



# Hypertension in adults with repaired coarctation of the aorta

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**Aims** In adults with coarctation of the aorta (CoA), hypertension (HTN) is a common long-term complication. We investigated the prevalence of HTN and analyzed factors associated with HTN.

**Methods and results** In the national register for congenital heart disease, 653 adults with repaired CoA were identified (mean age  $36.9 \pm 14.4$  years); 344 (52.7%) of them had HTN, defined as either an existing diagnosis or blood pressure (BP)  $\geq 140/90$  mmHg at the clinical visit. In a multivariable model, age (years) (odds ratio [OR] 1.07, CI 1.05-1.10), sex (male) (OR 3.35, CI 1.98-5.68), and body mass index (kilograms per square meter) (OR 1.09, CI 1.03-1.16) were independently associated with having HTN, and so was systolic arm-leg BP gradient where an association with HTN was found at the ranges of [10, 20] and  $>20$  mmHg, in comparison to the interval  $\leq 10$  mmHg (OR 3.58, CI 1.70-7.55, and OR 11.38, CI 4.03-32.11). This model remained valid when all patients who had increased BP ( $\geq 140/90$  mmHg) without having been diagnosed with HTN were excluded from the analyses.

**Conclusions** Hypertension is common in patients with previously repaired CoA and is associated with increasing age, male sex, and elevated body mass index. There is also an association with arm-leg BP gradient, starting at relatively low levels that are usually not considered for intervention. (*Am Heart J* 2016;181:1-6.)

Coarctation of the aorta (CoA) represents 5% to 10% of all congenital heart lesions. Surgical treatment of CoA has been possible since the mid-1940s,<sup>1-3</sup> but late complications such as hypertension (HTN) and left ventricular hypertrophy still pose a problem after intervention.<sup>4-9</sup>

Hypertension is the most common complication in patients with repaired CoA with a prevalence of between 25% and 68%. The large variation is primarily dependent on the definition of HTN, the studied population, and differences in the diagnostic methods.<sup>9</sup> Hypertension is also associated with early mortality in patients with repaired CoA.<sup>8,10</sup>

Several studies have identified risk factors associated with development of HTN in patients with repaired CoA.

Male sex, age at intervention, age at follow-up, type of intervention, systolic arm-leg blood pressure (BP) gradient, and high preoperative BP have, at some point, all been found to be associated with HTN in patients with CoA<sup>8,9,11-15</sup> while the outcome of multivariable models has varied.

In the present study, we investigated the prevalence and distribution of HTN among patients with repaired CoA in a national cohort and identified additional risk factors for HTN, both in the presence and absence of patients who had increased BP without having been previously diagnosed with HTN. Presently, an arm-leg difference in systolic BP of  $\geq 20$  mmHg is usually regarded as an indication for reintervention, but it is unknown if values  $<20$  mmHg are associated with HTN and thereby possibly with other late complications. Such an investigation was therefore a secondary goal of the study. Thus, in a large population of adults with repaired CoA, factors associated with HTN were investigated, as well as the significance of a residual arm-leg BP gradient.

## Patients and methods

### SWEDCON

This register study is based on data in the Swedish National Registry on Congenital Heart Disease (SWEDCON, [www.ucr.uu.se/swedcon/](http://www.ucr.uu.se/swedcon/)). Since 1998, the

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SWEDCON register has covered all 7 health care regions in Sweden, but registration started even earlier in some centers. In the beginning of 2013, the register contained data on approximately 9,800 adults (defined as age  $\geq 18$  years) with congenital heart disease. Data collected by each center contained information on diagnoses, interventions, demographics, functional class, symptoms, quality of life (EQ-5D), social variables, electrocardiogram, exercise tests, self-reported level of physical exercise, echocardiography, medication, and pacemakers/implanted cardioverter/defibrillators. At the first entry in the register, information is usually retrospective and based on access to relevant medical records such as surgical notes. After the first entry in the database, further data collection from clinic visits and investigations is prospective. All data collected up to February 17, 2013, were searched. For the present study, relevant data were then obtained from the last available clinic visit where systolic BP had been registered.

### Patients

SWEDCON was used to identify all patients with CoA (1,026/9,864 patients), who were at least 18 years of age at the time of their last clinic visit with systolic BP registered (916 patients). Patients with associated simple lesions, such as ventricular septal defect and aortic stenosis, were included, whereas those with major, complex pathologies or syndromes were excluded (leaving 810 patients). Only patients who had undergone repair of CoA were included, thus excluding those with mild coarctation without previous intervention (leaving 677 patients). Eleven patients whose interventions had taken place within 6 months before the clinic visit were excluded. Also excluded were 10 patients with insufficient data for determining whether they had been diagnosed with HTN, and 3 undiagnosed patients with insufficient diastolic BP data. This yielded a final population of 653 patients for inclusion in the study.

### Definition of HTN and systolic arm-leg BP gradient

Cases of HTN were defined as (a) previously diagnosed HTN identified by register diagnosis and/or by prescription medication— $\beta$ -blockers, angiotensin-converting enzyme-inhibitors, calcium blockers, diuretics, angiotensin II antagonists, or other medications prescribed for systemic HTN—or (b) BP  $\geq 140/90$  mmHg at the last clinic visit.

It is generally recommended that BP is measured in both arms in patients with CoA, and the highest value is registered. The last registered office BPs were compared to the recommended target values (ie,  $<140/90$  mmHg) and thus defined as within or above the recommended limits.<sup>16</sup> If either systolic or diastolic BP was found to exceed the currently recommended limits (ie,  $\geq 140/90$  mmHg), then the BP was classified as out of range. In cases where only one of the pressures, systolic or diastolic, was available, the BP was classified as out of

range if the available pressure exceeded the recommended limits. The comparison was otherwise considered indeterminate and thus classified as missing data.

Because a single increased BP is not diagnostic in itself, a secondary set of analyses was performed where the patients who had BP out of range, despite not having been previously diagnosed with HTN, were excluded.

The systolic arm-leg BP gradient was calculated using the registered office BP. Negative values, that is, higher BP in the lower extremity, were assumed to signify pulse wave reflections and were interpreted as no fall in pressure over the coarctation, that is, zero gradient. In the univariable and multivariable logistic regressions performed, the systolic arm-leg BP gradient was described by a scalar variable containing the ranges of [0, 10], (10, 20], and  $>20$  mmHg. The lowest range was used as reference in the analyses, and the listed odds ratios (ORs) described changes between the ranges.

### Statistics

All calculations and analyses were performed using SPSS 20-23 (IBM, Armonk, NY).

Differences in means and ratios between groups were tested with 1-way analysis of variance. Variables for multivariable analysis were selected from those significant in univariable logistic regression. Multivariable logistic regression was performed in a manual backward manner, excluding the variable with highest *P* value in each step. The null hypothesis was rejected for *P* values  $<.05$ .

### Ethics and funding

This study was approved by the Regional Ethical Review Board in Umeå, Sweden (Dnr 08-218M and 2012-445-32M). The study was supported by the Swedish Heart and Lung Foundation, the Heart Foundation of Northern Sweden, Umeå University, and the County Council of Västerbotten. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

### Results

Of the 653 patients, 414 (63.4%) were male. The mean age at the last registered clinic visit was  $36.9 \pm 14.4$  years, the mean age at intervention was  $9.5 \pm 11.0$  years, and the average time between intervention and follow-up was  $27.4 \pm 12.8$  years. In the entire study population, 344 patients (52.7%) met the criteria for HTN, and 97 (14.9%) of 649 patients had BP exceeding the recommended upper limit ( $\geq 140/90$  mmHg) despite not having been previously diagnosed with HTN (Table D).

In this population, the prevalence of HTN increased with age and was greater among men. To identify factors associated with HTN, variables that were significant in

**Table I.** Patient characteristics

Variable	All patients		Patients without diagnosed HTN and BP <140/90 mm Hg		Patients without diagnosed HTN and BP ≥140/90 mm Hg		Patients with diagnosed HTN	
	n	% or mean ± SD	n	% or mean ± SD	n	% or mean ± SD	n	% or mean ± SD
Sex (male)	414/653	63.4%	164/309	53.1%	69/97	71.1%	177/243	72.8%
Age (y)	653	36.9 ± 14.4	309	30.6 ± 10.2	97	35.7 ± 12.1	243	45.4 ± 15.3
Age at first intervention (y)	653	9.5 ± 11.0	309	6.3 ± 8.5	97	7.6 ± 8.3	243	14.3 ± 12.9
Time to follow-up (y)	653	27.4 ± 12.8	309	24.3 ± 9.1	97	28.0 ± 10.5	243	31.1 ± 16.3
Type of first intervention	–	–	–	–	–	–	–	–
End-to-end anastomosis	421/653	64.5%	193/309	62.5%	72/97	74.2%	153/243	63.0%
Subclavian flap	133/653	20.4%	88/309	28.5%	16/97	16.5%	29/243	20.7%
Percutaneous intervention	37/653	5.7%	9/309	2.9%	2/97	2.1%	26/243	10.7%
Other reconstruction	62/653	9.5%	19/309	6.1%	7/97	7.2%	35/243	14.4%
Reintervention*	108/653	16.5%	34/309	11.0%	18/97	18.6%	56/243	23.0%
Age at first reintervention (y)	108	22.7 ± 18.8	34	12.9 ± 12.2	18	19.0 ± 13.6	56	29.8 ± 19.9
Time from primary intervention to reintervention (y)	108	15.4 ± 15.6	34	9.6 ± 12.2	18	13.1 ± 13.0	56	19.7 ± 17.1
Height (cm)	567	173.9 ± 9.7	275	172.6 ± 9.2	79	174.7 ± 10.3	210	175.1 ± 10.0
Weight (kg)	496	75.8 ± 16.4	248	71.8 ± 15.6	68	78.2 ± 15.6	177	80.1 ± 16.5
BMI (kg/m <sup>2</sup> )	495	24.9 ± 4.5	248	24.0 ± 4.2	68	25.5 ± 5.1	176	25.9 ± 4.3
Systolic BP (mm Hg) <sup>†</sup>	653	131.8 ± 16.7	309	121.6 ± 10.1	97	145.9 ± 10.9	243	138.8 ± 17.6
Diastolic BP (mm Hg) <sup>†</sup>	649	75.2 ± 9.9	309	73.2 ± 7.5	97	81.1 ± 11.2	239	75.3 ± 11.1
Arm-leg BP gradient (mm Hg) <sup>‡</sup>	436	6.2 ± 9.6	218	4.2 ± 6.7	58	7.3 ± 11.2	156	8.7 ± 11.8
Other heart defects	324/653	49.6%	155/309	50.2%	51/97	52.6%	118/243	48.6%
Atrial septal defect	27/653	4.1%	12/309	3.9%	3/97	3.1%	12/243	4.9%
Ventricular septal defect	88/653	13.5%	58/309	18.8%	15/97	15.5%	15/243	6.2%
Patent ductus arteriosus	119/653	18.2%	77/309	24.9%	14/97	14.4%	28/243	11.5%
Aortic valve disease	206/653	31.5%	79/309	25.6%	33/97	34.0%	94/243	38.7%

\*In the study population, 108 patients had undergone at least 1 reintervention for CoA, with a total of 131 reinterventions performed. Of these, 34 (26.0%) were end-to-end anastomoses, 13 (9.9%) were subclavian flap procedures, 34 (26.0%) were percutaneous interventions, and 50 (38.2%) were classified as other reconstructions.

<sup>†</sup>Systolic and diastolic blood pressures were measured in the arm.

<sup>‡</sup>Blood pressure gradient denotes the systolic arm-leg BP gradient as a continuous variable, with negative values defined as no gradient.

univariable logistic regression were subsequently selected to be included in a multivariable logistic regression. The initial regression included sex, age, age at first intervention, type of first intervention, reintervention, body mass index (BMI), associated heart lesions (ventricular septal defect, patent ductus arteriosus, and aortic valve disease), and systolic arm-leg BP gradient divided into 3 ranges: [0, 10], (10, 20], and >20 mmHg with the first being used as reference. In the final model, age (years) (OR 1.07, CI 1.05-1.10), sex (male) (OR 3.35, CI 1.98-5.68), and BMI (kilograms per square meter) (OR 1.09, CI 1.03-1.16) were independently associated with having HTN, and so was systolic arm-leg BP gradient, where an association with HTN was found at the ranges of (10, 20] and >20 mmHg, in comparison to the interval [0, 10] mmHg (OR 3.58, CI 1.70-7.55, and OR 11.38, CI 4.03-32.11) (Table II). Subsequently, the procedure was repeated, excluding all patients who had BP out of range without having previously been diagnosed with HTN. This resulted in a similar final model containing the same variables as before (Table III).

β-Blockers were the most common antihypertensive medication class, prescribed to 144 (59.5%) of the 242

patients with previously diagnosed HTN, followed by angiotensin-converting enzyme inhibitors which were prescribed to 92 patients (38.0%).

## Discussion

### Population

Thus far, the present study is the largest follow-up of adult patients with repaired CoA, both in terms of the number of patients included and the number of years of follow-up. Unlike many previous studies of patients repaired solely at a single institution, this study drew patients from a large national register. Apart from the multicenter approach, the patients included have been, on average, followed up for almost 3 decades after their initial intervention, which provides a robust basis (17,892 patient years postintervention) for evaluating long-term effects after repair of CoA.

### Sex

Not only were there more men among this study's population of adults with repaired CoA, but the male patients more often had HTN. This seems consistent with

**Table II.** Univariable logistic regressions and the final multivariable logistic regression model, with hypertension as dependent variable

Variable	n	Univariable					Multivariable				
		Wald	OR	95% CI for OR		P	Wald	OR	95% CI for OR		P
				Lower	Upper				Lower	Upper	
Sex (male)*	414/653	26.46	2.35	1.70	3.26	<.001	20.28	3.35	1.98	5.68	<.001
Age (y)*	653	96.40	1.07	1.06	1.09	<.001	45.92	1.07	1.05	1.10	<.001
Age at first intervention (y)*	653	43.93	1.07	1.05	1.09	<.001					
Time to follow-up (y)	653	32.24	1.04	1.03	1.05	<.001					
Type of first intervention*,†	–	32.21	–	–	–	<.001					
End-to-end anastomosis	421/653	–	–	–	–	–					
Subclavian flap	133/653	16.25	0.43	0.29	0.65	<.001					
Percutaneous intervention	37/653	6.00	2.63	1.21	5.72	.014					
Other reconstruction	62/653	4.95	1.92	1.08	3.40	.026					
Reintervention†	108/653	12.61	2.22	1.43	3.44	<.001					
Age at first reintervention (y)	108	11.30	1.06	1.02	1.09	.001					
Time from primary intervention to reintervention (y)	108	6.27	1.05	1.01	1.08	.012					
Height (cm)	567	9.30	1.03	1.01	1.05	.002					
Weight (kg)	496	27.04	1.03	1.02	1.05	<.001					
BMI (kg/m <sup>2</sup> )*	495	20.54	1.11	1.06	1.16	<.001	7.66	1.09	1.03	1.16	.006
Arm-leg BP gradient*,‡	–	21.15	1.05	1.03	1.07	<.001	28.74	–	–	–	<.001
[0, 10] mm Hg	347/436	–	–	–	–	–	–	–	–	–	–
(10, 20] mm Hg	54/436	7.54	2.31	1.27	4.20	.006	11.26	3.58	1.70	7.55	.001
>20 mm Hg	35/436	15.25	6.06	2.45	14.96	<.001	21.11	11.38	4.03	32.11	<.001
Other heart defects	324/653	0.07	0.96	0.71	1.30	.792					
Atrial septal defect	27/653	0.09	1.13	0.52	2.45	.760					
Ventricular septal defect*	88/653	13.51	0.41	0.26	0.66	<.001					
Patent ductus arteriosus*	119/653	17.03	0.42	0.28	0.63	<.001					
Aortic valve disease*	206/653	9.63	1.70	1.22	2.39	.002					

The model includes 377 patients;  $P < .001$ .

\* Denotes variables included in the first step of the logistic regression. For each continuous variable, the OR is calculated per unit of measurement.

† End-to-end anastomosis is used as the reference category for type of first intervention.

‡ Arm-leg BP gradient denotes the systolic arm-leg BP gradient as a continuous variable, with negative values defined as no gradient.

our previous findings that showed that male adults with repaired CoA were more likely to have left ventricular hypertrophy and that left ventricular hypertrophy was associated with HTN.<sup>17</sup>

### Age and age at intervention

The association between age and HTN was expected, but it is noticeable that age at intervention was not associated with HTN in the final models, despite showing an association in the univariable analyses. Previous studies have reached different conclusions regarding the importance of age at intervention. Some studies suggest that late intervention is an important, or even the most important, predictor for the development of HTN in patients with CoA,<sup>8,10,12,14,15</sup> whereas others have provided models in which age at intervention is not significantly associated with HTN.<sup>11,13</sup> Our data suggest that age at intervention is indeed less important than age at follow-up. Because the patients in our study had been followed up for 3 decades after their original intervention, one might speculate that an early intervention is beneficial in the following years but that this effect eventually wears off as the patient ages.

### Systolic arm-leg BP gradient after intervention

Systolic arm-leg BP gradient was associated with HTN in patients with repaired CoA, even for gradients within the range of 10 to 20 mmHg, and there was no difference in the prevalence of HTN between patients with recorded gradient data and those without. This is interesting as the current guidelines recommend that all patients with a noninvasive systolic BP gradient >20 mmHg between upper and lower limbs, regardless of symptoms but with upper limb HTN (>140/90 mmHg in adults), pathologic BP response during exercise, or significant left ventricular hypertrophy, should be considered for reintervention.<sup>18</sup>

Our findings are consistent with previous studies that indicate that mild residual descending aortic narrowing in patients with repaired CoA is independently associated with mean daytime BP.<sup>19</sup> It has also been suggested that a lower threshold for reintervention of aortic narrowing might be desirable,<sup>13</sup> and our findings lend support to this suggestion. There may be reasons to consider reintervention at even smaller systolic arm-leg BP gradients than currently recommended, although further studies are necessary to properly evaluate the effects of such reinterventions because it is currently unknown whether

**Table III.** Univariable logistic regressions and the final multivariable logistic regression model, with diagnosed hypertension as dependent variable, excluding all undiagnosed patients with blood pressure  $\geq 140/90$  mm Hg

Variable	n	Univariable					Multivariable				
		Wald	OR	95% CI for OR		P	Wald	OR	95% CI for OR		P
Sex (male)*	341/552	22.06	2.37	1.65	3.40	<.001	13.46	3.09	1.69	5.66	<.001
Age (y)*	552	109.83	1.09	1.07	1.11	<.001	51.07	1.09	1.06	1.12	<.001
Age at first intervention (y)*	552	54.75	1.08	1.06	1.11	<.001					
Time to follow-up (y)	552	33.37	1.04	1.03	1.06	<.001					
Type of first intervention*,†	–	36.74	–	–	–	<.001					
End-to-end anastomosis	346/552	–	–	–	–	–					
Subclavian flap	117/552	13.39	0.42	0.26	0.67	<.001					
Percutaneous intervention	35/552	10.37	3.64	1.66	8.01	.001					
Other reconstruction	54/552	7.65	2.32	1.28	4.22	.006					
Reintervention*	90/552	13.91	2.42	1.52	3.86	<.001					
Age at first reintervention (y)	90	12.58	1.06	1.03	1.10	<.001					
Time from primary intervention to reintervention (y)	90	7.33	1.05	1.01	1.09	.007					
Height (cm)	485	8.14	1.03	1.01	1.05	.004					
Weight (kg)	425	24.00	1.03	1.02	1.05	<.001					
BMI (kg/m <sup>2</sup> )*	424	19.45	1.12	1.06	1.17	<.001	4.21	1.08	1.00	1.15	.040
Arm-leg BP gradient*,‡	–	22.62	–	–	–	<.001	30.71	–	–	–	<.001
[0, 10] mm Hg	300/374	–	–	–	–	–	–	–	–	–	–
(10, 20] mm Hg	44/374	6.97	2.37	1.25	4.51	.008	11.77	4.36	1.88	10.12	.001
>20 mm Hg	30/374	17.52	7.21	2.86	18.20	<.001	23.82	15.15	5.09	45.13	<.001
Other heart defects	273/552	0.14	0.94	0.67	1.31	.709					
Atrial septal defect	24/552	0.36	1.29	0.57	2.91	.547					
Ventricular septal defect*	73/552	17.10	0.28	0.16	0.52	<.001					
Patent ductus arteriosus*	105/552	15.18	0.39	0.25	0.63	<.001					
Aortic valve disease*	173/552	10.76	1.84	1.28	2.64	.001					

The model includes 325 patients;  $P < .001$ .

\*Denotes variables included in the first step of the logistic regression. For each continuous variable, the OR is calculated per unit of measurement.

† End-to-end anastomosis is used as the reference category for type of first intervention.

‡ Arm-leg BP gradient denotes the systolic arm-leg BP gradient as a continuous variable, with negative values defined as no gradient.

the gradient itself is the culprit or merely the result of unfavorable vascular mechanics. Presently, we do not know if treating a small residual gradient will affect either the current BP level or the future progression to HTN.

### Body mass index

It is well known that increased BMI is a risk factor for HTN, but how this pertains to CoA is not yet entirely clear. Previous studies have found both that obesity is common in patients with CoA<sup>20</sup> and that there seems to be no difference in mean BMI between patients with CoA and a reference population without cardiovascular lesions.<sup>21</sup> It is somewhat noteworthy that the average BMI in our study population was merely 24.9 kg/m<sup>2</sup> (generally classified as being within the normal range) despite the high prevalence of HTN. It might be that adults with repaired CoA are even more sensitive to increased BMI than the general population.

### Limitations

Age, sex, BMI, and systolic arm-leg BP gradient were independently associated with HTN, regardless of whether patients with BP out of range but no previously

diagnosed HTN, were counted as hypertensive or excluded from the analyses. That both sets of analyses led to the same final model suggests a similarity between the patients with diagnosed HTN and the undiagnosed patients who, nevertheless, had BP out of range. It seems likely that many of the undiagnosed patients have since been diagnosed and treated, but no such data are available in this study.

The present study is a retrospective register study, analyzing data from the last clinic visits where systolic BP measurements were available. The BP measurements and medications prescribed are therefore those recorded at these visits, and we do not have access to data pertaining to further attempts at treatment. Although single office BP measurements are less reliable than 24 hour registrations, it has previously been shown that elevated office BP is associated with left ventricular hypertrophy in patients with repaired CoA.<sup>17,22</sup>

The register did not include data pertaining to anatomy of the aortic arch, which might otherwise have been included in the analyses because previous studies have shown an association between late HTN and an angulated aortic arch in patients with repaired CoA.<sup>23</sup> However, although our study



does not include anatomical data regarding the area of the previously treated coarctation, the systolic arm-leg BP gradient can be considered to indirectly provide some information regarding the postinterventional aortic anatomy.

## Conclusions

Hypertension is common among patients with repaired CoA. In this relatively young population with a mean age of 37 years, 27 years after intervention, more than half of the patients had HTN, and there was an association with systolic arm-leg BP gradient as well as with BMI. Although calculated from noninvasive measurements, the clinically determined systolic arm-leg BP gradient may serve as an important predictor for HTN, and this appears to be true even for gradients below the currently recommended limit for reintervention. Thus, mild residual drops in pressure over the repaired coarctation may not be benign.

**Conflicts of interest.** None to report.

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