IJC Heart & Vasculature 28 (2020) 100530

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Increased prevalence of left ventricular diastolic dysfunction in adults with repaired coarctation of aorta

Alexander C. Egbe *, William R. Miranda, Heidi M. Connolly

The Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN 55905, United States

ARTICLE INFO

Article history:
Received 18 March 2020
Received in revised form 28 April 2020
Accepted 30 April 2020

Keywords:
Coarctation of aorta
Left ventricular diastolic dysfunction
Left ventricular hypertrophy

ABSTRACT

Background: Left ventricular (LV) pressure overload and coronary artery disease are common in patients with coarctation of aorta (COA), and they are risk factors for LV diastolic dysfunction. Patients with COA may have aortic vasculopathy that can result in LV pressure overload even in the absence of hemodynamically significant COA. We therefore hypothesized that patients with mild COA (without hemodynamically significant COA) will have more LV diastolic dysfunction compared to controls.

Methods: Adult patients with mild COA (Doppler peak velocity < 2.5 m/s) were matched 1:1 to patients without structural heart disease using propensity score method based on age, sex, body mass index, hypertension and blood pressure. The objective was to compare LV diastolic dysfunction (defined as E/e′ > 2 standard deviations above age-specific normative values) between adults with repaired COA and controls.

Results: Of 204 COA and 204 control patients (age 35 ± 12 years), patients with COA had higher septal and lateral E/e′ ratio (12 ± 4 vs 9 ± 4, p = 0.009) and (10 ± 3 vs 7 ± 3, p < 0.001), respectively. Compared to controls, the prevalence of LV diastolic dysfunction was higher in patients with COA for every age group: <40 years (63% vs 13%, p < 0.001); 41–60 years (87% vs 33%, p < 0.001); age > 60 years (82% vs 56%, p = 0.076). Left ventricular mass index (LVMI) was the strongest determinant of E/e′ (β = 2.71 per 10 g/m^2, standard error = 1.25, p < 0.001).

Conclusion: LV diastolic dysfunction was common in patients with COA, and the association with LVMI suggests that patients with COA may have ongoing LV pressure overload in the absence of hemodynamically significant re-coarctation.

1. Introduction

Patients with coarctation of aorta (COA) are exposed chronic (LV) pressure overload due to isthmus coarctation, increased arterial stiffness and endothelial dysfunction [1–4]. Chronic LV pressure overload is associated with LV remodeling which typically manifests as LV hypertrophy and diastolic dysfunction [2,5–7]. COA is also associated with increased risk of premature coronary artery disease, which further increases the risk LV remodeling [4]. Since aortic vasculopathy, hypertension and coronary artery disease affect left ventricular (LV) function [8–11], it is therefore important to determine if COA patients (without hemodynamically significant coarctation) have a higher than the expected risk of LV diastolic dysfunction. Understanding the risk and burden of LV diastolic dysfunction in patients with COA, is an important step towards formulating risk factor modification strategies tailored to this unique population.

The purpose of this study was to determine if patients with COA were at higher risk for LV diastolic dysfunction even in the absence of hemodynamically significant left heart obstruction, and to determine the predictors of LV diastolic function in this population. We therefore hypothesized that patients with mild COA (without hemodynamically significant coarctation) will have more LV diastolic dysfunction compared to controls matched by age, sex, body mass index, history of hypertension and systolic blood pressure. The scientific rationale for this hypothesis was based on previous data demonstrating aortic vasculopathy and endothelial dysfunction in patients with COA [2,3], and data linking aortic

Abbreviations: LV, Left ventricle; COA, coarctation of aorta; LVMI, left ventricular mass index; E, mitral inflow pulsed wave early velocity; e′, mitral annular tissue Doppler early velocity.

* Corresponding author at: Mayo Clinic and Foundation, 200 First Street SW, Rochester, MN 55905, United States.

E-mail address: egbe.alexander@mayo.edu (A.C. Egbe).

https://doi.org/10.1016/j.ijcha.2020.100530
2352-9067/

and peripheral vasculopathy to LV diastolic dysfunction in the acquired heart disease population [8,9].

2. Methods

2.1. Patient selection

We reviewed the MACHD (***M***ayo ***A***dult ***C***ongenital ***H***eart ***D***isease) database and identified patients (age $\geq$ 18 years) with COA that received care at Mayo Clinic Rochester, Minnesota from January 1, 2004 through December 31, 2018. The Mayo Clinic Institutional Review Board approved this study. Patients with repaired COA were eligible for the study if they met these 5 criteria based on transthoracic echocardiogram performed at rest. (1) Patients without hemodynamically significant COA defined as a continuous wave Doppler peak velocity < 2.5 m/s at the site of COA. (2) Patients without significant aortic valve disease defined as having a native aortic valve peak velocity < 2.5 m/s or $\leq$ mild aortic regurgitation. (3) Patients without significant mitral valve disease defined as a native mitral valve mean gradient < 3 mmHg or $\leq$ mild mitral regurgitation. (4) Outpatient cuff blood pressure measurement from the right arm in the absence of aberrant origin of right subclavian artery. (5) Tissue Doppler imaging data for the assessment of LV diastolic function. Patients with previous mitral and aortic valve surgery, and patients that were not in sinus rhythm were excluded. A prior study using the same cohort has been published [12].

For the control group, we identified patients without structural heart disease that underwent echocardiogram within the same period. The absence of structural heart disease was verified by manual review of report of echocardiogram. We performed 1:1 matching of patients with COA and controls using propensity score method based on age, sex, body mass index, history of hypertension and systolic blood pressure at the time of echocardiogram.

2.2. Study objectives and outcomes

The primary objective was to compare LV diastolic function indices and the prevalence of LV diastolic dysfunction between patients with COA and propensity-matched controls. The secondary objective was to determine the predictors of LV diastolic function, and the predictors of temporal change in LV diastolic function in the COA group. Temporal change in LV diastolic function was assessed in this subset of patients that had two echocardiograms performed > 10 years apart and no surgical procedure, transcatheter intervention, or initiation of new antihypertensive medication between the baseline and subsequent echocardiogram.

The main outcome of this study was LV diastolic function. LV diastolic function was assessed using mitral inflow pulsed wave early velocity (E), mitral inflow deceleration time, mitral annular tissue Doppler early velocity (e′), left atrial volume index, and tricuspid regurgitation velocity [13]. We defined LV diastolic dysfunction based on age-specific values of lateral and septal E/e′ [14]. A patient was considered to have LV diastolic dysfunction if E/e′ value was > 2 standard deviations above the age-specific normative value [14]. Two-dimensional and Doppler echocardiography was performed according to contemporary guidelines [13,15,16]. Two experienced sonographer (JW and KT) performed offline measurements of all echocardiographic indices. LV hypertrophy was assessed using LV mass index (LVMI) based on two-dimensional echocardiographic linear measurements of LV diastolic diameter and wall thickness [15]. The pattern of LV remodeling was classified based on the normative values for LVMI and relative wall thickness [15]. Relative wall thickness was calculated as (2 $\times$ posterior wall thickness)/LV end-diastolic diameter [15]. The following echo machines were used for image acquisition: Vivid E9 and E95 (General Electric Co, Fairfield, Connecticut); Philips EPIQ (Dallas, Tx); and Siemens Acuson (CA, USA).

2.3. Statistical analysis

Data were presented as mean ± standard deviation or count (%). Propensity score matching was used to balance the differences in baseline characteristics between the COA and control groups. A propensity score, the probability of having COA was estimated using logistic regression based on age, sex, body mass index, history of hypertension, and systolic blood pressure at the time of echocardiogram. One-to-one nearest neighbor caliper matching was used to match patients based on the logit of the propensity score using a caliper equal to 0.2 of the standard deviation of the logit of the propensity score [17]. The balance of covariates after matching was assessed using unpaired *t*-test and Fisher's exact test as appropriate.

The between-group differences in diastolic function indices, and prevalence of diastolic dysfunction were assessed using paired *t*-test and Fisher exact tests as appropriate. Because of the relationship between coronary artery disease and LV diastolic dysfunction, a sensitivity analysis was performed comparing the LV diastolic function indices in the subset of patients with COA and controls without known coronary artery disease diagnosis. Coronary artery disease was defined as history of acute coronary syndrome (ST-segment–elevation myocardial infarction, non–ST-–elevation myocardial infarction, or unstable angina), history of coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention) or > 50% stenosis in any vessel on invasive coronary or CT angiogram similar to our previous study [1].

Linear regression was used to determine the predictors of E/e′ and temporal change E/e′. The variables used in the full model were chosen *a priori* based on known association with LV diastolic function or clinical importance and we used stepwise backward selection based on likelihood ratio p value to arrive at the final model [13]. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed with JMP software (version 14.0; SAS Institute Inc, Cary NC).

Table 1
Baseline characteristics.

	COA (n = 204)	Control (n = 204)	p
Age, years	35 ± 12	35 ± 12	0.894
Male	117 (57%)	117 (57%)	0.999
Body mass index, kg/m^2	26 ± 5	26 ± 5	0.891
Systolic blood pressure, mmHg	126 ± 21	126 ± 16	0.517
Hypertension	119 (58%)	119 (58%)	0.999
Labs			
NT proBNP	135 ± 59	96 ± 36	0.04
Fasting glucose, mg/dl	103 ± 13	108 ± 11	0.3
Creatinine, mg/dl	1.1 ± 0.1	1.0 ± 0.2	0.6
NYHA II-IV	33/178 (19%)	18/164 (11%)	0.05
Diabetes	18 (9%)	16 (8%)	0.7
Medications			
Diuretics	16 (8%)	6 (3%)	0.028
Beta blockers	50 (25%)	17 (8%)	<0.001
Calcium channel blockers	21 (10%)	11 (5%)	0.066
RAAS antagonist	55 (25%)	31 (15%)	0.002
LV remodeling			
Concentric LV hypertrophy	55 (27%)	26 (13%)	<0.001
Eccentric LV hypertrophy	50 (24%)	51 (25%)	0.931
Eccentric remodeling	36 (18%)	29 (14%)	0.365
Normal	63 (31%)	98 (48%)	0.001

COA: Coarctation of aorta; RAAS: Renin-angiotensin-aldosterone system; LV: Left ventricle; NYHA: New York Heart Association.

3. Results

We enrolled 204 patients with COA and 204 controls in the study. In the COA group, 129 (63%) had bicuspid aortic valve, and the initial COA repair/intervention was resection and end-to-end anastomosis (n = 104, 51%), subclavian flap repair (n = 25, 12%), patch aortoplasty (n = 14, 7%), interposition graft repair (n = 37, 18%), extra-anatomic bypass graft (n = 10, 5%), balloon aortic dilation (n = 10, 5%), and aortic stent implantation (n = 4, 2%). The median age at the time of initial COA repair/intervention was 2.6 (0.7–8.5) years. In the control group, the indication for echocardiogram was screening for family history of congenital heart disease (n = 95, 47%), clinical evaluation for personal/family history of genetic arrhythmia (n = 54, 27%), hypertension (n = 39, 19%), non-cardiac dyspnea (n = 9, 4%), and others (n = 7, 3%). Table 1 shows a comparison of the baseline clinical characteristics of the COA and control groups. A diagnosis of coronary artery disease was more common in the COA group (n = 17, 8%) compared to controls (n = 5, 3%), p = 0.009. The upper to lower extremity blood pressure gradient in the COA group was 6 ± 3 mmHg.

Compared to the control group, the COA group had lower septal and lateral e′ velocities (9 ± 4 vs 11 ± 4 cm/s, p = 0.045) and (11 ± 3 vs 14 ± 4 cm/s, p = 0.021), respectively. Similarly the COA group had higher septal and lateral E/e′ ratio (12 ± 4 vs 9 ± 4,

Table 2
Echocardiography.

	COA (n = 204)	Control (n = 204)	Mean diff (95% CI)	p
LV ejection fraction, %	63 ± 8	60 ± 5	3 (−1 to 5)	0.104
LV end-diastolic dimension, mm	51 ± 7	52 ± 3	−1 (−3 to 1)	0.121
LV end-systolic dimension, mm	31 ± 6	33 ± 3	−2 (−4 to 1)	0.095
LV stroke volume index, mL/m^2	39 ± 11	46 ± 8	−5 (−7 to −3)	<0.001
Heart rate, bpm	73 ± 10	68 ± 7	4 (1–7)	0.014
LV mass index, g/m^2	109 ± 35	93 ± 22	16 (9–23)	<0.001
Relative wall thickness	0.41 ± 0.05	0.37 ± 0.04	0.04 (0.02–0.05)	<0.001
Mitral E velocity, m/s	1.1 ± 0.4	0.9 ± 0.1	0.2 (0.1–0.3)	0.012
Mitral A velocity, m/s	0.6 ± 0.2	0.6 ± 0.1	−1 (−3 to 2)	0.432
Mitral deceleration time, ms	189 ± 42	168 ± 36	19 (−11 to 37)	0.318
Septal e′ velocity, cm/s	9 ± 4	11 ± 4	−2 (−3 to −1)	0.045
Lateral e′ velocity, cm/s	11 ± 3	14 ± 4	−2 (−4 to −1)	0.021
Septal E/e	12 ± 4	9 ± 4	3 (1–5)	0.009
Lateral E/e	10 ± 3	7 ± 3	3 (2–4)	<0.001
Left atrial volume index, mL/m^2	33 ± 6	29 ± 5	4 (−1 to 9)	0.061
Tricuspid regurgitation velocity, m/s	2.6 ± 0.5	2.5 ± 0.4	0.1 (−0.3 to 0.3)	0.585

COA: Coarctation of aorta; LV: Left ventricle; E: Mitral early diastolic velocity; A: Mitral late diastolic velocity; e′: Mitral annular tissue Doppler early velocity; CI: Confidence.

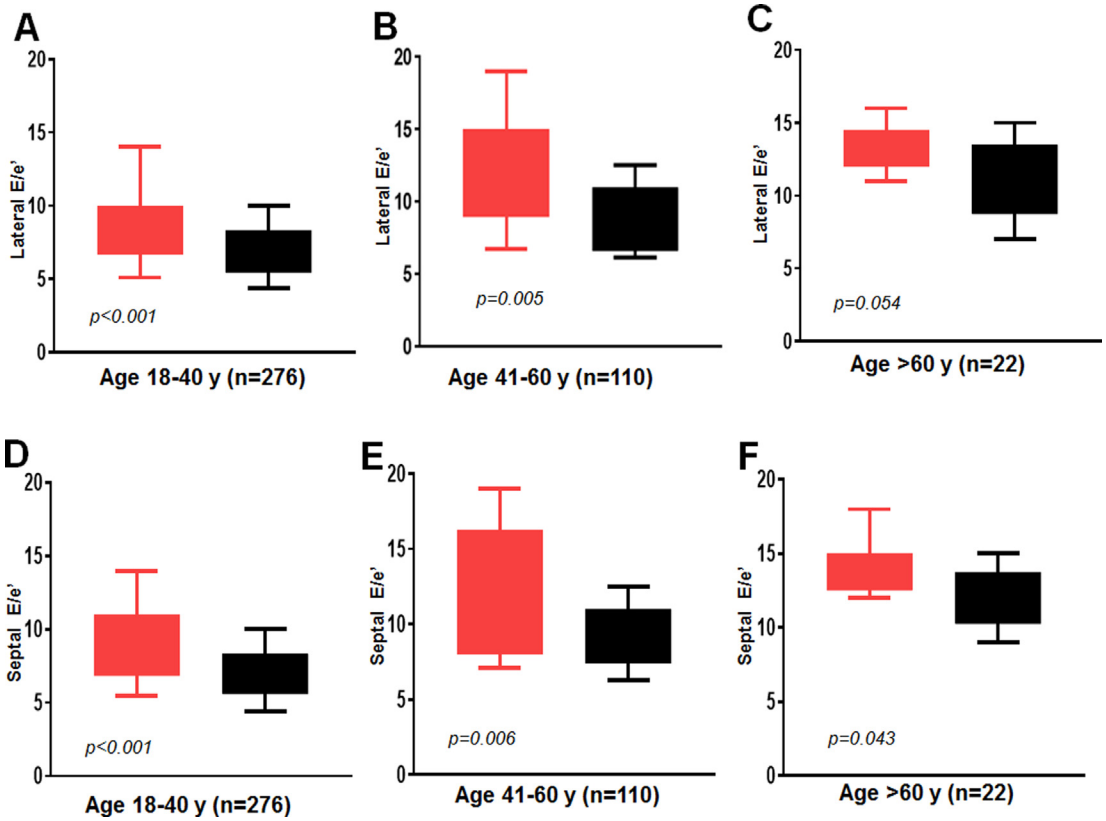

Fig. 1. (A–F) Box-and-whisker plot comparing E/e′ between patients with coarctation of aorta (red) and controls (black) across different age groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

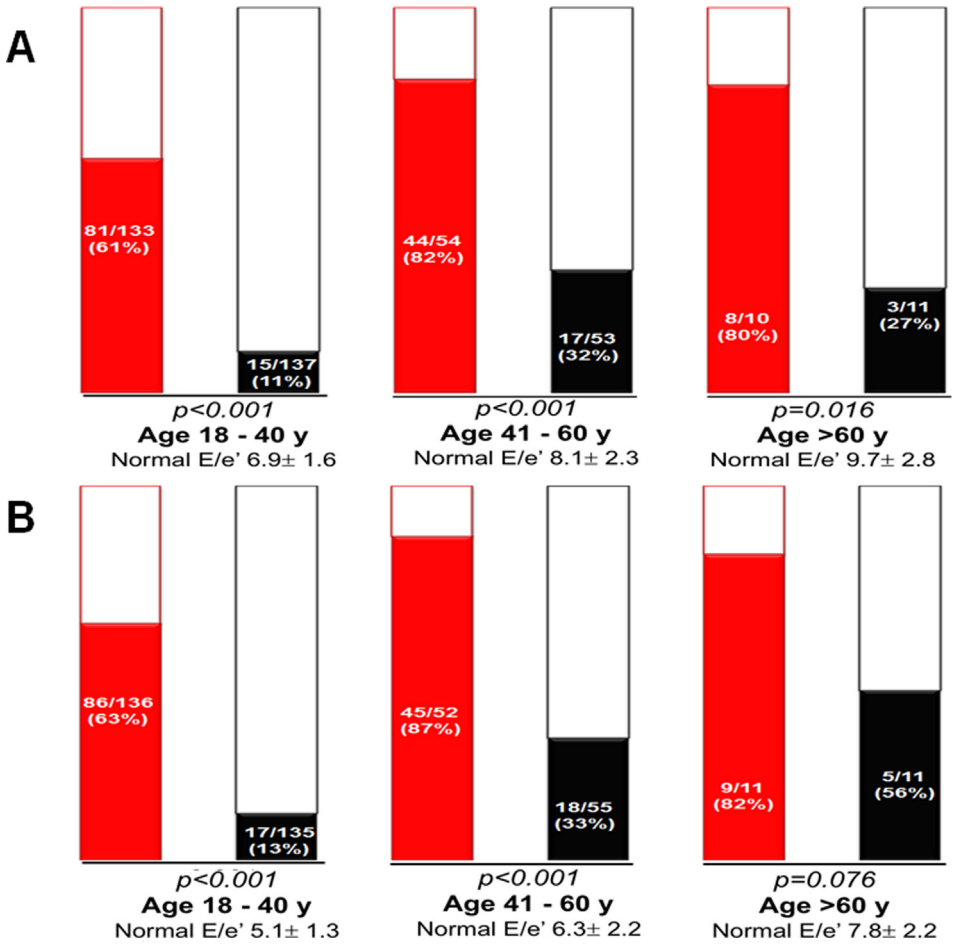

Fig. 2. Bar graphs comparing the prevalence of left ventricular (LV) diastolic dysfunction between patients with coarctation of aorta (red) and controls (black) across different age groups based on age-specific normative values for septal E/e′ (A) and lateral E/e′ (B) [14]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

p = 0.009) and (10 ± 3 vs 7 ± 3, p < 0.001), respectively (Table 2). This between-group difference was also significant for patients aged 18–40 years (septal E/e′ 9 ± 3 vs 7 ± 2, p < 0.001; lateral E/e′ 9 ± 3 vs 7 ± 2, p < 0.001) and patients aged 41–60 years (septal E/e′ 12 ± 4 vs 9 ± 2, p = 0.006; lateral E/e′ 11 ± 4 vs 9 ± 2, p = 0.005), Fig. 1. The prevalence of LV diastolic dysfunction was higher in the COA group in almost all the age groups, Fig. 2. Sensitivity analyses performed in patients without coronary artery disease (182 COA and 182 controls) showed similar between-group differences in e′, E/e′ and prevalence of LV diastolic dysfunction.

Exploratory analyses were performed in the COA group to assess difference in diastolic function based on diagnosis of hypertension and type of repair. Compared to the patients without history of hypertension, those with hypertension diagnosis had lower septal and lateral e′ velocities (8 ± 2 vs 10 ± 3 cm/s, p = 0.04) and (9 ± 2 vs 12 ± 3 cm/s, p = 0.02), respectively. Similarly, those with hypertension had higher septal and lateral E/e′ ratio (13 ± 2 vs 11 ± 3, p = 0.01) and (11 ± 3 vs 9 ± 3, p = 0.02) respectively. However, there were significant between-group differences (stent vs surgical COA repair) in septal e′ velocities (10 ± 3 vs 9 ± 3 cm/s, p = 0.09), lateral e′ (11 ± 4vs 12 ± 4 cm/s, p = 0.1), septal E/e′ ratio (12 ± 4 vs 12 ± 3, p = 0.3) and lateral E/e′ (10 ± 3 vs 11 ± 3, p = 0.08).

LVMI (β = 2.71 per 10 g/m^2, standard error = 1.25, p < 0.001) and age (β = 0.37 per 5 years, standard error = 0.14, p = 0.009) were the multivariate predictors of septal E/e′ while LVMI (β = 2.23 per 10 g/m^2, standard error = 0.85, p < 0.001) and coronary artery disease (β = 1.53 per 5 years, standard error = 0.09, p = 0.022) were the multivariate predictors of lateral E/e′ (Supplementary Tables 1 and 2). Of the 204 patients with COA, 92 (45%) had subsequent echocardiogram > 10 years from the baseline echocardiogram. The mean interval between echocardiograms was 12 ± 1 years, and the temporal changes in septal E/e′ and lateral E/e′ were 2.4 (95% confidence interval 2.3–2.6), and lateral E/e′ by 2.2 (95% confidence interval 2.0–2.7) respectively. LVMI was the only multivariate predictor of temporal change in septal E/e′ (β = 1.98 per 10 g/m^2, standard error = 0.82, p = 0.028) and lateral E/e′ (β = 1.85 per 10 g/m^2, standard error = 0.14, p < 0.001) (Supplementary Table 3 and 4). The interval change in LVMI between baseline and subsequent echocardiograms was 6.1 g/m^2 (95% confidence interval 3.2–9.6). There was a good correlation between LVMI and E/e′ (lateral r = 0.62, p < 0.001 and septal r = 0.59, p < 0.001) at baseline echocardiogram, Fig. 3A and B. There was also a modest correlation between temporal change in LVMI and E/e′ (lateral r = 0.46, p < 0.001 and septal r = 0.53, p < 0.001), Fig. 3C and D.

4. Discussion

Based on a propensity-matched cohort of patients with and without COA, we showed that patients with COA had worse LV diastolic function indices and more LV hypertrophy. Compared to controls, the prevalence of LV diastolic dysfunction was higher in patients with COA for every age group: age < 40 years of age (63% vs 13%, p < 0.001); age 41 to 60 years (87% vs 33%,

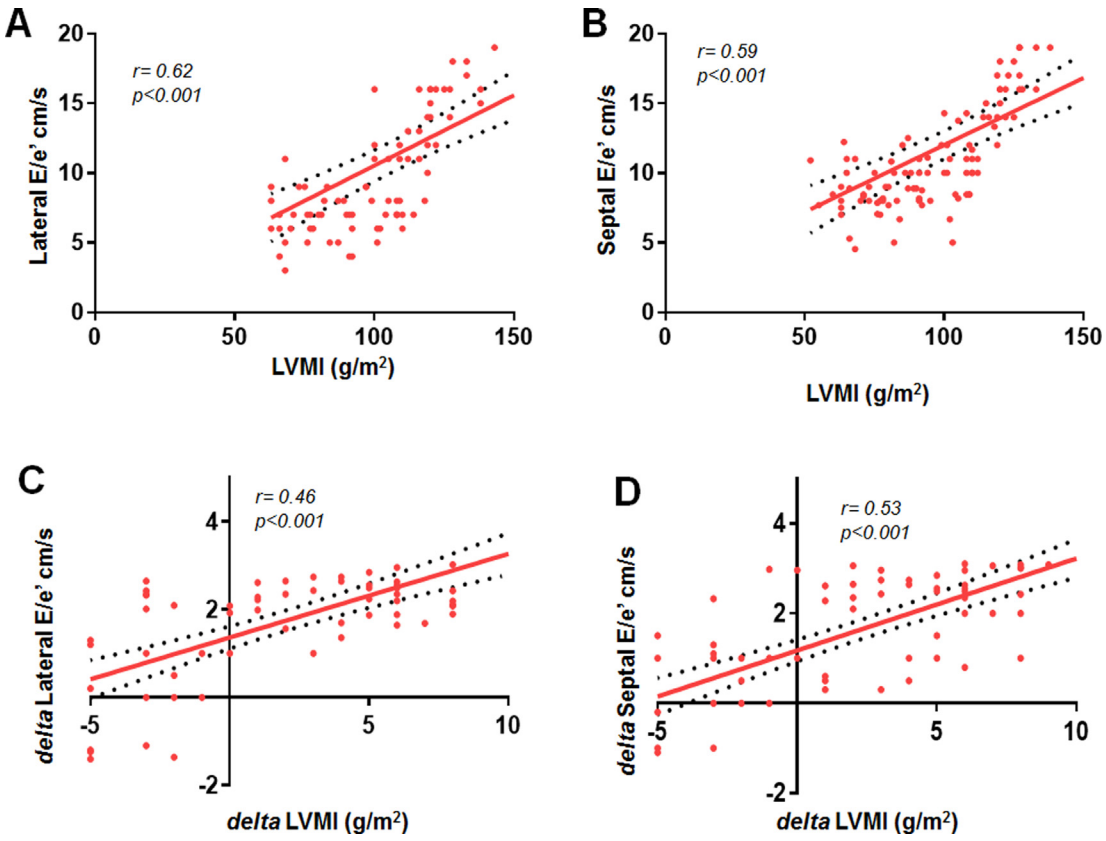

Fig. 3. Linear regression of LV mass index (LVMI) and E/e′ (A & B) and between temporal change in LVMI and temporal change in E/e′ (C & D).

p < 0.001); age > 60 years (82% vs 56%, p = 0.076). LV diastolic dysfunction was almost universal after the age of 40 years in patients with COA. This between-group difference in the prevalence of LV diastolic dysfunction was independent of coronary artery disease diagnosis. LV hypertrophy (LVMI) was a predictor of LV diastolic function indices (E/e′) at baseline and during follow-up. We also observed a correlation between temporal change in LVMI and temporal change in E/e′. Putting all these together, this study showed that patients with COA (without hemodynamically significant COA) have a higher than the expected risk of LV diastolic dysfunction.

Previous studies have described diastolic function indices in COA in children and adults. [18–23] The association between COA and LV diastolic dysfunction presented above is consistent with a previous study conducted in of 24 pediatric patients with COA.[11] In that study, Lombardi et al[11] reported a lower septal e′ in the patients with COA compared to controls, and an inverse correlation between septal e′ and aortic stiffness indices. In addition to matching by age, sex and weight as used in the previous study,[11] we also incorporated history of hypertension and systolic blood pressure in the propensity score matching. By controlling for these known confounders, the observed between-group difference in LV diastolic function is most likely related to COA diagnosis.

LVMI was a predictor of E/e′ at baseline and during follow-up, and temporal change in LVMI was associated with change in E/e′. Although the relationship between age, LV hypertrophy and diastolic dysfunction is well established in the literature,[7,11,13] we demonstrate for the first time that temporal changes in LV hypertrophy (LVMI) was associated with concordant changes in diastolic dysfunction (E/e′) in the COA population. There are two plausible mechanistic explanations for this finding. The first is that progression of LV hypertrophy (cause) results in progression of LV diastolic dysfunction (effect), while the second explanation is that progression of LV hypertrophy and diastolic dysfunction are both effects of aging and are accelerated/enhanced in patients with COA. Although the current study does not provide data about causality, we speculate that the progression of LV hypertrophy may be responsible for progression in diastolic dysfunction since prior studies have showed that therapies that reduce LV afterload and LVMI also results in improved diastolic function indices.[24,25]

LV diastolic dysfunction, especially when associated with elevated left heart filling pressures, is an important cause of heart failure-related symptoms and mortality.[26,27] Treatment of symptoms and modification of secondary causes of LV diastolic dysfunction is a cornerstone for the management of symptomatic patients. [28,29] The association between LV hypertrophy and LV diastolic dysfunction in the current study suggests that perhaps we should address the underlying causes of LV hypertrophy in this population. LV hypertrophy, as measured by LVMI, reflects LV adaptation to chronic abnormal loading conditions (pressure and/or volume overload).[30,31] Since we observed higher LVMI in the patients with COA after controlling for systolic blood pressure, hypertension history, and body mass index, we postulate that COA diagnosis is an independent risk factor for LV hypertrophy. Several studies have demonstrated that patients with COA have vascular and endothelial dysfunction, as well as an association between vascular and endothelial dysfunction and LV hypertrophy.[2,3,7,11] Patients with COA with vascular and endothelial dysfunction and normal blood pressure at rest sometimes have hypertension on ambulatory blood pressure monitoring.[2,3,7,11] This is likely because of the inability of the central arterial system to tolerate increased stroke volume during low intensity physical exertion required for activities of daily living. Putting all these together,

we speculate that compared to matched control, patients with COA (without hemodynamically significant COA) may have higher LV afterload due to vasculopathy which then results in maladaptive LV hypertrophy and subsequent diastolic dysfunction.

The guidelines for management of adults with congenital heart disease does not specify the systolic blood pressure target for antihypertensive therapy in patients with COA.[32] In our clinical practice, we typically titrate antihypertensive therapy to achieve systolic blood pressure < 140 mmHg at rest and absence of exercise-induced hypertension which is the same criteria used in the general cardiovascular population. The higher prevalence of LV diastolic dysfunction and its association with LV hypertrophy in the current study suggest that perhaps patients with COA represent the unique population and deserve more rigorous mechanistic investigations. Further studies are also required to determine if intensive blood pressure management will result in a reduction in LVMI and improvement of LV diastolic function indices.

5. Limitations

Although we demonstrated a correlation between LVMI and LV diastolic dysfunction as well as correlation between temporal changes in LVMI and diastolic function indices, the study design does not provide proof of causality. There were no standardized diagnostic criteria for hypertension and coronary artery disease in the current study, but rather we relied on diagnoses as documented in the clinical notes. However this should not have significant impact on the results since the same methodology was applied to both the case and controls. We controlled for known confounders with robust statistical methodology but this does not completely eliminate the risk of some residual confounders.

6. Conclusion

LV diastolic dysfunction was common in patients with COA even in absence of hemodynamically significant COA, and LVMI was an independent risk factor for LV diastolic dysfunction. Since LVMI reflects LV adaptation to chronic abnormal loading conditions, our data suggest that patients with COA may have ongoing LV pressure overload in the absence of hemodynamically significant re-coarctation.

Acknowledgements

James Welper (JW) and Katrina Tollefsrud (KT) for performing offline measurements of the echocardiographic indices used in this study.

Funding

Dr. Egbe is supported by National Heart, Lung, and Blood Institute (NHLBI) grant K23 HL141448-01.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100530.

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