSCORE	European System for Cardiac Operative Risk Evaluation
LA	Left atrial
LAVoli	Indexed left atrial volume
LGE	Late gadolinium enhancement
LV	Left ventricular
LVEDVi	Indexed left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESVi	Indexed left ventricular end systolic volume
LVMi	Indexed left ventricular mass
MF	Myocardial fibrosis
MR	Mitral regurgitation
NYHA	New York Heart Association
RF	Regurgitant fraction
SAVR	Surgical aortic valve replacement
SD	Standard deviation
SSFP	Standard steady-state free procession
TAVR	Trans-catheter aortic valve replacement

INTRODUCTION

Sex related differences in left ventricular (LV) remodeling in response to a wide range of diseases have been extensively explored[1], but the impact of sex on aortic stenosis (AS) and following aortic valve replacement (AVR) is less well described. AS is the commonest valve lesion in the developed world, and with an ageing population its incidence is increasing[2]. AVR has been shown to reduce mortality, and improve patient symptoms and health related quality of life[3-5]. Evidence suggests that women have higher pre-operative morbidity and mortality[6], and lower referral rates[7]. It remains controversial as to whether sex impacts on survival following surgical aortic valve replacement (SAVR)[8], however, females appear to have improved long term survival following trans-catheter aortic valve replacement (TAVR)[8-10]. The longer life expectancy of women or other factors such as LV remodeling and myocardial fibrosis (MF) may be implicated. Echocardiographic and Cardiac Magnetic Resonance (CMR) studies suggest that men and women remodel differently to the pressure overload of AS[11, 12] and may also reverse remodel differently following AVR[13, 14]. CMR imaging is the reference standard for LV mass and volume quantitation, with low intra-observer and inter-study variability. Moreover, sex-related differences in MF may play a key role in any reverse remodeling[15]. This can be accurately quantified non-invasively using the CMR late gadolinium enhancement (LGE) technique. The primary aim of this study was to determine whether any sex-related differences exist in severe AS in terms of LV remodeling, reverse remodeling after valve replacement and MF.

METHODS

Between January 2009 and April 2014, 135 patients (men, n=79 (59%), mean age 77±8) with severe AS undergoing either SAVR with or without concomitant coronary artery bypass grafting (CABG) or TAVR at a single tertiary centre (Leeds General Infirmary, Leeds, UK) were prospectively recruited (Figure 1). Severe AS was defined as an echocardiographically derived aortic valve area of ≤1.0cm^2, peak aortic velocity of >4m/sec or mean pressure gradient of >40mmHg[16]. Decision for aortic valve intervention was made by the multi-disciplinary heart team in accordance with international

guidelines [17]. Patients with contraindications to CMR were excluded. All patients provided written informed consent. The study was approved by the institutional ethics committee and complied with the declaration of Helsinki. This study was part-funded by the National Institute for Health Research Leeds Clinical Research Facility. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

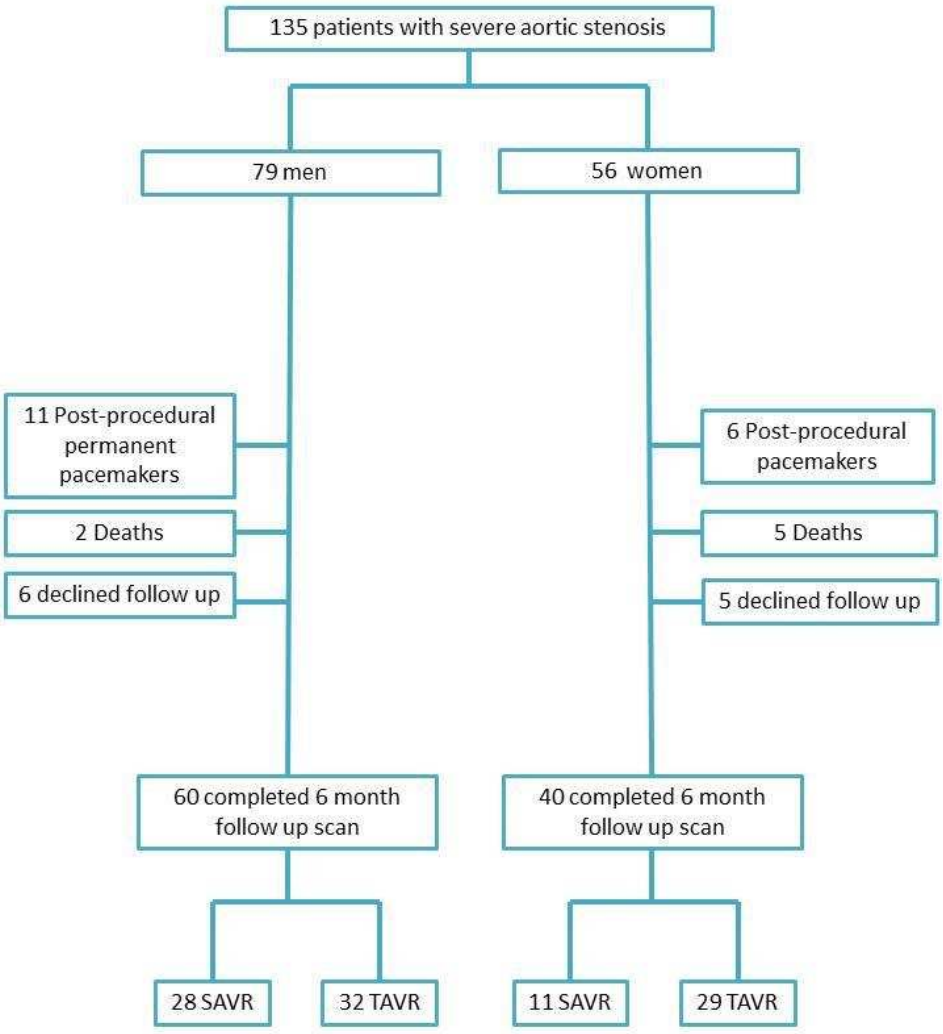

Figure 1. Patient recruitment pathway. SAVR: surgical aortic valve replacement, TAVR: Trans-catheter aortic valve replacement.

Aortic valve replacement

SAVR was performed in a standard manner on cardiopulmonary bypass via a midline sternotomy incision and mild systemic hypothermia using intraoperative transesophageal echocardiography guidance. Following standard heparinization the aorta was cross-clamped and cardiopulmonary bypass was initiated. The size and type of prosthesis was chosen according to annulus size, patient characteristics, surgical and patient preference. Concomitant coronary artery bypass was performed where indicated. TAVR was performed under general anaesthetic with X-ray fluoroscopy and TEE guidance using the self-expanding Medtronic CoreValve (Medtronic Inc., Minneapolis, Minnesota) or the mechanically expanded Boston Lotus valve (Boston Scientific Corporation, Natick, MA) via the femoral or subclavian route by two experienced, high-volume operators. All patients received heparin to maintain an activated clotting time >250s and were treated with dual anti-platelet therapy (aspirin and clopidogrel) for 3-6 months post-procedure.

CMR protocol

Identical CMR scans were obtained on the same imaging platform at baseline and at a median of 6 months (Q1-Q3 5-6 months) following aortic valve replacement using a 1.5T scanner (Intera, Philips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). Multi-slice, multi-phase cine imaging was performed using a standard steady-state free procession (SSFP) pulse sequence in the short axis (8mm thickness, 0mm gap, 30 phases, typical field of view 340mm) to cover both ventricles. Standard 4 chamber long axis and 2 chamber SSFP cine images were also acquired for measurement of atrial volume. Through-plane velocity encoded phase contrast (VENC) imaging was performed perpendicular to the aortic valve jet at the aortic sinotubular junction (VENC 250-500cm/sec, retrospective gating, slice thickness 6mm, 40 phases). LGE imaging (10-12 short axis slices, 10mm thickness, matrix 240x240) was performed with inversion time (TI) individually adjusted

according to TI scout, 10-15 minutes after the administration of 0.2mmol/kg of gadoteric acid (Dotarem, Guerbet, Villepinte).

CMR analysis

CMR analysis was performed by a single operator (LED) with 5 years' experience in CMR blinded to clinical data. Endocardial and epicardial borders were manually contoured at end-diastole and end-systole with papillary muscles and trabeculations excluded to allow the calculation of ventricular volumes (summation of discs methodology) and mass (epicardial volume – endocardial volume multiplied by myocardial density (1.05g/cm3)).. Values were indexed to body surface area (BSA). For analysis of the LGE images, each slice was visually inspected for the presence or absence of LGE, which was then categorised as either infarct pattern or focal/mid-wall pattern. In those slices positive for LGE, automated quantification was performed using dedicated computer software (cmr[42], Circle Cardiovascular Imaging Inc, Calgary, Alberta, Canada) using a threshold of 5 standard deviations method[18]. Left atrial area and length at end-systole was measured in the 4 chamber and 2 chamber cine views and a volume calculated based on the biplane area-length method[19]. Maximal septal and lateral wall thickness were measured at end diastole on the mid-ventricular short axis cine using electronic calliper measurement tools. Aortic flow was quantified using cross-sectional VENC images with contouring of the aortic lumen to provide a regurgitant fraction (%). Significant aortic regurgitation was defined as a regurgitant fraction >16%[20]. Mitral regurgitant fraction (%) was calculated using the equation: (LV stroke volume–aortic stroke volume/LV stroke volume*100. Significant mitral regurgitation was defined as a regurgitant fraction >40%[21]. The intraclass correlation (ICC) for LGE quantification was 0.995 for intraobserver variability and 0.979 for interobserver variability.

Statistical analysis

All statistical analyses were performed using the PASW software package (V21, SPSS, IBM, Chicago, Illinois, USA). Data are presented as mean±SD, median (Q1-Q3) or frequency (percentage). After testing for normality using the Shapiro-Wilks test, differences between means were evaluated using paired and unpaired (for independent group comparisons) Students *t* test for normally distributed data and the Mann Whitney or Wilcoxon signed rank test on non-parametric data. The Chi-squared test was used for comparing categories of data. Pearson correlation coefficients were used to investigate the relationship of aortic regurgitation to baseline cardiac remodeling. A two sided $P<0.05$ was considered statistically significant. Linear regression analysis was used to identify the main predictors of LV reverse remodeling and to derive parameter estimates for those predictors and for the differences in sex. Univariate regression analysis was performed using baseline measurements entered as covariate factors. All clinically significant variables and those with a $p<0.1$ on univariate analysis were subject to exploratory analysis to exclude those with weak or no correlation with the dependent variable, before entering them into a stepwise multiple linear regression model to identify the main predictor or combination of predictors in a multivariable model.

RESULTS

Study participants

135 patients were recruited into the study. 60 men and 40 women with severe AS completed both baseline and 6-month post-procedure CMR scans. Reasons for non-completion were varied and are depicted in Figure 1. There was no significant difference between the group that completed the 6 month CMR protocol and those that did not in terms of age (77±7 vs. 79±7yrs, p=0.267), baseline indexed aortic valve area (AVAi) (0.35±0.09 vs. 0.35±0.10cm/m^2, p=0.928), and European System for Cardiac Operative Risk Evaluation (EuroSCORE) II (4.04±4.27vs.4.96±3.60, p=0.257) indicating that the demographics of the analysed patients were representative of the larger population. Baseline demographic, clinical and echocardiographic characteristics of the final study population can be seen in Table 1.

	Total (n=100)	Men (n=60)	Women (n=40)	P value for sex difference
Age at intervention, years	77. ± 8	75 ± 7	80±9	0.004
Length of stay, days	8.3±4.7	7.9±3.0	8.8±6.5	0.883
BSA, m^2	1.86 ± 0.2	1.96 ± 0.18	1.71 ± 0.16	<0.001
Systolic blood pressure, mmHg	131 ± 23	129 ± 22	134 ± 24	0.20
NYHA (median)	2.9 ± 0.6, (3)	2.9 ± 0.6 (3)	3.0 ± 0.6 (3)	0.724
EuroSCORE II, %	4.0 ± 4.3	3.9 ± 3.7	4.5 ± 5.1	0.340
Hypertension	55 (55)	31 (52)	24 (60)	0.412
Hypercholesterolemia	67 (67)	44 (73)	23 (57.5)	0.10
Diabetes	21 (21)	11 (18)	10 (25)	0.42
Atrial Fibrillation	19 (19)	13 (22)	6 (15)	0.41
Previous myocardial infarction	15 (15)	9 (15)	6 (15)	1
Previous CABG	19 (19)	14 (23)	5 (12.5)	0.176
Any epicardial coronary artery stenosis >50%	53 (53)	38 (63)	15 (38)	0.011
Pulmonary hypertension	24 (24)	15 (25)	9 (22.5)	0.774
Peripheral vascular disease	16 (16)	11 (18)	5 (12.5)	0.436
Cerebrovascular disease	15 (15)	11 (18)	4 (10)	0.253
COPD	16 (16)	13 (22)	3 (7.5)	0.058
Indexed aortic valve area, cm/m^2	0.35 ± 0.09	0.35 ± 0.09	0.35 ± 0.10	0.928
Peak aortic velocity, m/sec	4.6±0.6	4.6±0.5	4.6±0.6	0.838
Mean pressure gradient, mmHg	48±13	48±12	49±14	0.974

Table 1. Baseline demographic, clinical and echocardiographic characteristics. BSA: Body surface area. BMI: Body mass index. NYHA: New York Heart Association classification. CABG: Coronary artery bypass grafting. COPD: Chronic obstructive pulmonary disease.

Baseline CMR left heart measurements

At baseline, women with severe AS had lower indexed LV mass (LVMi) than men (65.3± 18.4 vs. 81.5±21.3g/m^2, p<0.001) alongside smaller indexed LV end diastolic (LVEDVi) (87.3±17.5 vs. 101.2±28.6ml/m^2, p=0.002) and end systolic (LVESVi) (37.3±16.6 vs. 47.9±25.6ml/m^2, p=0.036) volumes. A typical example of the different patterns of remodeling can be seen in Figure 2. Further baseline differences according to sex can be seen in Table 2. Men had more aortic regurgitation (AR) at baseline (regurgitant fraction (RF) men 15.1±12.4 vs. women 9.6±9.2%, p=0.013). Significant AR at baseline was seen in 23 (38%) men and 7 (18%) women (p=0.026). There was a significant correlation

between baseline LVMi and AR fraction in men (r=0.455, p<0.01) and in women (r=0.577, p<0.001). There was also a relationship between AR fraction and LVEDVi in men (r=0.433, p<0.001), but not in women (r=0.140, p=0.400). When those with significant baseline AR were excluded, men still had greater LVMi than women (LVMi men 77.1±16.5 vs. women 61.9±13.8g/m^2, p=<0.001). Mitral regurgitation (MR) was similar for both sexes (RF men 33.8±19.8 vs. women 26.9±21.3%, p=0.09). Significant mitral regurgitation was seen in 24 (40%) men and 10 (25%) women at baseline (p=0.121). Baseline mitral regurgitant fraction was significantly associated with baseline LVMI and LVEDVi on univariate analysis, but was not found to be an independent predictor of baseline remodelling on multivariate analysis (Supplementary Table 1). Sex and baseline aortic and mitral regurgitation fraction were univariate predictors of baseline LVMi and baseline LVEDVi (Supplementary Table 1). Sex and baseline AR remained independent predictors of baseline LVMi on multiple regression analysis. Only baseline AR fraction was an independent predictor of baseline LVEDVI (Supplementary Table 2).

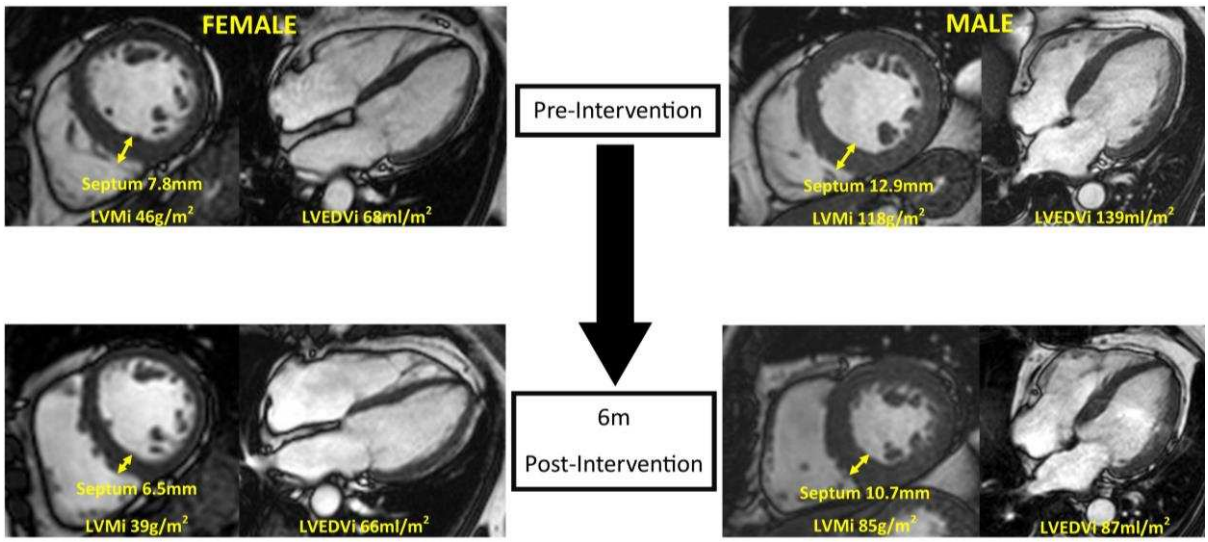

Figure 2. Short axis and 4 chamber cardiac magnetic resonance images of the left ventricle acquired at end diastole. The left sided panel depicts the typical female ventricle in severe aortic stenosis with a lower left ventricular (LV) mass and a small LV cavity size (top image) and subsequent LV mass regression 6 months (bottom image). The right hand panel shows a typical male pattern of remodeling with increased LV cavity size and greater LV mass at baseline (top image) and then reverse remodeling 6 months following valve replacement (bottom image). Both male and female ventricles exhibit reverse remodeling with LV mass regression 6 months following valve replacement.

	Total n=100	Men n=60	Women n=40	P Value for sex difference
LVMi, g/m^2				
Pre-intervention	75.1± 21.6	81.5±21.3	65.3±18.4	<0.001
Post-intervention	59.0±15.9	63.2±15.8	52.6±14.0	<0.001
P Value	<0.001	<0.001	<0.001	
LVM/LVEDV				
Pre-intervention	0.80±0.16	0.82±0.15	0.76±0.17	0.068
Post-intervention	0.69±0.15	0.72±0.15	0.65±0.14	0.006
P Value	<0.001	<0.001	<0.001	
Septal thickness, mm				
Pre-intervention	12.2±3.1	13.3±2.8	10.5±2.8	<0.001
Post-intervention	10.5±2.7	11.2±2.6	9.3±2.5	<0.001
P Value	<0.001	<0.001	<0.001	
Lateral wall thickness, mm				
Pre-intervention	8.0±2.2	8.6±2.1	7.1±2.1	<0.001
Post-intervention	7.0±1.9	7.8±1.8	5.9±1.6	<0.001

P Value	<0.001	0.001	<0.001	
Septal:Lateral wall thickness ratio				
Pre-intervention	1.58±0.41	1.56±0.36	1.55±0.48	0.458
Post-intervention	1.57±0.47	1.49±0.38	1.68±0.58	0.174
P Value	0.314	0.020	0.270	
LVEDVi, ml/m^2				
Pre-intervention	95.6 ±25.6	101.2±28.6	87.3±17.5	0.020
Post-intervention	86.5±20.7	89.6±21.2	81.9±19.2	0.075
P Value	<0.001	<0.001	0.019	
LVESVi, ml/m^2				
Pre-intervention	43.7±23.0	47.9±25.6	37.3±16.6	0.036
Post-intervention	37.9±17.1	40.1±17.1	34.4±16.9	0.045
P Value	<0.001	<0.001	0.088	
LVEF, %				
Pre-intervention	56.4±12.1	54.8±12.9	58.6±10.6	0.177
Post-intervention	58.0±10.8	56.5±10.5	60.2±11.0	0.042
P value	0.021	0.093	0.129	
LA Voli, ml/m^2				
Pre-intervention	67.2±20.8	67.8±21.8	66.2±19.3	0.578
Post-intervention	62.3±20.9	60.1±20.5	65.7±21.3	0.136
P Value	<0.001	<0.001	0.477	
Absolute myocardial fibrosis mass (g)				
Pre-intervention	2.0±3.3	2.3±4.1	1.3±1.1	0.714
Post-intervention	1.6±3.9	2.3±4.7	0.4±0.8	0.034
P value	0.022	0.412	0.010	
Myocardial fibrosis (% LV mass)				
Pre-intervention	1.2±1.5	1.2±1.8	1.2±1.1	0.435
Post-intervention	1.2±2.4	1.6±2.9	0.5±0.9	0.114
P Value	0.263	0.716	0.026	
Aortic maximum pressure gradient, mmHg				
Pre-intervention	42±36	46±43	36±16	0.171
Post-intervention	21±12	21±11	20±13	0.323
P value	<0.001	<0.001	<0.001	

Table 2. Cardiac magnetic resonance data pre and post intervention grouped according to sex.

LVMi: Indexed left ventricular mass. LVEDVi: Indexed left ventricular diastolic volume. LVESVi: Indexed left ventricular end systolic volume. LVEF: Left ventricular ejection fraction. LA Voli: Indexed left atrial volume. LV: Left ventricular.

Post-valve replacement

There was a similar length of post-procedure hospital stay between sexes (men 8±3 vs. women 9±7days, p=0.883). Reverse remodeling parameters according to sex can be seen in Table 2 and Figure 3. Following valve replacement there was a significant reduction in LVMi in both groups. Men experienced greater absolute LV mass regression than women (18.3±10.6 vs. 12.7±8.8g/m^2, p=0.007), however, when expressed as a percentage reduction of baseline LVMi, mass regression was similar between the sexes (men 21.7±10.1 vs. women 18.4±11.0%, p=0.121). A sex-related difference in LVMi regression was still evident when those with significant baseline AR were excluded from the analysis (men 16.2±10.4 vs. women 11.4±8.2g/m^2, p=0.034).

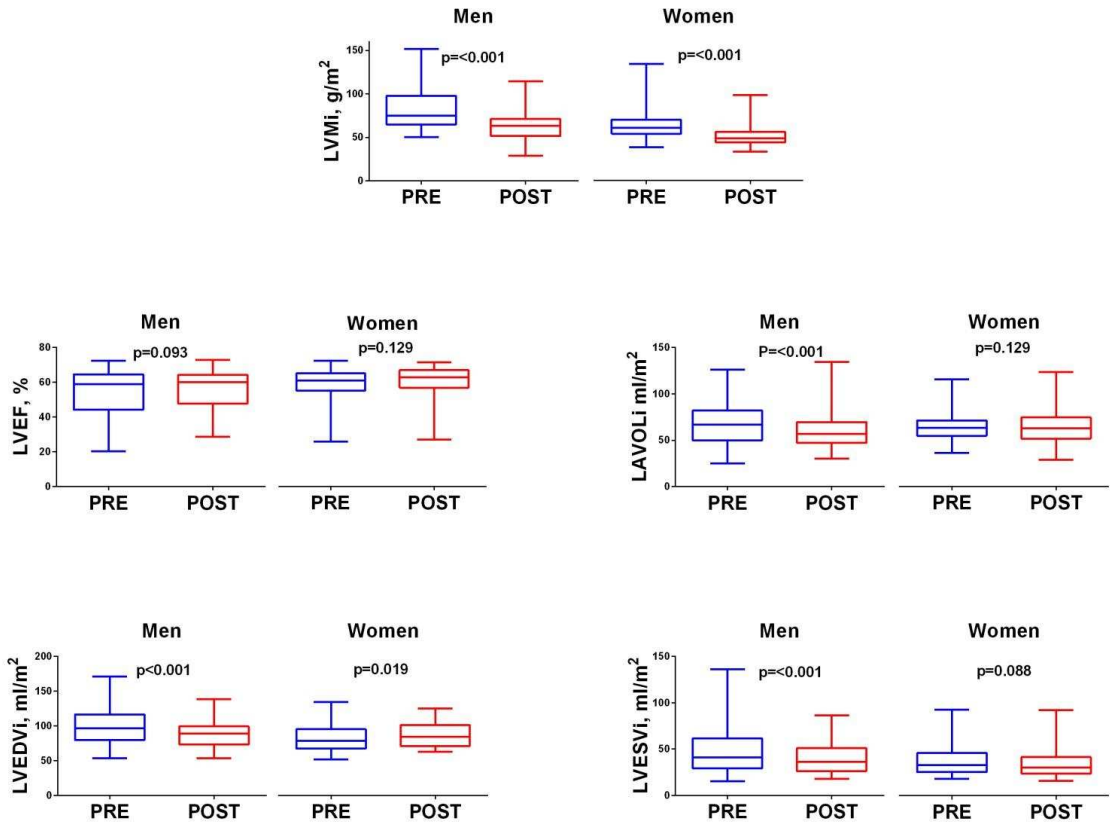

Figure 3. Values according to sex pre and post aortic valve replacement. Boxplots show median values (line within box), 50th percentile values (box outline) and maximum and minimum values (whiskers). LVMi: Indexed left ventricular mass. LVEF: Left ventricular ejection fraction. LAVOLi: Indexed left atrial volume. LVEDVi: Indexed left ventricular end diastolic volume. LVESVi: Indexed left ventricular end systolic volume.

There was no sex-related difference in post-procedural AR (RF men 8.4±8.0% vs women 6.9±6.8%, p=0.406). Significant post-procedural AR was seen in 9 (15%) men and 4 (10%) of women (p=0.347). Men experienced a significant reduction in MR following valvular intervention whereas women did not (men 33.8±19.8 to 17.6±18.1%, p<0.001, women: 26.9±21.3 to 20.5±19.6%, p=0.102). Significant post-procedural MR was seen in 5 (8%) of men and 6 (15%) women (p=0.297).

Results according to sex and procedure type can be seen in supplementary Table 3.

Myocardial fibrosis

LGE imaging was available for 95 patients. 5 patients (male, n=4) were not given a Gadolinium-based contrast agent due to pre-existing renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2. Patients were classified at baseline according to whether they had no LGE (men n=14 (25%), women n=16 (41%)), infarct pattern LGE (men n=14 (25%), women n=7 (18%)) or mid-wall/focal fibrosis pattern LGE (men n=28 (50%), women 16 (41%)).

The presence or absence of infarct pattern LGE did not impact on change in LVEF (men: infarct-LGE(+) 4.8±7.3 vs. infarct-LGE(-) 0.7±8.0%, p=0.099; women: infarct-LGE(+) 2.6±3.4 vs. infarct-LGE(-) 1.4±7.1%, p=0.670) or LVEDVi (men: infarct-LGE(+) 13.4±22.6 vs. infarct-LGE(-) 11.0±19.8ml/m^2, p=0.702; women: infarct-LGE(+) 3.7±19.4 vs. infarct-LGE(-) 5.8±13.1ml/m^2, p=0.726).

Of the patients with mid-wall fibrosis pattern LGE at baseline, there was a different distribution according to sex (Figure 4) but comparable total amounts when expressed as a percentage of LV mass (Table 2). Following valve replacement, only women experienced a significant reduction in total fibrosis burden both in absolute terms (men 2.3±4.1 to 2.3±4.7g, p=0.412, women 1.3±1.1 to 0.4±0.8g, p=0.010) and as a percentage of LV mass (men 1.2±1.8 to 1.6±2.9%, p=0.716, women 1.2±1.1 to 0.5±0.9%, p=0.026). The presence (MF(+)) or absence of MF (MF(-)) did not impact on change in LVEF (men: MF(+) 1.2±9.3 vs. MF(-) 2.6±6.5%, p=0.292; women: MF(+) 2.4±9.3 vs. MF(-) 1.2±3.9%, p=0.767),

LVEDVi (men: MF(+) 13.5±19.4 vs. MF(-) 12.1±21.0ml/m^2, p=0.823; women: MF(+) 13.4±19.4 vs. MF(-) 12.1±21.0ml/m^2, p=0.053) or LVMi (men: MF(+) -17.7±10.0 vs. MF(-) -19.4±11.6g/m^2, p=0.936; women: MF(+) -14.7±6.8 vs. MF(-) -11.8±9.9 vs. -14.7±6.8g/m^2, p=0.311).

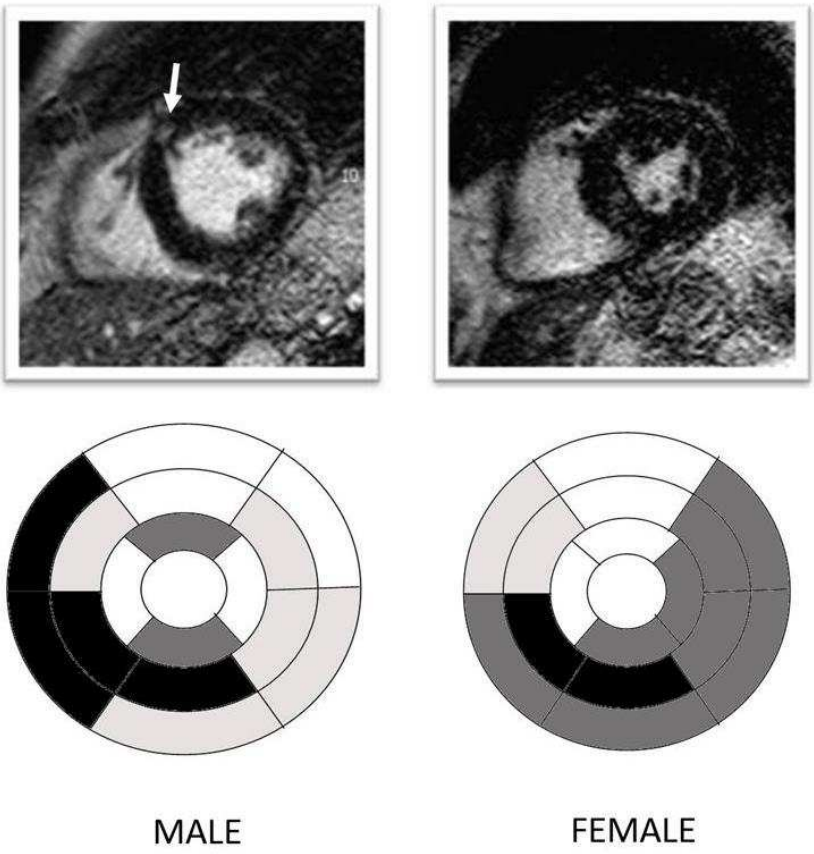

Figure 4. The distribution and frequency of focal mid-wall MF for 28 men and 16 women with severe AS as represented using the 17-segment American Heart Association (AHA) model. Focal fibrosis was greatest in the basal and septal regions in men (arrow) whereas women appeared to have a more varied distribution. The shaded diagram represents the proportion of patients with fibrosis in each numbered segment; <4% white, 4-8% light grey, 8-12% dark grey, >12% black.

Predictors of reverse remodeling

Clinical variables including patient demographics, co-morbidities and pre-operative cardiac measurements were analysed to determine predictors of reverse remodeling. These variables were each used as dependent variables in linear regression analysis. Results of the univariate analysis can be seen in Supplementary Table 1. For every dependent variable, the baseline level of the same measure emerged as the main predictor in a multivariable model. The relationship between each dependent and its baseline level is shown in Figure 5. Sex was only implicated as a factor for left atrial reverse remodeling but did not appear to influence LV reverse remodeling, and its inclusion in the multivariable model had minimal impact on the parameter estimates for the relevant baseline. Procedure type or the presence of coronary artery disease did not appear to predict reverse remodeling on univariate analysis. Baseline aortic regurgitation fraction was an independent predictor of change in LVMi alongside baseline LVMi, but was not an independent predictor in the multivariate model for any other reverse remodelling parameter. Results of the multiple regression analysis can be seen in Supplementary Table 2.

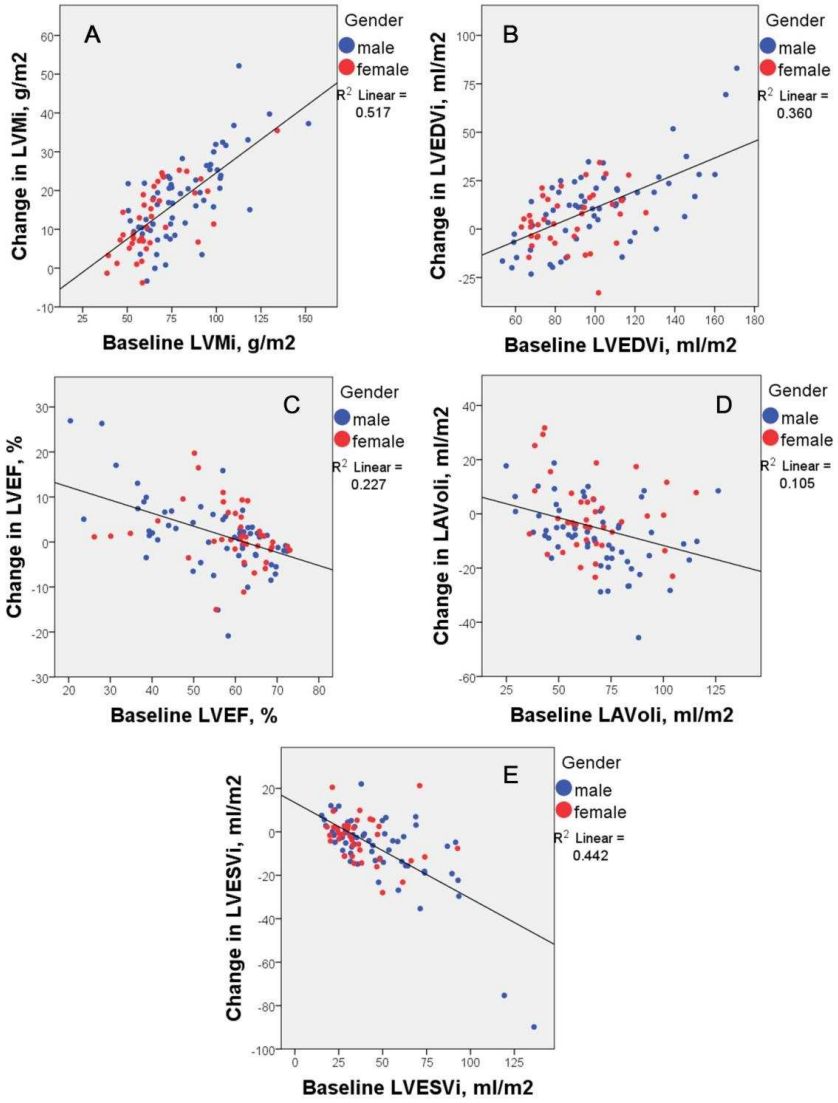

Figure 5. Relationship between cardiac reverse remodeling parameters following aortic valve replacement and baseline parameters displayed according to sex. A. Relationship between change in indexed LV mass (LVMi) and baseline LVMi. B. Relationship between change in indexed LV end diastolic volume (LVEDVi) and baseline LVEDVi. C. Relationship between change in LV ejection fraction (LVEF) and baseline LVEF. D. Relationship between change in indexed left atrial volume (LAVoli) and baseline LAVoli. E. Relationship between change in indexed left ventricular end systolic volume (LVESVi) and baseline LVESVi.

DISCUSSION

This study is the first using the reference standard of CMR to accurately assess the influence of sex on differences in LV remodeling in AS and the impact on reverse remodeling following AVR.

Our baseline CMR results demonstrating differing patterns of ventricular remodeling in response to AS are consistent with the published echocardiographic and CMR literature[11, 12, 22]. We have demonstrated that men and women with severe AS and similar co-morbidities remodel in different ways; women exhibit lower LV mass with a smaller LV cavity size, whereas men are prone to the development of a larger cavity size, greater LV wall thickness and increased LV mass. This pattern of remodeling is seen despite similar valvular gradients between groups but may be in part related to differing degrees of baseline aortic regurgitation. Hormonal influences may also be involved, with oestrogen limiting hypertrophy up to the menopause and its subsequent lack leading to accelerated (and possibly therefore different) patterns of hypertrophy in post-menopausal women compared to men[23].

In contrast to other studies evaluating sex in AS, our male and female groups were similar in terms of co-morbidity, cardiac risk score, NYHA classification and echo derived valve gradients. Only age, baseline aortic regurgitation and, expectedly, coronary artery disease prevalence and body size differed between the two groups. Previous reports of referral bias for men over women are seen again in our population, with male sex accounting for 74% of the SAVR population[7]. In our study, men and women had similar reverse remodeling 6 months following valve replacement. Multiple regression analysis suggested that the main predictor of reverse remodeling for each category was the baseline level of that variable. So, the greater absolute LV mass regression seen in men was a result of the fact that men have more LV mass at baseline than their female counterparts, rather than a sex-related difference *per se.* Stangl et al found a better LVEF at baseline and a more favourable LV remodeling response in women upon serial echocardiography following TAVR, but their female population had higher pre-TAVR aortic valve gradients than men, which may explain the greater degree of mass regression seen[13].In an echocardiographically based study of 92 patients undergoing SAVR for isolated

AS, Petrov et al [14] found a similar LVMi at baseline in men and women, but a greater degree of LVM regression in women after SAVR. This study was based on measurements taken only 3 days post-SAVR. The change in LVM reported was a reflection of a change in cavity size rather than a change in wall thickness, and it could be that the LVM regression reported was actually a reflection of the mathematical assumptions made by the echocardiographic estimation of LVM. Our study provides more robust data than that of Petrov et al; CMR is a well validated and accurate technique for LVM quantification, which does not rely to the same extent on mathematical assumptions and is independent of any change in cardiac geometry which may take place in the peri-operative period. Furthermore, the follow up of 6m (rather than 3 days), our larger sample size and the inclusion of other parameters of hypertrophy assessment in our study such as wall thickness, means that more robust conclusions about sex-related differences in reverse remodeling can be drawn.

AR has previously been suggested as a modulator of reverse remodeling following valve replacement and has been proposed as a mechanism for less favourable outcomes in men in the TAVR literature[24]. In our study, men had more AR at baseline which may in part contribute to their increased LV cavity size and mass pre-intervention. The AR regurgitant fraction following valve replacement was similar between sexes which may explain why our findings differ from those of Stangl et al where rates of residual AR were much higher in men than women[13]. A significant reduction in valve gradients was observed in both sexes, with no significant difference in CMR derived peak valve gradient according to sex, suggesting that patient prosthesis mismatch was not an implicating factor in remodeling parameters according to sex. Furthermore, post-procedure valve gradient was not associated with change in LVMi on univariate analysis. A reduction in mitral regurgitation was seen in men but not women. This, alongside the reduction in left atrial size seen in men but not women, may reflect a greater improvement in left ventricular cavity pressure, trans-mitral gradient and mitral valve tethering forces in men.

Myocardial Fibrosis

Myocardial fibrosis has been implicated in adverse clinical outcomes following both TAVR and SAVR[25, 26]. Men and women had similar levels of MF at baseline, in keeping with findings from previous studies[27, 28] but differing distributions. Our study shows that females develop a varied pattern of MF whereas men display most fibrosis in the basal and septal regions, suggesting that the pathogenesis may differ. The proportion of patients with MF was in keeping with those reported in previous studies; Rudolph et al[29] investigated 21 patients with AS and found MF in 62% once infarct pattern LGE had been excluded. Our absolute values for MF were lower than in previously reported studies[25, 29], however, these studies used different methods of MF quantification which most likely accounts for the increased values reported, rather than a true difference in absolute levels of MF.

Following AVR, there was a significant reduction in absolute MF and also MF as a proportion of LV mass in women but not in men. This finding is surprising given the greater degree of absolute LV mass reduction in the male cohort. Further studies exploring sex differences in MF are required to explain this finding. It is possible that the MF regression is different according to sex, with the more varied distribution 'female' pattern showing an early tendency to regress.. It is also possible that the regression in females is a reflection of the fact that more females underwent trans-catheter rather than surgical valve replacement, as it has previously been suggested that MF regression is seen following TAVR but not SAVR[15]. Failure of MF regression following AVR has been reported previously; Weidemann et al found no fibrosis regression following SAVR and also reported LV mass regression regardless of MF or MF burden[28]. Moreover, in our study the MF burden accounted for a very small proportion of total LV mass at both baseline and follow up, so one may not expect such a small amount of fibrosis to impact significantly on reverse remodeling.

Limitations

Patients in the two groups were similarly matched in terms of co-morbidities and clinical characteristics but were not comparable in terms of age. Due to age and referral patterns, the proportions of each sex undergoing TAVR and SAVR were different hampering any direct comparison

between the procedures. Due to their differing implant techniques and flow dynamics, there may be important differences between remodeling parameters in SAVR and TAVR, however, the procedure type did not influence reverse remodeling on univariate analysis. There was numerically (but not statistically significant) greater post-procedural AR in those undergoing TAVR compared with SAVR and therefore it is possible that this influenced findings given the different proportion of men and women undergoing each procedure. A quarter (26%) of the study population did not complete the study protocol, mainly due to permanent pacemaker implantation, which may have introduced bias, although the analysed population did not differ in terms of baseline characteristics from the original population. The post-procedure scan occurred 6m following valve replacement; although it is well documented that the majority of reverse remodeling occurs within the first 6m[30], this could still be too early to detect any subtle differences between the sexes. The follow up may also be too short to demonstrate reversal of MF. Caution may need to be exercised in the interpretation of mitral regurgitation pre-intervention. Mitral regurgitant fraction in the context of severe AS may be overestimated using CMR phase contrast imaging due to underestimation of aortic forward flow when sampling high velocities [31]. Any inferences related to MF are restrained to the technique of LGE imaging with its limited spatial resolution and variable inter-scan reproducibility. Our inter and intra-observer variability were in keeping with the published literature, supporting the notion that the MF findings are genuine, however, we accept that this is is a valid limitation of any paper reporting quantification of MF mass. T1 mapping is superior at detecting the often diffuse fibrosis seen in the pressure overloaded ventricle. T1 mapping was not widely performed at the time of the study design and absolute T1 values can vary between vendors, software release, pulse sequence and contrast agent making comparisons difficult in multivendor studies. This study was not designed as a clinical outcomes trial, but larger-scale mortality data would be useful to identify any independent prognostic markers between the sexes.

CONCLUSION

This study using the reference standard technique of CMR demonstrates that there are clear differences in the way that male and female hearts adapt to the pressure overload of AS. Despite similar co-morbidities and valvular gradients, women exhibit a lower indexed LV mass and smaller LV cavity size than men with a similar burden, but differing patterns of MF. Six months following surgical and trans-catheter aortic valve replacement, there are no sex-related differences *per* se, but superior reverse remodeling in men as a result of their more adverse remodeling at baseline.

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