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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Anatomical/Physiological Correlates of Functional Capacity in Adults With Repaired and Nonsevere Coarctation of the Aorta

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ABSTRACT

BACKGROUND There is limited data regarding the interplay of anatomic and physiologic parameters with exercise capacity in adults with native or recurrent nonsevere coarctation of the aorta (CoA).

OBJECTIVES The objective of this study was to use exercise stress echocardiography and cardiac magnetic resonance imaging to identify anatomic and physiologic correlates of exercise capacity in these patients.

METHODS We conducted a single-center retrospective analysis of 54 adults with nonsevere CoA (repaired or unrepaired) followed at our institution between 2015 and 2020. Resting coarctation gradients were obtained using echocardiography. Exercise gradients and functional capacity were assessed using exercise stress echocardiography. Aorta anatomy was obtained using magnetic resonance imaging.

RESULTS Coarctation-to-diaphragm ratio correlated with minutes of exercise ($r = 0.56$, $P < 0.01$) and metabolic equivalents ($r = 0.49$, $P < 0.01$). These relationships remained significant after controlling for use of beta-blockers, valvular disease, and type of coarctation repair. Minutes of exercise correlated with mean resting gradients ($r = -0.39$, $P < 0.05$). Coarctation-to-diaphragm ratio correlated with peak and mean resting gradients ($r = -0.34$, $P < 0.05$; $r = -0.48$, $P < 0.01$). Patients with coarctation-to-diaphragm ratio ≤0.7 achieved fewer metabolic equivalents (11.1 ± 1.9 vs 12.8 ± 2.2, $P < 0.05$) and minutes of exercise (10.3 ± 2.0 vs 12.6 ± 2.7, $P < 0.05$).

CONCLUSIONS In patients with nonsevere native or recurrent CoA, reduced exercise capacity is correlated with coarctation severity by anatomic size and gradients. Those with a coarctation-to-diaphragm ratio ≤0.7 may represent a subset of patients with nonsevere CoA whose clinical symptoms are only elicited with exercise stress testing. Exercise stress testing and cross-sectional imaging may help identify those who could be considered for earlier coarctation intervention. (JACC Adv 2023;2:100672) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CoA = coarctation of the aorta

ILW = inferolateral wall

IVS = interventricular septum

LV = left ventricle

MRI = magnetic resonance imaging

SBP = systolic blood pressure

Over the past several decades, various treatments have been developed to alleviate coarctation of the aorta (CoA), significantly improving patient outcomes.[1,2] While the American Heart Association/American College of Cardiology 2018 guidelines provide a Class 1 recommendation for surgical or catheter-based repair in adults with hypertension and severe native or recurrent CoA, the risk stratification and management of patients with nonsevere CoA is less well defined.[3]

However, long-term morbidity is still prevalent in patients with repaired CoA who do not have significant recurrent coarctation, including hypertension, left ventricular hypertrophy, and congestive heart failure.[4] Identification of patients with mild-moderate native or recurrent CoA who are at risk for long-term complications is therefore essential. While catheter angiography is the gold standard for assessing severity of coarctation, noninvasive imaging modalities such as echocardiography and magnetic resonance imaging (MRI) are more widely utilized and can provide valuable information regarding long-term outcomes, particularly when used in conjunction with functional testing such as exercise-stress testing.[5,6]

Patients with nonsevere CoA who have a hypertensive response to exercise are recognized as a group to be at higher risk for adverse cardiovascular events,[7] for which the American Heart Association/American College of Cardiology 2018 ACHD guidelines dedicate a Class 2B recommendation for evaluation.[3] However, the role for routine functional metrics is not well established but may provide important prognostication information. Exercise capacity, in particular, is of interest because of the association of decreased exercise capacity with a greater risk for hospitalization or death in adult patients with congenital heart disease.[8]

There is a paucity of data surrounding the interplay of anatomic and physiologic parameters with exercise capacity in adult patients with native or recurrent nonsevere CoA. Our objective is to use exercise stress echocardiography and MRI to identify such factors that correlate with exercise capacity in these patients. We hypothesized that exercise capacity measured by metabolic equivalents and duration of exercise would correlate with both coarctation size and gradients in this population.

METHODS

We conducted a single-center retrospective analysis of patients followed by the Adult Congenital Heart Disease Program at New York University Langone Health between 2015 and 2020. The New York University School of Medicine institutional review board approved the study and granted a waiver of written informed consent.

Patients were included if they had a diagnosis of CoA (repaired or unrepaired) and were over 18 years of age. Exclusion criteria included patients with complex congenital cardiac anatomy or at least moderate-severe aortic stenosis, multiple left-sided obstructive lesions (ie, Shone Complex), or patients with unrepaired severe coarctation (defined as mean resting coarctation gradient >20 mm Hg).

Electronic medical records were accessed for information on demographics, family history, vital signs, medications, and past medical and surgical history. Medical records and the Siemens SYNGO database (Siemens Medical Solutions USA Inc) were queried for clinical information related to echocardiograms, stress echocardiograms, and cardiac MRI. Resting and exercise coarctation gradients were obtained using echocardiography. Exercise stress echocardiography was performed using the Bruce protocol. Echocardiography machines, acquisition protocols, and measurement techniques were standardized in accordance with established guidelines adopted from the American Society of Echocardiography.[9] METs were provided by the treadmill program. Blood pressure information was collected at time of exercise stress echocardiography. Aorta anatomy was obtained using cardiac MRI reports. Aortic diameter at the coarctation and diaphragm were repeated and verified by investigators A.R. and D.G.H. Aortic isthmus/coarctation diameter divided by the aortic size at the level of the diaphragm was used to index the coarctation diameter to aortic size (coarctation-to-diaphragm ratio) per 2020 European Society of Cardiology guidelines.[10]

STATISTICAL ANALYSIS. Categorical variables were summarized using frequency and percent and compared using Pearson's chi-square test. Continuous variables were assessed for normality. Normally distributed continuous variables were presented as mean ± SD and compared by independent sample t-tests. Continuous variables with non-normal distributions were presented as median with interquartile range. Pearson correlation coefficients were generated to assess relationships between exercise capacity, echocardiogram findings (both with rest and stress), and cardiac MRI findings. Adjusted regression models were generated to account for use of beta-blockers, type of initial coarctation repair, and presence of moderate to moderate-severe valvular pathology in the relationships between exercise capacity and

coarctation anatomy. A P value <0.05 was considered statistically significant. Data were analyzed using STATA/IC 15.0 (StataCorp).

RESULTS

A total of 54 patients with CoA were included in this study, with a median age of 33 years (IQR: 27-38 years) (Table 1). Forty-one percent of patients were female. Most patients were non-Hispanic White (69%), followed by Hispanic (15%), Asian (7%), and Black (4%). The median body mass index was 24.9 kg/m^2 (IQR: 22.3-28.0 kg/m^2). Forty-eight patients had prior coarctation repair (89%), of whom 22 had surgical end-to-end repair (41%), 5 had surgical patch repair (9%), 8 had surgical subclavian flap repair (15%), 12 had transcatheter stenting (22%), and 1 had transcatheter balloon angioplasty (2%) as their initial coarctation repair. The most common comorbidities were bicuspid aortic valve (n = 39; 72%) and hypertension (n = 25; 46%). Most patients in our cohort took medications, with the most common being antiplatelets (n = 21; 39%), angiotensin converting enzyme inhibitors or angiotensin receptor blockers (n = 20; 37%), and beta-blockers (n = 13; 43%) (Table 1). Indications for medical therapy primarily included uncontrolled hypertension and aortic enlargement.

We assessed resting echocardiography and cardiac MRI for anatomic information. As seen in Table 2, despite 72% of patients having a bicuspid aortic valve, only 5 patients included in the analysis had significant valvular pathology: 2 patients with moderate aortic stenosis, 1 patient with moderate aortic insufficiency, and 2 patients with moderate-severe aortic insufficiency. Notably, patients with at least moderate-severe aortic stenosis were removed as a prespecified exclusion criterion. The median resting ejection fraction was 65% (IQR: 60%-65%), with 3 patients (6%) having a reduced ejection fraction by echocardiography. The average interventricular septal (IVS) and inferolateral wall thicknesses (ILW) were 1.0 ± 0.2 cm and 0.9 ± 0.2 cm, respectively. Average coarctation isthmus diameter was 14.2 ± 3.2 mm with the average coarctation-to-diaphragm ratio being 0.79 ± 0.17 (Table 3). Three patients had coarctation-to-diaphragm ratios ≤0.5.

Stress echocardiography was used to measure exercise capacity in conjunction with physiologic measurement of coarctation gradients with exercise. Patients exercised for on average 11.9 ± 2.6 minutes, achieving an average of 12.3 ± 2.2 METs. At maximal exertion, heart rate increased from 75 ± 14 beats/min to 171 ± 13 beats/min, and blood pressure increased from 127/76 to 171/72 mm Hg. Average peak coarctation gradients increased from 20.4 ± 12.0 mm Hg to 46.4 ± 23.0 mm Hg, and average mean coarctation gradients increased from 9.1 ± 5.7 mm Hg to 21.1 ± 10.9 mm Hg during maximal exertion (Table 2).

Exercise capacity as expressed by duration of exercise and METs were significantly correlated with anatomic measures of coarctation severity (Table 4, Central Illustration). Minutes of exercise were significantly correlated with coarctation isthmus diameter (r = 0.48, P < 0.01) and coarctation-to-diaphragm ratio (r = 0.56, P < 0.01). Similarly, METs were significantly correlated with coarctation isthmus

TABLE 1 Demographics and Clinical Characteristics (N = 54)

Age, y	33 (27-38)
BMI, kg/m^2	24.9 (22.3-28.0)
Female	22 (41%)
Race	
White	37 (69%)
Black	2 (4%)
Hispanic	8 (15%)
Asian	4 (7%)
Other/unknown	3 (6%)
Initial coarctation repair	48 (89%)
Surgical: end-to-end	22 (41%)
Surgical: patch	5 (9%)
Surgical: subclavian flap	8 (15%)
Transcatheter stent	12 (22%)
Transcatheter balloon angioplasty	1 (2%)
Comorbidity	
Bicuspid aortic valve	39 (72%)
Hypertension	25 (46%)
Hyperlipidemia	10 (19%)
Arrhythmia	7 (13%)
Genetic syndrome	6 (11%)
Asthma	6 (11%)
Reduced LVEF	3 (6%)
Type 2 diabetes mellitus	3 (6%)
History of stroke/TIA	3 (6%)
Cerebral aneurysm	2 (4%)
Obstructive sleep apnea	2 (4%)
Coronary artery disease	2 (4%)
Medications	
Antiplatelet	21 (39%)
Anticoagulant	7 (13%)
BB	13 (24%)
ACEI/ARB	20 (37%)
CCB	9 (17%)
MRA	2 (4%)
Statin	9 (17%)

Values are median (IQR) or n (%).

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BB = beta-blocker; BMI = body mass index; CCB = calcium-channel blocker; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; TIA = transient ischemic attack.

TABLE 2 Echocardiography

	Resting	Exercise
IVS thickness (cm)	1.0 ± 0.2	-
LV ILW thickness (cm)	0.9 ± 0.2	-
Valve disease (≥moderate)		
Mitral	0 (0%)	-
Tricuspid	0 (0%)	-
Aortic[a]	5 (9%)	-
Pulmonic	0 (0%)	-
Ejection fraction (%)	65 (60-65)	75 (70-80)
Coarctation gradient (mm Hg)		
Peak	20.4 ± 12.0	46.4 ± 23.0
Mean	9.1 ± 5.7	21.1 ± 10.9
Blood pressure (mm Hg)		
Systolic	127 ± 15	171 ± 23
Diastolic	76 ± 11	72 ± 11
Pulse pressure	51 ± 13	98 ± 23
Heart rate (beats/min)	75 ± 14	171 ± 13
METs	-	12.3 ± 2.2
Minutes of exercise (min)	-	11.9 ± 2.6

Values are mean ± SD, n (%), or median (IQR). [a]2 patients with mod AS, 1 patient with moderate AI, and 2 patients with moderate to severe AI.

AI = aortic insufficiency; AS = aortic stenosis; ILW = inferolateral wall; IVS = interventricular septum; LV = left ventricle.

TABLE 3 Aortic Dimensions by MRI

Location	Diameter (mm)
Aortic root	33.2 ± 6.1
Sinotubular junction	27.8 ± 5.2
Mid-ascending aorta	29.3 ± 6.1
Transverse aorta	18.2 ± 3.6
Coarctation	14.2 ± 3.2
Mid-descending aorta	20.9 ± 5.2
Diaphragm aorta	18.5 ± 3.2
Coarctation: diaphragm ratio[a]	0.79 ± 0.17

Values are mean ± SD. [a]Ratio given as unitless measurement.

diameter ($r = 0.54$, $P < 0.01$) and coarctation-to-diaphragm ratio ($r = 0.49$, $P < 0.01$). Adjusted regression models were done to account for potential confounders in the relationship between exercise capacity and coarctation anatomy (Table 5). Even with inclusion of use of beta-blockers, type of initial coarctation repair, and presence of moderate to moderate-severe valvular pathology, minutes of exercise maintained significant independent correlations with both coarctation isthmus diameter ($P < 0.01$) and coarctation-to-diaphragm ratio ($P < 0.01$). METs also maintained significant independent correlations with coarctation isthmus diameter ($P < 0.001$) and coarctation-to-diaphragm ratio ($P < 0.01$) after accounting for these confounding variables. Neither minutes of exercise nor METs had significant associations with blood pressure measurements at rest or exercise. Minutes of exercise correlated with mean coarctation gradient at rest ($r = -0.39$, $P < 0.05$) but did not correlate with mean coarctation gradient with exercise ($P = 0.19$) or with peak coarctation gradients (rest: $P = 0.28$; exercise: $P = 0.17$). On the other hand, METs did not correlate with any coarctation gradient measurements with rest or exercise.

While measurements of blood pressure during exercise did not correlate with anatomic size of the coarctation by MRI, they did have significant associations with echocardiographic data. Systolic blood pressure with exercise significantly correlated with mean coarctation gradient at rest ($r = 0.44$, $P < 0.05$) and left ventricular wall thickness (IVS: $r = 0.37$, $P < 0.05$; ILW: $r = 0.37$, $P < 0.05$). The delta rise in systolic blood pressure from rest to exercise also significantly correlated with left ventricular wall thickness (IVS: $r = 0.36$, $P < 0.05$; ILW: $r = 0.36$, $P < 0.05$) and had a nonsignificant association with mean coarctation gradient at rest ($r = 0.34$, 95% CI: −0.04 to 0.63, $P = 0.08$). Peak coarctation gradients during exercise were associated with diastolic blood pressure at rest ($r = -0.52$, $P < 0.05$) and exercise ($r = -0.53$, $P < 0.05$), but mean coarctation gradients during exercise were not correlated with blood pressure measurements.

In addition to having significant correlations with certain measurements of blood pressure, coarctation gradients had significant associations with coarctation isthmus anatomy. Coarctation isthmus diameter had significant associations with peak resting gradient ($r = -0.44$, $P < 0.01$), mean resting gradient ($r = -0.53$, $P < 0.01$), peak exercise gradient ($r = -0.78$, $P < 0.001$), and mean exercise gradient ($r = -0.60$, $P < 0.05$). However, when normalized for descending aortic diameter at the level of the diaphragm, they were only correlated with peak and mean resting gradients ($r = -0.34$, $P < 0.05$; $r = -0.48$, $P < 0.01$).

Given the significant correlation between anatomic severity of coarctation with exercise capacity, the cohort was divided into 2 groups based on their coarctation-to-diaphragm ratio with a cutoff of 0.7. As shown in Table 6 and in the Central Illustration, the cohort with a coarctation-to-diaphragm ratio ≤0.7 had significantly lower exercise capacity by both METs (11.1 ± 1.9 vs 12.8 ± 2.2, $P < 0.05$) and minutes of exercise (10.3 ± 2.0 vs 12.6 ± 2.7, $P < 0.05$). The cohort with a coarctation-to-diaphragm ratio ≤0.7 also had trends towards greater peak resting gradient (26.2 ± 10.7 vs 19.0 ± 11.3, $P = 0.09$), mean resting

TABLE 4 Pearson Correlation Coefficients

	Minutes of exercise	Metabolic equivalents	Coarctation: isthmus diameter	Coarctation: diaphragm ratio	Peak coarctation gradient at rest	Mean coarctation gradient at rest	Peak coarctation gradient with exercise	Mean coarctation gradient with exercise	Systolic blood pressure at rest	Diastolic blood pressure with rest	Systolic blood pressure with exercise	Diastolic blood pressure with exercise	Delta rise in systolic blood pressure
Coarctation isthmus diameter	**0.48**	**0.54**	-										
P value	**0.003**	**0.001**											
Coarctation Diaphragm ratio	**0.56**	**0.49**	0.68	-									
P value	**0.001**	**0.003**	0.000										
Peak coarctation gradient at rest	−0.21	−0.11	**−0.44**	**−0.34**	-								
P value	0.277	0.566	**0.006**	**0.042**									
Mean coarctation gradient at rest	**−0.39**	−0.22	**−0.53**	**−0.48**	0.97	-							
P value	**0.042**	0.265	**0.001**	**0.004**	0.000								
Peak coarctation gradient with exercise	−0.36	−0.42	**−0.78**	−0.48	0.74	0.71	-						
P value	0.169	0.103	**0.000**	0.060	0.001	0.003							
Mean coarctation gradient with exercise	−0.41	−0.41	**−0.60**	−0.33	0.84	0.70	0.90	-					
P value	0.187	0.187	**0.037**	0.291	0.001	0.008	0.000						
Systolic blood pressure at rest	0.12	0.16	0.04	−0.09	0.02	0.27	−0.03	0.07	-				
P value	0.476	0.343	0.821	0.597	0.921	0.153	0.923	0.833					
Diastolic blood pressure with rest	0.19	0.24	0.15	−0.09	−0.30	−0.13	**−0.52**	−0.46	0.56	-			
P value	0.258	0.148	0.397	0.617	0.103	0.515	**0.033**	0.112	0.000				
Systolic blood pressure with exercise	0.19	0.27	0.24	−0.04	0.24	**0.44**	0.12	0.27	0.68	0.33	-		
P value	0.268	0.112	0.169	0.815	0.198	**0.020**	0.648	0.404	0.000	0.043			
Diastolic blood pressure with exercise	0.23	0.22	0.32	0.26	−0.21	−0.19	**−0.53**	−0.38	0.34	0.42	0.21	-	
P value	0.180	0.199	0.060	0.132	0.268	0.346	**0.034**	0.229	0.039	0.010	0.210		
Delta rise in systolic blood pressure	0.14	0.22	0.24	−0.01	0.30	0.34	0.13	0.24	0.01	−0.06	0.74	−0.03	-
P value	0.395	0.201	0.167	0.950	0.106	0.080	0.619	0.457	0.954	0.703	0.000	0.874	
Interventricular septal thickness	−0.03	0.00	0.23	0.05	0.15	0.10	−0.07	0.31	0.17	0.01	**0.37**	0.16	**0.36**
P value	0.864	0.997	0.144	0.752	0.329	0.538	0.790	0.304	0.312	0.936	**0.026**	0.339	**0.031**
Inferolateral wall thickness	0.01	0.03	0.32	0.07	0.03	−0.06	0.09	0.51	0.17	−0.06	**0.37**	0.23	**0.36**
P value	0.942	0.844	0.038	0.676	0.840	0.701	0.744	0.075	0.301	0.712	**0.026**	0.172	**0.033**

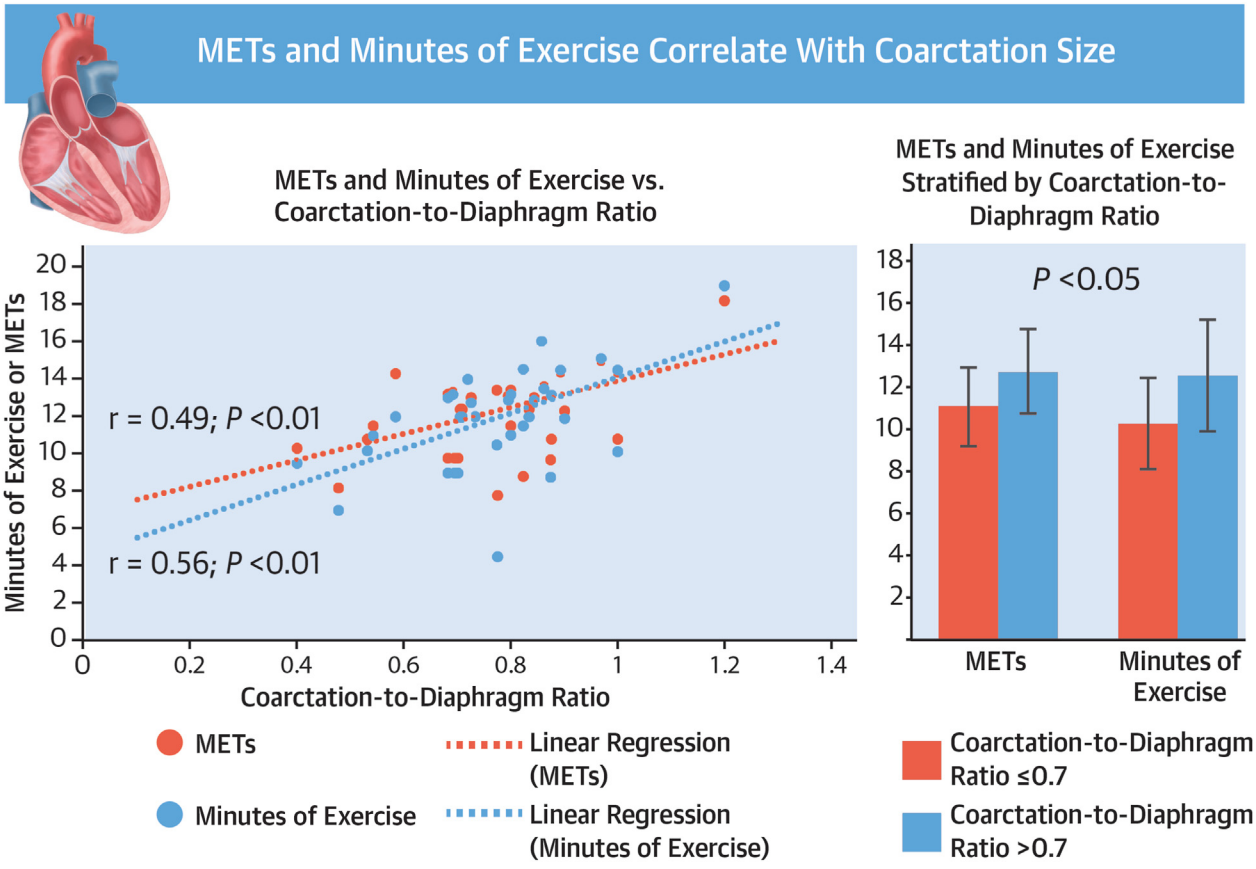
The **bold** values indicate: Exercise capacity measured by duration of exercise and metabolic equivalents were significantly correlated with coarctation severity by both coarctation isthmus diameter and coarctation-to-diaphragm ratio ($P < 0.01$). Coarctation-to-diaphragm ratio is also correlated with peak and mean resting coarctation gradients ($P < 0.05$; $P < 0.01$).

gradient (12.3 ± 5.1 vs 8.2 ± 5.5, $P = 0.06$), and peak exercise gradient (60.0 ± 28.4 vs 39.0 ± 18.8, $P = 0.098$). However, there were no significant differences in resting or exercise blood pressure or mean exercise coarctation gradient.

DISCUSSION

In this retrospective analysis of adults with both repaired and nonrepaired nonsevere CoA, minutes of exercise and METs during exercise stress testing

CENTRAL ILLUSTRATION **Exercise Capacity Correlated With Coarctation Size**



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Those with a coarctation-to-diaphragm ratio ≤0.7 may represent a subset of patients with nonsevere coarctation of the aorta who could be considered for earlier coarctation intervention.

had significant associations with coarctation diameter and with mean coarctation gradient, which confirmed our hypothesis. However, in this cohort with well-controlled blood pressure, there were no significant hypertensive responses, and exercise capacity did not correlate with blood pressure. While the relatively small sample size and retrospective nature of this study preclude the ability to make decisive statements on the applicability of these findings to clinical practice, we believe our data signals the presence of a subset of patients with nonsevere CoA who have clinical manifestations that can be elicited with exercise testing. There is potential that identification of these patients could lead to closer monitoring and consideration of earlier coarctation intervention to improve functional capacity.

Evaluation of physiologic response to exercise in patients with CoA has been growing as an important prognostic marker. However, there is limited data regarding how exercise capacity correlates with other noninvasive measurements of coarctation severity. Several studies have examined patients with repaired CoA who have exercise capacity similar to controls and/or age- and height-referenced values. Dijkema et al and Hanson et al looked at stented and surgically corrected patients, respectively, finding that long-term exercise capacity was similar to controls.[11,12] Conversely, Buys et al found that patients with CoA had reduced exercise tolerance by cardiopulmonary exercise testing (CPET) compared to controls and that these differences persisted despite CoA repair,[13,14] a finding that was corroborated by Hager et al[15] using

TABLE 5 Adjusted Regression Models for Minutes of Exercise and Metabolic Equivalents

	Minutes of Exercise			
	Coefficient	Standard Error	*P* Value	(95% CI)
Coarctation Isthmus Diameter vs Minutes of Exercise				
Coarctation isthmus diameter	0.43	0.15	**0.006**	(0.13 to 0.73)
Beta-blockers	−1.06	0.94	0.269	(−2.98 to 0.87)
Moderate to moderate-severe valvular disease	−1.88	1.21	0.132	(−4.37 to 0.61)
Repair type				
Surgical: end-to-end	−0.01	1.18	0.993	(−2.43 to 2.41)
Surgical: patch	1.12	1.58	0.483	(−2.12 to 4.37)
Surgical: subclavian flap	0.74	1.61	0.648	(−2.56 to 4.04)
Transcatheter stent	−2.51	1.50	0.106	(−5.58 to 0.57)
Transcatheter balloon angioplasty	3.15	2.42	0.205	(−1.83 to 8.13)
Coarctation-to-Diaphragm Ratio vs Minutes of Exercise				
Coarctation: diaphragm ratio	8.77	2.64	**0.003**	(3.34 to 14.20)
Beta-blockers	−1.03	0.90	0.261	(−2.89 to 0.82)
Moderate to moderate-severe valvular disease	−1.47	1.18	0.223	(−3.90 to 0.95)
Repair type				
Surgical: end-to-end	0.40	1.10	0.717	(−1.86 to 2.66)
Surgical: patch	0.94	1.54	0.546	(−2.22 to 4.10)
Surgical: subclavian flap	0.88	1.51	0.568	(−2.24 to 3.99)
Transcatheter stent	−2.43	1.45	0.105	(−5.40 to 0.55)
Transcatheter balloon angioplasty	1.28	2.45	0.605	(−3.75 to 6.32)
Metabolic Equivalents				
Coarctation Isthmus Diameter vs Metabolic Equivalents				
Coarctation isthmus diameter	0.46	0.10	**<0.001**	(0.24 to 0.67)
Beta-blockers	−1.08	0.67	0.119	(−2.45 to 0.30)
Moderate to moderate-severe valvular disease	−2.14	0.87	0.020	(−3.92 to −0.36)
Repair type				
Surgical: end-to-end	−0.45	0.84	0.600	(−2.18 to 1.28)
Surgical: patch	0.46	1.13	0.686	(−1.86 to 2.78)
Surgical: subclavian flap	−0.67	1.15	0.567	(−3.03 to 1.69)
Transcatheter stent	−2.82	1.07	0.014	(−5.02 to −0.62)
Transcatheter balloon angioplasty	2.15	1.73	0.226	(−1.41 to 5.71)
Coarctation-to-Diaphragm Ratio vs Metabolic Equivalents				
Coarctation: diaphragm ratio	6.74	2.21	**0.005**	(2.20 to 11.28)
Beta-blockers	−0.86	0.75	0.266	(−2.40 to 0.69)
Moderate to moderate-severe valvular disease	−1.82	0.99	0.076	(−3.84 to 0.21)
Repair type				
Surgical: end-to-end	0.21	0.92	0.818	(−1.68 to 2.10)
Surgical: patch	0.45	1.28	0.729	(−2.19 to 3.09)
Surgical: subclavian flap	0.09	1.26	0.941	(−2.51 to 2.69)
Transcatheter stent	−2.57	1.21	0.044	(−5.05 to −0.08)
Transcatheter balloon angioplasty	0.85	2.05	0.680	(−3.35 to 5.06)

The **bold** values indicate: Adjusted multivariate regression modeling shows coarctation anatomy is independently associated with exercise capacity.

symptom-limited exercise testing on patients who had received primary surgical CoA.

Notably, these trials do not provide data regarding how exercise capacity is related to relative severity of coarctation, whether anatomical or CoA gradient-based. Rog et al[16] compared patients with prior CoA repair to healthy controls using echocardiography and CPET and found that patients with prior CoA repair had significantly greater peak gradient of the coarctation and significantly lower exercise capacity, but did not find any associations between echocardiographic and CPET parameters. Similarly, 2 studies by Trojnarska et al[17,18] demonstrated that patients with prior surgically repaired CoA with recurrent coarctation had similar exercise tolerance to controls and that exercise capacity did not relate to whether

TABLE 6 Echocardiographic and Stress Test Parameters Stratified by Coarctation-to-Diaphragm Ratio

	CoA: Diaphragm Ratio		
	≤0.7 (n = 12)	**>0.7 (n = 33)**	***P* Value**
Blood Pressure (mm Hg)			
Resting systolic	128 ± 13	125 ± 16	0.663
Resting diastolic	79 ± 7	74 ± 11	0.223
Exercise systolic	171 ± 20	171 ± 25	0.993
Exercise diastolic	70 ± 12	73 ± 11	0.531
Heart rate (beats/min)			
Resting	74 ± 11	75 ± 15	0.797
Exercise	169 ± 13	172 ± 13	0.539
Coarctation gradient (mm Hg)			
Resting peak	26.2 ± 10.7	19.0 ± 11.3	0.089
Resting mean	12.3 ± 5.1	8.2 ± 5.5	0.060
Exercise peak	60.0 ± 28.4	39.0 ± 18.8	0.098
Exercise mean	26.0 ± 7.2	16.9 ± 12.6	0.179
METs	11.1 ± 1.9	12.8 ± 2.2	**<0.05**
Minutes of exercise (min)	10.3 ± 2.0	12.6 ± 2.7	**<0.05**

Values are mean ± SD. The **bold** values indicate: When stratified by coarctation severity using a coarctation-to-diaphragm ratio of 0.7, patients with a coarctation-to-diaphragm ratio ≤0.7 had significantly lower exercise capacity measured by both metabolic equivalents and minutes of exercise ($P < 0.05$).

CoA = coarctation of aorta.

patients had severe or nonsevere recoarctation, with severity defined by a mean coarctation gradient at rest >25 mm Hg by echocardiography. Only one prior study has examined exercise capacity in nonsevere CoA defined by anatomical parameters: Pedersen et al[19] studied a cohort of patients who had undergone primary surgical repair of CoA finding that patients with mild-moderate recoarctation based on a coarctation-to-diaphragm ratio of 0.46 to 0.79 did not have significantly different echocardiographic or exercise parameters.

We present results that contradict these prior findings. To our knowledge, this is the first study to demonstrate positive correlations between exercise capacity (by both minutes of exercise and metabolic equivalents) and coarctation isthmus diameter, a correlation that remained strong when CoA diameter was normalized to the descending aorta diameter at the level of the diaphragm. These correlations remained significant when they were adjusted for potential confounding variables, namely use of beta-blockers, type of initial coarctation repair, and presence of moderate to moderate-severe valvular pathology. Coarctation-to-diaphragm ratio was also associated with resting peak and mean coarctation gradients. In addition, we find significant negative correlations between exercise capacity by minutes of exercise and mean coarctation gradient at rest, suggesting a physiologic explanation for the reduced exercise capacity in patients with smaller CoA diameters. Exercise capacity has been shown to correlate with risk of hospitalization or death in adults with congenital heart disease, but there is scarce data in specifically patients with CoA.[8]

In our study, functional capacity was not associated with blood pressure either at rest or with exercise. Furthermore, we did not find an association between coarctation severity by anatomic size and blood pressure either at rest or with exercise, which corroborates previous findings.[20] We did find a nonsignificant association between the change in systolic blood pressure from rest to exercise and the mean coarctation gradient at rest, corroborating results found by prior studies finding a lack of significant relationship between peak systolic blood pressure during exercise and repair site gradients.[21] However, our findings are confounded by the fact that many of our subjects were on antihypertensives with well-controlled blood pressure. Our cohort did not exhibit significant hypertensive response, in part related to the milder degree of disease and well-controlled blood pressure. These observations suggest that there may be additional intrinsic vascular abnormalities driving hypertension in addition to the CoA anatomy.[22,23]

When our cohort was divided using a coarctation to diaphragm ratio of 0.7, those with a ratio ≤0.7 had significantly less functional capacity by both metabolic equivalents and minutes of exercise. Furthermore, the cohort with a ratio ≤0.7 had trends towards greater resting peak and mean gradients, as well as peak exercise gradients. While a cutoff of 0.7 is admittedly arbitrary, the use of such thresholds is already employed in clinical practice with the European Society of Cardiology guidelines providing a Class 2b recommendation for catheter intervention in patients with a coarctation to diaphragm ratio ≤0.5.[10] It's tempting to speculate on the value of identifying these patients, as prior studies demonstrate improvements in exercise capacity with stenting of mild-moderate coarctation.[24,25] Whether long-term cardiovascular morbidity is affected through this type of intervention remains to be seen, and future prospective studies on this population would help provide further understanding.

STUDY LIMITATIONS. This is a retrospective, single-center observational study, introducing the possibility of selection bias. The relatively small sample size meant our study was not powered to assess for adverse cardiovascular events or to perform large,

multivariable-adjusted analyses. We did not compare noninvasive imaging modalities with angiography results because not all patients underwent invasive hemodynamic investigation. Peak coarctation gradient was performed within 30 seconds after exercise cessation, but due to the time lapse, it may demonstrate lower gradients. Noninvasive imaging measurements, exercise stress testing, and echocardiography were not necessarily conducted on the same day leading to the possibility of changes in blood pressure and/or gradient at different testing time points. However, they were typically performed within several months of each other and are expected to correlate.

CONCLUSIONS

In patients with nonsevere native or recurrent CoA, reduced exercise capacity is correlated with more severe coarctation by anatomic size and coarctation gradient. Those with a coarctation-to-diaphragm ratio ≤0.7 may represent a subset of patients with nonsevere coarctation who have clinical effects of their disease, which can be elicited with exercise stress testing. Use of routine exercise stress testing and cross-sectional imaging in the follow-up of patients with nonsevere CoA may help identify those with subtle clinical effects of their coarctation who could be considered for sooner coarctation intervention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with nonsevere native or recurrent CoA, reduced exercise capacity correlates with coarctation severity by both anatomic size and coarctation gradients. Those with a coarctation-to-diaphragm ratio ≤0.7 may represent a subset of patients with nonsevere CoA whose clinical symptoms can be elicited with exercise stress testing.

TRANSLATIONAL OUTLOOK: Use of routine exercise stress testing and cross-sectional imaging in the follow-up of patients with nonsevere CoA may help identify those with subtle clinical effects of their coarctation who could be considered for earlier coarctation intervention.

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