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ORIGINAL ARTICLE

A Cross-Sectional Study of the Prevalence of Exercise-Induced Hypertension in Childhood Following Repair of Coarctation of the Aorta

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Background Exercise-testing may be a more tolerable method of detecting hypertension in children after coarctation repair compared to gold-standard 24-hour ambulatory blood pressure (BP) monitoring (ABPM). This study aims to determine the prevalence of exercise-induced hypertension and end-organ damage in children after coarctation repair, and the effectiveness of exercise-testing compared to 24-hour ABPM in this population.

Methods Exercise-testing (Bruce protocol), transthoracic echocardiogram, 24-hour ABPM, and pulse wave velocity were performed in 41 patients aged 8 to 18 years with previous coarctation repair. Median age at repair was 13 days. Exercise-testing data were compared to healthy paediatric controls. Hypertension was defined as BP >95th percentile on 24-hour ABPM compared to normalised data, and systolic BP (SBP) arbitrarily >200 mmHg on exercise-testing.

Results After 13 ± 3 years, 39% (14/36) were hypertensive on 24-hour ABPM and 12% (5/41) on exercise-testing. Coarctation patients had a higher peak exercise SBP and reduced endurance compared to controls (164 ± 26 mmHg vs. 148 ± 19 mmHg, p = 0.003; and 13.0 ± 1.7 mins vs. 14.2 ± 2.4 mins, p = 0.007; respectively). All patients with a peak exercise SBP >190 mmHg were hypertensive on 24-hour ABPM. Pulse wave velocity was higher in hypertensive patients on exercise-testing and 24-hour ABPM compared to normotensive patients (p = 0.004 and p = 0.06; respectively).

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Conclusions Exercise-testing may be a useful tool to detect hypertension in children and young adults after coarctation repair, particularly in those who do not tolerate 24-hour ABPM. Normative peak exercise BP data for age should be obtained to improve the accuracy of exercise-testing in detecting hypertension.

Keywords 24-hour ambulatory blood pressure monitoring • Coarctation of the aorta • Exercise test • Hypertension • Paediatrics • Pulse wave velocity

Introduction

Coarctation of the aorta can no longer be considered a benign condition [1] as up to 75% of patients may develop hypertension after coarctation repair, even as young children [2–7]. While the exact long-term impact of hypertension is still undetermined in this population, it has been reported that it may lead to a 20% reduction in long-term survival within 30 years after repair when compared to a matched population [8]. It is likely that early identification of the patients at risk of developing late hypertension will be beneficial in order to initiate earlier treatment. Several methods for detecting hypertension have been used, each of which carry their own merits and faults.

Twenty-four-hour (24-hr) ambulatory blood pressure monitoring (ABPM) is often considered the gold standard of detecting hypertension [2–4]. Similarly to others, we have noted the intolerance of the frequency of the blood pressure measurements over the 24-hour period in children [4]. Alternatively, an exaggerated blood pressure response to dynamic exercise in a repaired coarctation population has been demonstrated across numerous studies [7,9] and may be an effective and more tolerable method of assessing blood pressure in a paediatric population.

In this study, we investigated the prevalence of exercise-induced hypertension in children after coarctation repair and compared this to the prevalence of hypertension on 24-hour ABPM in order to assess the suitability and tolerability of exercise-testing to detect hypertension at an early age.

Material and Methods

Study Population

The design of this study was approved by The Royal Children's Hospital Human Research and Ethics Committee, and written informed consent was obtained from each patient or their parents if under 18 years of age. The hospital cardiac database was searched for survivors of a coarctation repair performed within the first year of life born between 1996 and 2007 such that potential patients were aged between 8 and 18 years of age at the time of the study. Exclusion criteria included living outside of the state of Victoria in Australia, severe intellectual disability, current use of an antihypertensive agent, and pregnancy. Of the 144 potential patients identified, 41 (28%) agreed to participate in the study. Patients who participated were comparable to the patients who did not participate in terms of age, gender ratio, and age at surgery.

The characteristics and surgical procedures of the patients are summarised in Table 1. Of the 41 patients, five (12%) underwent at least one arch reintervention for arch obstruction. The arch reintervention procedures included a single balloon angioplasty in three, two balloon angioplasties and subsequent resection and extended end-to-end anastomosis in one patient, and extended end-to-end anastomosis in one patient. None of the patients in our study had obvious scoliosis or chest wall deformities which could potentially contribute to respiratory performance with exercise.

Table 1 Patient characteristics and operative data.

Demographics	n = 41
Male: Female	27 (66%): 14 (34%)
Median age at surgical repair, *days*	13 (IQR: 9-51)
Median age at time of study, *years*	12 (IQR: 10-15)
Mean weight at study, *kgs*	48 ± 27
Mean height at study, *m*	1.55 ± 0.18
Mean body mass index at study, *kg/m²*	19.7 ± 9.6
Mean resting systolic BP, *mmHg*	111 ± 12
Mean resting diastolic BP, *mmHg*	65 ± 8
Associated cardiac anomalies	
Bicuspid aortic valve	25 (61%)
Patent ductus arteriosus	20 (49%)
Ventricular septal defect	14 (34%)
Atrial septal defect/patent foramen ovale	14 (34%)
Hypoplastic arch	13 (32%)
Transposition of the great arteries	2 (5%)
Associated non-cardiac anomalies	
Turners syndrome	1 (2%)
Pierre Robin sequence	1 (2%)
Chromosome 3 deletion with autism	1 (2%)
Arch repair technique	
Sternotomy	4 (10%)
End-to-side anastomosis	*4 (100%)*
Thoracotomy	37 (90%)
End-to-end anastomosis	*26 (70%)*
Extended end-to-end anastomosis	*7 (19%)*
End-to-side anastomosis	*3 (8%)*
Left subclavian flap repair	*1 (3%)*
Associated cardiac procedures	
Ventricular septal defect closure	7 (17%)
Arterial switch operation	2 (5%)
Pulmonary artery banding	2 (5%)

n (%) or mean ± standard deviation.
Abbreviation: BP, blood pressure; IQR, interquartile range.

Study Protocol

All patients underwent measurements of clinic resting and 24-hour ambulatory blood pressures, graded exercise-test on a treadmill, transthoracic echocardiogram, carotid ultrasound, and measurement of pulse wave velocity. Each patient was studied in the morning following 12 hours of no exercise and at least 6 hours of fasting.

Clinic Resting Blood Pressure

Measurements of clinic resting blood pressure were taken using an automatic oscillometric method (Dinamap PRO 100; GE Healthcare, Buckinghamshire, UK) after at least 30 minutes rest in a supine position using an appropriate-sized cuff on the right arm. Measurements were taken three times and the mean of the three readings was used.

Resting hypertension for children and adolescents was defined as a systolic blood pressure (SBP) or diastolic blood pressure (DBP) >95th percentile for age and height, and prehypertension was defined as between the 90th and 95th percentile [10].

Twenty-Four-Hour Ambulatory Blood Pressure Monitoring

A calibrated oscillometric device (Oscar 2; SunTech Medical, SunTech Medical Group, Oxfordshire, UK) was attached to the right arm of all patients using an appropriate-sized cuff. The monitor was programmed based on the approximation of each patient's awake-time and asleep-time. Blood pressure measurements were performed automatically every 30 minutes during the awake-time and every 60 minutes during asleep-time. Patients were advised to continue with their normal daily activities with the exception of participation in sports or swimming activities.

Hypertension on 24-hour ABPM was defined as a mean 24-hour SBP or DBP ≥95th percentile for height for a separate reference population [11].

Graded Exercise-test

Exercise-testing was performed on a motorised treadmill with incremental increases in speed and incline according to the standard Bruce Protocol [12]. Continuous electrocardiogram monitoring on patients' heart rate and rhythm were performed. Patients were encouraged to exercise until they reached 80% of their age-specific maximum heart rate (220–age) or until exhaustion. Patients were laid supine on an examination bed immediately post-exercise. Blood pressure measurements were conducted using a standard mobile sphygmomanometer (Welch Allyn (Tycos), Skaneateles Falls, NY, USA) prior to exercise, immediately post-exercise, and after the 10-minute recovery period the right arm of all patients using an appropriate-sized cuff. The blood pressure value immediately post-exercise was used to imitate maximum blood pressure during exercise. Exercise endurance and achieved heart rates at peak exercise were assessed using age-adjusted references values [13]. Age-adjusted reference values for blood pressure at peak exercise currently do not exist.

Exercise-induced hypertension was defined as SBP at maximal exercise of ≥200 mmHg as per the current definition in the validated adult population [14]. Blood pressure responses were compared to 44 age- and gender-matched controls with structurally and functionally normal hearts from our paediatric exercise-testing database.

Transthoracic Echocardiography

A transthoracic echocardiogram was performed using a standard ultrasound machine (Vivid 7, GE Healthcare, Buckinghamshire, UK). Patients were placed in the left lateral decubitus position.

Arch re-obstruction was defined as a peak gradient ≥25 mmHg across the repair site. The aortic diameter was measured in five regions including the ascending aorta, proximal transverse arch (between the brachiocephalic and the left common carotid arteries), distal transverse arch (between the left subclavian and left carotid arteries), aortic isthmus, and descending aorta. Measurements were converted to z-scores using a separate paediatric reference population [15]. A segment with a z-score diameter of <-2.0 was considered hypoplastic.

Left ventricular mass was calculated from a two-dimensional guided M-mode measurement of the left ventricle using the recommended formula from the American Society of Echocardiography [16]. Left ventricular mass index was calculated by dividing the left ventricular mass by (height in metres)$^{2.7}$ to reduce the impact of age, gender, ethnicity, and body mass index. Left ventricular hypertrophy in a paediatric and adolescent population was defined as left ventricular mass index >95th percentile (38.6 g/m$^{2.7}$) for healthy children and adolescents [17].

Carotid Ultrasound

A carotid ultrasound study was performed using a standard ultrasound machine (Vivid 7, GE Healthcare). Patients were placed supine with the head rotated to 45° from the midpoint and the ultrasound transducer placed above the right carotid artery in the ear-to-ear plane. Images were acquired with simultaneous electrocardiogram gating. Carotid measurements were taken from magnified images of the near and far walls of the right carotid artery approximately 1 cm from the carotid bulbus in its long axis to derive the mean carotid intimal-medial thicknesses in accordance with guidelines from the American Society of Echocardiography [18]. The images obtained were analysed using automated wall-tracking software (Carotid Analyser for Research, Medical Imaging Applications, Coralville, IA, USA).

The following indices of arterial elasticity were calculated: *carotid arterial distensibility* $= [\Delta D/D_{min}] \times 100\%$ and *arterial stiffness index*, $\beta = \ln(SBP/DBP)/(\Delta D/D_{min})$; where D_{min} is carotid artery diameter in diastole; D_{max}, the carotid artery diameter in systole; and ΔD, the difference between the diameters [19].

Pulse Wave Velocity

A SphygmoCor® system (Atcor Medical, Sydney, NSW, Australia) was used to record carotid and femoral waveforms. Waveforms were acquired using an appropriatelysized blood pressure cuff for the femoral artery and tonometer pressure sensor for the carotid artery. The distances between the carotid and femoral arteries were measured (carotid to sternal notch, sternal notch to cuff, and cuff to femoral artery) and the pulse waves were recorded over a pre-set time. The pulse wave velocity was automatically determined by dividing the distance measured by the pulse transit time and the average of three pulse wave values was calculated for each patient.

Statistical Analysis

All data were exported and analysed using the Stata version 13.1 (StataCorp, College Station, TX, USA). Numerical data was expressed as a mean ± standard deviation. Unpaired student *t*-tests or Fisher's exact test were used to perform intergroup comparisons of all outcomes between hypertensive patients and normotensive patients, and to compare exercise-testing data between coarctation patients and the control population. Linear regression was used to assess correlations between 24-hour SBP and resting or peak-exercise SBPs. A p-value ≤0.05 was considered statistically significant.

Results

The mean follow-up time between surgical repair and the study was 13 ± 3 years. Prior to taking part in this study, all patients were actively involved in at least one sporting interest.

Clinic Resting Blood Pressure

Of the 41 patients, two (5%) had resting hypertension, seven (17%) had prehypertension, and 32 (78%) had normal resting blood pressure.

Twenty-Four-Hour Ambulatory Blood Pressure Monitoring

Of the 41 patients, the 24-hour ABPM results of five patients were excluded as they failed to wear the monitor overnight, leaving a total of 36 blood pressure results (88%) for analysis. Hypertension and prehypertension on 24-hour ABPM was present in 39% (14/36) and 11% (4/36) of patients, respectively.

Exercise-Testing

All 41 patients underwent exercise-testing and reached at least stage four of the standard Bruce protocol (Table 2). The overall endurance of the coarctation population was reduced compared to the control group (13.0 ± 1.7 mins vs. 14.2 ± 2.4 mins, respectively; $p = 0.007$). Mean SBP at peak exercise was higher in the coarctation population compared to the control group (164 ± 26 mmHg vs. 148 ± 19 mmHg, respectively; $p = 0.003$) (Table 2). Five of the 41 (12%) coarctation patients had a peak exercise SBP >200 mmHg and were therefore considered to have exercise-induced hypertension. All five were identified as being hypertensive on 24-hour ABPM. There was a significant association between peak exercise SBP and resting SBP ($p < 0.0001$) (Figure 1A) and with 24-hour SBP ($p < 0.0001$) (Figure 1B).

All patients with a peak exercise SBP >190 mmHg were also hypertensive on 24-hour ABPM (Figure 2). Patients with hypertension on 24-hour ABPM had a peak exercise SBP range of 120 to 240 mmHg (Figure 2). The mean peak exercise SBP of patients with hypertension on 24-hour ABPM was higher than those with normal blood pressure or prehypertension (180 ± 32 mmHg vs. 153 ± 18 mmHg, $p = 0.003$). There was no significant difference in study age, gender, or exercise endurance between patients who were hypertensive on both 24-hour ABPM and exercise-testing compared to patients who were hypertensive only on 24-hour ABPM and normotensive on exercise-testing ($p = 0.09$, $p = 0.09$, and $p = 0.2$, respectively).

Arch Reobstruction

Measurement of the maximum velocity in the descending aorta was obtained in 39 of the 41 patients (95%). Maximum velocity in the descending aorta was significantly higher in patients with hypertension on both 24-hour ABPM and exercise-testing (2.3 ± 0.3 m/s vs. 1.9 ± 0.5 m/s, $p = 0.009$; and 2.6 ± 0.2 m/s vs. 2.0 ± 0.5 m/s, $p = 0.007$; respectively). Arch

Table 2 Comparison of demographics and exercise performance between coarctation patients and controls.

	Coarctation (*n* = *41*)	Controls (*n* = *44*)	P-value
Demographics			
Male	27 (66%)	29 (66%)	1.0
Mean age at study, *years*	12.5 ± 3.2	12.4 ± 3.1	0.9
Exercise performance			
Mean peak exercise systolic BP, *mmHg*	164 ± 26	148 ± 19	0.003
Mean peak exercise diastolic BP, *mmHg*	64 ± 9	63 ± 12	0.6
Mean maximum heart rate, *beats/min*	193 ± 10	196 ± 11	0.1
Mean endurance, *mins*	13.0 ± 1.7	14.2 ± 2.4	0.007

Mean ± standard deviation.
Abbreviation: BP, blood pressure.

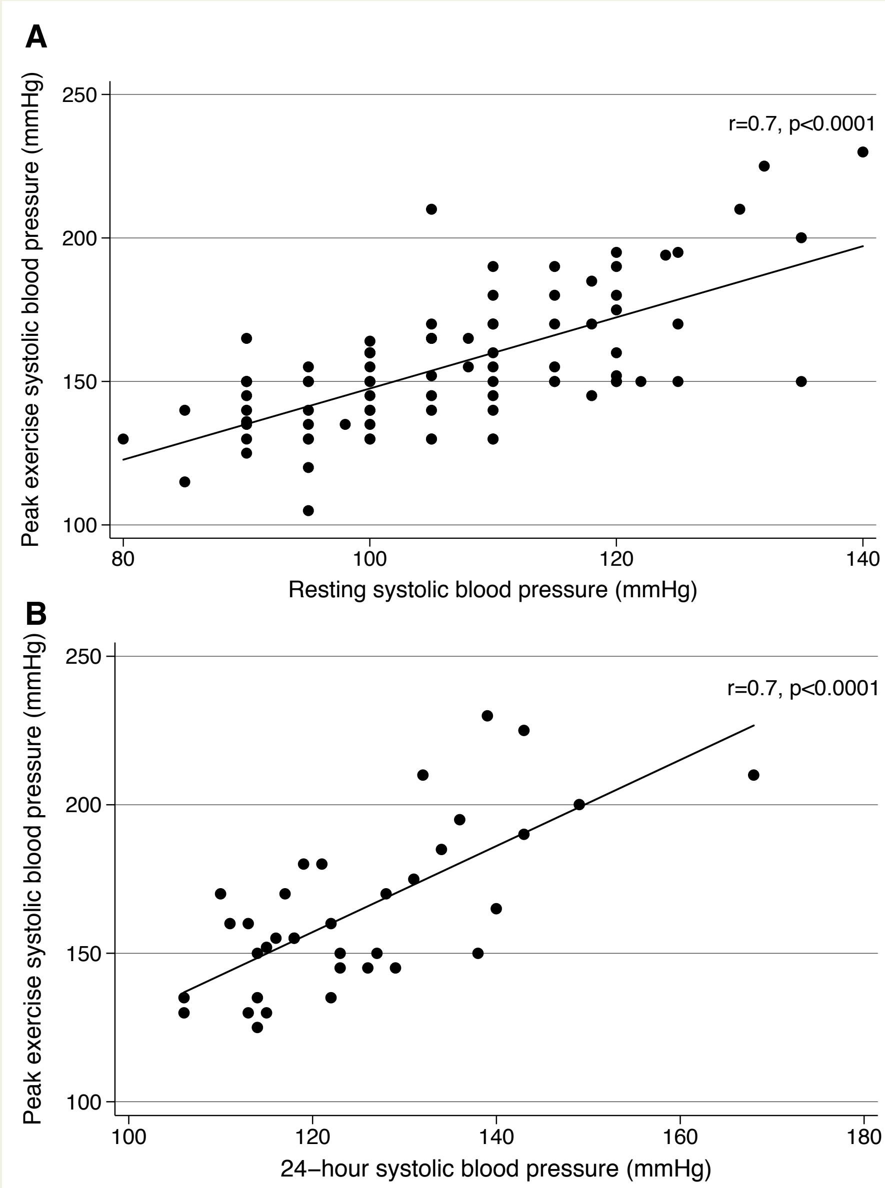

Figure 1 Relationship between peak exercise systolic blood pressure (SBP) and: **A**. Resting SBP; **B**. Mean 24-hour SBP.

reobstruction was present in 18% (7/39) of patients with 43% (3/7) of them hypertensive on both 24-hour ABPM and exercise-testing. Conversely, arch reobstruction was present in only 31% (4/13) and 60% (3/5) of patients with hypertension on 24-hour ABPM and exercise-induced hypertension, respectively.

Arch Hypoplasia

Measurements of the diameters of the proximal and distal transverse arches, the isthmus and the descending aorta were obtained in 38 (93%), 40 (98%), 40 (98%) and 40 (98%) of the 41 patients, respectively. One patient had a hypoplastic proximal arch, two patients had a hypoplastic isthmus, and three patients had a hypoplastic descending aorta. The patient with a hypoplastic proximal arch was hypertensive on 24-hour ABPM, while the patient with a hypoplastic descending aorta was prehypertensive on 24-hour ABPM.

Left Ventricular Hypertrophy

Transthoracic echocardiographic measurements of the left ventricle were obtained in 39 of the 41 patients (95%). No patients met the criteria for left ventricular hypertrophy.

Pulse Wave Velocity

Pulse wave velocity was significantly higher in coarctation patients who were hypertensive on exercise-testing (>200 mmHg) and trending towards significance in patients who were hypertensive on 24-hour ABPM compared to normotensive coarctation patients ($p = 0.004$ and $p = 0.06$, respectively) (Table 3).

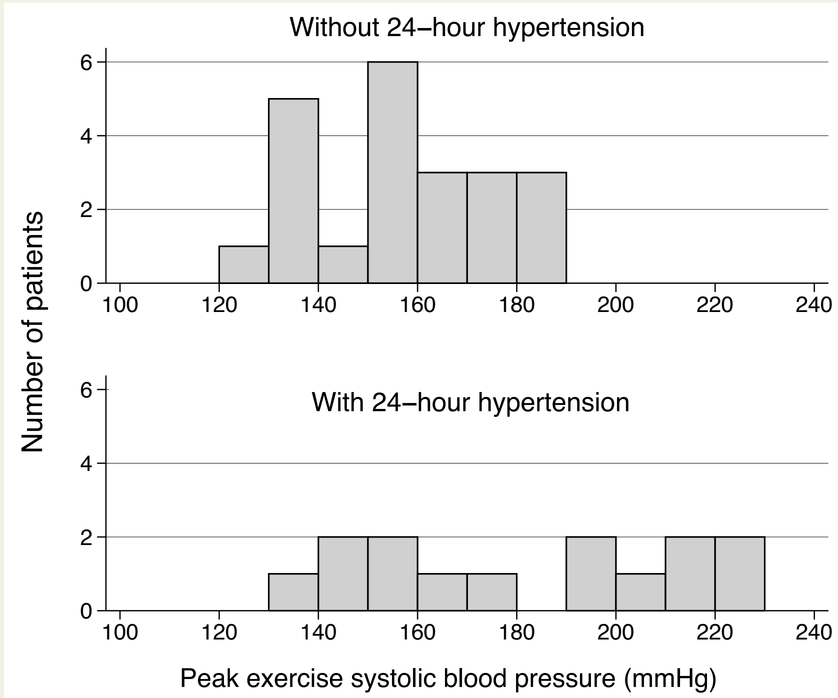

Figure 2 Histogram of peak exercise systolic blood pressure (SBP) distribution between patients without hypertension on 24-hour ambulatory blood pressure monitoring (ABPM) (**top**) and patients with hypertension on 24-hour ABPM (**bottom**). All patients with a peak exercise SBP >190 mmHg were also hypertensive on 24-hour ABPM.

Carotid Intima-medial Thickness and Elasticity

There was no significant difference in carotid intima-medial thickness between the hypertensive and normotensive coarctation patients on both 24-hour ABPM (p = 0.8) or exercise-testing (p = 0.6) (Table 3). There was no significant difference in arterial distensibility or β stiffness index between hypertensive and normotensive patients on both 24-hour ABPM (p = 0.6 and p = 0.5, respectively) or exercise-testing (p = 0.5 and p = 0.4, respectively) (Table 3).

Discussion

Up to 75% of patients may develop late hypertension after coarctation repair [2–7] which may lead to mortality at a young age [8]. Our study once again confirms that these patients are predisposed to developing hypertension at a young age, even with previous successful coarctation repair [4]. We demonstrated half of our patients, even as young as 8.5 years of age, to have hypertension or prehypertension on 24-hour ABPM. Although the most intuitive cause for this hypertension is an arch reobstruction, less than a third of

Table 3 Comparison of vascular results of coarctation patients on exercise-testing and 24-hour ABPM.

	Exercise-testing (n = 41)				*24-hour BP monitoring (n = 36)*		
	Total	**Normal BP**	**HTN**	**P-value (Normal/ HTN)**	**Normal/ PreHT**	**HTN**	**P-value (Normal/ HTN)**
	(n = 41)	**(n = 36)**	**(n = 5)**		**(n = 22)**	**(n = 14)**	
PWV, *m/s*	4.0 ± 0.8	3.9 ± 0.7	5.0 ± 0.6	0.004	4.0 ± 0.6	4.4 ± 0.6	0.06
Mean cIMT, *mm*	0.57 ± 0.15	0.58 ± 0.14	0.54 ± 0.18	0.6	0.58 ± 0.06	0.57 ± 0.12	0.8
Arterial distensibility, *%*	16.0 ± 4.7 *(n = 40)*	15.8 ± 4.4 *(n = 35)*	17.3 ± 6.6	0.5	16.3 ± 3.7	17.1 ± 4.9	0.6
β stiffness index	2.1 ± 0.3 *(n = 40)*	2.1 ± 0.3 *(n = 35)*	2.0 ± 0.2	0.4	2.1 ± 0.3	2.0 ± 0.2	0.5

Mean ± standard deviation.

Abbreviations: BP, blood pressure; cIMT, carotid intima-media thickness; HTN, hypertension; PreHT, prehypertension; PWV, pulse wave velocity, ABPM, ambulatory blood pressure monitoring.

patients with hypertension on 24-hour ABPM had an arch reobstruction. Despite all patients normally participating in at least one sporting activity, functional limitations were also demonstrated with decreased exercise endurance and increased peak exercise SBP in the coarctation patients compared to controls. Alarmingly, we also demonstrated increased pulse wave velocity and vascular stiffness to be already present in these young hypertensive patients.

Unfortunately, the identification of individuals at risk of late hypertension is difficult in the paediatric population. Twenty-four-hour (24-hr) ABPM is often considered the gold standard method to detect hypertension in adults as it is more closely related to end-organ damage than screening with casual blood pressure measurements [20]. However, concerns exist over the re-test reliability of 24-hour ABPM [21] and the intolerance of this method of blood pressure measurement in younger patients [4]. This prompted us to investigate exercise-testing as a method of detecting hypertension in these younger patients.

Exercise-testing was better tolerated by this young population than 24-hour ABPM. More than 10% of patients were unable to tolerate the frequent recordings of the 24-hour ABPM but all patients successfully completed the graded exercise test. Peak exercise SBP was correlated with SBP on both resting and 24-hour ABPM measurements. Unfortunately, the current definition of exercise-induced hypertension of >200 mmHg leaves exercise-testing a poor tool to identify the paediatric patients at risk. We suspect this is related to the lack of normative paediatric data for age, gender, or body size, resulting in a likely underestimation of the real prevalence of exercise-induced hypertension in our population. Interestingly, our study revealed that patients with a peak exercise SBP of >190 mmHg were clearly identified as being hypertensive on 24-hour ABPM. We suspect that this cut-off point may be even lower in an even younger population.

Investigations for early cardiovascular changes within our young population demonstrated increased vascular stiffness in our hypertensive patients. Although increased pulse wave velocity has been linked to cardiovascular events in adults [22,23], its usefulness as a long-term prognostic tool in a young coarctation population remains unclear. In our previous studies of predominantly young adult patients with previous coarctation repair, almost half of patients had left ventricular hypertrophy [2,3]. None of the patients in this study met the criteria for left ventricular hypertrophy but it is possible that it may develop within the next few years as these patients reach early adulthood. Additionally, there were no differences observed in the measurements of carotid intima-media thickness but this data is difficult to interpret as there are no normative data or cut-off criteria in the paediatric population.

Limitations

Echocardiographic estimation of arch reobstruction and left ventricular hypertrophy may not be as accurate as the use of magnetic resonance imaging.

The lack of normative paediatric data and validated cut-offs for exercise-testing and carotid intima-medial thickness may have underestimated those with exercise-induced hypertension and atherosclerotic cardiovascular disease, respectively.

We did not perform blood pressure measurements during the stages of the exercise-testing to allow our young coarctation patients to focus solely on running on the treadmill. We also did not perform cardiopulmonary testing in our patients so we are unable to compare other measures of endurance such as metabolic equivalent (MET) or VO_2max between coarctation patients and controls.

We did not have measurements of pulse wave velocity or carotid intima-medial thickness and elasticity in our control patients so we were unable to compare the difference in these variables between coarctation patients and controls.

The participation rate for the study was within expected range. However, we cannot exclude that the population studied was not representative.

Conclusion

Exercise-testing may be a useful tool to detect hypertension in children and young adults after coarctation repair, particularly in those who do not tolerate 24-hour ABPM. Normative peak exercise blood pressure data for age should be obtained to improve the accuracy of exercise-testing in detecting hypertension.

Previous Presentations

Poster presentation at the 64th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand; Adelaide, Australia; 4-7th August 2016.

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Disclosures

Yves d'Udekem is a consultant for Actelion and MSD. There are no disclosures for the remaining authors.

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