Exercise-induced hypertension after aortic coarctation repair: Our experience and a systematic review

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DOI: 10.33963/v.phj.100636

Received:
February 15, 2024

Accepted:
May 9, 2024

Early publication date:
May 16, 2024

ABSTRACT

Background: The exact prevalence and clinical significance of excessive increase in blood pressure in response to exercise in patients with repaired coarctation of aorta (CoA) remains unknown.

Aim: This study aimed to investigate the impact of different definitions of exercise-induced hypertension (EIH) on the prevalence rates in our adult patients with repaired CoA. A systematic review of the available literature was also performed.

Methods: We retrospectively analyzed exercise test data from adult patients with repaired CoA followed at the national referral center for adult congenital heart disease between 1998 and 2021. The three most reported definitions of EIH in patients with repaired CoA were used for the analysis of EIH prevalence. We also performed a systematic search of the PubMed electronic bibliographic database. Full-text versions of all potentially relevant articles on EIH in CoA were reviewed for relevance.

Results: Our registry included 161 adult CoA patients. Complete exercise test results were available in 74 patients (59% male, median age 39 years [range 20–68 years]). The prevalence of EIH in our cohort varied from 24 to 41%, depending on the definition used. We identified eleven eligible articles from 184 publications. The reported prevalence rate of EIH in the studies ranged from 13% to 82%.

Conclusion: EIH is common in patients with repaired CoA; however, the rates of EIH vary greatly depending on the definition used. A standardized and uniform EIH definition is needed to accurately assess the prevalence and clinical relevance of EIH in this population.

Key words: adult congenital heart disease, aortic coarctation, exercise, hypertension

INTRODUCTION

Coarctation of aorta (CoA) is a common congenital heart disease, accounting for 5%–10% of all congenital heart defects [1]. It is characterized by a narrowing in the descending aorta that creates a blood pressure gradient leading to upper body arterial hypertension. However, according to the European Society of Cardiology guidelines, CoA is considered as part of generalized arteriopathy, and not only as a narrowing of the aorta [2]. Therefore, even after successful surgical or percutaneous repair of CoA, arterial hypertension is common in these patients and has been associated with a higher incidence of premature cardiovascular disease and reduced life expectancy compared to the healthy population [3, 4]. Early detection and treatment of arterial hypertension is, therefore, crucial to prevent long-term complications.

In addition to arterial hypertension at rest, patients after CoA repair often show an exaggerated increase in blood pressure in response to exercise. The exact prevalence of exercise-induced hypertension (EIH) in these patients is unknown since there is no consensus on what normal blood pressure during exercise is, and several different definitions of EIH are used in medical practice. The prognostic value of EIH in patients after successful repair of CoA is unknown. In the general population, EIH is associated with a higher incidence of cardiovascular and all-cause mortality [5, 6]. It is also prognostic for the development of arterial hypertension at rest, which is the strongest risk factor for cardiovascular diseases [7, 8].

WHAT'S NEW?

Patients after successful repair of coarctation of the aorta often show an exaggerated increase in blood pressure in response to exercise. The reported prevalence of exercise-induced hypertension (EIH) among these patients is high; however, it varies greatly depending on the EIH definition used. Until a consensus is reached on a standardized definition of EIH in patients with repaired coarctation of the aorta, we cannot precisely assess the prevalence and clinical relevance of EIH in this population.

This study aimed to determine the prevalence of EIH in our adult patients with repaired CoA according to the different definitions of EIH in use. In addition, a systematic review of the literature on EIH in patients with repaired CoA was performed to determine the prevalence of EIH and its association with cardiovascular morbidity.

METHODS

Our experience

We retrospectively analyzed the demographic and exercise test data from all consecutive adult patients (age ≥18 years) with CoA followed at the national referral center for adult congenital heart disease between 1998 and 2021. Only patients with complete exercise testing data and repaired CoA were included. Exercise stress testing was performed on a cycle ergometer or treadmill following the Bruce protocol. A cardiopulmonary exercise test was performed on a cycle ergometer following the Ramp protocol. Blood pressure was measured on the right arm by a conventional sphygmomanometer before the start of the test and every 2 to 3 minutes during exercise. Systolic blood pressure at peak exercise was obtained from the reports. The prevalence of EIH in our patients with repaired CoA was estimated using the three most commonly used definitions of EIH [9–11]:

- systolic blood pressure (SBP) >200 mm Hg;
- SBP ≥220 mm Hg;
- SBP ≥210 mm Hg for men and ≥190 mm Hg for women.

The study was approved by the National Ethics Committee (approval number 0120-560/2020/7), and it has been carried out in accordance with the Declaration of Helsinki. Participants gave informed consent.

Literature review

A systematic literature search was performed to examine the evidence on the prevalence of EIH in adult patients (age ≥18 years) after repaired CoA. A literature search was conducted in the PubMed (1955–2022) electronic bibliographic database. The search query was: ([coarctation of the aorta] OR [aortic coarctation] OR [coarctation of aorta]) AND (arterial hypertension) AND (exercise). We included all studies published in English-language journals, regardless of the year of publication or study design. All main outcomes were acceptable if EIH data were available. Studies that did not report EIH data were excluded. Full-text versions of all potentially relevant articles were obtained and reviewed. All reasons for exclusion were recorded.

Data extraction and assessment of study quality

A common template was used for data extraction of participants, study type, methods, type of intervention, age at intervention, comorbidities, regular medication, definitions of EIH, incidence of EIH, and conclusions regarding EIH.

The quality of the studies was assessed using relevant components (questions 1–4, 6, 7, 9–13, 16–18, 20) of the Downs and Black scoring system [12] assigning each article a maximum score of 15.

Statistical analysis

Continuous variables were presented as means (SDs) or medians (ranges), and categorical variables as numbers and percentages. The Mann–Whitney U test was used to compare continuous variables. Categorical variables were analyzed using the McNemar–Bowker's test. The kappa coefficient was calculated to assess the level of agreement between the three most commonly used definitions of EIH. All statistical analyses were performed using SPSS version 27.0 software. Values of P <0.05 were considered statistically significant.

RESULTS

Our experience

Over 23 years, 161 patients with CoA were examined at our national referral center for adult congenital heart disease. Of 161 patients, complete exercise test results were available for 74 (46%) patients with repaired CoA who were included in this study. Baseline characteristics of the study population are presented in Table 1. Most of the patients in our cohort had the first repair done in childhood (median age 6 [0–47] years). Surgical repair of CoA was performed in 71 (96%) patients, and 9 (12%) patients required an additional procedure. Forty-three patients (58%) had arterial hypertension at rest and were treated with anti-hypertensive medication, with 25 (34%) patients requiring more than one anti-hypertensive medication. A bicuspid aortic valve was the most commonly associated congenital heart disease (n = 19; 26%). The majority of the patients underwent exercise stress testing on a treadmill or cycle ergometer following the Bruce protocol, and 11 (15%) patients underwent cardiopulmonary exercise tests on a cycle ergometer following the Ramp protocol. The prevalence of EIH varied widely in our cohort, depending on the definition used (Table 2). When EIH was defined as SBP >200 mm Hg, 30 patients (41%) had EIH. On the other

Table 1. Baseline characteristics

	All patients (n = 74)
Age, median (range)	39 (20–68) years
Male sex, n (%)	44 (59%)
BMI, kg/m^2, mean (SD)	23.7 (4.4)
Resting hypertension, n (%)	43 (58%)
Use of anti-hypertensive medication, n (%)	43 (58%)
Resting SBP, mm Hg, mean (SD)	142 (20)
Resting DBP, mm Hg, mean (SD)	78 (11)
Resting HR, bpm, mean (SD)	81 (18)
HR at maximal exercise, bpm, mean (SD)	169 (18)
Type of anti-hypertensive medication, n (%)	
ACEIs	32 (43%)
ARBs	5 (7%)
Beta-blockers	28 (38%)
CCBs	4 (5%)
Associated congenital heart defects	
Bicuspid aortic valve, n (%)	19 (26%)
Atrial septal defect, n (%)	2 (3%)
Ventricular septal defect, n (%)	3 (4%)
Patent foramen ovale, n (%)	1 (1.5%)
Patent ductus arteriosus, n (%)	2 (3%)
Transposition of great arteries, n (%)	1 (1.5%)
Type of 1st repair	
Surgical, n (%)	71 (96%)
Percutaneous, n (%)	3 (4%)
Age at 1st repair, median (range)	6 (0–47) years
Additional repair, n (%)	9 (12%)

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BMI, body mass index; CCBs, calcium channel blockers; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure

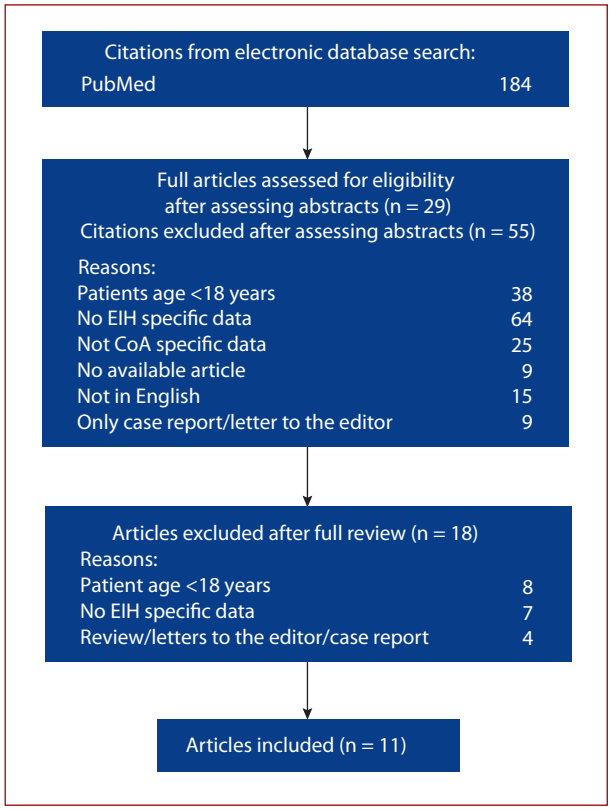

Figure 1. Results of the literature search on exercise-induced hypertension in patients after repaired coarctation of aorta

Abbreviations: CoA, coarctation of aorta; EIH, exercise-induced hypertension

hand, only 18 patients (24%) had EIH when a SBP cut-off of 220 mm Hg was used. With sex-specific cut-off values, 30 (41%) patients had EIH, with a higher rate of EIH observed in women than with the other definitions. The level of agreement between the three most commonly used EIH definitions was assessed using kappa coefficient and the results are presented in Supplementary material, *Table S1*.

Overall, 66% of patients with EIH had resting hypertension, regardless of the EIH definition used, and were more likely to have hypertension at rest compared to those without EIH (Supplementary material, *Table S2*). There were no differences between groups (EIH according to each definition versus patients without EIH) in the age at first repair. However, patients with EIH defined as SBP >200 mm Hg were younger compared to those without EIH (median age 32.5 years vs. 42.5 years; $P = 0.01$).

Literature review

The electronic database search identified a total of 184 articles (Figure 1). After review, 11 articles were included in this review. The majority of included studies were prospective cohort studies (Table 3). The quality of the studies was high (mean 13.6 of 15, range 11–15). These studies included a total of 2122 participants (range 22–675 per study), of whom 1298 (61%) were men. Arterial hypertension was the most reported comorbidity in patients with repaired CoA (n = 1106; 52%) and bicuspid aortic valve (BAV) was the most commonly associated congenital heart defect (n = 877; 41%). Arterial hypertension was treated in 780 patients (37%). A total of 699 cases of EIH were reported (range 8–299 per study). Definitions of EIH varied between studies. Most commonly, EIH was defined as peak exercise SBP ≥210 mm Hg in men and peak exercise SBP ≥190 mm Hg in women (n = 4) [11, 13–15] and as peak exercise SBP >200 mm Hg (n = 3) [16–18]. Two studies defined EIH as peak exercise SBP ≥220 mm Hg [9, 10]. The remaining two studies defined it as age and sex-specific SBP >95th percentile and peak SBP >2 SD above the load-dependent reference value [19, 20].

Table 2. Prevalence of exercise induced hypertension depending on exercise induced hypertension definition used

	SBP >200 mm Hg	SBP ≥220 mm Hg	SBP ≥210 mm Hg (men), ≥190 mm Hg (women)
Men (n = 44)	24 (55%)	14 (32%)	21 (48%)
Women (n = 30)	6 (20%)	4 (13%)	9 (30%)
Total (n = 74)	30 (41%)	18 (24%)	30 (41%)

Abbreviations: see — Table 1

Table 3. Characteristics of studies included in the review

Publication	Study type	Objective	Population	Methods	EIH prevalence	Grade
Vriend et al., 2004 [17]	Prospective cohort study	To investigate if EIH in patients with repaired CoA is associated with arterial hypertension on 24-h blood pressure measurement and increased LV mass	n = 144 (91 men) Age: mean 31.5 (11.2) years Age at repair: mean 7.9 years (range 0.01–45.7 years)	One exercise test between 2001 and 2002 EIH: maximal SBP ≥200 mm Hg	n = 38 (32% of 117 normotensive patients at rest)	13/15
Vriend et al., 2005 [10]	Prospective cohort study	To investigate the relation between EIH and carotid intima media thickness in patients with repaired CoA	n = 137 (89 men) Age: median 31 years (range 17–74 years) Age at repair: median 7.8 years (range 0.1–46 years)	One exercise test between 2001 and 2002 EIH: peak SBP ≥200 mm Hg	n = 18 (13%)	11/15
Luijendijk et al., 2011 [16]	Prospective cohort study	Evaluation of predictive value of EIH for chronic arterial hypertension in patients with repaired CoA	n = 74 (45 men) Age: mean 30.9 (9.5) years Age at repair: mean 8.0 (6.8) years	Two exercise tests from 2001 to 2009 EIH: peak exercise SBP ≥200 mm Hg	n = 16 (22%)	15/15
Yogeswaran et al., 2018 [18]	Retrospective cohort study	To determine the prevalence of EIH and its association with cardiovascular adverse events in patients with repaired CoA	n = 138 (82 men) Age: mean 40 (13) years Age at repair: mean 9 (3) years	EIH: peak SBP >200 mm Hg	n = 26 (19%)	15/15
Correia et al., 2013 [14]	Retrospective cohort study	To assess the prevalence of EIH in patients with repaired CoA	n = 65 (40 men) Age: mean 30 (8) years	EIH: peak SBP ≥210 mm Hg for men and peak SBP ≥190 mm Hg for women	n = 11 (22%)	13/15
Egbe et al., 2019 [13]	Retrospective case control study	Patients with repaired CoA will have a higher rise in SBP during exercise compared to matched controls	n = 149 patients and 149 controls (87 men) Age: mean 37 (12) years Age at repair: mean 4 (2) years	Exercise test between 1985 and 2018 EIH: peak exercise SBP >210 mm Hg for men and peak exercise SBP >190 mm Hg for women	n = 37 (26%)	15/15
Meijs et al., 2022 [11]	Prospective cohort study	To determine the prevalence of a hypertensive response to exercise, to identify factors associated with peak exercise SBP and to explore association of peak exercise SBP with resting SBP and CV events during follow-up	n = 675 (403 men) Age: median 24 years (range 16–72 years) Age at repair: median 3 years (0–67 years)	Exercise stress test between 2002 and 2018 EIH: peak SBP ≥210 mm Hg for men and peak SBP ≥190 mm Hg for women	n = 299 (44%)	13/15
Egbe et al., 2022 [15]	Retrospective cohort study	To assess the relationship between EIH and cardiovascular events and to determine if exercise BP improved risk stratification in this population	n = 327 (201 men) Age: mean 35 (13) years Age at repair: median 3 years (1–6 years)	Exercise stress test between 2003 and 2019 EIH: peak SBP >210 mm Hg for men and peak SBP >190 mm Hg for women	n = 116 (35%)	13/15
Hager et al., 2008 [20]	Prospective cohort study	To evaluate if patients with repaired CoA have reduced exercise capacity	n = 260 (176 men) Age: mean 30.2 (11.4) years Age at repair: 11.5 (11.2) years	EIH: peak SBP >2 SD above the age-and workload-dependent reference value	n = 73 (28.1%)	12/15
Pedersen et al., 2011 [9]	Prospective cohort study	To assess late morbidity in patients with repaired CoA and its association with residual aortic arch obstruction	n = 133 (84 men) Age: median 44 years (range 26–74 years) Age at repair: median 10 years (range 0.1–40 years)	EIH: peak SBP >220 mm Hg	n = 47 (37%)	15/15
Dijkema et al., 2019 [19]	Prospective case control study	To assess exercise capacity and blood pressure response in patients with repaired CoA in relation to LV and vascular function	n = 22 patients and 22 controls Age: mean 30 (10.6) years Age at repair: mean 5.9 years (range 0.35–14.4 years)	Cardiopulmonary exercise test EIH: age- and sex-specific systolic blood pressure above the 95th percentile	n = 18 (82%)	15/15

Grade: Assigned to each study based on quality assessment using the relevant components (questions 1–4, 6, 7, 9–13, 16–18, 20) of Downs and Black scoring system [12]
Continuous variables are presented as mean (SD), mean (range) or median (range), and categorical variables as numbers and percentage

Abbreviations: BP, blood pressure; CoA, coarctation of aorta; CV, cardiovascular; EIH, exercise-induced hypertension; LV, left ventricle; SBP, systolic blood pressure

The estimated prevalence of EIH in 9 of the included studies was 20%–45%, while two studies reported the estimated prevalence at 13% and 82%.

A summary of other important findings on EIH derived from the systematic review is reported in parentheses as the number of studies and total number of participants assessed. Even after repair, patients frequently experienced arterial hypertension and aortopathy (1 article, n = 133). Patients with repaired CoA had a higher risk of EIH and achieved a higher peak SBP during exercise than the healthy population (2 articles, n = 171). EIH was an independent risk factor for the development of chronic arterial hypertension in patients after CoA repair (3 articles, n = 771). Peak exercise SBP was also associated with higher mean

daytime SBP at ambulatory blood pressure monitoring (1 article, n = 144). The severity of vascular dysfunction correlated with exercise-induced SBP changes (1 article, n = 149) and EIH was also an independent predictor of common carotid intima-media thickness (1 article, n = 137). No correlation was found between peak SBP and left ventricular mass (3 articles, n = 893). EIH seemed to be less prevalent in patients without residual gradient (measured as systolic brachial-ankle blood pressure difference) and in those treated with diuretics (1 article, n = 260). However, patients under antihypertensive therapy with angiotensin-converting enzyme inhibitors may be at greater risk of EIH (1 article, n = 65).

DISCUSSION

The results of our single-center retrospective study and systematic review of the related literature show that EIH is common in patients with repaired CoA, but the observed prevalence varies considerably depending on the EIH definition used.

Currently, there is no consensus on what is considered a normal blood pressure response during exercise [21]. In clinical practice, several different definitions of EIH in patients with repaired CoA are used leading to conflicting results. The 11 studies included in the systematic review used 5 different definitions of EIH. In nine of the studies, the reported prevalence of EIH was between 20% and 45%. However, in two studies the estimated prevalence of EIH was 13% and 82%. The prevalence of EIH in our cohort of patients with repaired CoA, whose clinical characteristics were comparable to those of other described CoA cohorts, varied from 24% to 41%, depending on the definition used.

The three most common definitions of EIH in the articles included in this review were exercise-associated peak SBP >200 mm Hg or SBP ≥220 mm Hg for both sexes and exercise-associated peak SBP ≥210 mm Hg and ≥190 mm Hg for men and women, respectively. Based on the kappa coefficients there is overall a substantial agreement between these three EIH definitions. However, sex-specific sub-analysis revealed only moderate agreement between definitions 1 and 2 in men and between definitions 2 and 3 in women, indicating the potential for a significant mismatch between definitions, which may have implications for research and routine clinical care (Supplementary material; *Table S1*). Our results also show higher prevalence of EIH in women in gender specific EIH definition when compared to other definitions. However, a recent study in a large cohort of healthy individuals demonstrated that the cut-offs used in the sex-specific EIH definition are less reliable in young adults, especially in the second and third decades of life, because the 90th percentile of peak exercise SBP did not reach or exceed 210 mm Hg in men or 190 mm Hg in women until the fourth decade of life [22]. Therefore, applying this EIH definition in young patients with repaired CoA is questionable.

The blood pressure response to exercise is complex and peak exercise SBP may not be the most optimal marker of EIH. Among other factors that influence blood pressure response during exercise, workload plays an important role. SBP has been shown to rise linearly with increasing workload [23]. A large study recently established age- and sex-specific reference values and equations for the workload-indexed SBP response during exercise in apparently healthy individuals [24]. As the exercise capacity of patients with repaired CoA is lower compared to healthy individuals, using the workload-indexed SBP response during exercise may eliminate the confounding effect of early exercise termination on peak SBP [25, 26]. In this regard, workload-indexed SBP may be a better marker of EIH than peak SBP. However, studies in patients with repaired CoA are lacking.

In an otherwise healthy population, EIH causes cardiac remodeling and increases the risk of the development of arterial hypertension in the future [27]. The clinical significance of EIH in patients with CoA remains a matter of debate. The current American Heart Association guidelines for the management of adults with congenital heart disease consider exercise testing for screening of EIH as a class IIb recommendation [28]. EIH appears to be a predictor of the development of chronic arterial hypertension [11, 15, 16, 19]. In comparison to patients with normotensive response to exercise, EIH patients had significantly increased intima-media thickness, a validated and reproducible end-point for atherosclerosis [10, 29].

The correlation between EIH and adverse cardiovascular events, as well as with left ventricular mass, remains to be investigated, as the results of available studies are conflicting [11, 15–17, 30].

Currently, there is insufficient evidence to support early antihypertensive treatment in patients with EIH. Future studies are needed to evaluate the benefit of exercise testing for follow-up and monitoring of patients with repaired CoA and the potential benefit of early antihypertensive treatment in patients with EIH. However, a consensus on a uniform definition of EIH is a prerequisite for such studies.

We acknowledge some limitations of our study. Only half of all our CoA patients were included in the study; complete data on exercise testing were not retrospectively available in others. Since most of the patients in our cohort had the first repair done in childhood, surgical repair was most commonly performed, therefore the effect of the treatment method on the incidence of EIH cannot be compared. The main limitation of the systematic review is the paucity of available literature on EIH in patients with repaired CoA. Although the quality of the studies was high, they included a heterogeneous patient population and mostly had a small sample size.

CONCLUSION

Our study in patients with repaired CoA showed that the prevalence of EIH varies greatly depending on the EIH defi-

nition used. Until a consensus is reached on a standardized definition of EIH in patients with repaired CoA, we cannot precisely assess the prevalence and clinical relevance of EIH in this population. In patients with repaired CoA, workload-indexed SBP may be a better marker of EIH than peak exercise SBP.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/polish_heart_journal.

Article information

Conflict of interest: None declared.

Funding: None.

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