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ORIGINAL PAPER

Alterations in left atrial and left ventricular coupling in mixed aortic valve disease

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Aims To characterize left atrial (LA) and left ventricular (LV) function and atrioventricular (AV) coupling in patients with moderate mixed aortic valve disease (MMAVD) against those with isolated moderate or severe aortic valve disease and controls.

Methods and results Retrospective LA and LV peak longitudinal strain (LS) analysis were performed on 260 patients [46 MMAVD, 81 moderate aortic stenosis (AS), 50 severe AS, 48 moderate aortic regurgitation (AR), and 35 severe AR] and 66 controls. Peak LV and LA LS and AV coupling, assessed by combined peak LA and LV strain, was compared between the groups. Analysis of variance and two-sided *t*-tests were used, and a *P*-value of <0.01 was considered significant. LV strain was significantly lower in those with MMAVD compared with controls and those with moderate or severe isolated AR but comparable to those with moderate or severe AS (−17.1 ± 1.1% MMAVD vs. −17.7 ± 1.5% moderate AS, $P = 0.02$, vs. −17.0 ± 1.5% severe AS, $P = 0.74$). AV coupling was significantly lower in those with MMAVD compared with controls and those with moderate AS or AR but comparable to those with severe AS or AR (47.1 ± 6.8% MMAVD vs. 45.1 ± 5.6% severe AS, $P = 0.13$, vs. 50.4 ± 9% severe AR, $P = 0.07$).

Conclusion Impairments in AV coupling are comparable for patients with MMAVD and those with severe isolated AS or AR. Impairments in LV GLS in MMAVD mirror those found in severe AS. These findings suggest that haemodynamic consequences and adverse remodelling are similar for patients with MMAVD and isolated severe disease.

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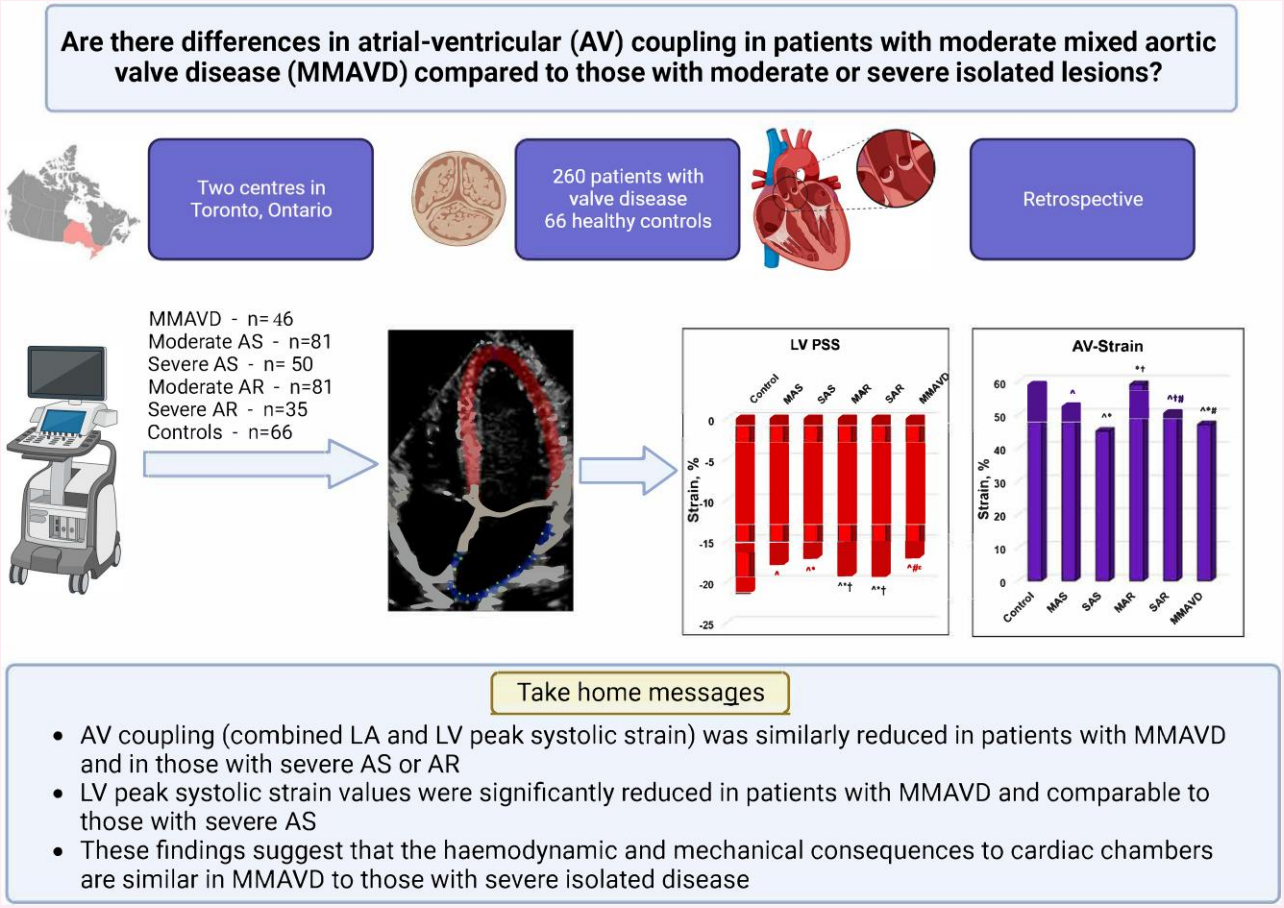
Graphical Abstract



Keywords mixed aortic valve disease • aortic stenosis • aortic regurgitation • longitudinal strain • atrioventricular coupling

Introduction

Patients with moderate mixed aortic valve disease (MMAVD) defined as the presence of moderate aortic stenosis (mAS) and moderate aortic regurgitation (mAR) are known to experience adverse cardiovascular events, such as hospitalizations and mortality, at rates similar to if not worse than those with isolated severe AS (sAS) or regurgitation (sAR).[1–9] This may be due to the unique haemodynamic impact of combined pressure and volume overload that both stenotic and regurgitant lesions have on patients with MMAVD. In those with MMAVD, the concomitant moderate lesions may cause greater changes to left atrial (LA) and left ventricular (LV) structure and function than that observed with isolated aortic valve disease.[10,11]

Studies have demonstrated that the LA and LV also do not operate in isolation but are functionally interdependent.[12,13] Historically, the impact of disease processes on the LV or LA has been studied in isolation, ignoring this important relationship. Recent technological advancements allow direct assessment of this interchamber coupling by various methods and have established normal function.[14] Alterations in LA and LV volume and longitudinal function predict the occurrence of incidence of atrial fibrillation, cardiac arrest, congestive heart failure, and death in patients with heart disease.[5,15–17] Therefore, atrioventricular coupling could be a better assessment of global heart dysfunction. Little is known regarding the effects of MMAVD on LA function and LA–LV coupling. This study aims to (i) describe the impact of MMAVD on LA function and (ii) left atrioventricular coupling and (iii) compare left atrioventricular coupling in MMAVD patients to patients with isolated AS and isolated AR.

Methods

Patient selection

Patients were retrospectively identified with MMAVD, a combination of mAS and mAR, on transthoracic echocardiography (TTE) from 1 January 2009 to 1 January 2016, at St. Michael's Hospital. Isolated AS and AR patients and controls were identified at the University Health Network from 1 January 2017 to 1 January 2019. The Research Ethics Boards of both institutions approved this study.

We included patients with MMAVD who were ≥18 years of age, in sinus rhythm, and had normal LV function [ejection fraction (EF) ≥ 50%]. Those with MMAVD were compared with four isolated disease groups and a control group. The isolated disease groups comprised patients with isolated mAS, isolated sAS, isolated mAR, and isolated sAR. The control group consisted of healthy adults free of cardiac disease. Exclusion criteria included (i) prior valve intervention, (ii) mitral, tricuspid, or pulmonic valve disease of moderate or greater in severity, and (iii) acute valvular disease (i.e. from trauma, infective endocarditis, or aortic dissection).

Echocardiographic data

All selected patients underwent a standard comprehensive echocardiographic study including M-mode, 2D echocardiogram, Doppler, tissue Doppler, and the use of multiple transducer positions to record aortic valve jet velocity. Aortic valve area (AVA) was calculated using the continuity equation as per the American Society of Echocardiography (ASE) guidelines.[18] Doppler parameters of pressure half-time, and the presence of flow reversal in the thoracic and descending aorta, and the quantitative measure of vena contracta width, jet area as a percentage of the left ventricular outflow tract (LVOT), and regurgitant volume were also measured as per the ASE guidelines.[19]

Valve severity classification

An integrated and stepwise approach was used for AS and AR quantification as per current guidelines.[18,19] sAS was defined by any two of the following criteria: AVA < 1.0 cm^2, $V_{max} \geq 4$ m/s, or mean gradient ≥40 mmHg, and mAS by an AVA of 1.0–1.5 cm^2, V_{max} of 3.0–3.9 m/s, or mean gradient of 20–39 mmHg. As the presence of concomitant AR may lead to a higher volume flow rate and so overestimation of gradients, an indexed AVA of 0.60–0.85 cm^2/m^2 and/or dimensionless index 0.25–0.50 for mAS were also assessed in accordance with the ASE guideline.

sAR was defined as having at least two of the following: vena contracta width > 0.6 cm, pressure half-time < 200 ms, jet width ≥ 65% of LVOT, enlarged LV, and the presence of prominent holodiastolic flow reversal in the descending aorta. mAR was defined as having at least two of the following: vena contracta width: 0.3–0.6 cm, pressure half-time: 200–500 ms or jet width 25–64% of LVOT, and intermediate flow reversal in the descending aorta.

LV, LA, and right ventricular parameters

The following parameters were measured offline from each study as per the ASE guidelines: LV wall thickness, volumes, and EF.[20] E-wave velocity, A-wave velocity, and septal and lateral e′ velocities were measured from mitral valve inflow and mitral annulus tissue Dopplers. Tricuspid annular plane systolic excursion (TAPSE) and tricuspid valve lateral annulus S′ were measured from tricuspid annular M-mode and tissue Doppler, respectively. LV stroke volume (SV) was derived from the LVOT. The biplane Simpson's method was used to measure LV and LA volumes, which are reportedly indexed to body surface area (BSA). A volumetric ratio of LA:LV end-systolic volumes was calculated and reported.

Speckle tracking strain analysis

Offline 2D speckle tracking strain analysis was performed to measure LA and LV longitudinal strain on the same image and cardiac cycle to eliminate the beat-to-beat variability, using vendor-independent software EchoInsight® (Epsilon Imaging®) for full heart analysis (*Figure 1*).[14] Analysed image frame rates were ≥30 frames/s. End-diastole was defined as one frame before the corresponding mitral valve closure, and end-systole was defined to coincide with the closure of the aortic valve.[21,22] LA cardiac cycles were defined as follows: (i) reservoir phase: starts at ventricular end-diastole and continues until the mitral valve opens; (ii) conduit phase: from mitral valve opening through diastasis until the onset of atrial contraction; and (iii) contractile phase: onset of atrial contraction until the end of ventricular diastole.[22,23] Endocardial border tracing was performed manually. Segments with persistently inadequate tracking after manual adjustment were excluded.

LV myocardial systolic function and LA phasic function were studied on apical four-chamber views. The following myocardial and chamber function values were recorded: LV global longitudinal peak systolic strain (GLS), LA reservoir, LA contractile and conduit strains (LA Sct and LA Scd, respectively), and LA biplane EF. The time to peak strain for both chambers was also recorded. Strain analysis was feasible in 98.9% of LV and 98.8% of LA segments.

Atrioventricular strain, as a measure of AV coupling, was calculated as the sum of the absolute values of LV GLS (converted to positive values) and LA reservoir strain.[24] Time to peak values were corrected to heart rate by dividing by the R-R interval and multiplying by 100% to account for variable heart rate.

Reproducibility

Intra- and interobserver variability of LV GLS and LA reservoir strain were calculated after blinded repeat analysis was performed on 20 randomly chosen patients. Intraobserver variability was performed over 12 months after the first reading to avoid recall bias. Intra- and interobserver agreement are presented by Bland–Altman (differences vs. means) plots and intraclass correlation coefficients (ICCs). The ICCs were calculated by two-way random-effects models with 95% confidence intervals (CIs).

Statistical analysis

Categorical variables were expressed as percentages, whereas continuous variables were expressed as mean ± SD unless otherwise noted. Comparison of categorical variables was performed using χ^2 or Fisher's exact test. Comparison of continuous variables was performed with analysis of variance

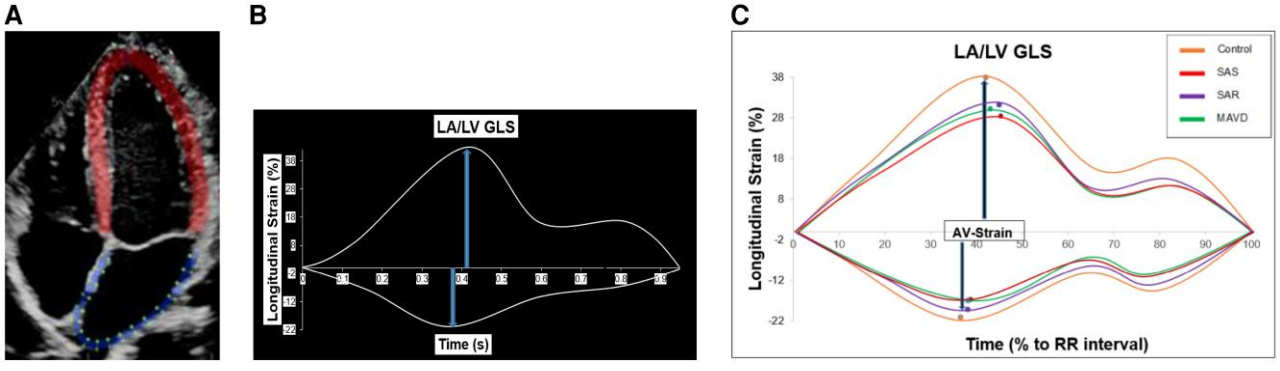


Figure 1 (*A*) Image of 2D STE global longitudinal strain analysis of LA and LV with the zero strain reference at the end-diastole. (*B*) The line plot shows the average GL strain curves for LA (top) and LV (bottom) per one cardiac cycle. The LV peak systolic strain and LA reservoir strain with the time to peak strain are indicated by arrows. (*C*) Mean LS curves of LA and LV for MAVD, severe disease groups, and control were superimposed to show the peak and time to peak strain differences. AV strain was calculated as sum of absolute values of global longitudinal LV peak systolic strain and LA reservoir strain.

followed by *post hoc* Tukey's test if needed or two-sided *t*-tests. A $P < 0.01$ was considered significant.

Results

Baseline clinical characteristics of the study population

A total of 260 patients with valve disease (46 MMAVD, 81 isolated mAS, 50 isolated sAS, 48 isolated mAR, and 35 isolated sAR) and 66 healthy controls were included in this study. Baseline clinical characteristics are shown in *Table 1*. Those with moderate or severe AS were older than the other groups. The most common cause of AS was calcific disease. For those with AR, the most common cause was a dilated ascending aorta. The MMAVD group consisted predominantly of those with congenital and dilated ascending aorta. Echocardiographic AV measurements are presented in *Table 2*.

Echocardiographic and strain parameters of the study population

LA geometry and function

Echocardiographic parameters of LA volumes and function are summarized in *Table 2*. Those with MMAVD had significantly larger BSA-indexed left atrial end-diastolic volume (LAEDV) compared with controls and those with moderate isolated AS or AR (LAEDV indexed 20.7 ± 9.6 mL/m^2 MMAVD vs. 11.4 ± 2.9 mL/m^2 controls vs. 15.3 ± 4.8 mL/m^2 mAS vs. 15.2 ± 5.7 mL/m^2 mAR; all $P < 0.001$), but not compared with those with isolated severe AS or AR (20.7 ± 9.6 mL/m^2 MMAVD vs. 19.1 ± 5.1 mL/m^2 sAS ($P = 0.30$) vs. 18.8 ± 8.8 mL/m^2 sAR ($P = 0.37$). MMAVD patients had significantly lower LA EF compared with controls and those with isolated mAS or AR ($P < 0.001$), but similar values compared with those with isolated severe AS or AR [$48.6 \pm 11.8\%$ MMAVD vs. $48.9 \pm 8.3\%$ sAS ($P = 0.89$) vs. $52.1 \pm 9.4\%$ sAR ($P = 0.15$)].

LA reservoir and contractile strains (LA Sr and LA Sct, respectively) were significantly lower in the MMAVD group compared with controls and those with moderate isolated AS or AR (LA Sr and LA Sct values 29.9 ± 6.4 and $-10.1 \pm 3.7\%$ MMAVD vs. 37.6 ± 5.5 and $-13.2 \pm 2.2\%$ controls vs. 34.7 ± 5.6 and $-13.0 \pm 2.2\%$ mAS vs. 39.9 ± 4.4 and $-13.9 \pm 2.3\%$ mAR; all $P < 0.001$) but similar to those with isolated severe AS or AR (29.9 ± 6.4 and $-10.1 \pm 3.7\%$ MMAVD vs. 28.1 ± 4.9 and $-10.3 \pm 2.6\%$ sAS; $P = 0.11$ and $P = 0.80$ vs. 30.9 ± 7.2 and $-10.4 \pm 3.6\%$ sAR; $P = 0.51$ and $P = 0.72$, *Figure 2A*). LA Scd in MMAVD patients was significantly reduced compared with controls and those with isolated mAR and mAS (LA Scd $-19.5.1 \pm 5.1\%$ MMAVD vs. $-24.4 \pm 4.8\%$ controls vs. $-26.5 \pm 5.1\%$ mAR, both $P < 0.001$ vs. $-21.8 \pm 4.2\%$ mAS, $P = 0.007$) but was not significantly different compared with isolated severe AS or AR ($19.5.1 \pm 5.1\%$ MMAVD vs. $-17.9 \pm 4.7\%$ sAS, $P = 0.10$ vs. $-20.5 \pm 5.8\%$ sAR, $P = 0.43$) (*Figure 3*). There was no significant difference in LA corrected time to peak strain values between all the groups. E/A ratio in MMAVD patients was not significantly different from those with moderate or

Table 1 Baseline clinical characteristics of the study population

		Aortic stenosis		Aortic regurgitation		Mixed aortic valve disease
	Control $n = 66$	Moderate (mAS) $n = 81$	Severe (sAS) $n = 50$	Moderate (mAR) $n = 48$	Severe (sAR) $n = 35$	Moderate (mAS + mAR) $n = 46$
Age, years	59 ± 12	65 ± 16	71 ± 16^{a}	$53 \pm 23^{b,c}$	$46 \pm 17^{a,b,c}$	$54 \pm 21^{b,c}$
Female, *n* (%)	27 (41)	34 (42)	21 (42)	20 (42)	14 (40)	19 (40)
BSA, m^2	1.83 ± 0.19	1.97 ± 0.26	1.90 ± 0.22	1.84 ± 0.38	1.92 ± 0.23	1.91 ± 0.27
SBP, mmHg	119.9 ± 13.9	137.4 ± 21.0^{a}	137.1 ± 20.4^{a}	135.4 ± 19.6^{a}	138.2 ± 19.4^{a}	131.3 ± 18.7
DBP, mmHg	73.2 ± 7.3	74.9 ± 9.1	73.5 ± 8.5	73.3 ± 9.3	69.9 ± 9.3	68.9 ± 11.7^{b}
HR, bpm	62.1 ± 9.4	69.1 ± 12.1^{a}	67.8 ± 12.2	64.5 ± 10.4	67.2 ± 11.4	66 ± 10.2
AV aetiology						
Unicuspid, no. (%)	N/A	2 (3)	N/A	N/A	N/A	N/A
Bicuspid, no. (%)	N/A	14 (17)	8 (16)	15 (31)	16 (46)	21 (46)
Tricuspid, no. (%)	66 (100)	39 (48)	19 (38)	33 (69)	19 (54)	22 (48)
Unknown, no. (%)	N/A	26 (32)	23 (46)	N/A	N/A	3 (6)
Medical history						
Hypertension, no. (%)	N/A	45 (56)	31 (62)	20 (42)	20 (57)	14 (30)
Diabetes, no. (%)	N/A	16 (20)	11 (22)	3 (6)	1 (3)	3 (7)
Hyperlipidaemia, no. (%)	N/A	41 (51)	29 (58)	8 (17)	5 (14)	14 (30)
Smoking, no. (%)	N/A	24 (30)	3 (6)	3 (6)	2 (6)	6 (13)
CAD, no. (%)	N/A	19 (23)	27 (56)	3 (6)	8 (23)	10 (22)

Data are presented as mean ± standard deviation or *n* (%).
AS, aortic stenosis; AR, aortic regurgitation; AV, aortic valve; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CAD, coronary artery disease; N/A, not applicable.
[a]$P < 0.01$ compared with control.
[b]$P < 0.01$ compared with MAS.
[c]$P < 0.01$ compared with SAS.
[d]$P < 0.01$ compared with MAR.
[e]$P < 0.01$ compared with SAR.

Table 2 Echocardiographic parameters of the study population

		Aortic stenosis		Aortic regurgitation		Mixed aortic valve disease
	Control $n = 66$	Moderate (mAS) $n = 81$	Severe (sAS) $n = 50$	Moderate (mAR) $n = 48$	Severe (sAR) $n = 35$	Moderate (mAS + mAR) $n = 46$
Aortic valve						
V_{max}, m/s	1.3 ± 0.2	3.3 ± 0.4[a]	4.4 ± 0.6[a,b]	1.7 ± 0.5[a,b,c]	2.0 ± 0.4[a,b,c]	3.6 ± 0.4[a,c,d,e]
MG, mmHg	3.4 ± 1.0	26.6 ± 6.0[a]	47.8 ± 13.5[a,b]	6.5 ± 3.8[b,c]	8.6 ± 4.3[b,c]	29.6 ± 6.3[a,c,d,e]
PG, mmHg	6.7 ± 1.9	45.3 ± 9.8[a]	78.5 ± 21.0[a,b]	12.9 ± 6.8[b,c]	17.3 ± 7.5[a,b,c]	50.7 ± 10.5[a,c,d,e]
AVA, cm^2	2.91 ± 0.69	1.14 ± 0.23[a]	0.77 ± 0.16[a,b]	2.75 ± 0.90[b,c]	3.34 ± 1.03[a,b,c,d]	1.28 ± 0.27[a,c,d,e]
AVA index, cm^2/m^2	1.58 ± 0.31	0.59 ± 0.12[a]	0.41 ± 0.09[a,b]	1.48 ± 0.45[b,c]	1.75 ± 0.53[b,c,d]	0.67 ± 0.14[a,c,d,e]
DI (dimensionless index)	0.82 ± 0.1	0.32 ± 0.05[a]	0.22 ± 0.05[a,b]	0.62 ± 0.13[a,b,c]	0.64 ± 0.12[a,b,c]	0.31 ± 0.07[a,c,d,e]
TFR, mL/s	247.7 ± 54.4	263.6 ± 56.6	233.8 ± 47.2	299.00 ± 98.2[c]	417.5 ± 86.29[a,b,c,d]	308.9 ± 74.1[a,b,c,e]
VC, mm	N/A	N/A	N/A	0.35 ± 0.10	0.56 ± 0.16[d]	0.42 ± 0.09[d,e]
Jet width/LVOT	N/A	N/A	N/A	0.28 ± 0.08	0.35 ± 0.10	0.41 ± 0.12[d]
PHT, ms	N/A	N/A	N/A	397.4 ± 62.4	283.6 ± 67.3[d]	391.6 ± 88.1[e]
Left ventricle						
LVEDV index, mL/m^2	66.2 ± 13.4	75.6 ± 15.3	65.7 ± 11.7	96.8 ± 20.5[a,b,c]	146.1 ± 37.9[a,b,c,d]	103.3 ± 25.2[a,b,c,e]
LVESV index, mL/m^2	27.7 ± 6.4	32.8 ± 7.2	28.3 ± 5.9	41.2 ± 9.5[a,b,c]	65.1 ± 18.5[a,b,c,d]	45.2 ± 12.6[a,b,c,e]
RWT	0.28 ± 0.04	0.39 ± 0.06[a]	0.37 ± 0.07[a]	0.29 ± 0.06[b,c]	0.27 ± 0.05[b,c]	0.38 ± 0.09[a,d,e]
LV mass index, g/m^2	62.4 ± 13.8	85.2 ± 20.2[a]	81.9 ± 16.3[a]	88.9 ± 18.6[a]	123.1 ± 23.5[a,b,c,d]	105.7 ± 30.7[a,b,c]
SV index, mL/m^2	42.9 ± 8.5	42.8 ± 9.3	41.5 ± 9.4	49.8 ± 11.4[b,c]	70.3 ± 15.5[a,b,c,d]	55.4 ± 11.8[a,b,c,e]
LV EF (BP), %	58.6 ± 2.3	56.6 ± 2.0[a]	57.3 ± 2.6	57 ± 2.8	55.5 ± 2.8[a]	56.2 ± 3.3[a]
LV GLS, %	−21.4 ± 1.5	−17.7 ± 1.5[a]	−17.0 ± 1.5[a]	−19.3 ± 1.3[a,b,c]	−19.4 ± 2.6[a,b,c]	−17.1 ± 1.1[a,d,e]
LV CTTP, %	36.5 ± 4.5	36.9 ± 4.5	38.9 ± 6.2	35.5 ± 5.4	38.3 ± 5.6	38.3 ± 5.6
Left atrium						
LAESV index, mL/m^2	28.9 ± 6.1	35.7 ± 9.0[a]	37.2 ± 7.4[a]	35.6 ± 10.5	38.2 ± 11.8[a]	39.0 ± 10.6[a]
LAEDV index, mL/m^2	11.4 ± 2.9	15.3 ± 4.8[a]	19.1 ± 5.1[a,b]	15.2 ± 5.7[a,c]	18.8 ± 8.8[a,b]	20.7 ± 9.6[a,b,d]
LA EF, %	60.6 ± 5.1	57.2 ± 6.2[a]	48.9 ± 8.3[a,b]	58.2 ± 6.3[c]	52.1 ± 9.4[a,b,d]	48.6 ± 11.8[a,b,d]
LA Sr, %	37.6 ± 5.5	34.7 ± 5.6	28.1 ± 4.9[a,b]	39.9 ± 4.4[b,c]	30.9 ± 7.2[a,b,d]	29.9 ± 6.4[a,b,d]
LA Scd, %	−24.4 ± 4.8	−21.8 ± 4.2	−17.9 ± 4.7[a,b]	−26.5 ± 5.1[b,c]	−20.5 ± 5.8[a,d]	−19.5 ± 5.1[a,b,d]
LA Sct, %	−13.2 ± 3.4	−12.9 ± 2.2	−10.3 ± 2.6[a,b]	−13.9 ± 2.3[c]	−10.4 ± 3.6[a,b,d]	−10.1 ± 3.7[a,b,d]
LA CTTP, %	42.4 ± 5.9	43.2 ± 4.8	45.2 ± 6.5[c]	41.7 ± 5.6	45.5 ± 5.8	43.2 ± 7.2
Diastolic function						
E/A	1.1 ± 0.37	0.99 ± 0.4	0.95 ± 0.5	1.36 ± 0.84	1.48 ± 0.94[b,c]	1.33 ± 0.63
Lateral e′, cm/s	9.12 ± 2.37	8.06 ± 2.49	6.7 ± 1.98[a]	9.24 ± 2.62[c]	8.91 ± 2.48[c]	8.52 ± 3.27[c]
Septal e′, cm/s	7.27 ± 1.78	6.41 ± 1.83	5.48 ± 1.75[a]	7.07 ± 1.85[c]	7.16 ± 1.92[c]	6.17 ± 1.65
Average E/e′	8.8 ± 2.59	12.90 ± 4.94[a]	14.29 ± 5.22[a]	9.74 ± 3.40[c]	10.57 ± 3.90	13.07 ± 5.44[a]
Atrioventricular coupling						
LAESV: LVESV	1.08 ± 0.28	1.12 ± 0.30	1.36 ± 0.32[a]	0.91 ± 0.32[a,b,c]	0.62 ± 0.20[a,b,c,d]	0.90 ± 0.31[b,c,e]
AV-S, %	58.9 ± 5.8	52.5 ± 6.3[a]	45.1 ± 5.6[a,b]	59.1 ± 4.7[b,c]	50.4 ± 9.0[a,c,d]	47.2 ± 6.8[a,b,d]
LA stiffness	24.0 ± 8.2	37.6 ± 17.0	52.9 ± 22.5[a,b]	24.7 ± 9.7[c]	35.0 ± 15.8	46.3 ± 24.7[a,d]
LA:LV CTTP	1.16 ± 0.07	1.17 ± 0.09	1.17 ± 0.09	1.18 ± 0.08	1.20 ± 0.11	1.14 ± 0.12
Right ventricle						
TAPSE, cm	2.23 ± 0.31	2.22 ± 0.39	2.15 ± 0.32	2.25 ± 0.35	2.28 ± 0.47	2.21 ± 0.41
S′, cm/s	12.49 ± 2.12	12.03 ± 2.45	11.9 ± 2.07	12 ± 2.22	12.63 ± 3.06	11.96 ± 2.19

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; RWT, relative wall thickness; SV, stroke volume; EF, ejection fraction; LAESV, left atrial end-systolic volume; LAEDV, left atrial end-diastolic volume; V_{max}, maximum transvalvular velocity; MG, mean gradient; PG, peak gradient; DI, dimensionless index; TFR, transvalvular flow rate; VC, vena contracta; PHT, pressure half-time; LVOT, left ventricular outflow tract; GLS, global longitudinal strain; CTTP, corrected time to peak; LA Sr, left atrial reservoir strain; LA Sct, left atrial contractile strain; LA Scd, left atrial conduit strain; AV-S, atrioventricular strain; TAPSE, tricuspid annular plane systolic excursion; N/A, not applicable.

[a] $P < 0.01$ compared with control.

[b] $P < 0.01$ compared with MAS.

[c] $P < 0.01$ compared with SAS.

[d] $P < 0.01$ compared with MAR.

[e] $P < 0.01$ compared with SAR.

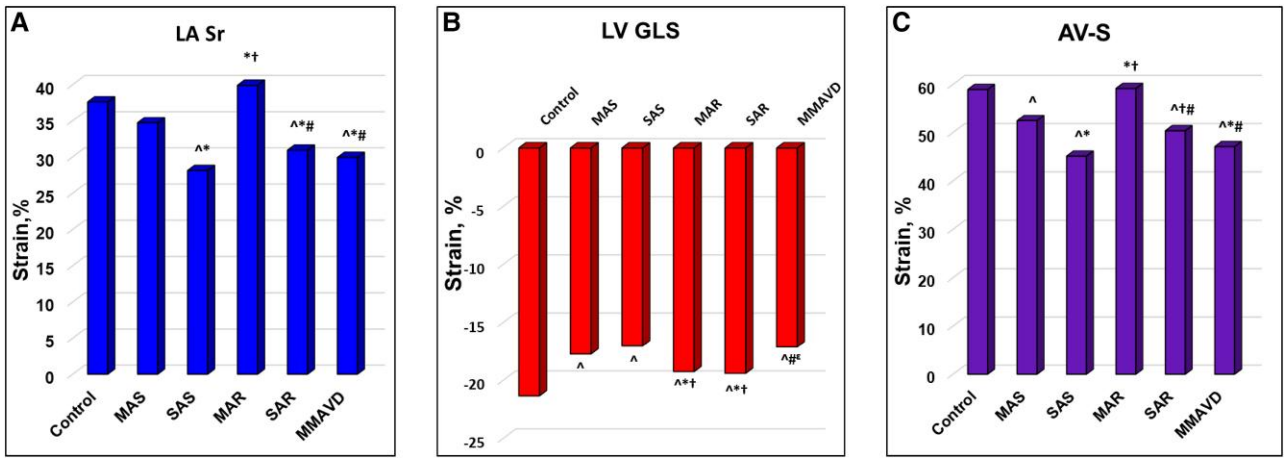


Figure 2 (*A*) LA global longitudinal reservoir strain. (*B*) LV global longitudinal peak systolic strain. (*C*) Global longitudinal atrioventricular strain value among the groups.

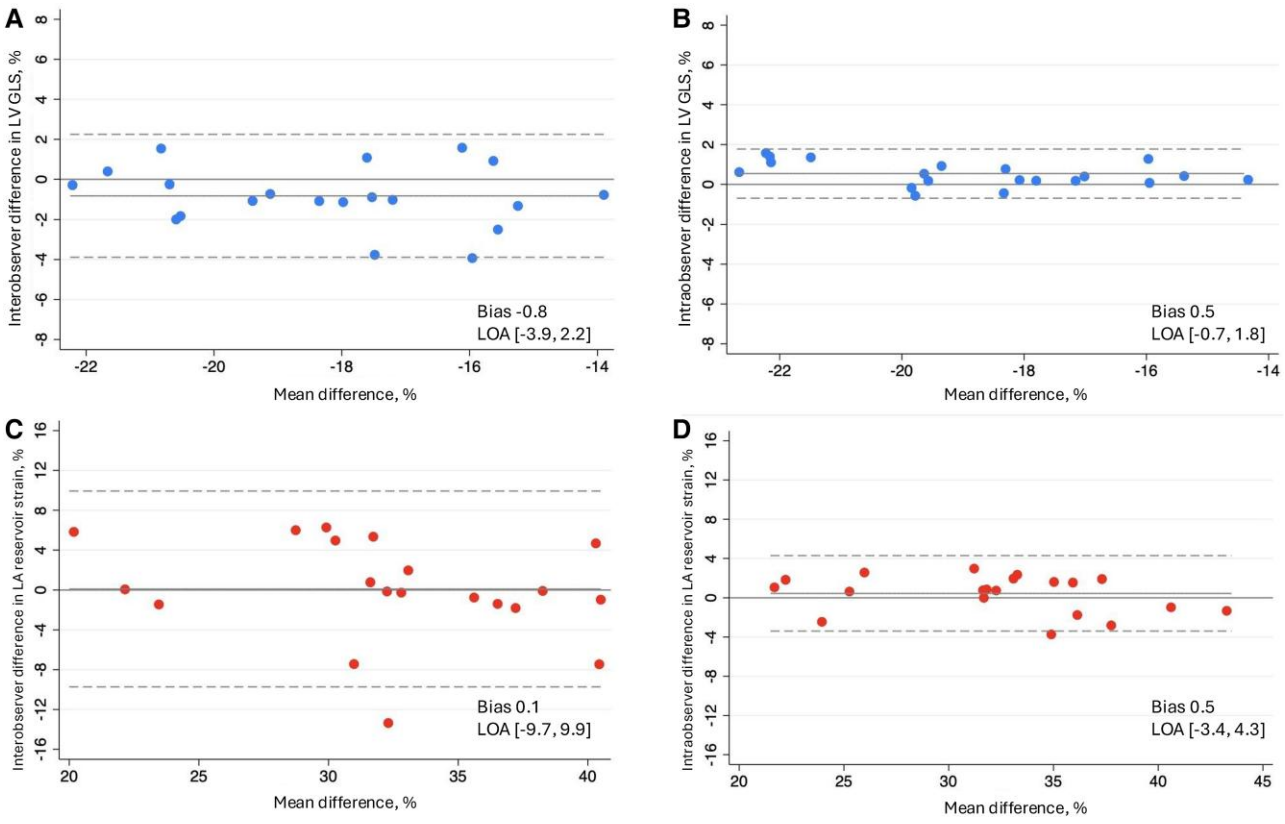


Figure 3 Bland–Altman plots of interobserver and intraobserver variability for LV GLS (*A* and *B*) and LA reservoir strain (*C* and *D*), respectively.

severe AS or AR. However, patients with isolated sAR had higher E/A ratios compared with patients with isolated moderate or severe AS. Patients with MMAVD and moderate or severe isolated AR had higher lateral and septal e′ compared with patients with isolated sAS, who in turn had lower lateral and septal e′ compared with controls.

LV geometry and function

Echocardiographic parameters detailing LV size and function in each group are presented in *Table 2*. Patients with MMAVD had significantly larger indexed left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) compared with patients with

isolated moderate or severe AS and controls ($P < 0.001$), but significantly smaller volumes compared with isolated severe AR (LVEDV 103.3 ± 25.2 mL/m^2 MMAVD vs. 146.1 ± 37.9 mL/m^2; $P < 0.001$). They had similar indexed LVEDV and LVESV to those with isolated mAR ($P = 0.18$ and $P = 0.90$, respectively).

BSA-indexed LV mass was significantly higher in MMAVD patients compared with all the other groups ($P < 0.001$) but smaller compared with the isolated sAR group (105.7 + 30.7 g/m^2 MMAVD vs. 123.1 + 23.5 g/m^2 sAR, $P = 0.009$).

Those with MMAVD had significantly lower LV peak GLS compared with controls and those with isolated moderate or severe AR (−17.1 ± 1.1% MMAVD vs. −21.4 ± 1.5% controls vs. −19.3 ± 1.3% mAR vs. −19.4 ± 2.6% sAR, all $P < 0.01$). There was no difference in LV peak GLS compared with those with isolated moderate or severe AS (−17.1 ± 1.1% MMAVD vs. −17.7 ± 1.5% mAS, $P = 0.02$ vs. −17.0 ± 1.5% severe AS, $P = 0.74$) (*Figure 2B*). There was no significant difference in LV corrected time to peak GLS values between all the groups.

Atrioventricular coupling

The LA:LV end-systolic volumetric ratio was significantly lower in MMAVD compared with controls and those with isolated moderate or severe AS (0.90 ± 0.31 MMAVD vs. 1.08 ± 0.28 controls, $P = 0.001$ vs. 1.12 ± 0.30 mAS vs. 1.36 ± 0.32 sAS, both $P < 0.001$) but larger than those with isolated sAR (0.90 ± 0.31 MMAVD, 0.62 ± 0.20 sAR, all $P < 0.01$). There was no significant difference in LA:LV volume ratio between MMAVD and isolated mAR ($P = 0.93$).

Combined LA and LV peak strain values (AV-S) were significantly lower in those with MMAVD compared with controls and those with isolated moderate AS or AR (47.1 ± 6.8% MMAVD vs. 58.9 ± 5.8% controls vs. 52.5 ± 6.3% mAS vs. 59.1 ± 4.7% mAR, all $P < 0.001$), but comparable to those with isolated severe AS or AR (47.1 ± 6.8% MMAVD vs. 45.1 ± 5.6% severe AS, $P = 0.13$ vs. 50.4 ± 9% severe AR, $P = 0.07$) (*Figure 2C*). There was no difference in the ratio between LA and LV corrected time to peak longitudinal strain.

Reproducibility

There was good interobserver ICC for both LV GLS (0.87, 95% CI 0.65–0.95, $P < 0.001$) and LA reservoir strain (0.82, 95% CI 0.54–0.93, $P < 0.001$) and intraobserver for LV GLS (0.97, 95% CI 0.83–0.99, $P < 0.001$) and LA reservoir strain (0.97, 95% CI 0.03–0.99, $P < 0.001$). Bland–Altman plots (*Figure 3*) demonstrated small biases and limits of agreement (LOA) for both interobserver LV GLS (bias −0.8%, LOA −3.9 to 2.2%) and LA reservoir strain (bias 0.1%, LOA −9.7 to 9.9%) and intraobserver LV GLS (bias 0.5%, LOA −0.7 to 1.8%) and LA reservoir strain (bias 0.5%, 95% CI −3.4 to 4.3%).

Discussion

To our knowledge, this is the first paper to examine the impact of MMAVD on LA and LV function and in turn atrioventricular coupling. We have found that in patients with MMAVD, (i) LA function is impaired, and this impairment is similar to that found in isolated sAS or isolated AR; (ii) LV GLS is impaired to a similar degree as in isolated sAS; (iii) the combined end-systolic atrioventricular volume is similar to that in isolated mAR; and (iv) the combined atrioventricular strain is similar to that observed in isolated sAS and isolated AR patients.

The similarities in impaired LA function and AV coupling in patients with MMAVD and isolated severe AS or AR, together with demonstrated associations between impaired AV coupling and adverse events in various cardiovascular conditions,[17,25] suggest that AV coupling could be used to identify those with MMAVD who may benefit from earlier intervention. Current valve disease guidelines provide guidance on optimal timing of valve intervention based on the presence of symptoms, which are subjective, and/or the haemodynamic consequences of the valve lesion, which are typically late manifestations and may not be reversible.[26,27] Guidance for mixed valvular disease is particularly lacking. It is unclear if a mixed moderate lesion should be treated equivalent to an isolated severe lesion in terms of follow-up and when referring for intervention. Our research demonstrates the haemodynamic and mechanical impact of mixed aortic valve disease parallels that of isolated severe lesions, suggesting that MMAVD should be considered as significant as isolated severe disease.

LA remodelling and function in MAVD

In patients with MMAVD, like those with isolated severe AS or AR, we found that the LA increases in size, while function decreases. Changes to LA volumes and function have been previously demonstrated in isolated severe AS and AR and have been associated with higher mortality.[28–32] Less is known for those with MMAVD. Changes in LA size in those with MMAVD likely reflect impaired LA mechanics and the impact of MAVD on LA remodelling and function.

LV function in MAVD

Patients with MMAVD have a reduction in GLS that is as substantial as that found in severe isolated AS and significantly worse when compared with those with mAR or sAR. The degree of myocardial dysfunction found in MMAVD suggests that the combined impact of the mixed valve lesion can lead to more significant changes than would be observed with isolated moderate disease.

The observed reduction in LV longitudinal strain in those with MMAVD was not as severe as that found in the study by Saijo *et al.*[33] They reported an average GLS value of −15.3 ± 2.9% for their MMAVD cohort, considerably worse compared with that obtained in our study (GLS −17.1 ± 1.1%). This may be due to differences in age, sex, co-morbidities, and LV remodelling between the two studies.[14,34–37] Saijo *et al.*[33] proposed that the differences in GLS reductions in MMAVD compared with those with moderate or severe AR may reflect the combination of greater afterload with resultant higher relative wall thickness in MMAVD vs. volume overloaded states and larger LV volumes in those with AR. However, in our cohort, those with MMAVD had similar indexed LVEDV to those with mAR, favouring the former as a more likely explanation.

Previous research in patients with isolated sAS has demonstrated that reductions in LV GLS are associated with poorer outcomes.[38] This reduction in GLS may reflect a process of more irreversible myocardial damage including replacement fibrosis,[26,39] which may help identify those with MMAVD who may benefit from surgical or transcatheter intervention at an earlier stage. The high afterload associated with sAS can also lead to reductions in GLS values.[26] Those with MMAVD are likely to have less afterload than those with sAS yet have similarly impaired strain values, which may suggest a greater burden of fibrosis or scar contributing to impaired GLS.

Atrioventricular coupling in MMAVD

In a normal heart, the LA and LV volumetric relationships are coupled. Studies have shown that coupling can be deranged in patients with cardiovascular disease[17,25] and in states of pressure and volume overload such as in severe AS and AR.[28,40] When we examined the impact of coupling on atrioventricular remodelling, we found that the increase in combined end-systolic atrioventricular volume in patients with MMAVD is similar to that in isolated mAR group. Maximal LA volumes [left atrial end-systolic volume (LAESV)] were not significantly different between groups whereas LVESV was significantly higher in MMAVD compared with moderate or severe AS. This translates as a lower LA:LV volume ratio in MMAVD compared with moderate or severe AS. This ratio was lowest in those with sAR, confirming that this

reduced LA:LV ratio in MMAVD is driven primarily by a volume overloaded LV in AR rather than the effects of pressure overload from AS on LA size.

AV coupling is a surrogate marker of the haemodynamic relationship between the LV and LA and may be a more sensitive marker of adverse remodelling. Compared with the control group and those with moderate isolated lesions, AV coupling was significantly abnormal in those with MMAVD and comparable to those with severe isolated lesions. In patients with heart failure, abnormal AV coupling (assessed by the ratio of LA volume/tissue Doppler-derived a′) was found to be independently associated with greater mortality.[41] Others have also demonstrated the incremental value, on top of existing LA parameters and traditional risk factors, of volumetric-derived AV coupling in predicting adverse events or incident disease.[17,42,43] It is reasonable to predict that this independent prognostic relationship holds true in those with valvular disease, but further study is needed.

Limitations

Limitations of this study include its retrospective nature. LA and LV are functionally coupled; for this reason, we assessed LA and LV deformation in the same image and same cardiac cycle to eliminate the beat-to-beat variability. However, this prevented us from obtaining global strain analysis by including assessment of the LV and LA walls in the apical two- and three-chamber views as suggested by guidelines.[20,23] Other research groups have defined LA–LV coupling as a volumetric ratio at end-diastole or as a ratio of LA volume to tissue Doppler-derived a′ rather than a sum of strain-derived values as in our paper.[17,25,41] There is currently no universally accepted method to assess AV coupling. We have chosen our methods to include both volumetric and mechanical (strain) measures of AV coupling. We also do not have catheterization or cardiac MRI correlations.

Conclusion

Impairments in LA function and AV coupling are comparable for patients with MMAVD and those with severe isolated AS or AR. Impairments in LV GLS in those with MMAVD mirror those found in severe AS. Taken together, these findings suggest that haemodynamic consequences and reverse remodelling are similar for patients with MMAVD and isolated severe disease. Further research is required to validate our findings, determine their prognostic implications, and ideally provide a threshold justifying surgical or transcatheter intervention.

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Data availability

All data are incorporated into the article.

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