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ABSTRACT

Objective The clinical and prognostic implications of a hypertensive response to exercise after repair of coarctation of the aorta (CoA) remain controversial. We aimed to determine the prevalence of a hypertensive response to exercise, identify factors associated with peak exercise systolic blood pressure (SBP) and explore the association of peak exercise SBP with resting blood pressure and cardiovascular events during follow-up.

Methods From the Dutch national CONgenital CORvitia (CONCOR) registry, adults with repaired CoA who underwent exercise stress testing were included. A hypertensive response to exercise was defined as a peak exercise SBP ≥210 mm Hg in men and ≥190 mm Hg in women. Cardiovascular events consisted of coronary artery disease, stroke, aortic complications and cardiovascular death.

Results Of the original cohort of 920 adults with repaired CoA, 675 patients (median age 24 years (range 16–72 years)) underwent exercise stress testing. Of these, 299 patients (44%) had a hypertensive response to exercise. Mean follow-up duration was 10.1 years. Male sex, absence of a bicuspid aortic valve and elevated resting SBP were independently associated with increased peak exercise SBP. Peak exercise SBP was positively predictive of office SBP (β=0.11, p<0.001) and 24-hour SBP (β=0.05, p=0.03) at follow-up, despite correction for baseline SBP. During follow-up, 100 patients (15%) developed at least 1 cardiovascular event. Peak exercise SBP was not significantly associated with the occurrence of cardiovascular events (HR 0.994 (95% CI 0.987 to 1.001), p=0.11).

Conclusions A hypertensive response to exercise was present in nearly half of the patients in this large, prospective cohort of adults with repaired CoA. Risk factors for increased peak exercise SBP were male sex, absence of a bicuspid aortic valve and elevated resting SBP. Increased peak exercise SBP independently predicted hypertension at follow-up. These results support close follow-up of patients with a hypertensive response to exercise to ensure timely diagnosis and treatment of future hypertension.

INTRODUCTION

Coarctation of the aorta (CoA) is referred to as a local stenosis of the proximal descending aorta, often at the level of the duct. While CoA was previously regarded as a simple, curable condition, it is now increasingly recognised as the expression of a complex, generalised arteriopathy that requires lifelong monitoring.[1 2] Pathological vascular mechanisms contribute to the high prevalence of resting hypertension, which should be adequately treated to avoid late cardiovascular complications.[3] In addition to resting hypertension, 19%–35% of patients with CoA show a hypertensive response to exercise.[4–8] This is rather inconsistently defined but is commonly referred to as a systolic blood pressure (SBP) ≥210 mm Hg in men and ≥190 mm Hg in women during maximal exercise.[9] Like resting hypertension, it is often observed in the absence of restenosis at the repair site.[10 11] Hence, it remains unclear which patients with CoA are at high risk of a hypertensive response to exercise and may therefore require more intensive monitoring.

In the general population, a hypertensive response to exercise carries significant prognostic implications, as it is associated with an increased risk of future hypertension, cardiovascular events and mortality.[12 13] Although some studies have identified a hypertensive response to exercise as a risk factor for chronic hypertension in patients with CoA, these studies were limited by a relatively small sample size or did not correct for potentially important confounding factors, such as baseline blood pressure (BP).[14 15] In particular, the prognostic significance of this hypertensive response during exercise in the setting of a normal resting BP is subject of debate, which was recognised as a 'gap in knowledge' in the recent 2020 European Society of Cardiology (ESC) guidelines.[3] Furthermore, although it is well known that patients with repaired CoA are at increased risk to experience cardiovascular events, including coronary artery disease, stroke and aneurysm formation, the impact of a hypertensive response to exercise on the incidence of these cardiovascular complications remains to be elucidated.[16]

Using a multicentre, prospective cohort of adults with repaired CoA, we aimed to determine the prevalence of a hypertensive response to exercise, identify factors associated with peak exercise SBP and examine the association of peak exercise SBP with resting SBP and the occurrence of cardiovascular events during follow-up.

METHODS

Study design

Adult patients with CoA from five tertiary referral centres who underwent exercise stress testing on enrolment in the CONgenital CORvitia (CONCOR) registry were included in this study. CONCOR is a prospective registry of adult patients with congenital heart disease in the Netherlands and was founded in 2001. Patients provided informed consent at the time of study entry. The short-term and medium-term outcomes of patients in one participating centre have been previously published.[14 17 18] Patients were only included when prior surgical or transcatheter repair of CoA was performed. Exclusion criteria comprised a functionally univentricular circulation or transposition of the great arteries not repaired by an arterial switch procedure. Patients were enrolled between 2002 and 2018 and followed until their last clinic visit or death. The study was designed and performed without patient or public involvement.

Data collection and definitions

Patients underwent maximal exercise stress testing on a treadmill or cycle ergometer. The test was symptom-limited, unless other reasons for termination were present according to ESC guidelines.[19] Exercise workload was expressed as metabolic equivalents (METs). One MET equals an energy expenditure of 3.5 mL O_2/kg/min. BP was measured in upright position before the start of the test and during exercise using standardised intervals, generally every 2–3 min. A hypertensive response to exercise was defined as a peak exercise SBP ≥210 mm Hg in men and ≥190 mm Hg in women.[9] Resting BP status was determined at baseline and at last follow-up. Resting BP was measured at the right arm at the outpatient clinic. In case the BP was only measured at the left arm or it was unclear which arm was used, these values were recorded to reduce the number of missing BP readings. Resting hypertension was regarded as an office SBP ≥140 mm Hg, office diastolic blood pressure (DBP) ≥90 mm Hg and/or the use of ≥1 antihypertensive agents. Additionally, 24-hour ambulatory BP monitoring (ABPM) was performed at follow-up. Left ventricular (LV) mass was assessed by echocardiography at baseline and follow-up, and was indexed for body surface area. LV hypertrophy was defined as an LV mass index >115 g/m^2 for men and >95 g/m^2 for women.[20] Other collected data included demographics, prior CoA interventions and associated congenital defects.

Outcome measures

Outcomes at follow-up consisted of office SBP, 24-hour SBP as determined by ABPM and LV mass index. Additionally, two independent researchers (TAM and SCSM) recorded cardiovascular events during the follow-up period, based on the written medical correspondence by the treating cardiologist. Cardiovascular events consisted of coronary artery disease, stroke, aortic complications and cardiovascular death. Coronary artery disease was defined as myocardial infarction, coronary revascularisation or medical therapy for angina. Aortic complications comprised thoracic aortic aneurysms and dissections. An aortic aneurysm was defined as an aortic diameter >50% larger than predicted based on sex and aortic segment, and/or surgical treatment of the aneurysm.[21] Aortic dissection also included pseudoaneurysm, intramural haematoma and aortic rupture. The definitions of the Standardized Data Collection for Cardiovascular Trials Initiative/Food and Drug Administration consensus report were used to determine whether mortality was due to a cardiovascular or non-cardiovascular cause.[22] In case of uncertainty, this was resolved by discussion with a third study member (MV).

Statistical analyses

Baseline characteristics were compared between patients with and without a hypertensive response to exercise using the independent-samples t-test, Mann-Whitney U test or Fisher's exact test, where appropriate. To identify factors associated with peak exercise SBP, univariable and multivariable linear regression were performed. Covariates were included when a potential association with the outcome was conceivable based on previous findings or pathophysiological mechanisms. All covariates were entered into the multivariable model without any selection based on significance. Residual analyses (normality, homoscedasticity and linearity) were performed to assess the validity of the model. Potential multicollinearity was assessed by inspection of the variance inflation factor values. Similar linear regression models were created for the outcomes office SBP, 24-hour SBP and LV mass index at follow-up.

A potential association between peak exercise SBP and cardiovascular events was explored by Cox proportional-hazards regression. Patients were followed until the occurrence of a cardiovascular event or censored at the time of the last follow-up visit. A delayed entry model with age as the time scale was used to correct for left-truncated, right-censored data. The model was adjusted for potential confounding factors, which were included by forced entry and consisted of sex, age at initial CoA repair, end-to-end anastomosis, prior intervention for re-CoA, bicuspid aortic valve, ventricular septal defect, aortic and/or mitral mechanical heart valve, resting SBP and DBP and LV mass index. Fitted penalised B-spline curves and scaled Schoenfeld residuals were examined for each individual covariate and the multivariable model to determine whether or not the proportional-hazards assumption was violated. Due to a relatively low number of events per covariate, Firth's correction was applied to reduce bias associated with monotone likelihood.[23] Statistical analyses were performed using IBM SPSS Statistics V.25 (Armonk, New York, USA) and SAS V.9 (Cary, North Carolina, USA). A p value <0.05 was considered to represent statistical significance.

RESULTS

Baseline characteristics

Of the original cohort of 920 adult patients with CoA from the CONCOR registry, 675 patients (73%) underwent exercise stress testing and were therefore included in the current study. Of these, 299 patients (44%) showed a hypertensive response to exercise. Baseline characteristics are presented in table 1. In the group with a hypertensive response to exercise, 195 patients (65%) had resting hypertension vs 181 patients (48%) in the group without a hypertensive response to exercise (p<0.001). Exercise workload was comparable between the groups (11.2±3.6 vs 11.0±3.9 METs, respectively; p=0.46). Mean follow-up duration was 10.1±4.7 years. Figure 1 depicts the study cohort stratified by resting BP status and the presence or absence of a hypertensive response to exercise.

Baseline characteristics were compared with patients from the original cohort who were excluded from this study, that is, patients who did not undergo exercise stress testing (online supplemental table 1). Patients in the study cohort were younger at the time of initial repair, less frequently treated by graft interposition and more likely to have LV hypertrophy.

Factors associated with peak exercise SBP

Table 2 displays the results of linear regression analysis to identify factors associated with peak exercise SBP. In multivariable analysis, resting SBP at baseline (β=0.53; p<0.001) was positively associated with peak exercise SBP. Female sex (β=−11.68;

Table 1 Baseline characteristics

	All patients n=675	Hypertensive response to exercise n=299	No hypertensive response to exercise n=376	P value*
Age (y), median (range)	24 (16–72)	25 (16–65)	24 (16–72)	0.66
Female sex, n (%)	272 (40)	127 (42)	145 (39)	0.31
BMI (kg/m^2), mean±SD	23.9±4.3	24.1±3.8	23.8±4.6	0.47
Age at initial CoA repair (y), median (range)	3 (0–67)	4 (0–54)	2 (0–67)	0.37
Type of initial CoA repair, n (%)				
End-to-end anastomosis	344 (51)	154 (52)	190 (51)	0.82
Patch angioplasty	72 (11)	27 (9)	45 (12)	0.26
Subclavian flap angioplasty	65 (10)	33 (11)	32 (9)	0.29
Graft interposition	19 (3)	10 (3)	9 (2)	0.49
Ascending-to-descending BG	5 (1)	1 (0.3)	4 (1)	0.39
Surgery, technique unknown	127 (19)	58 (19)	69 (18)	0.77
Balloon angioplasty	15 (2)	8 (3)	7 (2)	0.80
Stenting	28 (4)	8 (3)	20 (5)	0.17
Prior intervention for re-CoA, n (%)	140 (21)	69 (23)	71 (19)	0.21
Bicuspid aortic valve, n (%)	389 (58)	158 (53)	231 (61)	**0.03**
Ventricular septal defect, n (%)	155 (23)	63 (21)	92 (24)	0.31
Aortic and/or mitral MHV, n (%)	41 (6)	15 (5)	26 (7)	0.33
Resting hypertension, n (%)	376 (56)	195 (65)	181 (48)	**<0.001**
Resting SBP (mm Hg), mean±SD	134±18	139±18	130±17	**<0.001**
Resting DBP (mm Hg), mean±SD	76±11	77±11	76±11	0.28
Resting arm-leg gradient (mm Hg), mean±SD†	1±17	3±16	−1±17	0.06
Exercise workload (METs), mean±SD	11.1±3.8	11.2±3.6	11.0±3.9	0.46
Peak exercise SBP (mm Hg), mean±SD	196±33	225±20	174±22	**<0.001**
Use of any AHM, n (%)	224 (33)	111 (37)	113 (30)	0.06
LV mass index (g/m^2), mean±SD‡	96±31	96±30	95±31	0.87
LV hypertrophy, n (%)‡	187 (29)	87 (29)	100 (28)	0.73

P values <0.05 are indicated in bold.
*Indicates the difference between patients with and without a hypertensive response to exercise, as determined by the independent-samples t-test, Mann-Whitney U test or Fisher's exact test, where appropriate.
†Unavailable for 449 patients (67%), of whom 188 patients (63%) with and 261 patients (69%) without a hypertensive response to exercise.
‡Unavailable for 26 patients (4%), of whom 4 patients (1%) with and 22 patients (6%) without a hypertensive response to exercise.
AHM, antihypertensive medication; BG, bypass graft; BMI, body mass index; CoA, coarctation of the aorta; DBP, diastolic blood pressure; LV, left ventricular; MET, metabolic equivalent; MHV, mechanical heart valve; SBP, systolic blood pressure; y, years.

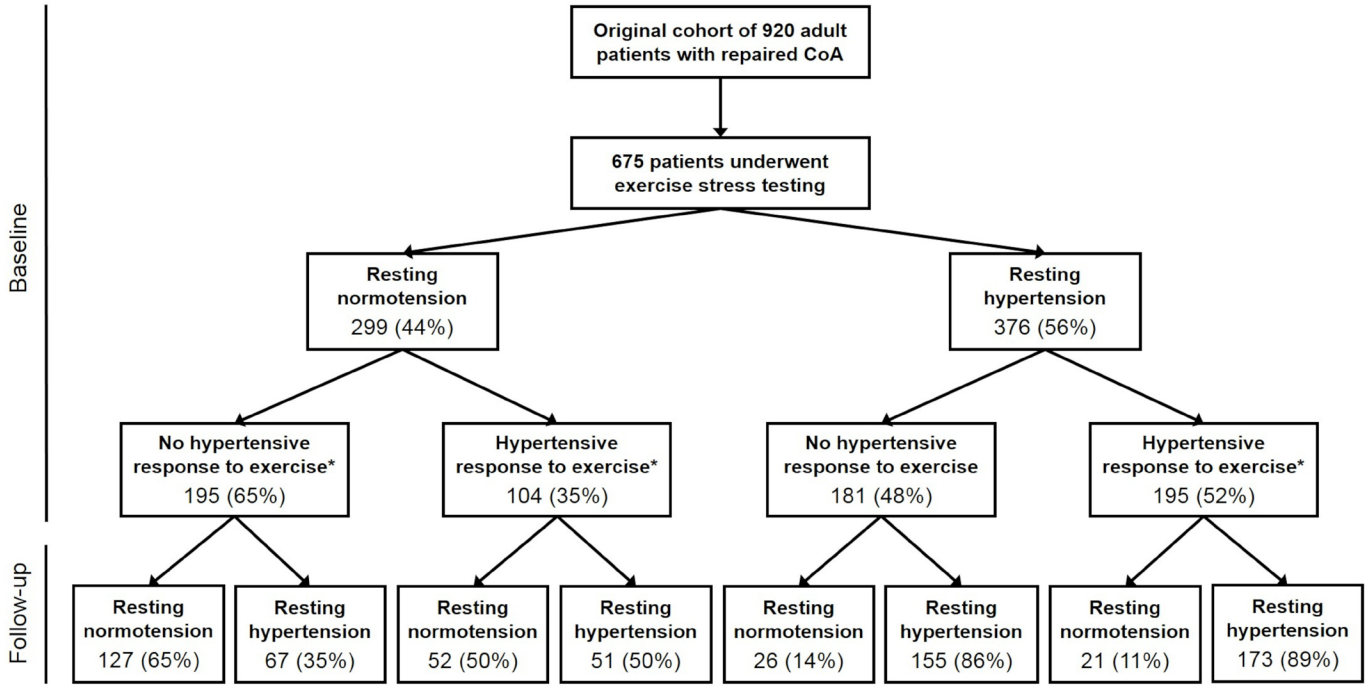

Figure 1 Flow chart displaying the stratification of patients based on the presence or absence of resting hypertension (office) and a hypertensive response to exercise at baseline. The prevalence of hypertension at follow-up is shown for the various subgroups. *Blood pressure status at follow-up was unknown for one patient in this group. CoA, coarctation of the aorta.

Table 2 Factors associated with peak exercise SBP

	Peak exercise SBP (mm Hg)			
	Univariable		Multivariable	
	β (SE)*	P value	β (SE)*	P value
Age (y)	−0.13 (0.11)	0.23	−0.28 (0.15)	0.06
Female sex	−16.57 (2.50)	**<0.001**	−11.68 (2.69)	**<0.001**
BMI (kg/m^2)	0.31 (0.30)	0.30	0.29 (0.32)	0.37
Age at initial CoA repair (y)	−0.12 (0.14)	0.37	0.25 (0.21)	0.23
Type of initial CoA repair				
End-to-end anastomosis	3.03 (2.53)	0.23	3.89 (3.40)	0.25
Patch angioplasty	−2.74 (4.10)	0.50	−4.59 (4.92)	0.35
Subclavian flap angioplasty	5.89 (4.29)	0.17	8.25 (5.02)	0.10
Graft interposition	5.78 (7.66)	0.45	8.81 (8.56)	0.30
Balloon angioplasty	2.70 (8.33)	0.75	−6.23 (8.89)	0.48
Stenting	−12.03 (6.45)	0.06	−16.32 (8.30)	0.05
Prior intervention for re-CoA	6.58 (3.12)	**0.04**	5.88 (3.12)	0.06
Bicuspid aortic valve	−5.42 (2.56)	**0.04**	−6.52 (2.43)	**0.007**
Resting SBP (mm Hg)	0.54 (0.07)	**<0.001**	0.53 (0.07)	**<0.001**
Use of any AHM	1.21 (0.54)	**0.02**	0.56 (0.57)	0.33
LV mass index (g/m^2)	0.10 (0.04)	**0.02**	0.02 (0.04)	0.61

In multivariable analysis, there was additionally adjusted for exercise workload in METs. A total of 644 complete cases were included in the multivariable model.
P values <0.05 are indicated in bold.
*Represents the change in peak exercise SBP per unit increase of the covariate.
AMH, antihypertensive medication; BMI, body mass index; CoA, coarctation of the aorta; LV, left ventricular; MET, metabolic equivalent; SBP, systolic blood pressure; y, years.

p<0.001) and the presence of a bicuspid aortic valve (β=−6.52; p=0.007) were negatively associated with peak exercise SBP.

Change in resting SBP and antihypertensive medication from baseline to follow-up

Online supplemental table 2 shows that office SBP and DBP remained similar during the follow-up period, both in patients with and without a hypertensive response to exercise. The proportion of patients taking any antihypertensive medication and the number of antihypertensive agents increased in both groups, although the increase in antihypertensive agents was more outspoken in patients with a hypertensive response to exercise (0.52 vs 0.35; p=0.03).

Value of peak exercise SBP in predicting resting SBP at follow-up

As shown in table 3, peak exercise SBP positively predicted office SBP at follow-up (β=0.11; p<0.001). This association was independent of resting SBP at baseline and other potential confounding factors. Resting SBP at baseline (β=0.23; p<0.001) and the use of any antihypertensive medication (β=0.63; p=0.02) were also independent positive predictors of office SBP at follow-up, whereas stent implantation as initial CoA repair (β=−9.76; p=0.01) was an independent negative predictor. When limiting this analysis to normotensive patients at baseline, peak exercise SBP was similarly predictive of office SBP at follow-up (β=0.08; p=0.002; online supplemental table 3).

In 244 patients (36%) 24-hour ABPM was performed at follow-up. Higher peak exercise SBP was associated with increased 24-hour SBP at follow-up in a multivariable model (β=0.05; p=0.03; table 3).

Peak exercise SBP was univariably predictive of LV mass index at follow-up (β=0.10; p=0.006), but this association was no longer observed in multivariable analysis (β=0.04; p=0.23; online supplemental table 4). Similarly, peak exercise SBP was not an independent predictor of LV mass index at follow-up when the analysis was limited to patients who were normotensive at baseline (β=0.06; p=0.27; online supplemental table 5).

Peak exercise SBP and the risk of cardiovascular events

During follow-up, 113 cardiovascular events were observed: 12 cases of coronary artery disease, 15 strokes, 69 aortic complications and 17 cardiovascular deaths (online supplemental table 6). These events occurred in 100 individual patients. Peak exercise SBP was not associated with the risk of cardiovascular events in univariable (HR 0.996 (95% CI 0.990 to 1.002); p=0.19) nor multivariable (HR 0.994 (95% CI 0.987 to 1.001); p=0.11) Cox proportional-hazards regression (table 4). In contrast, older age at initial repair, the presence of a bicuspid aortic valve and elevated LV mass index at baseline were independent risk factors for the occurrence of cardiovascular events.

DISCUSSION

In this multicentre, prospective cohort of adult patients with CoA, we sought to investigate the prevalence, potential risk factors and prognostic consequences of a hypertensive response to exercise. A hypertensive response to exercise occurred in 44% of patients in our cohort, which is even higher than previously reported.[4–8] Patients with an increased peak exercise SBP were more often male, had less frequently a bicuspid aortic valve and had a higher resting SBP. Increased peak exercise SBP was predictive of elevated resting SBP at follow-up, even after correction for baseline SBP (figure 2). These findings underline the prognostic impact of a hypertensive response to exercise in the adult CoA population. However, in this study no association between peak exercise SBP and the occurrence of cardiovascular events was demonstrated.

Prevalence and associations of a hypertensive response to exercise

In our cohort, a hypertensive response to exercise was observed in 299 out of 675 patients (44%), whereas in previous literature

Table 3 Value of peak exercise SBP in predicting office and 24-hour SBP at follow-up

	Office SBP at follow-up (mm Hg)				24-hour SBP at follow-up (mm Hg)			
	Univariable		Multivariable		Univariable		Multivariable	
	β (SE)*	P value	β (SE)*	P value	β (SE)*	P value	β (SE)*	P value
Age (y)	0.21 (0.05)	**<0.001**	0.09 (0.07)	0.18	0.03 (0.07)	0.71	−0.09 (0.09)	0.30
Female sex	−3.00 (1.28)	**0.02**	−0.004 (1.26)	1.00	−0.69 (1.73)	0.69	0.06 (1.77)	0.97
BMI (kg/m^2)	0.63 (0.15)	**<0.001**	0.19 (0.15)	0.20	0.24 (0.21)	0.25	0.22 (0.21)	0.29
Age at initial CoA repair (y)	0.15 (0.07)	**0.02**	0.14 (0.10)	0.15	0.03 (0.09)	0.73	0.00 (0.15)	1.0
Type of initial CoA repair								
End-to-end anastomosis	−2.02 (1.25)	0.09	−2.61 (1.62)	0.11	−1.21 (1.63)	0.46	−2.97 (2.07)	0.15
Patch angioplasty	1.16 (2.04)	0.57	−1.67 (2.27)	0.46	−0.81 (2.64)	0.76	−3.07 (2.95)	0.30
Subclavian flap angioplasty	−1.00 (2.12)	0.64	−0.81 (2.37)	0.73	−3.38 (3.19)	0.29	−7.20 (3.40)	**0.04**
Graft interposition	−0.78 (3.79)	0.84	−6.21 (4.08)	0.13	4.73 (3.92)	0.23	3.08 (4.80)	0.52
Balloon angioplasty	−1.89 (4.12)	0.65	−8.22 (4.22)	0.05	−3.71 (4.87)	0.45	−7.61 (5.49)	0.17
Stenting	−4.97 (3.19)	0.12	−9.76 (3.95)	**0.01**	−1.87 (3.77)	0.62	−2.04 (5.05)	0.69
Prior intervention for re-CoA	2.01 (1.54)	0.05	1.27 (1.48)	0.39	0.52 (1.89)	0.79	−0.21 (1.90)	0.91
Bicuspid aortic valve	−1.87 (1.27)	0.14	−0.41 (1.17)	0.73	2.30 (1.66)	0.17	3.58 (1.60)	**0.03**
Resting SBP at baseline (mm Hg)	0.35 (0.03)	**<0.001**	0.23 (0.04)	**<0.001**	0.22 (0.05)	**<0.001**	0.25 (0.05)	**<0.001**
Use of any AHM	1.46 (0.26)	**<0.001**	0.63 (0.27)	**0.02**	0.71 (0.33)	**0.03**	0.25 (0.33)	0.46
Peak exercise SBP (mm Hg)	0.15 (0.02)	**<0.001**	0.11 (0.02)	**<0.001**	0.07 (0.02)	**0.003**	0.05 (0.02)	**0.03**
LV mass index (g/m^2)	0.06 (0.02)	**0.007**	0.02 (0.02)	0.47	−0.03 (0.03)	0.37	−0.05 (0.03)	0.08

A total of 645 (office SBP) and 239 (24-hour SBP) complete cases were included in the multivariable model.
P values <0.05 are indicated in bold.
*Represents the change in SBP per unit increase of the covariate.
AHM, antihypertensive medication; BMI, body mass index; CoA, coarctation of the aorta; LV, left ventricular; SBP, systolic blood pressure; y, years.

Table 4 Cox proportional-hazards regression to assess the association between peak exercise SBP and the risk of cardiovascular events

	Cardiovascular event			
	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Female sex	0.51 (0.32 to 0.79)	**0.003**	0.70 (0.42 to 1.15)	0.15
BMI (kg/m^2)	1.04 (1.01 to 1.08)	**0.02**	1.02 (0.98 to 1.06)	0.30
Age at initial CoA repair (y)	1.030 (1.010 to 1.050)	**0.004**	1.027 (1.004 to 1.049)	**0.02**
End-to-end anastomosis	0.72 (0.48 to 1.09)	0.12	0.79 (0.51 to 1.23)	0.30
Prior intervention for re-CoA	0.79 (0.46 to 1.35)	0.39	0.79 (0.44 to 1.43)	0.44
Bicuspid aortic valve	2.29 (1.43 to 3.69)	**0.001**	2.23 (1.34 to 3.70)	**0.002**
Ventricular septal defect	0.89 (0.52 to 1.52)	0.68	1.16 (0.67 to 2.00)	0.61
Aortic and/or mitral MHV	1.73 (0.96 to 3.14)	0.07	1.27 (0.69 to 2.34)	0.45
Resting SBP (mm Hg)	1.005 (0.994 to 1.016)	0.37	1.006 (0.993 to 1.020)	0.37
Resting DBP (mm Hg)	1.017 (0.997 to 1.036)	0.09	1.015 (0.993 to 1.038)	0.19
Peak exercise SBP (mm Hg)	0.996 (0.990 to 1.002)	0.19	0.994 (0.987 to 1.001)	0.11
LV mass index (g/m^2)	1.009 (1.005 to 1.014)	**<0.001**	1.009 (1.003 to 1.014)	**0.003**

A total of 648 complete cases were included in the multivariable model, of whom 94 patients developed a cardiovascular event (composite of coronary artery disease, stroke, aortic complications and cardiovascular death).
P values <0.05 are indicated in bold.
BMI, body mass index; CoA, coarctation of the aorta; DBP, diastolic blood pressure; LV, left ventricular; MHV, mechanical heart valve; SBP, systolic blood pressure; y, years.

the reported prevalence ranged from 19% to 35%.[4–8] A possible explanation for the higher prevalence in the current study is that patients were younger (median of 24 years vs a mean between 30 and 40 years in four previous studies) and younger patients tend to have a higher peak exercise SBP.[4–7] Only 10% of people in the general population shows a hypertensive response to exercise, as the definition of a peak exercise SBP ≥210 mm Hg in men and ≥190 mm Hg in women roughly corresponds to the 90th percentile.[24] The mechanisms underlying this response have not been fully elucidated, although endothelial dysfunction, increased arterial stiffness, activation of the renin-angiotensin-aldosterone system and elevated sympathetic tone are considered key processes.[24] In patients with CoA, a hypertensive response to exercise may also be a clue to the presence of re-coarctation, especially in the setting of normal BP at rest.[7] Recently, we demonstrated that mimicking exercise by epinephrine administration during cardiac catheterisation may be useful in detecting haemodynamically relevant re-coarctation.[25]

In this study, male sex was predictive of higher peak exercise SBP. This is reflected by the current definition of a hypertensive

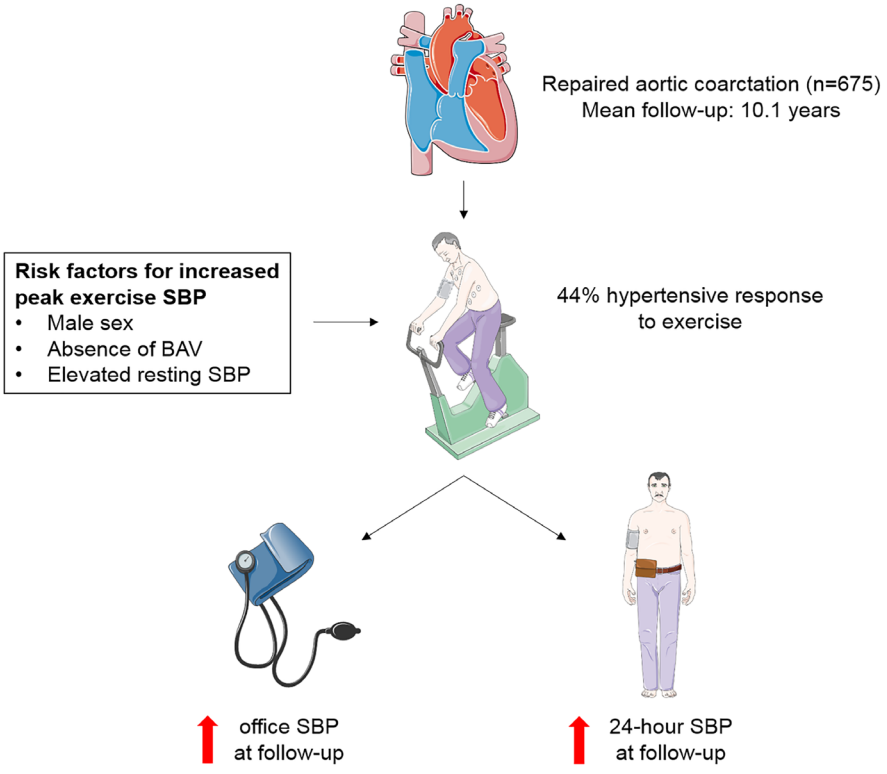

Figure 2 Graphical summary of the main findings in this study. Images from Servier Medical Art (smart.servier.com) were used to create this figure. BAV, bicuspid aortic valve; SBP, systolic blood pressure.

response to exercise, which applies a higher cut-off value for men compared with women (210 vs 190 mm Hg, respectively), even though some earlier studies used a cut-off value of 200 mm Hg for both men and women.[14 18] Furthermore, elevated resting SBP was a predictor of increased peak exercise SBP, despite several previous studies reporting no association between resting SBP and SBP response to exercise.[4 11] Lastly, patients with a bicuspid aortic valve showed a lower BP response to exercise, which may be related to the degree of aortic valve stenosis in this specific patient subset. However, it was previously found that patients with moderate-to-severe aortic valve stenosis (regardless of the presence of a bicuspid aortic valve) may have a hypertensive response to exercise, even though a blunted BP response to exercise was more frequent (21% vs 37%, respectively).[26]

Value of a hypertensive response to exercise in predicting hypertension and LV afterload

Although the BP response to exercise is frequently assessed in patients with CoA, there is uncertainty regarding its prognostic consequences. We found that peak exercise SBP was predictive of resting SBP at follow-up, which is in line with previous findings.[14 15] Importantly, this association was observed independently of resting SBP at baseline, which suggests that the BP response to exercise may have additional value in clinical decision making besides resting BP. Our results indicate that this also applies to normotensive patients with an isolated hypertensive response to exercise. Of note, stent implantation was associated with a lower resting BP at follow-up, which is consistent with the previously reported favourable haemodynamic effects of stenting.[27] However, patients who undergo stenting as primary repair generally have less complex disease compared with those surgically treated and therefore this finding should be interpreted with caution.

Hypertensive response to exercise and the risk of cardiovascular events

Despite the association between a hypertensive response to exercise and late hypertension, we found no conclusive evidence that this response predisposes for cardiovascular complications in the CoA population. One possible reason is that our follow-up time was not long enough. In addition, our patients were still relatively young and perhaps patients with CoA with a hypertensive response to exercise may not be at increased risk to experience cardiovascular events in early adulthood, but rather beyond the age of 50 years. In contrast, a previous study identified a hypertensive response to exercise as a risk factor for adverse cardiovascular events in patients with CoA.[4] However, events occurred only in 24 patients and aortic aneurysm formation, a hypertension-related complication frequently observed in CoA, was not included as an outcome. In our study, on the contrary, patients with a low peak exercise SBP tended to experience more events, although not statistically significant. We observed a particularly high incidence of ascending aortic aneurysms, despite correction for the presence of a bicuspid aortic valve. Obviously, aneurysm formation is a gradual process, and it is likely that these patients already had some degree of aortic dilatation at the time of the exercise stress test. It has been shown that the elasticity of the ascending aorta decreases during exercise to increase pulse wave velocity, which indicates that the ascending aorta plays a crucial role in elevating central BP during exercise.[28] It is conceivable that patients with ascending aortic dysfunction, as a result of aortic dilatation, are less capable of this adaptive BP response to exercise, which may result in a relatively low peak exercise SBP. However, further detailed study is necessary to elucidate these underlying mechanisms.

Implications for management

The results of this study suggest that patients with CoA with a hypertensive response to exercise are prone to develop hypertension during follow-up. Therefore, close surveillance of these patients is indicated in order to adequately identify and treat future hypertension. However, it remains unclear whether to start antihypertensive medication in normotensive patients with a hypertensive response to exercise, since some of these patients may never develop hypertension but would be exposed to potential side effects. Furthermore, a clear association between a hypertensive response to exercise and cardiovascular events has not yet been demonstrated. These questions need to be addressed in future studies to further clarify the clinical value of exercise stress testing in addition to conventional office and ABPM measurements, which have logistical advantages.

Limitations

This study has several limitations. As this was a multicentre study, there was a lack of uniformity in the protocols for exercise stress testing. Particularly, differences in interval duration between BP measurements may have affected peak exercise SBP. Furthermore, patients in the study cohort were more likely to have LV hypertrophy compared with patients from the original cohort who did not undergo exercise stress testing, which may have introduced selection bias. Bias may also have been caused by the fact that 24-hour ABPM at follow-up was only available in a subset of patients. In addition, the presence of aortic arch hypoplasia was not systematically assessed in this study, even though arch hypoplasia

Key messages

What is already known on this subject?

- It is well known that patients with previous repair of coarctation of the aorta (CoA) are at increased risk of resting hypertension and consequent cardiovascular complications.
- Previous studies suggest that a hypertensive response to exercise is also frequent in these patients, even when normotensive in rest; however, the clinical and prognostic consequences of a hypertensive response to exercise remain subject of debate.

What might this study add?

- This prospective cohort study demonstrates that 44% of adults with repaired CoA has a hypertensive response to exercise, which is higher than previously reported.
- Male sex, absence of a bicuspid aortic valve and elevated resting systolic blood pressure (SBP) were risk factors for increased peak exercise SBP.
- Peak exercise SBP was independently predictive of hypertension at follow-up.

How might this impact on clinical practice?

- The outcomes of this study advocate stringent follow-up of patients with CoA with a hypertensive response to exercise to timely identify and treat future hypertension.
- Subsequent studies are needed to investigate associations with cardiovascular events and to determine the optimal management of normotensive patients with an isolated hypertensive response to exercise.

may contribute to the development of resting hypertension in patients with CoA.[29] Also, since the majority of surgical repairs was performed prior to 1990, surgical reports were frequently unavailable. Hence, determination of the surgical technique was primarily based on the correspondence by the treating cardiologist. In this correspondence, it was often not specified whether a simple or extended end-to-end repair was performed. Furthermore, the surgical technique was unknown in a substantial number of patients (19%).

CONCLUSIONS

In this large nationwide study involving adults with repaired CoA, the prevalence of a hypertensive response to exercise was 44%, which is higher than previously reported. Independent risk factors for increased peak exercise SBP were male sex, absence of a bicuspid aortic valve and elevated resting SBP. Peak exercise SBP was positively predictive of resting SBP at follow-up independently of baseline SBP. Close monitoring of patients with CoA with a hypertensive response to exercise is required to timely identify and treat future hypertension.

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Supplemental Material

Hypertensive Response to Exercise in Adult Patients with Repaired Aortic Coarctation

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Supplemental Table 1. Baseline characteristics in patients who underwent exercise stress testing (study cohort) versus patients who did not undergo exercise stress testing (excluded cohort).

	EST (study cohort) n = 675	**No EST (excluded cohort) n = 245**	***p*-value[a]**
Age (y), median (range)	24 (16-72)	24 (16-74)	0.45
Female sex, n (%)	272 (40)	93 (38)	0.54
BMI (kg/m^2), mean ± SD	23.9 ± 4.3	24.3 ± 5.3	0.35
Age at initial CoA repair (y), median (range)	3 (0-67)	6 (0-61)	**0.004**
Type of initial CoA repair, n (%)			
End-to-end anastomosis	344 (51)	130 (53)	0.60
Patch angioplasty	72 (11)	16 (7)	0.08
Subclavian flap angioplasty	65 (10)	24 (10)	1.0
Graft interposition	19 (3)	14 (6)	**0.045**
Ascending-to-descending BG	5 (1)	2 (1)	1.0
Surgery, technique unknown	127 (19)	45 (18)	0.92
Balloon angioplasty	15 (2)	4 (2)	0.62
Stenting	28 (4)	10 (4)	1.0
Prior intervention for re-CoA, n (%)	140 (21)	38 (16)	0.09
Bicuspid aortic valve, n (%)	389 (58)	130 (53)	0.23
Ventricular septal defect, n (%)	155 (23)	53 (22)	0.72
Aortic and/or mitral MHV, n (%)	41 (6)	19 (8)	0.37
Resting hypertension, n (%)[b]	376 (56)	138 (59)	0.36
Resting SBP (mmHg), mean ± SD[b]	134 ± 18	137 ± 20	0.05
Resting DBP (mmHg), mean ± SD[b]	76 ± 11	76 ± 12	0.97
Resting arm-leg gradient (mmHg), mean ± SD[c]	1 ± 17	5 ± 25	0.27
Use of any AHM, n (%)[d]	224 (33)	72 (30)	0.38
LV mass index (g/m^2), mean ± SD[e]	96 ± 31	91 ± 31	**0.04**
LV hypertrophy, n (%)[e]	187 (29)	46 (21)	**0.04**

[a] Determined by the independent samples t-test, Mann-Whitney U test or Fisher's exact test, where appropriate.

[b] Unavailable for 12 patients (5%) in the excluded cohort.

[c] Unavailable for 449 patients (67%) in the study cohort and 178 patients (73%) in the excluded cohort.

[d] Unavailable for 5 patients (2%) in the excluded cohort.

[e] Unavailable for 26 patients (4%) in the study cohort and 31 patients (13%) in the excluded cohort.

AHM, antihypertensive medication; BG, bypass graft; BMI, body mass index; DBP, diastolic blood pressure; EST, exercise stress testing; LV, left ventricular; SBP, systolic blood pressure; y, years.

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Supplemental Table 2. Change in office blood pressure and antihypertensive medication from baseline to follow-up.

	Office SBP (mmHg) mean ± SD			**Office DBP (mmHg)** mean ± SD			**Use of any AHM** n (%)			**No. of antihypertensives** mean ± SD			
	Baseline	**FU**	***p*-value**	**Baseline**	**FU**	***p*-value**	**Baseline**	**FU**	***p*-value**	**Baseline**	**FU**	***p*-value**	p_{diff}[a]
All patients	134 ± 18	134 ± 16	0.43	76 ± 11	77 ± 10	0.06	224 (33)	354 (52)	**<0.001**	0.51 ± 0.85	0.93 ± 1.13	**<0.001**	
Hypertensive response to exercise	139 ± 18	138 ± 16	0.73	77 ± 11	78 ± 10	0.15	111 (37)	173 (58)	**<0.001**	0.56 ± 0.88	1.08 ± 1.19	**<0.001**	**0.03**
No hypertensive response to exercise	130 ± 17	130 ± 15	0.44	76 ± 11	77 ± 10	0.22	113 (30)	181 (48)	**<0.001**	0.47 ± 0.83	0.82 ± 1.06	**<0.001**	

Baseline and follow-up data were compared using the paired t-test for office SBP and office DBP, McNemar test for use of any AHM, and Wilcoxon signed rank test for no. of antihypertensives.

[a] This *p*-value indicates whether the change in no. of antihypertensives (from baseline to follow-up) was different between patients with and without a hypertensive response to exercise, as determined by the independent-samples t-test.

AHM, antihypertensive medication; DBP, diastolic blood pressure; FU, follow-up; SBP, systolic blood pressure.

Supplemental Table 3. Value of peak exercise SBP in predicting office SBP at follow-up when the analysis is limited to normotensive patients at baseline (n = 299).

	Office SBP at follow-up (mmHg)			
	Univariable		**Multivariable**	
	β (SE)[a]	***p*-value**	**β (SE)[a]**	***p*-value**
Age (y)	0.26 (0.09)	**0.006**	0.06 (0.11)	0.59
Female sex	-4.64 (1.63)	**0.005**	-2.71 (1.69)	0.11
BMI (kg/m^2)	0.64 (0.24)	**0.008**	0.48 (0.23)	**0.04**
Age at initial CoA repair (y)	0.10 (0.12)	**0.048**	0.12 (0.17)	0.46
Type of initial CoA repair				
End-to-end anastomosis	-4.42 (1.64)	**0.007**	-8.50 (2.22)	**<0.001**
Patch angioplasty	1.88 (2.96)	0.53	-3.91 (3.30)	0.24
Subclavian flap angioplasty	0.50 (2.46)	0.84	-4.99 (2.94)	0.09
Graft interposition	-3.59 (7.13)	0.62	-12.97 (6.74)	0.06
Balloon angioplasty	-2.08 (5.84)	0.72	-12.73 (5.70)	**0.03**
Stenting	-5.57 (5.07)	0.27	-17.57 (6.40)	**0.006**
Prior intervention for re-CoA	-1.03 (2.27)	0.65	-1.61 (2.17)	0.46
Bicuspid aortic valve	-1.21 (1.68)	0.47	0.07 (1.55)	0.96
Resting SBP at baseline (mmHg)	0.42 (0.08)	**<0.001**	0.33 (0.08)	**<0.001**
Peak exercise SBP (mmHg)	0.12 (0.03)	**<0.001**	0.08 (0.03)	**0.002**
LV mass index (g/m^2)	0.04 (0.03)	0.18	0.01 (0.03)	0.84

A total of 285 complete cases were included in the multivariable model.

[a] Represents the change in office SBP per unit increase of the covariate.

BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

Supplemental Table 4. Value of peak exercise SBP in predicting LV mass index at follow-up.

	LV mass index at follow-up (g/m^2)			
	Univariable		**Multivariable**	
	β (SE)[a]	***p*-value**	**β (SE)[a]**	***p*-value**
Age (y)	0.48 (0.10)	**<0.001**	0.41 (0.13)	**0.001**
Female sex	-20.07 (2.19)	**<0.001**	-19.00 (2.22)	**<0.001**
BMI (kg/m^2)	0.77 (0.29)	**0.007**	0.40 (0.28)	0.15
Age at initial CoA repair (y)	0.45 (0.12)	**<0.001**	0.15 (0.18)	0.40
Type of initial CoA repair				
End-to-end anastomosis	-3.73 (2.28)	0.10	0.06 (2.99)	0.98
Patch angioplasty	9.85 (3.63)	**0.007**	11.16 (4.10)	**0.007**
Subclavian flap angioplasty	-5.51 (3.82)	0.15	1.64 (4.36)	0.71
Graft interposition	-7.84 (6.89)	0.26	-5.96 (7.14)	0.40
Balloon angioplasty	18.99 (7.50)	**0.01**	14.38 (7.91)	0.07
Stenting	-1.24 (5.78)	0.83	-4.40 (7.17)	0.54
Prior intervention for re-CoA	-0.90 (2.81)	0.75	0.23 (2.70)	0.93
Bicuspid aortic valve	4.38 (2.30)	0.06	4.22 (2.12)	**0.047**
Resting SBP at baseline (mmHg)	0.12 (0.06)	0.06	-0.07 (0.07)	0.27
Use of any AHM	1.97 (0.48)	**<0.001**	0.70 (0.49)	0.16
Peak exercise SBP	0.10 (0.03)	**0.006**	0.04 (0.04)	0.23

A total of 638 complete cases were included in the multivariable model.

[a] Represents the change in LV mass index per unit increase of the covariate.

AHM, antihypertensive medication; BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

Supplemental Table 5. Value of peak exercise SBP in predicting LV mass index at follow-up when the analysis is limited to normotensive patients at baseline (n = 299).

	LV mass index at follow-up (g/m^2)			
	Univariable		**Multivariable**	
	β (SE)[a]	***p*-value**	**β (SE)[a]**	***p*-value**
Age (y)	0.04 (0.18)	0.82	0.22 (0.21)	0.28
Female sex	-20.02 (2.76)	**<0.001**	-19.53 (2.99)	**<0.001**
BMI (kg/m^2)	0.31 (0.45)	0.49	0.25 (0.43)	0.56
Age at initial CoA repair (y)	0.10 (0.21)	0.64	0.04 (0.31)	0.90
Type of initial CoA repair				
End-to-end anastomosis	-1.13 (3.03)	0.71	2.57 (4.15)	0.54
Patch angioplasty	9.26 (5.16)	0.07	11.43 (5.93)	0.06
Subclavian flap angioplasty	-3.04 (4.49)	0.50	0.38 (5.48)	0.95
Graft interposition	12.44 (12.67)	0.33	21.25 (12.42)	0.09
Balloon angioplasty	14.27 (10.36)	0.17	11.25 (10.50)	0.29
Stenting	-5.29 (9.03)	0.56	-4.78 (11.79)	0.69
Prior intervention for re-CoA	3.15 (4.09)	0.44	1.65 (3.96)	0.68
Bicuspid aortic valve	5.96 (3.06)	0.05	6.64 (2.85)	**0.02**
Resting SBP at baseline (mmHg)	0.25 (0.14)	0.08	-0.01 (0.14)	0.97
Peak exercise SBP (mmHg)	0.15 (0.05)	**0.002**	0.06 (0.05)	0.27

A total of 282 complete cases were included in the multivariable model.

[a] Represents the change in LV mass index per unit increase of the covariate.

BMI, body mass index; LV, left ventricular; SBP, systolic blood pressure; SE, standard error; y, years.

Supplemental Table 6. Overview of cardiovascular events.

	No. of cases
Coronary artery disease	**12**
Myocardial infarction	6
Coronary revascularization	5
Medical treatment for angina	1
Stroke	**15**
Ischemic stroke	14
Hemorrhagic stroke, intracerebral	0
Hemorrhagic stroke, subarachnoidal	1
Aortic complication	**69**
Aneurysm	64
Dissection	5
CV death	**17**
Total CV events	**113**
No. of individual patients with CV event	**100**

CV, cardiovascular.