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Temporal changes in prevalence and severity of pulmonary hypertension, and relationship to outcomes in coarctation of aorta

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ABSTRACT

Background: Pulmonary hypertension (PH) affects 20% of adults with coarctation of aorta (COA). What is not known is whether PH prevalence and severity increased over time, and the prognostic implications of such changes. The purpose of this study was to assess temporal changes in PH prevalence and severity (PH progression), and to determine the correlates and prognostic implications of pH progression in adults with COA.
Method: Retrospective cohort study of adults with repaired COA with ≥ 2 echocardiograms > 5 years apart. PH was defined as Doppler-derived right ventricular systolic pressure (RVSP) > 40 mmHg.
Results: Of 392 patients (age 35 years [24–49]; females 154 [39 %]), median RVSP was 30 (26–35) mmHg, and 76 (19 %) had PH at baseline echocardiogram. There was a temporal increase in PH severity (ΔRVSP 6 ± 9 mmHg, p = 0.008), and PH prevalence (19 % versus 27 %, p = 0.01). The correlates of Δ RVSP were older age, left atrial (LA) dysfunction, left ventricular (LV) hypertrophy, high LV global afterload, and atrial fibrillation. Of 392 patients, 50 (13 %) died, and Δ RVSP was associated with mortality (adjusted hazard ratio 1.19 [1.08–1.31] per 5 mmHg increase, p = 0.006) after adjustment for baseline RVSP, demographic indices, comorbidities, and echocardiographic indices.
Conclusions: These findings underscore the clinical importance of pH in COA and supports the need for new strategies for prevention and treatment of LA and LV dysfunction, which should in turn, slow the pace of pH progression in this population. Such strategies should include early detection and treatment of hypertension and atrial fibrillation.

1. Introduction

Pulmonary hypertension (PH) is present in 20 % of the adults with repaired coarctation of aorta (COA), and it is associated with right ventricular (RV) systolic dysfunction, right heart failure, and all-cause mortality. [1–3] The etiology of pH in COA is multifactorial, but it is predominantly due to chronic elevation in left atrial (LA) pressures leading to pulmonary vascular remodeling, elevated pulmonary artery pressures, and RV dysfunction. [2–8] The data about PH prevalence in COA were derived from cross-sectional studies, and average age of the patients at the time of sampling was 30–35 years. [2–4] What is not known is whether PH prevalence and severity increased over time in adults with COA, and the prognostic implications of such changes.

Since PH in COA is attributed to left-sided heart disease, and the severity of left-sided heart disease increased with age, it is logical to expect ongoing pulmonary vascular remodeling and worsening PH over time in this population. [7–10] Based on this premise, we hypothesized that adults with COA would experience a temporal increase in the PH prevalence and severity over time (PH progression), and that PH progression would be associated with all-cause mortality in this population. The purpose of this study was to assess temporal change in PH prevalence and severity, and to determine the correlates and prognostic implications of pH progression in adults with COA.

Abbreviations: COA, COA: Coarctation of aorta; CI, Confidence interval; HR, Hazard ratio; IQR, Interquartile range; LA, Left atrium; LV, Left ventricle; LVOT, Right ventricular outflow tract; PH, Pulmonary hypertension; RA, Right atrium; RVSP, Right ventricular systolic pressure.

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2. Methods

2.1. Study population

This is a retrospective cohort study of adults (age ≥ 18 years) with repaired COA that received care at Mayo Clinic from January 1, 2003, to December 31, 2017. From this cohort, we selected consecutive patients that met the following inclusion criteria: (1) Two or more transthoracic echocardiograms with > 5 years interval between studies and no surgical or transcatheter cardiovascular interventions between echocardiograms. (2) Adequate echocardiographic images for the estimation of Doppler-derived RV systolic pressure (RVSP) in both studies. (3) Absence of pulmonary valve stenosis defined as pulmonary valve peak velocity < 2 m/s. (4) Absence of left ventricular (LV) inflow disease (Shone complex) defined as having any of the following conditions: mitral valve prosthesis, sub-valvular, valvular, or supra-valvular mitral stenosis (mean gradient > 3 mmHg) or ≥ moderate mitral regurgitation.

Because of the known association between COA and left-sided heart lesions, we divided the cohort into patients with isolated COA versus COA with concomitant LVOT disease. LVOT disease was defined as any of the following conditions: aortic valve prosthesis, sub-valvular, valvular, or supra-valvular aortic stenosis (mean gradient > 20 mmHg) or ≥ moderate aortic regurgitation.

2.2. Study objectives

The study objectives were to: (1) Assess temporal change in PH prevalence and severity (PH progression). PH severity was estimated using Doppler-derived RVSP, temporal change in PH severity was assessed as Δ RVSP between echocardiograms. PH was defined as RVSP > 40 mmHg, and temporal change in PH prevalence was assessed as the difference in PH prevalence between echocardiograms. [1] (2) Identify clinical and hemodynamic factors associated with PH progression (Δ RVSP). (3) Determine the prognostic implications of pH progression. This was assessed as the relationship between Δ RVSP and all-cause mortality.

2.3. Echocardiography

The first echocardiogram performed within the study period was designated as the baseline echocardiogram (Echo #1), and the first echocardiogram performed > 5 years from the baseline echocardiogram was designated as the follow-up (Echo #2). Offline image analyses and measurements were performed in all patients as previously described. [2,5,11] Tricuspid regurgitation velocity was assessed from multiple windows, and the Doppler signal with the highest velocity that was visible through at least one half of the systolic period was selected for analysis. [12,13] RVSP was estimated using the modified Bernoulli equation 4 x (tricuspid regurgitation peak velocity)^2 + estimated right atrial (RA) pressure. RA pressure was estimated based on the size and collapsibility of the inferior vena cava using standard technique. [13–15] In the absence of pulmonary valve stenosis, estimated RVSP was used as a surrogate for pulmonary artery systolic pressure. [2–4] Temporal change in PH severity (Δ RVSP) was calculated as: RVSP from Echo #2 minus RVSP from Echo #1, whereby a positive value signifies an increase in PH severity, while a negative value signifies a decrease in PH severity. Cardiac chamber size and function was assessed by 2D, Doppler, and speckle tracking echocardiography using standard techniques. [16–18].

2.4. Reproducibility analysis

The reproducibility of estimated RVSP (estimated RA pressure and tricuspid regurgitation velocity) was assessed in 20 studies from 10 randomly selected patients (10 from Echo #1 and 10 from Echo #2). There was an excellent intraobserver and interobserver agreement for RVSP in Echo #1 (intraclass coefficient 0.95, 95 % confidence interval [CI] 0.92–0.98, and intraclass coefficient 0.89, 95 % CI 0.84–0.94, respectively), and RVSP in Echo #2 (intraclass coefficient 0.92, 95 % CI 0.89–0.95, and intraclass coefficient 0.88, 95 % CI 0.83–0.93, respectively).

2.5. Statistical analysis

Data were presented as mean ± standard deviation, median (interquartile range, IQR), and count (%). Normality was assessed using Shapiro-Wilk test of normality. Between-group comparisons were performed using unpaired *t*-test, Wilcoxon rank sum test, analysis of variance test, and Fisher's exact test, as appropriate. Temporal change in PH severity was assessed using Δ RVSP and was calculated for each patient using paired *t* test. The Δ RVSP for the group was expressed as mean difference (95 % CI), mean ± standard deviation, and median (range). Temporal change in PH prevalence was assessed by comparing PH prevalence at Echo #1 versus Echo #2 using McNemar test.

To assess the relationship between baseline characteristics and temporal change in PH severity, we divided the cohort into quartiles based on Δ RVSP and compared the baseline characteristics across the quartiles. Linear regression analysis was used to assess the correlates of Δ RVSP. First, we created multiple univariable linear regression models using the following covariates: demographic/anatomic indices (age, sex, COA repair, and LVOT disease), vital signs and laboratory indices (blood pressure, heart rate, hemoglobin, and estimated glomerular filtration rate), comorbidities (hypertension, diabetes, coronary artery disease, atrial fibrillation, and sleep apnea), echocardiographic indices of chamber size and function, and LV afterload indices (aortic valve Doppler mean gradient, COA Doppler mean gradient, valvuloarterial impedance [Zva]). Zva was used as a measure of LV global afterload, and was calculated as (aortic valve Doppler mean gradient + brachial systolic blood pressure)/LV stroke volume index. [19] Covariates with $p < 0.1$ on univariable analysis, were used to create the multivariable model, and the final variable selection was based on stepwise backwards selection with $p < 0.1$ required for a covariate to remain in the model.

All-cause mortality was assessed as time-to-event outcome from Echo #2 until death, last clinical encounter, or December 31, 2023. Cox regression analysis was used to assess the relationship between Δ RVSP and all-cause mortality. The models were adjusted for RVSP at baseline echocardiogram, demographic/anatomic indices, comorbidities, echocardiographic indices of chamber size and function, and LV afterload. The final variable selection was also based on stepwise backwards selection with $p < 0.1$ required for a covariate to remain in the model.

Some patients underwent cardiovascular interventions (i.e., surgical or transcatheter COA reintervention or surgical LVOT intervention) between Echo #2 and end of the study period. To adjust for the confounding effect of these interventions, we modeled cardiovascular interventions (COA intervention [yes/no] and LVOT intervention [yes/no]) as time-dependent covariates in the Cox models. Additionally, we performed subgroup analysis assessing the relationship between Δ RVSP and mortality in the subset of patients that did not undergo cardiovascular interventions. All statistical analyses were performed with BlueSky Statistics software (version. 7.10; BlueSky Statistics LLC, Chicago, IL, USA), and JMP statistical software (version 17.1.0, JMP Statistical Discovery LLC, NC). P value < 0.05 was considered to be statistically significant for all analyses.

3. Results

3.1. Baseline characteristics

There were 651 adults with COA that received care at Mayo Clinic within the study period. Of the 651 patients, 259 (40 %) patients were excluded because of lack of serial echocardiograms, inadequate tricuspid regurgitation Doppler signal, or presence of concomitant LV

inflow disease or pulmonary valve stenosis (exclusion group; N = 259, 40 %). The rest of the patients comprised the study group (N = 392, 60 %). Supplementary Table S1 compares the baseline clinical and echocardiographic characteristics of the study group versus the exclusion group. Compared to the exclusion group, the study group had higher prevalence of bicuspid aortic valve (260 [66 %] versus 146 [56 %], p = 0.01), type 2 diabetes (29 [7 %] versus 8 [3 %], p = 0.2), and coronary artery disease (33 [8 %] versus 10 [4 %], p = 0.02). The other clinical characteristics were similar between the 2 groups (Supplementary Table S1).

3.2. Pulmonary hypertension

3.2.1. Baseline echocardiogram (Echo #1)

Of the 392 patients in the study group, the median age at baseline echocardiogram was 35 years (IQR 24–49), and 154 (39 %) were females. The median tricuspid regurgitation velocity and estimated RVSP were 2.5 m/s (IQR 2.3–2.7) and 30 mmHg (IQR 26–35), respectively. The prevalence of pH was 19 % (76/392). Table 1 shows a comparison of the baseline clinical and echocardiographic indices of patients with PH (N = 76, 19 %) versus the patients without PH (N = 316, 81 %). Compared to patients without PH, those with PH were older, more likely to be females, and had more comorbidities (Table 1). Similarly, the PH subgroup had worse RA function (RA reservoir strain 33 % [IQR 21–46] versus 46 % [IQR 37–56], p < 0.001), worse RV function (RV free wall strain −25 ± 4 % versus −28 ± 6 %, p < 0.001), worse LA function (LA reservoir strain 39 % [IQR 31–45] versus 28 % [IQR 20–42], p < 0.001), lower LV stroke volume index (44 ± 19 versus 50 ± 14 ml/m^2, p = 0.03), and higher LV filling pressures (lateral E/e' 15 ± 8 versus 9 ± 4, p = 0.004) (Table 1). Similarly, the PH group had higher LV global afterload (Zva 3.34 ± 0.74 versus 2.74 ± 0.51 mmHg/ml*m^2, p < 0.001), and higher LV mass index (118 ± 29 versus 98 ± 24 g/m^2, p = 0.008) (Table 1).

3.2.2. Follow-up echocardiogram (Echo #2)

The median interval between Echo #1 and Echo #2 was 6.2 (5.1–7.4) years, and during this period, RVSP increased from 30 mmHg (IQR 26–35) to 36 (IQR 31–42) mmHg, yielding a Δ RVSP 6 ± 9 mmHg (mean difference 5.6 mmHg [95 % CI 2.7, 8.8]; median 5 mmHg [range −9 to 23 mmHg]) (Fig. 1). The prevalence of pH increased from 19 % (76/392) at Echo #1 to 27 % (104/392) at Echo #2 (p = 0.01) (Fig. 1). Temporal change in RVSP was similar in males versus females (Δ RVSP 5 ± 8 mmHg versus 6 ± 9 mmHg, respectively, p = 0.4), and in patients with isolated COA versus concomitant LVOT disease (Δ RVSP 6 ± 8 mmHg versus 5 ± 7 mmHg, respectively, p = 0.2).

Table 2 shows a comparison of the baseline characteristics of the cohort across the quartiles of Δ RVSP. Compared to the patients in the lower 2 quartiles, those in the upper 2 quartiles (higher Δ RVSP) were older and had more comorbidities. Similarly, patients in the upper 2 quartiles had worse atrial function, as well as higher LV filling pressures, LV mass index, and LV global afterload (Table 2).

Table 3 compares echocardiographic indices between Echo #1 and Echo #2. There was a temporal increase in RVSP (mean difference 5.6 mmHg, 95 % CI 2.7, 8.8), RA pressure (mean difference 1.9 mmHg, 95 % CI 0.7, 3.1), and LV filling pressures (lateral E/e' mean difference 1.8, 95 % CI 0.7, 2.9), as well as a temporal decrease in RA reservoir strain (mean difference −3.6 %, 95 % CI −5.4, −1.8), and absolute value of RV free wall strain (mean difference −2.3 mmHg, 95 % CI −3.7, −0.9), and LA reservoir strain (mean difference −3.9 mmHg, 95 % CI −5.7, −2.1), (Table 3).

Clinical and Echocardiographic Indices Associated with PH Progression (Δ RVSP).

Table 4 shows univariable and multivariable linear regression models of the correlates of Δ RVSP. Older age (β ± SE 0.09 ± 0.04, p = 0.007), atrial fibrillation (β ± SE 1.04 ± 0.78, p = 0.01), LA reservoir strain (β ± SE −0.12 ± 0.06, p = 0.005), LV mass index (β ± SE 0.18 ±

Table 1
Baseline characteristics.

	All (N = 392)	PH (N = 76,19 %)	No PH (N = 316, 81 %)	p
Age, years	35 (24–49)	40 (26–54)	33 (22–47)	0.003
Female sex	154 (39 %)	39 (51 %)	115 (36 %)	0.01
Age of COA repair, years	4 (1–7)	5 (2–8)	4 (0.8–7)	0.5
Associated LVOT disease	80 (20 %)	15 (20 %)	65 (21 %)	0.9
Bicuspid aortic valve	260 (66 %)	45 (59 %)	215 (68 %)	0.1
Body mass index, kg/m^2	27 ± 5	27 ± 7	27 ± 6	0.9
Vitals and labs				
Systolic BP, mmHg	131 ± 21	134 ± 20	128 ± 19	0.4
Diastolic BP, mmHg	72 ± 13	73 ± 11	70 ± 10	0.1
Pulse pressure, mmHg	59 ± 14	59 ± 17	58 ± 19	0.8
ULE BP gradient, mmHg	8 (0–17)	6 (0–15)	8 (0–18)	0.7
Heart rate, beats per minute	73 ± 15	76 ± 13	71 ± 14	0.2
Hemoglobin, g/dl	13.9 ± 1.3	13.6 ± 1.5	14.1 ± 1.4	0.1
eGFR, ml/min/1.73 m^2	89 ± 27	82 ± 22	92 ± 24	0.008
Comorbidities				
Hypertension	202 (52 %)	47 (62 %)	155 (49 %)	0.04
Diabetes	29 (7 %)	8 (11 %)	21 (7 %)	0.3
Coronary artery disease	33 (8 %)	14 (18 %)	19 (6 %)	0.002
Atrial fibrillation	31 (8 %)	12 (16 %)	19 (6 %)	0.009
Obstructive sleep apnea	20 (5 %)	7 (9 %)	13 (4 %)	0.09
Medications				
ACEI/ARB	161 (41 %)	34 (45 %)	127 (40 %)	0.5
Beta blockers	114 (29 %)	26 (34 %)	88 (29 %)	0.3
Calcium channel blockers	83 (21 %)	19 (25 %)	64 (20 %)	0.5
Diuretics	45 (12 %)	11 (15 %)	34 (11 %)	0.6
Echocardiography				
Right heart indices				
RA reservoir strain, %	43 (35–50)	33 (21–46)	46 (37–56)	<0.001
RA volume, ml/m^2	23 (18–30)	31 (21–39)	22 (17–290	<0.001
RA pressure, mmHg	6 ± 3	9 ± 4	5 ± 1	<0.001
RV FWS, %	−27 ± 5	−25 ± 4	−28 ± 6	<0.001
RV EDA, cm^2	21 ± 6	23 ± 6	21 ± 5	0.06
RV FAC, %	46 ± 8	42 ± 8	46 ± 7	0.009
≥Moderate TR	19 (5 %)	11 (15 %)	8 (2 %)	0.001
TR velocity, m/s	2.5 (2.3–2.7)	3.1 (2.7–3.4)	2.4 (2.2–2.6)	<0.001
RVSP, mmHg	30 (26–35)	47 (38–59)	28 (24–32)	<0.001
Pulm valve peak velocity, m/s	1.2 ± 0.3	1.3 ± 0.4	1.2 ± 0.3	0.2
Left heart indices				
LA volume index, mL/m^2	28 (23–35)	33 (26–49)	27 (22–34)	<0.001
LA reservoir strain, %	39 (28–45)	28 (20–42)	39 (31–45)	<0.001
Lateral e', cm/s	12 ± 4	10 ± 5	13 ± 4	0.009
Lateral E/e'	11 ± 6	15 ± 8	9 ± 4	0.004
LV GLS, %	−20 ± 3	−20 ± 4	−21 ± 3	0.3
LV ejection fraction, %	61 ± 9	59 ± 11	62 ± 9	0.6
LV mass index, g/m^2	107 ± 30	118 ± 29	98 ± 24	0.008
AV mean gradient, mmHg	10 (6–18)	13 (8–24)	9 (6–16)	0.07
COA mean gradient, mmHg	14 (9–21)	12 (7–21)	14 (9–21)	0.8
Zva, mmHg/ml*m^2	2.91 ± 0.58	3.34 ± 0.74	2.74 ± 0.51	<0.001
LV stroke volume index, ml/m^2	48 ± 16	44 ± 19	50 ± 14	0.03

Abbreviations.
AV: Aortic valve; BP: Blood pressure; COA: Coarctation of aorta; eGFR: Estimated glomerular filtration rate; EDA: End-diastolic area; E/e': Ratio of pulsed wave mitral inflow early velocity to tissue Doppler early velocity; FAC: Fractional area change; FWS: Free wall strain; GLS: Global longitudinal strain; LA: Left atrium; LV: Left ventricle; LVOT: Left ventricular outflow tract; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TR: Tricuspid regurgitation; ULE: Upper-to-lower extremity; Zva: Valvuloarterial impedance.

Footnote: Data were presented as mean ± standard deviation, median (interquartile range), count (%), as appropriate. P values were derived from between-group comparisons using unpaired *t*-test, Wilcoxon rank sum test, or Fisher's exact test, as appropriate. LVOT disease was defined as any of the following conditions: aortic valve prosthesis, sub-valvular, valvular, or supra-valvular aortic stenosis (mean gradient > 20 mmHg) or ≥ moderate aortic regurgitation.

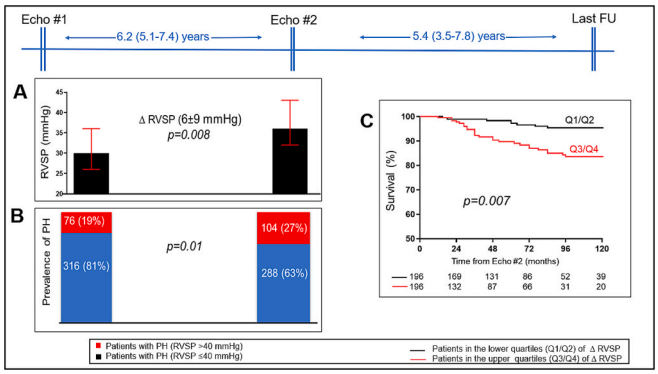

Fig. 1. Temporal changes in pulmonary hypertension (PH) prevalence and severity, and prognostic implications. Caption: Echo #1 signifies baseline echocardiogram, and Echo #2 signifies follow-up echocardiogram > 5 years from the baseline echocardiogram. **A**: Box and whisker plots showing in temporal increase in RVSP from Echo #1 to Echo #2. Δ RVSP signifies increase in RVSP between echocardiograms. The box and error bars signify median and interquartile range of RVSP. **B**: Bar chart showing increase in PH prevalence from 19 % in Echo #1 to 27 % in Echo #2. **C**: Kaplan Meier curves showing a lower survival in the patients with greater Δ RVSP (upper 2 quartiles of Δ RVSP) compared to patients with less Δ RVSP (lower 2 quartiles of Δ RVSP), 82 % versus 95 % at 10 years, respectively.

0.11, p = 0.02), and valvuloarterial impedance, Zva (β ± SE 0.13 ± 0.07, p = 0.009), were associated with temporal increase in RVSP (Table 4).

3.3. PH and all-cause mortality

Of the 392 patients, 50 (13 %) died during a median follow-up of 5.4 (IQR 3.5–7.8) years. There was a 19 % increase in the risk of mortality for every 5 mmHg increase in Δ RVSP (hazard ratio [HR] 1.19, 95 % CI 1.08–1.31, p = 0.006) after adjustment for baseline RVSP, demographic indices, comorbidities, and echocardiographic indices (Table 5). Table 6 shows a set of Cox regression models assessing the relationship between pulmonary hypertension (as measured by RVSP as baseline and temporal change in RVSP) and all-cause mortality, with stepwise adjustments for confounders (Models A-C). These model showed similar results whereby a 5 mmHg increase in Δ RVSP was associated with a 21 % increase in the risk of all cause mortality (adjusted HR 1.21, 95 % CI 1.09–1.33, p = 0.009). The patients with more PH progression (upper 2 quartiles of Δ RVSP) had lower 10-year survival compared to those with less PH progression (lower 2 quartiles of Δ RVSP); 82 % versus 95 %, p = 0.007 (Fig. 1).

Subgroup analyses were performed to assess the prognostic implications of pH progression in males, females, and patients without cardiovascular intervention during follow-up, while adjusting for age, baseline RVSP, and RV free wall strain. We observed that Δ RVSP was

Table 2
Baseline Characteristics Stratified Across Quartiles of Temporal Change in RVSP.

	Q1 (N = 98) Δ RVSP −4 ± 3 −4 (−9 – −3)	Q2 (N = 98) Δ RVSP 1 ± 4 1 (−3 – 5)	Q3 (N = 98) Δ RVSP 9 ± 5 8 (5—12)	Q4 (N = 98) Δ RVSP 16 ± 8 17 (12—23)	p
Age, years	31 (22–40)	34 (20–47)	36 (25–48)	39 (24–67)	0.002
Female sex	29 (30 %)	32 (33 %)	33 (34 %)	37 (38 %)	0.7
Age of COA repair, years	4 (1–7)	3 (1–6)	5 (2–8)	4 (2–7)	0.1
Associated LVOT disease	20 (20 %)	16 (16 %)	29 (30 %)	15 (15 %)	0.07
Body mass index, kg/m^2	26 ± 4	28 ± 6	27 ± 5	27 ± 6	0.5
Vitals and labs					
Systolic BP, mmHg	128 ± 18	130 ± 21	132 ± 20	138 ± 26	0.03
ULE BP gradient, mmHg	12 (0–19)	8 (3–17)	7 (2–15)	6 (0–13)	0.5
Heart rate, beats per minute	73 ± 14	75 ± 13	72 ± 14	74 ± 13	0.6
Hemoglobin, g/dl	13.8 ± 1.4	14.2 ± 1.1	14.1 ± 1.3	13.6 ± 1.6	0.4
eGFR, ml/min/1.73 m^2	87 ± 18	92 ± 22	83 ± 26	78 ± 23	0.02
Comorbidities					
Hypertension	48 (49 %)	59 (60 %)	49 (50 %)	46 (47 %)	0.3
Diabetes	4 (4 %)	7 (7 %)	7 (7 %)	11 (11 %)	0.3
Coronary artery disease	4 (4 %)	6 (6 %)	5 (5 %)	18 (18 %)	0.001
Atrial fibrillation	7 (7 %)	3 (3 %)	8 (8 %)	13 (13 %)	0.06
Echocardiography					
Right heart indices					
RA reservoir strain, %	43 ± 10	44 ± 12	44 ± 9	37 ± 10	0.004
RA volume, ml/m^2	23 ± 7	22 ± 8	24 ± 9	29 ± 8	0.003
RA pressure, mmHg	5 ± 2	5 ± 1	6 ± 2	9 ± 4	<0.001
RV FWS, %	−28 ± 5	−27 ± 5	−28 ± 5	−26 ± 6	0.1
RV EDA, cm^2	22 ± 5	20 ± 6	21 ± 5	22 ± 6	0.4
RV FAC, %	45 ± 7	46 ± 8	46 ± 7	43 ± 9	0.09
≥Moderate TR	3 (3 %)	1 (1 %)	4 (4 %)	11 (11 %)	0.007
TR velocity, m/s	2.5 (2.2–2.6)	2.4 (2.1–2.7)	2.7 (2.5–2.8)	2.9 (2.5–3.3)	<0.001
RVSP, mmHg	26 (22–31)	28 (23–32)	33 (29–38)	36 (31–40)	<0.001
Pulm valve peak velocity, m/s	1.0 ± 0.4	0.9 ± 0.3	1.2 ± 0.4	1.1 ± 0.6	0.2
Left heart indices					
LA volume index, mL/m^2	27 ± 9	29 ± 11	33 ± 13	35 ± 16	<0.001
LA reservoir strain, %	40 ± 12	38 ± 10	39 ± 11	32 ± 13	<0.001
Lateral e', cm/s	14 ± 5	13 ± 5	12 ± 4	9 ± 4	0.004
Lateral E/e'	8 ± 4	9 ± 5	9 ± 3	13 ± 8	0.002
LV GLS, %	−21 ± 3	−20 ± 3	−21 ± 3	−20 ± 4	0.2
LV ejection fraction, %	61 ± 9	63 ± 7	62 ± 7	59 ± 13	0.3
LV mass index, g/m^2	96 ± 18	104 ± 26	116 ± 24	121 ± 32	<0.001
AV mean gradient, mmHg	9 (6–17)	9 (5–14)	11 (6–19)	12 (7–21)	0.2
COA mean gradient, mmHg	12 (9–19)	16 (9–22)	13 (9–23)	15 (7–21)	0.7
Zva, mmHg/ml*m^2	2.84 ± 0.52	2.79 ± 0.42	2.96 ± 0.54	3.14 ± 0.72	<0.001
LV stroke volume index, ml/m^2	49 ± 16	45 ± 13	47 ± 14	44 ± 12	0.1

Abbreviations.
AV: Aortic valve; BP: Blood pressure; COA: Coarctation of aorta; eGFR:

Estimated glomerular filtration rate; EDA: End-diastolic area; E/e': Ratio of pulsed wave mitral inflow early velocity to tissue Doppler early velocity; FAC: Fractional area change; FWS: Free wall strain; GLS: Global longitudinal strain; LA: Left atrium; LV: Left ventricle; LVOT: Left ventricular outflow tract; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TR: Tricuspid regurgitation; ULE: Upper-to-lower extremity; Zva: Valvuloarterial impedance.

Footnote: Data were presented as mean ± standard deviation, median (interquartile range), count (%), as appropriate. P values were derived from between-group comparisons using analysis of variance test, Wilcoxon rank sum test, or Fisher's exact test, as appropriate. LVOT disease was defined as any of the following conditions: aortic valve prosthesis, sub-valvular, valvular, or supra-valvular aortic stenosis (mean gradient > 20 mmHg) or ≥ moderate aortic regurgitation.

Table 3
Comparison of Echocardiographic Indices Between Echo #1 and Echo #2.

	Echo #1 (N = 392)	Echo #2 (N = 392)	Difference (95 % CI)	p
Right heart indices				
RA reservoir strain, %	43 (35–50)	40 (32–47)	−3.6 (−5.4, −1.8)	0.008
RA volume, ml/m^2	23 (18–30)	25 (17–32)	2.1 (−0.6, 4.4)	0.3
RA pressure, mmHg	6 ± 3	8 ± 4	1.9 (0.7, 3.1)	0.009
RV FWS, %	−27 ± 5	−25 ± 6	−2.3 (−3.7, −0.9)	0.006
RV EDA, cm^2	21 ± 6	20 ± 4	−0.8 (−2.7,1.6)	0.2
RV FAC, %	46 ± 8	45 ± 6	−1.2 (−4.6, 3.9)	0.3
≥Moderate TR	19 (5 %)	21 (5 %)	NA	0.5
TR velocity, m/s	2.5 (2.3–2.7)	2.8 (2.5–3.1)	0.34 (0.19, 0.48)	0.01
RVSP, mmHg	30 (26–35)	36 (31–42)	5.6 (2.7,8.8)	0.008
Pulm valve peak velocity, m/s	1.2 ± 0.3	1.1 ± 0.4	−0.09 (−0.32,0.16)	0.4
Left heart indices				
LA volume index, mL/m^2	28 (23–35)	31 (24–39)	3.4 (−0.8, 7.2)	0.2
LA reservoir strain, %	39 (28–45)	35 (24–41)	−3.9 (−5.7, −2.1)	0.007
Lateral E/e'	11 ± 6	13 ± 7	1.8 (0.7, 2.9)	0.01
LV GLS, %	−20 ± 3	−19 ± 5	−1.2 (−2.8,0.9)	0.3
LV ejection fraction, %	61 ± 9	57 ± 12	−4.2 (−9.9,0.8)	0.5
LV mass index, g/m^2	107 ± 30	113 ± 27	6.4 (−3.8,15.2)	0.2
LV stroke volume index, ml/m^2	48 ± 16	46 ± 21	−3.7 (−9.5, 0.6)	0.4

Abbreviations.
EDA: End-diastolic area; E/e': Ratio of pulsed wave mitral inflow early velocity to tissue Doppler early velocity; FAC: Fractional area change; FWS: Free wall strain; GLS: Global longitudinal strain; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TR: Tricuspid regurgitation.

Footnote: Temporal changes in echocardiographic indices were calculated as Echo #2 minus Echo #1 for each patient using paired t −test and expressed as mean difference (95% confidence interval). A positive value signifies a temporal increase, while a negative value signifies a temporal decrease in value for each of the different echocardiographic indices.

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associated with all-cause mortality in males (N = 238) (adjusted HR 1.14, 95 % CI 1.05–1.26, p = 0.008) as well as in females (N = 153) (adjusted HR 1.22, 95 % CI 1.03–1.41, p = 0.01) with no sex difference (interaction p = 0.2). Of the 392 patients, 31 required COA interventions (transcatheter n = 18, and surgical n = 13) while 17 required LVOT interventions (surgical aortic valve replacement). Of the 344 patients without COA or LVOT interventions during follow-up, Δ RVSP was associated with all-cause mortality (adjusted HR 1.15, 95 % CI 1.09–1.21, p = 0.005).

4. Discussion

In this study, we assessed temporal change in PH prevalence and severity of PH, as well as the correlates and prognostic implications of pH progression in adults with COA. The main findings were as follows: (1) PH prevalence and severity increased over time, and the correlates of pH progression were older age, atrial fibrillation, LA dysfunction, LV hypertrophy, and high LV pressure afterload. (2) PH progression was associated with all-cause mortality, independent of pH severity at baseline echocardiogram.

Three previous studies have described the prevalence and outcomes of pH in adults with COA. [1–3] Two of these studies, Egbe et al and Oliver et al, defined PH as Doppler-derived RVSP > 40 mmHg, and observed that PH was present in about 20 % of adults with COA. [1,2]

Table 4
Linear Regression Showing Correlates of Temporal Change in RVSP.

	Univariable analysis		Multivariable analysis	
	β ± SE	p	β ± SE	p
Age, years	0.11 ± 0.03	<0.001	0.09 ± 0.04	0.007
Female sex	0.57 ± 0.84	0.3		
Age of COA repair, years	0.05 ± 0.11	0.2		
Associated LVOT disease	0.03 ± 0.91	0.6		
Body mass index, kg/m^2	0.03 ± 0.09	0.4		
Vitals and labs				
Systolic BP, per 10 mmHg	0.15 ± 0.04	<0.001		
ULE BP gradient, mmHg	0.02 ± 0.04	0.6		
Heart rate, per 10 beats per minute	0.01 ± 0.06	0.8		
Hemoglobin, g/dl	0.64 ± 0.98	0.7		
eGFR, per 10 ml/min/1.73 m^2	−0.09 ± 0.04	<0.001		
Comorbidities				
Hypertension	1.05 ± 0.53	0.003		
Diabetes	−0.07 ± 0.05	0.1		
Coronary artery disease	0.41 ± 0.23	0.04		
Atrial fibrillation	1.32 ± 0.68	<0.001	1.04 ± 0.78	0.01
Obstructive sleep apnea	0.28 ± 0.74	0.3		
Echocardiography				
Right heart indices				
RA reservoir strain, %	−0.11 ± 0.02	<0.001		
RA volume, ml/m^2	0.21 ± 0.07	<0.001		
RA pressure, mmHg	1.81 ± 0.17	<0.001		
RV FWS, %	−0.15 ± 0.13	0.01		
RV EDA, cm^2	0.21 ± 0.09	0.002		
RVSP, mmHg	0.47 ± 0.11	<0.001		
Left heart indices				
LA volume index, mL/m^2	0.26 ± 0.06	<0.001		
LA reservoir strain, %	−0.16 ± 0.07	<0.001	−0.12 ± 0.06	0.005
Lateral E/e'	0.58 ± 0.19	<0.001		
LV GLS, %	−0.51 ± 0.18	0.006		
LV mass index, per 10 g/m^2	0.31 ± 0.16	<0.001	0.18 ± 0.11	0.02
AV mean gradient, mmHg	0.06 ± 0.04	0.04		
Zva, mmHg/ml*m^2	0.16 ± 0.05	0.003	0.13 ± 0.07	0.009
COA mean gradient, mmHg	0.08 ± 0.11	0.6		

Abbreviations.
AV: Aortic valve; BP: Blood pressure; COA: Coarctation of aorta; eGFR: Estimated glomerular filtration rate; EDA: End-diastolic area; E/e': Ratio of pulsed wave mitral inflow early velocity to tissue Doppler early velocity; FAC: Fractional area change; FWS: Free wall strain; GLS: Global longitudinal strain; LA: Left atrium; LV: Left ventricle; LVOT: Left ventricular outflow tract; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; SE: Standard error; TR: Tricuspid regurgitation; ULE: Upper-to-lower extremity; Zva: Valvuloarterial impedance.

Footnote: Covariates with p < 0.1 in the univariable model were entered into the multivariable mode. The final covariate selection was based on stepwise backward selection with p < 0.1 required for a covariate to remain in the model.

Table 5

	HR (95 % CI)	p	HR (95 % CI)	p
Pulmonary hypertension				
Δ RVSP, per 5 mmHg	1.34 (1.29–1.48)	<0.001	1.19 (1.08–1.31)	0.006
RVSP at baseline echo, per 5 mmHg	1.22 (1.16–1.28)	<0.001	1.05 (1.01–1.09)	0.03
Demographic indices				
Age, per year	1.05 (1.03–1.07)	<0.001	1.03 (1.01–1.05)	0.01
Female sex	1.16 (0.66–2.03)	0.6		
Anatomic/surgical indices				
Age of COA repair, years	1.02 (0.99–1.05)	0.3		
Associated LVOT disease	1.98 (1.15–3.39)	0.009		
Comorbidities				
Hypertension	1.64 (1.22–1.98)	0.007		
Diabetes	1.55 (0.73–3.29)	0.3		
Coronary artery disease	2.45 (1.37–4.36)	0.002		
Atrial fibrillation	3.39 (1.74–6.61)	<0.001		
CKD ≥ III	4.12 (2.02–7.73)	0.005		
Echocardiography				
RA reservoir strain, %	0.93 (0.91–0.96)	<0.001		
RV FWS, %	0.86 (0.81–0.92)	<0.001	0.93 (0.89–0.97)	0.008
LA reservoir strain, %	0.92 (0.89–0.96)	<0.001		
Lateral E/e'	1.11 (1.07–1.15)	0.02		
LV GLS, %	0.84 (0.76–0.93)	0.008		
LV mass index, per 10 g/m^2	1.03 (1.01–1.05)	0.007	1.02 (1.00–1.04)	0.04
Zva, mmHg/ml*m^2	1.48 (1.13–1.89)	0.002	1.34 (1.11–1.68)	0.009
AV mean gradient, mmHg	1.02 (0.98–1.06)	0.2		
COA mean gradient, mmHg	0.97 (0.91–1.02)	0.3		
Cardiovascular interventions				
COA intervention*	0.98 (0.92–1.04)	0.3		
LVOT intervention *	1.08 (1.01–1.15)	0.02		

Abbreviations.
AV: Aortic valve; COA: Coarctation of aorta; CI: Confidence interval; CKD: Chronic kidney disease; E/e': Ratio of pulsed wave mitral inflow early velocity to tissue Doppler early velocity; FWS: Free wall strain; GLS: Global longitudinal strain; HR: Hazard ratio; LA: Left atrium; LV: Left ventricle; LVOT: Left ventricular outflow tract; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; Zva: Valvuloarterial impedance.
Footnote: Covariates with $p < 0.1$ in the univariable model were entered into the multivariable mode. The final covariate selection was based on stepwise backward selection with $p < 0.1$ required for a covariate to remain in the model. COA intervention (defined as surgical or transcatheter COA reintervention) and LVOT intervention (defined as aortic valve replacement or subaortic membrane resection) were modeled as time dependent covariate.

The third study by Jain et al defined PH as invasively measured mean pulmonary artery pressure > 20 mmHg and observed that PH was present in 96 % of patients with Shones complex referred for right heart catheterization. [3] The significantly higher PH prevalence reported by Jain el al was due to the clinical characteristics of the study sample, because the study was based exclusively on patients with concomitant LV inflow disease, as well as significant symptoms or hemodynamic abnormalities to require cardiac catheterization. [3] The current study builds on the existing literature, and provides new insight into the ongoing risk of pH progression and its prognostic implications. The prevalence of pH at baseline observed in the current study (prevalence of 19 %) was consistent with estimates from prior studies (prevalence of 20 %). [1,2] The novel finding from the current study was an increase in PH severity as measured by Doppler-derived RVSP, resulting in more than a 40 % increase in PH prevalence (from 19 % to 27 %) within a relatively short follow-up. This is concerning given the young age of the poulation and association of pH progression with mortality.

The risk factors for PH progression (high LV afterload, LV hypertrophy, LA dysfunction, and atrial fibrillation) in the current study are consistent with the underlying anatomic and physiologic lesions of COA. The anatomic lesions include aortic isthmus stenosis and LVOT disease, while the physiologic lesions include increased aortic stiffness and afterload due to endothelial dysfunction, abnormal arterial smooth muscle reactivity, and increased wave reflection to the proximal aorta. [20–22] While the anatomic lesions can be effectively treated with surgical and transcatheter interventions with good long-term results, the physiologic lesions persist throughout the lifespan of the patients resulting in high LV afterload. [5,23–27] Chronic exposure to high LV afterload invariably leads to LV hypertrophy (increased LV mass) and LA dysfunction (reduced LA reservoir strain), which in turn, leads to pulmonary vascular remodeling and PH and mortality in this subset of patients. [8,10] This is similar to the pathophysiologic process resulting in PH in patients with acquired forms of heart failure, where PH has been reported in up to 40 % of the population. [28–31].

PH progression has also been described in the acquired heart disease population. [12] In a recent study utilizing longitudinal echocardiographic data from the ARIC (Atherosclerosis Risk in Communities) registry, Zierath et al observed a temporal increase in Doppler-derived RVSP over a 6-year period, and the risk factors associated with PH progression were older age, LV hypertrophy, LV diastolic function (both indices of impaired relaxation and increased filling pressures), pulmonary dysfunction, and renal dysfunction. [12] Although the demographic characteristics of the ARIC cohort (mean age 75 year) differed significantly from that of the current study, some of the risk factors for PH progression (age, LV hypertrophy, LV diastolic dysfunction) were consistent across the 2 studies. That supports the paradigm of LV and LA dysfunction as key the drivers for PH progression.

4.1. Clinical implications and Future Directions

The current study demonstrates that PH progression is clinically relevant because of its association with mortality in patients with COA. As a result, there is a need for new strategies to prevent and manage LA and LV dysfunction, since left heart dysfunction is a linchpin in the pathogenesis of pH in this population. Such strategies should focus on early detection and treatment of anatomic lesions (aortic isthmus stenosis and LVOT disease) using multimodality imaging and invasive hemodynamic assessment. Strong emphasis should be placed on accurate and frequent blood pressure monitoring since systemic hypertension is almost universal in this population. Blood pressure measurement should not rely solely on brachial blood pressure measurement at rest, as this has been shown to underestimate arterial load in patients with COA. [32–34] Other methods of blood pressure assessment such as 24-hour ambulatory blood pressure monitoring and exercise testing should be part of routine clinical evaluation, and should be used for the titration of antihypertensive therapy in this population. [32–34].

Another important observation from this study was the consistent association between high LV afterload and LV hypertrophy, and subsequent PH progression and mortality. An accurate assessment of LV afterload in COA is challenging because of multiple in-series anatomic and physiologic lesions (concomitant LVOT disease, increased aortic stiffness and wave reflection, and residual aortic isthmus stenosis). [8,19,25,35] However, the net hemodynamic effect of these lesions can be assessed using valvuloarterial impedance as a measure of global LV

Table 6
Cox Regression Showing Relationship Between Temporal Change in RVSP and Mortality.

	Model A		Model B		Model C	
	HR (95 % CI)	p	HR (95 % CI)	p	HR (95 % CI)	p
Pulmonary hypertension						
Δ RVSP, per 5 mmHg	1.31 (1.26–1.43)	<0.001	1.27 (1.14–1.39)	0.002	1.21 (1.09–1.33)	0.009
Baseline RVSP, per 5 mmHg	1.26 (1.15–1.25)	<0.001	1.13 (1.08–1.18)	0.008	1.08 (1.03–1.13)	0.01

Abbreviations.
CI: Confidence interval; LVOT: Left ventricular outflow tract; HR: Hazard ratio; RVSP: Right ventricular systolic pressure.
Model A: Model adjusted for demographic indices (age, sex) and anatomic/surgical indices (age of COA repair, associated LVOT disease).
Model B: Model adjusted for demographic indices, anatomic/surgical indices, and comorbidities (hypertension, diabetes, coronary artery disease, atrial fibrillation, and chronic kidney disease).
Model C: Model adjusted for demographic indices, anatomic/surgical indices, and comorbidities echocardiographic indices (atrial and ventricular strain, LV mass index) and cardiovascular interventions (COA interventions and LVOT intervention).

afterload. In a previous study from our group, we demonstrated that patients with COA and aortic stenosis had higher valvuloarterial impedance compared to non-COA patients with similar severity of aortic stenosis, and that the residual valvuloarterial impedance after aortic valve replacement was a determinant of regression of LV hypertrophy and long-term survival after aortic valve replacement. [19] Valvuloarterial impedance has been shown to be prognostic older patients with degenerative aortic stenosis. [36] Perhaps, valvuloarterial impedance should be part of routine clinical assessment in adults with COA since it can easily be calculated using routinely available clinical indices (blood pressure, aortic valve mean gradient, and Doppler-derived LV stroke volume). Finally, the prevention and treatment of atrial fibrillation is important for the prevention of pH progression since atrial fibrillation is both a cause and effect of LA dysfunction.

5. Limitations

This is a retrospective cohort study of adults with COA followed in a single tertiary center, and it is prone to selection and ascertainment bias. We included only patients with more than 5 years of imaging follow-up, thereby introducing selection bias. However, this is unlikely to have impacted the results since most of the clinical and hemodynamic indices were comparable between the patients included in the study and those that were excluded. We relied on Doppler echocardiography for PH assessment, rather than invasive hemodynamic assessment which is the gold standard. This limits our ability to provide in depth hemodynamic phenotyping of the contribution of pulmonary vascular disease to progressive pulmonary hypertension. However, the high E/e' and LA dysfunction supports that pulmonary hypertension was likely driven predominantly by post-capillary mechanisms in the study population.

6. Conclusion

There was a temporal increase in PH prevalence and severity in adults with COA, and the risk factors associated with PH progression were older age, atrial fibrillation, LA dysfunction, LV hypertrophy, and high LV pressure afterload. PH progression was associated with all-cause mortality, independent of pH severity at baseline. These findings underscore the clinical importance of pH in COA and supports the need for new strategies for the prevention and treatment of LA and LV dysfunction, which should in turn, slow the pace of pH progression in this population. Such strategies should include early detection and treatment of hypertension and atrial fibrillation. Further studies are required to determine whether these strategies would modify the natural history of the disease and improve outcomes.

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CRediT authorship contribution statement

Ahmed Younis: Writing – review & editing, Writing – original draft. **Yogesh N.V. Reddy:** . **William R. Miranda:** Writing – review & editing, Writing – original draft. **Ahmed T. Abdelhalim:** Writing – review & editing, Writing – original draft. **Barry A. Borlaug:** Writing – review & editing, Writing – original draft. **Heidi M. Connolly:** Writing – review & editing, Writing – original draft. **Alexander C. Egbe:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101626.

References

[1] J.M. Oliver, P. Gallego, A.E. Gonzalez, A. Sanchez-Recalde, M. Bret, A. Aroca, Pulmonary hypertension in young adults with repaired coarctation of the aorta: an unrecognised factor associated with premature mortality and heart failure, *Int J Cardiol.* 174 (2014) 324–329, https://doi.org/10.1016/j.ijcard.2014.04.060.
[2] A.C. Egbe, W.R. Miranda, C.C. Jain, H.M. Connolly, Right Heart Dysfunction in Adults With Coarctation of Aorta: Prevalence and Prognostic Implications, *Circ Cardiovasc Imaging.* 14 (2021) 1100–1108, https://doi.org/10.1161/CIRCIMAGING.121.013075.
[3] C.C. Jain, C.A. Warnes, A.C. Egbe, F. Cetta, H.M. DuBrock, H.M. Connolly, W. R. Miranda, Hemodynamics in Adults With the Shone Complex, *Am J Cardiol.* 130 (2020) 137–142, https://doi.org/10.1016/j.amjcard.2020.06.024.
[4] J.M. Oliver, P. Gallego, A. Gonzalez, A. Aroca, M. Bret, J.M. Mesa, Risk factors for aortic complications in adults with coarctation of the aorta, *J Am Coll Cardiol.* 44 (2004) 1641–1647, https://doi.org/10.1016/j.jacc.2004.07.037.
[5] A.C. Egbe, A. Younis, W.R. Miranda, C.C. Jain, H.M. Connolly, B.A. Borlaug, Determinants and Prognostic Implications of Left Atrial Reverse Remodeling After Coarctation of Aorta Repair in Adults, *Eur Heart J Cardiovasc Imaging.* (2023), https://doi.org/10.1093/ehjci/jead203.
[6] A.C. Egbe, W.R. Miranda, C.C. Jain, C.R. Bonnichsen, J.H. Anderson, B.A. Borlaug, H.M. Connolly, Prognostic Value of Cardiac Remodeling Staging in Adults With Repaired Coarctation of Aorta, *J Am Coll Cardiol Img.* 16 (2023) 864–865, https://doi.org/10.1016/j.jcmg.2022.12.012.
[7] F. Labombarda, M. Bonopera, P. Maragnes, P. Milliez, A. Manrique, F. Beygui, Impaired left atrial function in adults and adolescents with corrected aortic coarctation, *Pediatr Cardiol.* (2020), https://doi.org/10.1007/s00246-020-02471-3.
[8] K.C. Lombardi, V. Northrup, R.L. McNamara, L. Sugeng, C.G. Weismann, Aortic stiffness and left ventricular diastolic function in children following early repair of aortic coarctation, *Am J Cardiol.* 112 (2013) 1828–1833, https://doi.org/10.1016/j.amjcard.2013.07.052.

[9] A.C. Egbe, W.R. Miranda, H.M. Connolly, Increased prevalence of left ventricular diastolic dysfunction in adults with repaired coarctation of aorta, *Int J Cardiol Heart Vasc*. 28 (2020) 100530, https://doi.org/10.1016/j.ijcha.2020.100530.

[10] A.C. Egbe, W.R. Miranda, H.M. Connolly, B.A. Borlaug, Coarctation of aorta is associated with left ventricular stiffness, left atrial dysfunction and pulmonary hypertension, *Am Heart J*. 241 (2021) 50–58, https://doi.org/10.1016/j.ahj.2021.07.005.

[11] A.C. Egbe, W.R. Miranda, M. Ahmed, L.J. Burchill, C.C. Jain, S. Karnakoti, S. Kandlakunta, H.M. Connolly, Diagnostic and Prognostic Role of Left Ventricular Strain Imaging in Adults with Coarctation of aorta, *Am J Cardiol*. 211 (2024) 98–105, https://doi.org/10.1016/j.amjcard.2023.10.082.

[12] R. Zierath, B. Claggett, V. Arthur, Y. Yang, H. Skali, K. Matsushita, D. Kitzman, S. Konety, T. Mosley, A.M. Shah, Changes in Pulmonary Artery Pressure Late in Life: The Atherosclerosis Risk in Communities (ARIC) Study, *J Am Coll Cardiol*. 82 (2023) 2179–2192, https://doi.org/10.1016/j.jacc.2023.09.821.

[13] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2010;23:685-713; quiz 786-688. doi: 10.1016/j.echo.2010.05.010.

[14] A.C. Egbe, H.M. Connolly, P.A. Pellikka, J.H. Anderson, W.R. Miranda, Role of Inferior Vena Cava Dynamics for Estimating Right Atrial Pressure in Congenital Heart Disease, *Circ Cardiovasc Imaging*. 15 (2022) e014308.

[15] A.C. Egbe, O. Abozied, W.R. Miranda, A. Younis, L. Burchill, S. Kandlakunta, M. H. Ahmed, S. Karnakoti, H.M. Connolly, Prognostic role of inferior vena collapsibility index in congenital heart disease: A validation study, *Int J Cardiol*. 394 (2024) 131399, https://doi.org/10.1016/j.ijcard.2023.131399.

[16] R.M. Lang, L.P. Badano, V. Mor-Avi, J. Afilalo, A. Armstrong, L. Ernande, F. A. Flachskampf, E. Foster, S.A. Goldstein, T. Kuznetsova, et al., Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging, *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography*. 28 (1–39) (2015) e14.

[17] M. Padeletti, M. Cameli, M. Lisi, A. Malandrino, V. Zaca, S. Mondillo, Reference values of right atrial longitudinal strain imaging by two-dimensional speckle tracking, *Echocardiography*. 29 (2012) 147–152, https://doi.org/10.1111/j.1540-8175.2011.01564.x.

[18] C. Mitchell, P.S. Rahko, L.A. Blauwet, B. Canaday, J.A. Finstuen, M.C. Foster, K. Horton, K.O. Ogunyankin, R.A. Palma, E.J. Velazquez, Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography, *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography*. 32 (2019) 1–64, https://doi.org/10.1016/j.echo.2018.06.004.

[19] A.C. Egbe, J.K. Oh, P.A. Pellikka, Cardiac Remodeling and Disease Progression in Patients With Repaired Coarctation of Aorta and Aortic Stenosis, *Circ Cardiovasc Imaging*. 14 (2021) 1091–1099, https://doi.org/10.1161/CIRCIMAGING.121.013383.

[20] M.G.Y. Lee, R.A. Hemmes, J. Mynard, E. Lambert, G.A. Head, M.M.H. Cheung, I. E. Konstantinov, C.P. Brizard, G. Lambert, Y. d'Udekem, Elevated sympathetic activity, endothelial dysfunction, and late hypertension after repair of coarctation of the aorta, *Int J Cardiol*. 243 (2017) 185–190, https://doi.org/10.1016/j.ijcard.2017.05.075.

[21] M. de Divitiis, C. Pilla, M. Kattenhorn, M. Zadinello, A. Donald, P. Leeson, S. Wallace, A. Redington, J.E. Deanfield, Vascular dysfunction after repair of coarctation of the aorta: impact of early surgery, *Circulation*. 104 (2001) I165–I170, https://doi.org/10.1161/hc37t1.094900.

[22] C.A. Jesus, J.E. Assef, S.R. Pedra, W.P. Ferreira, T.A. Davoglio, A.C. Petisco, M. H. Saleh, D.C. Le Bihan, R.B. Barretto, C.A. Pedra, Serial assessment of arterial structure and function in patients with coarctation of the aorta undergoing stenting, *Int J Cardiovasc Imaging*. 32 (2016) 729–739, https://doi.org/10.1007/s10554-015-0827-3.

[23] A.C. Egbe, J.H. Anderson, N.M. Ammash, N.W. Taggart, Left Ventricular Remodeling After Transcatheter Versus Surgical Therapy in Adults With Coarctation of Aorta, *J Am Coll Cardiol Img*. 13 (2020) 1863–1872, https://doi.org/10.1016/j.jcmg.2020.01.016.

[24] A.C. Egbe, W.R. Miranda, H.M. Connolly, Predictors of left ventricular reverse remodelling after coarctation of aorta intervention, *Eur Heart J Cardiovasc Imaging*. (2020), https://doi.org/10.1093/ehjci/jeaa199.

[25] A.C. Egbe, C.A. Warnes, H.M. Connolly, Critical Appraisal of the Indications for Intervention in Adults With Coarctation of Aorta, *J Am Coll Cardiol*. 75 (2020) 1089–1090, https://doi.org/10.1016/j.jacc.2019.12.047.

[26] T.J. Forbes, D.W. Kim, W. Du, D.R. Turner, R. Holzer, Z. Amin, Z. Hijazi, A. Ghasemi, J.J. Rome, D. Nykanen, et al., Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium), *J Am Coll Cardiol*. 58 (2011) 2664–2674, https://doi.org/10.1016/j.jacc.2011.08.053.

[27] A.C. Egbe, W.R. Miranda, C.A. Warnes, C. Bonnichsen, J. Crestanello, J. H. Anderson, H.M. Connolly, Persistent Hypertension and Left Ventricular Hypertrophy After Repair of Native Coarctation of Aorta in Adults, *Hypertension*. 78 (2021) 672–680, https://doi.org/10.1161/HYPERTENSIONAHA.121.17515.

[28] W.L. Miller, D.E. Grill, B.A. Borlaug, Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure, *JACC Heart Fail*. 1 (2013) 290–299, https://doi.org/10.1016/j.jchf.2013.05.001.

[29] M. Obokata, B.A. Borlaug, Right ventricular dysfunction and pulmonary hypertension in heart failure with preserved ejection fraction, *Eur J Heart Fail*. 18 (2016) 1488–1490, https://doi.org/10.1002/ejhf.666.

[30] T.M. Gorter, E.S. Hoendermis, D.J. van Veldhuisen, A.A. Voors, C.S. Lam, B. Geelhoed, T.P. Willems, J.P. van Melle, Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis, *Eur J Heart Fail*. 18 (2016) 1472–1487, https://doi.org/10.1002/ejhf.630.

[31] L. Tastet, C. Tribouilloy, S. Marechaux, E.M. Vollema, V. Delgado, E. Salaun, M. Shen, R. Capoulade, M.A. Clavel, M. Arsenault, et al., Staging Cardiac Damage in Patients With Asymptomatic Aortic Valve Stenosis, *J Am Coll Cardiol*. 74 (2019) 550–563, https://doi.org/10.1016/j.jacc.2019.04.065.

[32] A.C. Egbe, Y.N.V. Reddy, M. Obokata, B.A. Borlaug, Doppler-Derived Arterial Load Indices Better Reflect Left Ventricular Afterload Than Systolic Blood Pressure in Coarctation of Aorta, *Circ Cardiovasc Imaging*. 13 (2020) e009672.

[33] A.C. Egbe, W.R. Miranda, C.R. Bonnichsen, C.A. Warnes, H.M. Connolly, Potential Benefits of Ambulatory Blood Pressure Monitoring in Coarctation of Aorta, *J Am Coll Cardiol*. 75 (2020) 2089–2090, https://doi.org/10.1016/j.jacc.2020.02.053.

[34] A.C. Egbe, T.G. Allison, N.M. Ammash, Mild Coarctation of Aorta is an Independent Risk Factor for Exercise-Induced Hypertension, *Hypertension*. 74 (2019) 1484–1489, https://doi.org/10.1161/HYPERTENSIONAHA.119.13726.

[35] M.A. Quail, R. Short, B. Pandya, J.A. Steeden, A. Khushnood, A.M. Taylor, P. Segers, V. Muthurangu, Abnormal Wave Reflections and Left Ventricular Hypertrophy Late After Coarctation of the Aorta Repair, *Hypertension*. 69 (2017) 501–509, https://doi.org/10.1161/HYPERTENSIONAHA.116.08763.

[36] Z. Hachicha, J.G. Dumesnil, P. Pibarot, Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis, *J Am Coll Cardiol*. 54 (2009) 1003–1011, https://doi.org/10.1016/j.jacc.2009.04.079.