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Original Article

Sex Differences in Outcomes of Adults with Repaired Coarctation of Aorta and Concomitant Aortic Valve Disease

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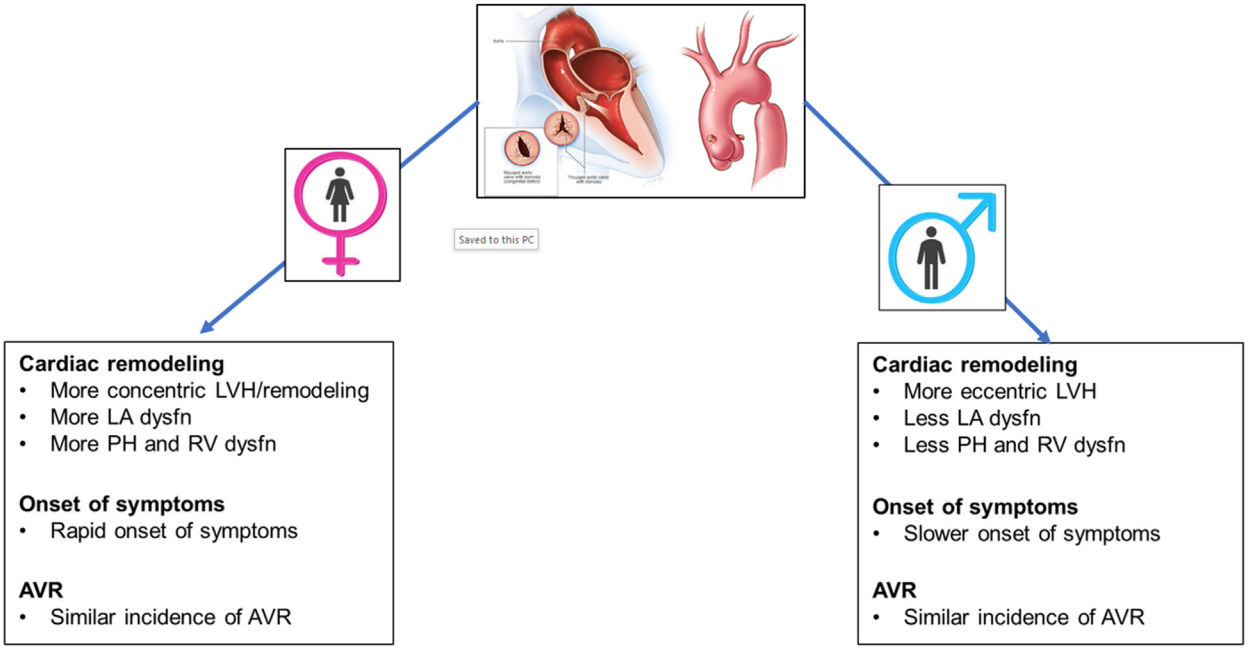

ABSTRACT

Background: Aortic valve disease is common in adults with coarctation of aorta. However, no systematic comparative analyses have been performed of the clinical course of aortic valve disease for male vs female patients in this population. The purpose of this study was to compare cardiac remodelling, onset of symptoms, and incidence of aortic valve replacement (AVR) for male vs female patients.

Methods: A retrospective study was conducted of adults with repaired coarctation of aorta and $\geq$ moderate aortic stenosis and/or aortic regurgitation. Cardiac remodelling (left ventricular [LV], left atrial, right ventricular [RV], and right atrial structure and function) and symptomatic and/or functional class were determined at the baseline encounter. Development of new-onset symptoms and the incidence of AVR were ascertained for the period from baseline to last encounter.

RÉSUMÉ

Contexte : La valvulopathie aortique est fréquente chez les adultes atteints de coarctation de l'aorte. Cependant, aucune analyse comparative systématique de l'évolution clinique de la maladie valvulaire aortique n'a été réalisée chez les hommes par rapport aux femmes dans cette population. L'objectif de cette étude était de comparer le remodelage cardiaque, l'apparition des symptômes et l'incidence du remplacement valvulaire aortique (RVA) chez les hommes et les femmes.

Méthodes : Une étude rétrospective a été menée sur des adultes ayant subi une correction de la coarctation de l'aorte et présentant une sténose aortique $\geq$ modérée et/ou une régurgitation aortique. Le remodelage cardiaque (structure et fonction du ventricule gauche [VG], de l'oreillette gauche, du ventricule droit [VD] et de l'oreillette droite) et

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Results: We identified 214 patients (121 male [57%], 93 female [43%]). Although both groups had a similar aortic valve gradient, aortic valve area indexed to body surface area, aortic regurgitation severity, and functional status at baseline, female patients had more LV concentric hypertrophy and remodelling, left atrial hypertension and dysfunction, elevated RV systolic pressure, and RV systolic dysfunction. Of 151 patients without symptoms at baseline,102 (72%) developed symptoms. Female sex was independently associated with new-onset symptoms (adjusted hazard ratio 1.14, [95% confidence interval 1.05-1.23]). Of 214 patients, 191 (89%) underwent AVR. Female sex was not associated with AVR upon multivariable analysis. However, LV concentric hypertrophy and remodelling (both of which were more common in female patients) were associated with new-onset symptoms and AVR.

Conclusions: Female patients, compared to male patients, had more-advanced cardiac remodelling, and more-rapid onset of symptoms, but a similar risk of AVR.

la classe symptomatique et/ou fonctionnelle ont été déterminés lors de la consultation initiale. L'apparition de nouveaux symptômes et l'incidence du RVA ont été déterminées pour la période allant de la consultation initiale à la dernière consultation.

Résultats : Nous avons identifié 214 patients (121 hommes [57 %], 93 femmes [43 %]). Bien que les deux groupes aient présenté une similarité de profil concernant le gradient valvulaire aortique, la surface valvulaire aortique indexée sur la surface corporelle, la sévérité de régurgitation aortique et leur état fonctionnel au départ, les patientes avaient plus d'hypertrophie concentrique et de remodelage du VG, d'hypertension et de dysfonction de l'oreillette gauche, de pression systolique élevée du VD et de dysfonction systolique du VD. Sur 151 patients sans symptômes au départ, 102 (72 %) ont développé des symptômes. Le sexe féminin a été associé de manière indépendante à l'apparition de nouveaux symptômes (rapport de risque ajusté 1,14, [1,05-1,23]). Sur 214 patients, 191 (89 %) ont subi un RVA. Le sexe féminin n'était pas associé à un RVA lors de l'analyse multivariée. Cependant, l'hypertrophie et le remodelage concentrique du VG (tous deux plus fréquents chez les femmes) étaient associés à l'apparition de nouveaux symptômes et à un RVA.

Conclusions : Les femmes, comparées aux hommes, présentaient un remodelage cardiaque plus avancé et une apparition plus rapide des symptômes, mais un risque similaire de RVA.

Transcatheter and surgical therapies are effective for the management of native and recurrent coarctation of aorta (COA).[1-3] However, patients may experience ongoing left ventricular (LV) pressure overload even in the absence of residual or recurrent COA.[4-9] This overload is due to the high prevalence of systemic arterial hypertension, which is present in more than 50% of adults with repaired COA.[10-14] The high prevalence of systemic arterial hypertension in this population is attributed to endothelial dysfunction, abnormal arterial smooth-muscle reactivity, and wave reflection due to changes in the material properties of the thoracic aorta.[12,15-17] In addition to systemic arterial hypertension, bicuspid aortic valve is present in more than 50% of adults with COA, and this in turn, increases the lifetime risk of aortic valve disease (AVD), and LV pressure and/or volume overload in this population.[12,15-17]

In previous studies, we demonstrated that COA patients presenting with aortic valve disease (aortic stenosis [AS] or aortic regurgitation [AR]) had a more aggressive clinical course, as evidenced by rapid onset of symptoms and need for aortic valve replacement (AVR), and had a higher risk of cardiovascular (CV) events during follow-up, compared to patients without COA presenting with a similar degree of AVD.[18,19] The adverse clinical course of AVD in patients with COA was attributed to increased LV stiffness and diastolic dysfunction from hypertension, which in turn, impaired the ability of the left ventricle to adapt to pressure or volume overload from concomitant AVD.[18,19] What is not known is whether the clinical course of AVD in patients with COA differ between male vs female patients. This knowledge gap is important, as significant sex-related differences in LV remodelling, clinical presentation, and outcomes of AVD have been demonstrated in patients with degenerative AVD.[20,21] The purpose of this study was to compare cardiac remodelling, the onset of symptoms, and the need for AVR between male and female patients with COA presenting with concomitant AVD.

Methods

Study population

This retrospective study focused on adults (aged $\geq$ 18 years) with repaired COA, and concomitant AVD, who received care at the Mayo Clinic, Rochester, Minnesota, between January 1, 2003 and December 31, 2022. We defined AVD as the presence of any of the following conditions: $\geq$ moderate AS and/or $\geq$ moderate AR at the time of baseline echocardiogram. $\geq$ moderate AS was defined as an aortic valve peak velocity of $>$ 3.0 m/s, and $\geq$ moderate AR was defined as the presence of $\geq$ 2 of the following criteria: vena contracta of 0.3-0.6 cm; an effective regurgitant office area of 0.10-0.29 cm^2; a regurgitant volume by proximal isovelocity surface area of 30-59 mL/beat; and a regurgitant fraction of 30%-49%.The severity of AR was determined by qualitative assessment in the patients who had quantitative Doppler indices that were insufficient to quantify the severity of AR.[22] The patients were divided into 3 mutually exclusive AVD subgroups, as follows: (i) isolated AS, defined as an aortic valve peak velocity $>$ 3 m/s and $<$ moderate AR; (ii) isolated AR, defined as $\geq$ moderate AR and aortic valve peak velocity of $\leq$ 3 m/s; and (iii) mixed AVD, defined as an aortic valve peak

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See page 1393 for disclosure information.

velocity of $>$ 3 m/s and $\geq$ moderate AR. The rationale for enrolling only patients with $\geq$ moderate AVD was that these patients were the ones who had pressure and/or volume overload of sufficient severity to allow for the assessment of between-sex differences in CV remodelling.

We excluded patients with the following conditions: (i) LV inflow disease, defined as having mitral valve prosthesis, subvalvular and/or valvular and/or supravalvular mitral stenosis (mean gradient of $>$ 3 mm Hg) or $\geq$ moderate mitral regurgitation; and (ii) subvalvular or supravalvular AS.

Study objectives

The study objectives were as follows. The first was to compare the the onset of symptoms and the incidence of AVR for male vs female patients from the time of the baseline encounter (time zero). Onset of symptoms was defined as the occurrence of new-onset (New York Heart Association [NYHA] II/III) angina or dyspnea, and it was assessed in the subset of patients who were asymptomatic at the baseline encounter. NYHA classes II and III denote symptoms with moderate vs mild exertion, respectively. The second objective was to compare cardiac remodelling at the baseline encounter for male vs female patients. We assessed cardiac remodelling using the following indices: (i) left ventricle—LV mass index, relative wall thickness, ejection fraction, and global longitudinal strain; (ii) left atrium)—left atrial (LA) volume index, and LA reservoir strain; (iii) right ventricle—right ventricular (RV) free-wall strain and RV systolic pressure; and (iv) right atrium—-right atrial volume index, and right atrial reservoir strain.

The exploratory objective was to compare the incidence of CV adverse events among male vs female patients in the subset that underwent AVR using the date of AVR as time zero. A CV adverse event was defined as the composite endpoint of new-onset atrial fibrillation, sustained or non-sustained ventricular tachycardia, heart failure hospitalization, or CV death.

Data collection

The first clinical encounter in the adult congenital heart disease clinic within the study period was considered the baseline encounter. Clinic notes, echocardiograms, and exercise-test reports obtained within 12 months from the baseline encounter were reviewed; these were used to define the baseline characteristics of the cohort. Surgical notes were reviewed for the patients who underwent AVR, to determine the indications for AVR. The indications, as follows, were based on the guidelines for the management of valvular heart disease[23]: (i) symptoms; (ii) progressive LV enlargement; (iii) LV systolic dysfunction, defined as an LV ejection fraction $<$ 50%.

Echocardiography

All patients underwent comprehensive 2-dimensional, Doppler, and speckle tracking transthoracic echocardiograms, based on contemporary guidelines.[24] Chamber structure and function (volume, area, strain, fractional area change, and ejection fraction) were assessed using standard techniques.[24] We assessed the severity of AVD using the multiparametric approach described in the Study Population section. Offline image analysis was performed in all patients by research sonographers in the Mayo Adult Congenital Heart Disease imaging core laboratory. The reproducibility analyses of echocardiographic indices from the program at this laboratory have been described in previous studies.[10,25,26]

LV mass index (LVMI) was calculated using end-diastolic linear measurements of the interventricular septum, LV inferolateral wall thickness, and LV internal diameter derived from 2-dimensional echocardiography measured at the tissue—blood interphase.[27] Relative wall thickness was calculated as follows: (2 x LV posterior wall thickness) / LV end-diastolic diameter.[27] The patients were classified into 4 groups based on LV geometry, as follows: (i) normal LV geometry (LVMI $\leq$ 95 g/m^2 in female patients, and $\leq$ 115 g/m^2 in male patients, and relative wall thickness $\leq$ 0.42); (ii) LV concentric remodelling (LVMI $\leq$ 95 g/m^2 in female patients, and $\leq$ 115 g/m^2 in male patients, and relative wall thickness $>$ 0.42); (iii) LV concentric hypertrophy (LVMI $>$ 95 g/m^2 in female patients, and $>$ 115 g/m^2 in male patients, and relative wall thickness $>$ 0.42); and (iv) LV eccentric hypertrophy (LVMI $>$ 95 g/m^2 in female patients, and $>$ 115 g/m^2 in male patients, and relative wall thickness $\leq$ 0.42).[27]

Statistical analysis

Data were presented as mean $\pm$ standard deviation, median (interquartile range [IQR]), or count (%). Between-group comparisons were performed using an unpaired t test, for continuous variables with normal distribution, the Wilcoxon rank-sum test for continuous variables with skewed distribution, and the χ^2 test for categorical variables. The onset of symptoms was assessed as a time-to-event outcome from the time of the baseline echocardiogram (time zero) to the occurrence of symptoms, AVR, death, or last clinical encounter. Similarly, AVR was assessed as a time-to-event outcome from the time of the baseline echocardiogram (time zero) to the occurrence of AVR, death, or last clinical encounter. The patients who did not have the outcome of interest were censored on December 31, 2022. The 5-year cumulative incidence of symptoms and AVR was estimated using Kaplan-Meier methods, and comparisons between male and female patients were performed using the log-rank test.

The relationships between sex and outcomes were assessed using Cox regression. The Cox models were adjusted for the following: demographic indices (age, COA repair status, age of initial COA repair); comorbidities (hypertension, diabetes, coronary artery disease, atrial flutter and/or tachycardia, atrial fibrillation); office blood pressure (systolic and diastolic blood pressure); and echocardiographic indices (COA Doppler mean gradient, LVMI, relative wall thickness, LV geometry [modelled as categorical variable with normal geometry as the reference group], LV global longitudinal strain, LV septal ratio of mitral inflow pulse wave Doppler early velocity to tissue Doppler early velocity [E/e], LA reservoir strain, RV free wall strain, and RV systolic pressure). These variables were chosen based on their clinical relevance and known association with outcomes. Because of the limited sample size, we first performed univariable Cox regression analysis assessing the relationship between the above variables and outcomes. The variables with $P < 0.1$ on univariable analyses were then entered into the multivariable model, and the final covariate selection was based on stepwise backwards selection, with $P < 0.1$ required for a covariate to remain in the model. All statistical analyses were

Table 1. Baseline characteristics

Characteristic	All patients (N = 214)	Male patients (N = 121; 56%)	Female patients (N = 93; 44%)	*P*
Demographic or anatomic Indices				
Age, y	33 (22−47)	35 (22−49)	31 (22−44)	0.1
Bicuspid aortic valve	168 (79)	95 (79)	73 (79)	0.9
Body mass index, kg/m^2	26.1 (22.8−29.8)	26.3 (24.1−29.6)	25.2 (22.1−30.4)	0.2
Body surface area, m^2	1.91 (1.71−2.07)	2.02 (1.89−2.13)	1.71 (1.60−1.88)	< 0.001
Age of initial COA repair, y	4.1 (0.7−7.6)	4.3 (0.8−8.4)	3.8 (0.6−7.4)	0.6
# of COA interventions prior to baseline	1 (1−3)	1 (1−3)	1 (1−2)	0.8
Office BP				
Systolic BP, mm Hg	133 ± 36	134 ± 24	131 ± 16	0.6
Diastolic BP, mm Hg	65 ± 15	65 ± 16	64 ± 14	0.8
Pulse pressure, mm Hg	68 ± 19	69 ± 20	66 ± 18	0.4
ULE systolic BP gradient, mm Hg	11 (2−19)	10 (1−21)	11 (2−22)	0.4
Heart rate, bpm	75 ± 13	73 ± 18	76 ± 16	0.3
Comorbidities				
Hypertension	98 (45)	62 (51)	35 (38)	0.03
Coronary artery disease	16 (8)	12 (10)	4 (4)	0.1
Diabetes	12 (6)	7 (6)	5 (5)	0.8
Atrial fibrillation	19 (9)	11 (9)	8 (9)	0.9
Atrial flutter and/or tachycardia	3 (1)	2 (2)	1 (1)	0.7
Prior stroke	4 (2)	2 ()	2 (2)	0.6
Medications				
Beta-blockers	88 (41)	56 (46)	32 (34)	0.08
Calcium-channel blockers	26 (12)	18 (15)	8 (9)	0.2
Diuretics	36 (17)	22 (18)	14 (15)	0.5
ACEI and/or ARB	81 (38)	51 (42)	30 (32)	0.1
Mineralocorticoid antagonist	10 (5)	6 (5)	4 (4)	0.8
Functional status				0.6
NYHA I	151 (71)	85 (70)	66 (71)	
NYHA II or III	63 (29)	36 (30)	27 (29)	
Laboratory data				
NT proBNP, pg/L	218 (68−255)	196 (61−233)	229 (76−261)	0.3
Exercise data				
Exercise time, min	6.7 ± 2.5	7.2 ± 2.5	5.9 ± 2.3	0.06
Peak VO_2, mL/kg/min	23.7 ± 8.7	25.9 ± 8.5	20.4 ± 8.1	0.01
Predicted peak VO_2, %	66 ± 21	68 ± 18	64 ± 19	0.7

Values are mean ± standard deviation, for continuous variables with normal distribution, median (interquartile range), for continuous variables with skewed distribution, and count (%) for categorical variables. The *P* values were derived from between-group comparisons using an unpaired *t* test, for continuous variables with normal distribution, the Wilcoxon rank-sum test, for continuous variables with skewed distribution, and the χ^2 test for categorical variables. Hypertension was defined as having a diagnosis of hypertension that requires the use of antihypertensive therapy prior to presentation at the Mayo Adult Congenital Heart Disease clinic or having a BP ≥ 140/90 mm Hg at 2 different settings at the time of presentation to the clinic.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; bpm, beats per minute; COA, coarctation of aorta; NT proBNP, N-terminal pro-hormone brain natriuretic peptide; NYHA, New York Heart Association; ULE, upper-to-lower extremity; VO_2, oxygen consumption.

performed with BlueSky Statistics software (version 7.10, BlueSky Statistics, Chicago, IL), and JMP statistical software (version 17.1.0, JMP Statistical Discovery, Cary, NC). A *P* value of < 0.05 was considered to be statistically significant for all analyses.

Results

Baseline characteristics

Of 891 patients with COA, we identified 214 consecutive patients (24%) who met the study inclusion criteria. Of these 214 patients, 121 (57%) and 93 (43%) were male and female, respectively. Of the female patients, 3 (3%) had a diagnosis of Turner syndrome. Table 1 shows a comparison of the baseline characteristics of male vs female patients. Female patients had a smaller body surface area than male patients (2.02 [IQR 1.89-2.13] vs 1.71 [IQR 1.60-1.88] m^2, $P < 0.001$) and were less likely to have hypertension (35 female patients [38%] vs 62 male patients [51%], $P = 0.03$). Otherwise, no significant between-group differences occurred in the prevalence of bicuspid aortic valve, comorbidities, NYHA functional class, or office blood pressure (Table 1).

Echocardiography

Table 2 shows a comparison of the aortic valve indices and cardiac remodelling indices between male and female patients. No significant between-group differences occurred in the severity of AVD (Doppler mean gradient, Doppler-derived aortic valve area indexed to body surface area, and severity of AR), or the distribution of AVD subgroups (Table 2). However, male patients had larger LV volumes (LV end-diastolic volume index, 78 [IQR 58-91] vs 69 [IQR 46-82] mL/m^2, $P < 0.001$; LV end-systolic volume index, 28 [IQR 21-38] vs 20 [IQR 16-25] mL/m^2, $P < 0.001$) and LV mass (LVMI, 129 ± 24 vs 114 ± 22 69 g/m^2, $P < 0.001$), even after adjustment was made for body surface area (Table 2).

We observed significant between-group differences in LV geometry. Female patients were more likely to have LV concentric hypertrophy (29% vs 20%, $P = 0.002$) and LV

Table 2. Cardiac remodelling indices

Indices	All patients (N = 214)	Male patients (N = 121; 56%)	Female patients (N = 93; 44%)	*P*
Aortic valve				
Mean gradient, mm Hg	36 (22−58)	34 (21−56)	37 (24−62)	0.2
Area, cm^2	1.06 ± 0.36	1.14 ± 0.31	0.92 ± 0.29	0.008
Area, cm^2/m^2	0.54 ± 0.21	0.55 ± 0.19	0.54 ± 0.16	0.4
≥ moderate regurgitation	89 (42)	49 (41)	40 (43)	0.8
Severe stenosis	93 (44)	52 (43)	41 (44)	0.7
Disease subgroup				0.8
Isolated stenosis	125 (58)	72 (60)	53 (57)	
Isolated regurgitation	40 (19)	21 (17)	19 (20)	
Mixed	29 (23)	28 (23)	21 (23)	
LV				
End-diastolic volume index, mL/m^2	72 (52−81)	78 (58−91)	69 (46−82)	< 0.001
End-systolic volume index, mL/m^2	24 (18−31)	28 (21−38)	20 (16−25)	< 0.001
Ejection fraction, %	63 ± 8	59 ± 7	69 ± 9	0.03
Global longitudinal strain, %	−18 ± 4	−19 ± 4	−17 ± 3	0.1
Mass index, g/m^2	121 ± 29	129 ± 24	114 ± 22	0.006
RWT	0.42 ± 0.18	0.40 ± 0.21	0.43 ± 0.23	< 0.001
Geometry				
Normal	62 (29)	38 (31)	24 (26)	0.002
Concentric remodelling	35 (16)	13 (17)	22 (24)	
Eccentric hypertrophy	66 (31)	46 (38)	20 (22)	
Concentric hypertrophy	51 (24)	24 (20)	27 (29)	
LA				
Reservoir strain, %	32 (27−41)	34 (28−41)	30 (25−37)	0.009
Volume index, mL/m^2	30 (24−37)	30 (24−36)	31 (24−40)	0.9
Septal E/e'	14.1 (10.0−17.6)	12.9 (10.0−16.8)	15.3 (10.1−20.4)	0.02
Lateral E/e'	12.1 (9.0−15.2)	10.7 (8.7−14.9)	13.7 (9.7−16.2)	0.01
RV				
FWS, %	−27 ± 5	−29 ± 5	−25 ± 6	0.02
SP, mm Hg	39 (31−46)	37 (28−41)	43 (32−49)	0.06
FWS/SP, % / mm Hg	−0.69 ± 0.26	−0.78 ± 0.27	−0.58 ± 0.23	< 0.001
RA				
Pressure, mm Hg	6 ± 3	6 ± 2	7 ± 3	0.08
Volume index, mL/m^2	24 (18−30)	25 (19−31)	23 (18−29)	0.2
Reservoir strain, %	41 (32−49)	43 (34−52)	39 (30−47)	0.07
Other, mm Hg				
COA Doppler peak gradient	21 (14−29)	19 (14−28)	23 (14−29)	0.4
COA Doppler mean gradient	12 (7−16)	11 (7−16)	12 (8−17)	0.4
Recoactation (mean gradient > 20)	20 (9)	12 (10)	8 (9)	0.8

Values are mean ± standard deviation, for continuous variables with normal distribution, median (interquartile range), for continuous variables with skewed distribution, and count (%) for categorical variables. The *P* values were derived from between-group comparisons using an unpaired *t* test, for continuous variables with normal distribution, a Wilcoxon rank-sum test, for continuous variables with skewed distribution, and a χ^2 test, for categorical variables. Relative wall thickness (RWT) was calculated as follows: (2 x left ventricular [LV] posterior wall thickness) / LV end-diastolic diameter. The 3 mutually exclusive aortic valve disease subgroups were as follows: (i) isolated aortic stenosis, defined as an aortic valve peak velocity > 3 m/s and < moderate aortic regurgitation (AR); (ii) isolated AR, defined as ≥ moderate AR and aortic valve peak velocity of ≤ 3 m/s; and (iii) mixed, defined as an aortic valve peak velocity of > 3 m/s and ≥ moderate AR. The 4 groups based on LV geometry were as follows: (i) normal LV geometry (LV mass index [MI] ≤ 95 g/m^2 in female patients, and ≤ 115 g/m^2 in male patients, and RWT ≤ 0.42); (ii) LV concentric remodelling (LVMI ≤ 95 g/m^2 in female patients, and ≤ 115 g/m^2 in male patients, and RWT > 0.42); (iii) LV concentric hypertrophy (LVMI > 95 g/m^2 in female patients, and > 115 g/m^2 in male patients, and RWT > 0.42); and (iv) LV eccentric hypertrophy (LVMI > 95 g/m^2 in female patients, and > 115 g/m^2 in male patients, and RWT ≤ 0.42).

COA, coarctation of aorta; E/e', ratio of mitral inflow pulse wave Doppler early velocity to tissue Doppler early velocity; FWS, free wall strain; LA, left atrial; RA, right atrial; RV, right ventricular; SP, systolic pressure.

concentric remodelling (24% vs 17%, $P = 0.002$), whereas males were more likely to have LV eccentric hypertrophy (38% vs 22%, $P = 0.002$; Table 2). Furthermore, female patients had higher LV filling pressures, worse LA function, worse RV free-wall strain, and higher RV systolic pressure (Table 2).

Outcomes

New-onset symptoms. Of 151 patients (85 male, 66 female) without symptoms at baseline encounter, 109 patients (72%; 53 male, 56 female) developed NYHA class II and/or III symptoms during follow-up. The 5-year cumulative incidence of new-onset symptoms was higher in female patients (83% vs 57%, unadjusted $P = 0.009$; Fig. 1A). Female sex was associated with a higher risk of new-onset symptoms during follow-up (unadjusted hazard ratio [HR] 1.33, 95% confidence interval [CI] 1.14-1.49), $P = 0.008$). Supplemental Table S1 shows the correlates of new-onset symptoms, based on univariable analyses. Multivariable analysis showed that female sex (adjusted HR 1.14, 95% CI 1.05-1.23, $P = 0.01$), older age (adjusted HR 1.02, 95% CI 1.01-1.03, $P = 0.008$), mixed AVD (adjusted HR 1.21, 95% CI 1.07-1.39, $P = 0.009$), concentric LV remodelling (adjusted HR 1.09, 95% CI 1.03-1.14, $P = 0.01$), concentric LV hypertrophy (adjusted HR 1.13, 95% CI 1.05-1.21, $P = 0.008$), and RV

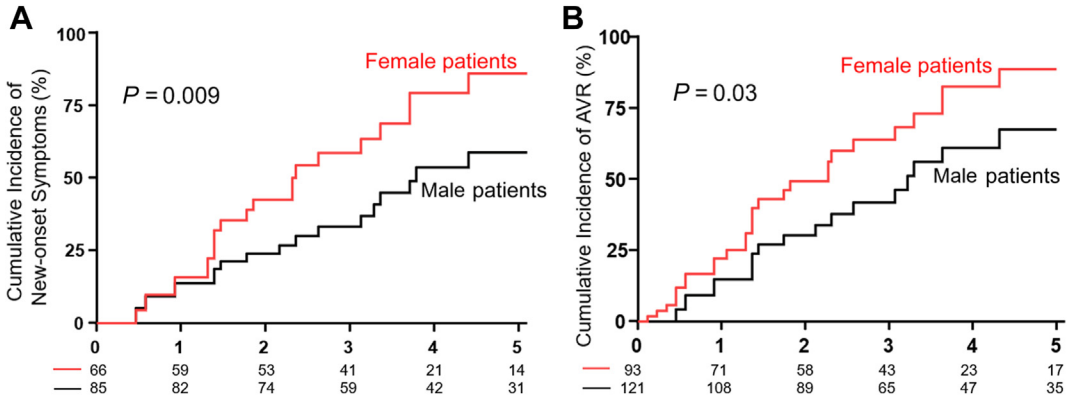

Figure 1. (**A**) Kaplan–Meier curves comparing cumulative incidence of new-onset symptoms between female patients (**red**) and male patients (**black**). The analysis was based on the subgroup of patients who were asymptomatic at the baseline encounter (n = 151). The patients with onset of symptoms were censored at the time of last clinical encounter, death, or aortic valve replacement (AVR). The *P* value was derived from the log-rank test. (**B**) Kaplan–Meier curves comparing the cumulative incidence of AVR between female patients (**red**) and male patients (**black**). The analysis was based on the entire cohort (n = 214). The patients who did not undergo AVR during follow-up were censored at the time of either the last clinical encounter or death. The *P* value was derived from thelog-rank test.

systolic pressure (adjusted HR 1.04, 95% CI 1.03-1.05, $P = 0.01$) were associated with new onset of symptoms (Table 3).

Aortic valve replacement. Of the 214 patients in the study, 191 patients (89%, 102 male, 89 female) underwent AVR (isolated AVR, n = 158; and AVR with root and/or ascending aorta replacement, n = 33). The indications for AVR were symptoms (n = 172; 80%), progressive LV enlargement (n =16; 8%), and LV systolic dysfunction (n = 14; 7%). Of note, 11 (5%) had more than one indication for AVR. Males patients were more likely to undergo AVR with root and/or ascending aorta, compared to female patients (20% [24 of 121] vs 9% [9 of 193], $P = 0.04$).

The 5-year cumulative incidence of AVR was higher in female patients (88% vs 71%, unadjusted $P = 0.03$; Fig. 1B). Female sex was associated with a higher risk of AVR during follow-up (unadjusted HR 1.26, 95% CI 1.10-1.42, $P = 0.01$) upon univariable analysis (Supplemental Table S2) but not upon multivariable analysis (Table 4). The correlates of AVR, as shown by multivariable analysis, were as follows: mixed AVD (adjusted HR 1.07, 95% CI 1.02-1.13, $P = 0.01$); LV concentric remodelling (adjusted HR 1.07, 95% CI 1.01-1.11, $P = 0.03$); and LV concentric hypertrophy (adjusted HR 1.10, 95% CI 1.04-1.19, $P = 0.01$; Table 4).

Of the 191 patients who underwent AVR, 176 patients (92%) received a mechanical prosthesis, and 15 patients (8%) received a bioprosthesis. No significant difference occurred in the proportion of male vs female patients who received bioprosthetic valves (6% [6 of 102] vs 10% [9 of 89], respectively, $P = 0.3$). No early postoperative mortality occurred. The average prosthesis size was 23 ± 2 mm. No between-group difference occurred in the postoperative aortic valve Doppler gradient at the time of hospital discharge (10 ± 3 mm Hg vs 9 ± 3 mm Hg, $P = 0.4$, for male and female patients, respectively).

CV adverse events. The 191 patients who underwent AVR were followed for 4.3 ± 2.5 years after AVR. During this period, the composite CV-adverse-event endpoint occurred in 34 patients (18%; atrial fibrillation, n = 16; nonsustained ventricular tachycardia, n = 9; sustained ventricular tachycardia, n = 2; heart failure hospitalization, n = 5; and death, n = 8). The cause of the death was due to heart failure (n = 2), sudden death (n = 1), endocarditis and/or sepsis (n = 1), or unknown factors (n = 4). No significant difference occurred in the 5-year cumulative incidence of CV events for male vs female patients (10% vs 13%, respectively, $P = 0.3$).

Discussion

In this study, we compared cardiac remodelling and outcomes of male patients vs female patients with repaired COA and concomitant AVD. The main findings were as follows: (i) both groups had similar severity and types of AVD, and functional status at baseline; (ii) female patients had more LV concentric hypertrophy and remodelling, LA hypertension and dysfunction, pulmonary hypertension, and RV systolic

Table 3. Multivariable Cox regression model showing correlates of new-onset symptoms

Covariates	HR (95% CI)	*P*
Female sex	1.14 (1.05–1.23)	0.01
Age, y	1.02 (1.01–1.03)	0.008
Aortic valve disease subgroup		
Isolated stenosis	Reference	
Isolated regurgitation	0.92 (0.76–1.25)	0.5
Mixed	1.21 (1.07–1.39)	0.009
LV geometry		
Normal	Reference	
Concentric remodelling	1.09 (1.03–1.11)	0.01
Eccentric hypertrophy	0.97 (0.78–1.14)	0.3
Concentric hypertrophy	1.13 (1.05–1.21)	0.008
RV systolic pressure, mm Hg	1.04 (1.03–1.05)	< 0.001

Covariates in this multivariable model were derived from the univariable analysis shown in Supplemental Table S1. Aortic valve disease subgroups and left ventricular (LV) geometry were modeled as categorical variables with isolated aortic stenosis and normal LV geometry, respectively, used as the reference for each group.

CI, confidence interval; HR, hazard ratio; RV, right ventricular.

Table 4. Multivariable Cox regression model showing correlates of aortic valve replacement

Covariates	HR (95% CI)	*P*
Female sex	1.05 (1.00−1.10)	0.08
Age, y	1.01 (0.99−1.03)	0.1
Aortic valve disease subgroup		
Isolated stenosis	Reference	
Isolated regurgitation	0.96 (0.82−1.10)	0.3
Mixed	1.07 (1.02−1.13)	0.01
LV geometry		
Normal	Reference	
Concentric remodelling	1.07 (1.01−1.11)	0.03
Eccentric hypertrophy	0.95 (0.76−1.10)	0.5
Concentric hypertrophy	1.10 (1.04−1.19)	0.01

Covariates in this multivariable model were derived from the univariable analysis shown in Supplemental Table S2. Aortic valve disease subgroup was modeled as a categorical variable with isolated aortic stenosis used as the reference for each group.

CI, confidence interval; HR, hazard ratio; LV, left ventricular.

dysfunction; and (iii) female sex was independently associated with onset of symptoms but not with AVR.

AVD is common in adults with repaired COA because of the high prevalence of bicuspid aortic valve in this population.[18,19] The presence of AVD creates additional LV pressure and/or volume overload, leading to more LV remodelling, LA and pulmonary vascular remodelling, and RV systolic dysfunction.[18,19,28] Because of the impaired ability of the left ventricle to cope with the additional pressure and/or volume overload from AVD, COA patients with concomitant AVD have a more aggressive clinical course, compared to that of patients without COA.[18,19] The current study provides new insight into the pathophysiology and outcomes of AVD in COA, by demonstrating sex-related differences in cardiac remodelling and outcomes in this population. The higher prevalence of LV concentric hypertrophy and remodelling observed in this cohort is similar to data from patients with degenerative AVD.[20] In a retrospective cohort study of 927 patients with AS (mean age, 74 years), Ito et al. observed that female patients had more LV concentric hypertrophy and higher LV filling pressures, similar to the findings of the current study.[20] In contrast to our findings, Ito et al. observed a lower aortic valve gradient, and aortic valve area indexed to body surface area, and in turn, a higher prevalence of low-flow, low-gradient AS in female patients.[20] These differences may be explained by the different inclusion criteria of the 2 studies; Ito et al. studied patients with isolated AS, whereas the current study included the entire spectrum of AVD. We postulate that the LA dysfunction, pulmonary hypertension, and RV systolic dysfunction observed in female patients may be due to the more-advanced LV remodelling that occurred in this group, which in turn, might have contributed to the rapid onset of symptoms in female patients. This postulate is supported by previous data showing that female patients, compared to male patients, had more LV fibrosis, and their LV fibrosis and hypertrophy were associated with higher LV filling pressure and mortality incidence.[21,29,30]

Another potential explanation for the observed differences in cardiac remodelling and the onset of symptoms may be related to differences in the duration of exposure to abnormal loading conditions. However, this possibility is unlikely, as both groups had similar ages and aortic valve hemodynamics at the time of their baseline encounter, and similar ages at the time of their COA repair. Hence, the observed differences in cardiac remodelling and symptomatic progression more likely are due to sex-related differences and the intrinsic ability of the left ventricle to adapt to abnormal loading conditions. Of note, sex-related differences in cardiac adaptation to AS have been demonstrated by Tastet et al. who showed that female patients had more focal and diffuse myocardial fibrosis, compared to that of male patients with AS, in spite of having a lower prevalence of atherosclerotic CV disease risk factors.[30]

Another interesting observation from this study was that, although female patients had more-rapid onset of symptoms, compared to male patients, the adjusted risk of AVR was not significantly different between the 2 groups. This finding may reflect the complex decision process involved in the timing of AVR, which relies on objective metrics, such as aortic valve hemodynamics and cardiac remodelling indices, subjective reports of symptoms by the patient, and subjective interpretation of symptoms by the treating physician. This process is consistent with previously described late referral for AVR, and worse outcomes after AVR in female patients, compared to those in male patients.[31,32]

To the best of our knowledge, this study is the first to systematically assess sex-related differences in cardiac remodelling and outcomes of AVD in COA, which is a common and important comorbidity in this population. The results of the current study may have important clinical implications with regard to the monitoring and timing of AVR in this population. Perhaps, female patients with COA and concomitant AVD should be monitored more closely because of the more-advanced cardiac remodelling at baseline and the more-rapid onset of symptoms during follow-up. Thresholds of reinterventions should be reassessed, depending on these parameters.

Limitations

This retrospective cohort study focused on adults with COA, followed at a single tertiary centre; hence, it is prone to selection and ascertainment bias. However, the age and clinical characteristics of the cohort were similar to those in prior reports in the literature, suggesting that the results of the current study should be generalizable to other COA patients. We did not perform subgroup analysis based on AVD subgroups and LV geometry, because of the small sample size. Finally, the study carries a risk of overfitting of the models, because of the multiple covariates and small sample size.

Conclusions

Although male and female patients had similar AVD severity and CV comorbidities, female patients had more adverse cardiac remodelling, and more-rapid onset of symptoms, compared to male patients. LV concentric hypertrophy and remodelling were more common in female patients and were associated with onset of symptoms and AVR. These findings highlight important sex-related differences that occur in the clinical course of AVD in COA patients and suggest that more studies are needed to determine whether a sex-specific monitoring protocol and criteria for interventions

would be required in this population. Also needed is a delineation of the effect of pregnancy on CV remodelling and the progression of valvular heart disease in this population.

Ethics Statement

Research work adhered to the guidelines stipulated by the Mayo Clinic institutional review board.

Patient Consent

The authors confirm that patient consent is not applicable to this article because this is a retrospective chart review, and therefore, the institutional review board did not require consent from the patient.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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