Cardiology in the Young (2013), **23**, 416–422
doi:10.1017/S1047951112001114

Original Article

Predictors of exaggerated exercise-induced systolic blood pressures in young patients after coarctation repair

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Abstract *Background:* In normotensive subjects, an exaggerated blood pressure response to exercise is associated with the development of resting hypertension. We sought to determine the prevalence of elevated blood pressures during exercise in post-operative coarctation patients with normal resting blood pressure, and investigate associations with exercise-induced hypertension in this population. *Methods:* A total of 38 patients were enrolled after end-to-end anastomosis repair and resting normotension. All patients underwent anthropometric and blood pressure measurements, echocardiographic evaluation of function, arterial stiffness assessment by pulse wave velocity, and a graded exercise test. An abnormal response was defined as a maximum systolic blood pressure greater than the 95th percentile of published normal values. Correlation analyses and stepwise regression analyses were performed. *Results:* The mean age was 12.7 years, including 79% male patients. The mean resting systolic blood pressure was 111.3 millimetres of mercury and the mean exercise systolic blood pressure was 178.1 millimetres of mercury. The prevalence of a systolic blood pressure greater than the 95th percentile was 16.7%. In multivariate analysis, the exercise systolic blood pressure index was associated with body mass index, age, aortic valve annulus, shortening fraction, and pulse wave velocity (R^2 equal to 0.79, p equal to 0.0009). Estimates of ventricular filling and indexed left ventricular mass were elevated. *Conclusions:* There is a risk of elevated systolic blood pressure during exercise in normotensive patients after coarctation repair. Resting blood pressures are useful but not sufficient. Echocardiography demonstrated abnormalities suggestive of a chronic cardiac burden despite resting normotension. Regular imaging may be necessary to improve long-term outcomes. New paradigms for the continued follow-up of these patients are necessary.

Keywords: End-to-end resection; exercise-induced hypertension; pulse wave velocity; graded exercise test

Received: 2 December 2011; Accepted: 24 June 2012; First published online: 12 September 2012

COARCTATION OF THE AORTA IS A COMMON congenital heart defect accounting for approximately 5–8% of all congenital heart diseases.[1] The prevalence of post-operative resting hypertension within this population has previously been reported to be as high as 45%.[2] A subset of patients with aortic coarctation who are normotensive at rest can demonstrate elevated systolic blood pressures only in response to exercise.[3–6] An exaggerated blood pressure response to exercise has previously been associated with progression to clinical hypertension, which is a risk factor for morbidity in adults.[7,8] Managing patients who are normotensive at rest, yet hypertensive during exercise, has proven to be a clinical challenge. Specific management guidelines are not well established, largely because the mechanism of exercise-induced hypertension in this population is unknown. The purpose of the study was to investigate the determinants of abnormal blood pressure response to exercise in post-operative coarctation patients who were normotensive at rest. We hope to demonstrate that these patients are in need of alternative management strategies to minimise long-term morbidity.

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Methods

Study population

All patients between the ages of 7 and 21 years who had undergone repair of aortic coarctation via end-to-end resection were eligible for prospective enrolment (n equal to 166). Only end-to-end resection repairs were analysed in this initial study to minimise bias due to alternative repair techniques, such as catheter interventions that typically occur in older age children. Patients were identified using the hospital echocardiographic database, Vericis (Camtronics, Milwaukee, Wisconsin, United States of America). Exclusion criteria included known genetic syndromes, any associated congenital heart lesions – except a normally functioning bicuspid aortic valve – history of alternate cardiac surgical intervention, clinically documented hypertension at rest, and current anti-hypertensive medications. A total of 42 patients (25%) had documented clinical hypertension or were on anti-hypertensive medications, and were therefore excluded before any testing. Prior approval was obtained from the Cincinnati Children's Hospital Medical Center Institutional Review Board. Informed and written consent was obtained from all study participants. Resting blood pressure was measured before exercise testing as indicated below. We obtained standard demographic information including age, weight, height, gender, body surface area, and body mass index.

Echocardiography

Complete echocardiograms were obtained while at rest using a Vivid 7 GE Medical Systems ultrasound imaging system (Milwaukee, Wisconsin, United States of America) in a standard supine position. Testing was performed by paediatric registered sonographers, and images were obtained in three standard views – parasternal, apical, and suprasternal – in accordance with the American Society of Echocardiography guidelines.[9] Systolic function was assessed via shortening fraction (shortening fraction % = left ventricular end-diastolic dimension − left ventricular end-systolic dimension/left ventricular end-diastolic dimension) and global strain as a measure of global function. Diastolic function was assessed via both transmitral velocity and tissue Doppler imaging. The lateral and septal ventricular annular wall velocities were assessed during peak systole and diastole. Mitral inflow velocities including early diastolic transmitral peak velocity and late diastolic transmitral peak velocity were measured. Estimates of ventricular filling pressures were assessed by comparing the ratio of pulsed wave inflow velocity with the myocardial annular velocity. The relationship between ventricular filling pressures and peak exercise systolic blood pressure was analysed. Left ventricular mass was obtained via M-mode in the parasternal long-axis view using the equation:[10]

$$\text{Left ventricular mass (g)} = (1.04)(0.8)[(\text{LVID}_d + \text{IVS}_d + \text{LVPW}_d)^3 - (\text{LVID}_d)^3] + (0.6)$$

where $LVID_d$ is the left ventricular internal diameter in diastole, IVS_d the interventricular septal diameter in diastole, and $LVPW_d$ the left ventricular posterior wall diameter in diastole. The left ventricular mass was indexed by dividing by the patient's height, raised to an exponential power of 2.7.[11] Global longitudinal strain was measured in the apical four- and two-chamber views. The automated function imaging feature on the Vivid 7 GE machine analysed myocardial motion by tracking two points along the medial and lateral mitral valve annuli, and one point at the left ventricular apex. Aortic arch diameters indexed to the body surface area were measured in the parasternal and suprasternal long-axis views. All measurements and values were obtained in triplicate and averaged. Inter- and intra-observer variability for these measurements in our laboratory was less than or equal to 5% (unpublished data).

Vascular testing

Vascular function testing was conducted at rest in the supine position. Pulse wave velocity was measured with a SphygmoCor SCOR-PVx System (Atcor Medical, Sydney, Australia) according to the manufacturer's protocol. Pulse wave velocity is the difference in the carotid-to-femoral length divided by the difference in R wave to waveform foot times. The average distance of three measurements from the sternal notch to the femoral artery was entered into the software. Arterial waveforms gated to the R wave on the electrocardiogram tracing were recorded from the carotid to the femoral artery (Fig 1). The mean of three values was used in the analyses. Recent data published by our laboratory demonstrated excellent reproducibility with coefficients of variability less than 7% even in obese adolescents.[12]

Graded exercise test

Each patient underwent a Graded Exercise Test. The testing was performed by licensed exercise technicians at the Cincinnati Children's Hospital Medical Center on an upright calibrated cycle ergometer (Lode Corival Cycle 400, Groningen, The Netherlands) as per the James protocol.[13] Heart rates and 12-lead electrocardiograms were recorded at rest; during each minute of exercise; immediately after exercise; and 1, 3, 5, 10, and 15 minutes after exercise. Blood pressures were measured in the right arm and right leg while supine at rest; during upright exercise; and while

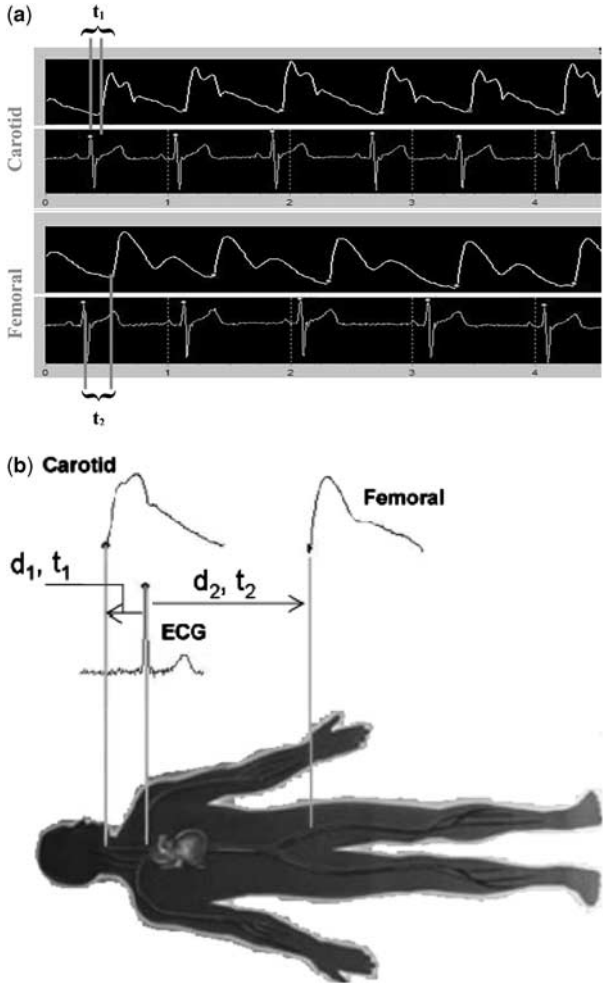

Figure 1.
*(**a**) Electrocardiographic tracing depicting the time measured from the R wave on the electrocardiogram (ECG) to the foot of the pressure wave for the carotid artery (t_1) and the femoral artery (t_2). The difference between these two times is the Δt. (**b**) The distance from the sternal notch to the femoral artery ($d_2 - d_1$) is divided by the difference in time ($\Delta t = t_2 - t_1$) between the carotid and femoral arteries to calculate the pulse wave velocity.*

supine 1, 3, and 5 minutes after exercise using the auscultation method and a manual mercury sphygmomanometer. Cuff sizes were chosen on the basis of a bladder length and width of 80% and 40% of the arm circumference, respectively. The stethoscope was placed over the antecubital fossa of the right arm.[14,15] Systolic blood pressure was determined by the onset of the first Korotkoff sound.[16] The highest systolic blood pressure obtained was used in the analysis. An exaggerated blood pressure response to exercise was defined as a maximum exercise systolic blood pressure greater than or equal to the 95th percentile.[13] Maximum systolic blood pressure index was generated by dividing the observed systolic blood pressure by the expected systolic blood pressure based on the 95th percentile. Expected systolic blood pressure values for age, gender, and height were taken from established data on similar cycle ergometers reported by James in 1980.[13] Various additional exercise indices, including working capacity, oxygen consumption, heart rate, and heart rhythm were obtained. Perceived exertion was obtained during each workload using the Borg Scale.[17] The exercise tests were judged as maximal if two of the following criteria were met: (a) respiratory quotient (carbon dioxide production/oxygen consumption) greater than 1.1, (b) maximal heart rate greater than or equal to 85% of the age-predicted maximal heart rate, or (c) maximal perceived exertion greater than or equal to 18.

Ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring was obtained in all patients. Measurements were performed using a validated oscillometric device (Spacelabs 90207 or 90217, Issaquah, Washington, United States of America) with appropriate cuff sizes for age in the non-dominant arm. Blood pressure measurements were recorded automatically every 20 minutes from 7:00 am to 11:00 pm and every 60 minutes from 11:00 pm to 7:00 am. All recordings were visually inspected for artefact and were edited according to paediatric ambulatory blood pressure monitoring guidelines.[18] Blood pressure load, night-time dip, average systolic blood pressure for daytime and night-time, and 24-hour ambulatory blood pressure measurements were used for analysis with the peak systolic blood pressure attained during exercise. Ambulatory hypertension was defined as a mean ambulatory systolic blood pressure greater than the 95th percentile and a systolic blood pressure load greater than 25%.[18]

Data analysis

All data analyses were performed using SAS® statistical software (version 9.2; SAS® Institute Incorporation, Cary, North Carolina, United States of America). Demographic and clinical characteristics of the study sample were summarised using measures of central tendency, variability, and frequency. Mean and standard deviation were reported for continuous variables. Frequencies and proportions were reported for categorical variables as indicated. Primary analyses were performed using Pearson's correlation coefficient to determine associations between the independent variables and maximum systolic blood pressure index during exercise. Stepwise regression modelling and analysis of covariance were performed to identify the independent predictors of an elevated systolic blood pressure during exercise. Covariates included resting systolic blood pressure, pulse wave velocity, body mass index, aortic valve annulus, indexed left ventricular

https://doi.org/10.1017/S1047951112001114 Published online by Cambridge University Press

mass, night-time systolic blood pressure, proximal arch diameter, transverse arch diameter, and age.

Results

Demographics

Of all eligible subjects, a total of 38 subjects were recruited for the study. Study population characteristics are summarised in Table 1. The patient cohort was predominately male (79%). A bicuspid aortic valve was present in 76.3% of the study subjects. The remaining patients refused to participate for personal reasons, were lost to follow-up, or failed to show up for their appointment.

Ambulatory blood pressure and exercise results

All the subjects were normotensive at rest on the day of testing. A maximum exercise systolic blood pressure greater than the 95th percentile occurred in 16.7% of the study subjects. Ambulatory hypertension – daytime, night-time, or both – was demonstrated in 28% of patients based on elevated mean systolic blood pressures and elevated systolic blood pressure load, defined as greater than 25% of readings spiking above the 95th percentile.[18,19] Mean ambulatory blood pressure and exercise data can be seen in Table 2. In correlation analysis, ambulatory blood pressure measurements demonstrated that night-time systolic blood pressure was significantly associated with maximum exercise systolic blood pressure index (r equal to 0.43, p equal to 0.04). No significant correlations were observed between maximum exercise systolic blood pressure index and exercise capacity.

Echocardiography results

Mean values for shortening fraction were mildly elevated in comparison with accepted normal ranges of 28–40%, as can be seen in Table 2.[20] The mean values for indexed left ventricular mass were elevated compared with normal values used in our laboratory.[21]

Table 1. Study population characteristics (means ± SD) – number of subjects = 38.

Age (years)	12.7 ± 3.9
Male (%)	79
Height (cm)	154.3 ± 18.3
Weight (kg)	47.6 ± 17.5
BMI (kg/m^2)	19.3 ± 3.6
BSA (m^2)	1.4 ± 0.3
Resting SBP (mmHg)	112 ± 14
Max SBP (mmHg)	178 ± 26
Bicuspid aortic valve (%)	76.3

BMI = body mass index; BSA = body surface area; SBP = systolic blood pressure; SD = standard deviation

The mean values for estimates of ventricular filling (E/Ea) were elevated when compared with published normal values.[22] No significant correlations were observed with the indices of diastolic function when they were compared with maximum systolic blood pressure index. The transverse aortic arch diameter demonstrated a significant negative correlation with maximum systolic blood pressure index (r equal to −0.38, p equal to 0.03). The aortic valve annulus diameter demonstrated a negative correlation that trended towards significance with multivariate analysis (r equal to −0.33, p equal to 0.06). When we evaluated the correlation between aortic valve annulus diameter and the transverse aortic arch diameter, we found a significant correlation (r equal to 0.47, p equal to 0.006). No significant correlations were observed with the other diameters of the aortic arch.

Table 2. Haemodynamic data (means ± SD).

Echocardiography	
Shortening fraction (%)	41 ± 7
Global strain (%)	−20 ± 3
Aortic arch gradient (mm)	9.3 ± 5.4
Left ventricular mass/height$^{2.7}$	48 ± 11
Aortic valve annulus (mm)	1.9 ± 0.3
Aortic root (cm)	2.5 ± 0.4
Proximal arch (cm)	1.7 ± 0.4
Transverse arch (cm)	1.5 ± 0.3
Distal arch (cm)	1.4 ± 0.2
Aortic isthmus (cm)	1.3 ± 0.3
E/A	2.2 ± 0.6
Ea/Aa septal	2.4 ± 0.6
Ea/Aa lateral	3.2 ± 1.1
E/Ea septal	9.6 ± 1.8
E/Ea lateral	7.1 ± 1.5
Vascular	
Pulse wave velocity (m/s)	4.8 ± 0.6
Graded exercise test	
Exercise hypertension (%)	16.7
Total working capacity (kpm)	5562 ± 4065
Maximum heart rate (bpm)	189 ± 9
Maximum SBP (mmHg)	178 ± 26
Maximum workload (kpm/min)	859 ± 298
Maximum VO_2 (ml/min)	40 ± 6
Ambulatory blood pressure	
Daytime ambulatory hypertension (%)	33
Night-time ambulatory hypertension (%)	20
Daytime and night-time hypertension (%)	9
24 hour SBP (mmHg)	117 ± 10
24 hour DBP (mmHg)	70 ± 7
Daytime SBP (mmHg)	122 ± 11
Daytime DBP (mmHg)	75 ± 6
Night-time SBP (mmHg)	105 ± 8
Night-time DBP (mmHg)	59 ± 6
SBP dip (%)	13 ± 5
DBP dip (%)	20 ± 6

A = late diastolic transmitral velocity; Aa = late diastolic myocardial annular velocity; DBP = diastolic blood pressure; E = early diastolic transmitral velocity; Ea = early diastolic myocardial annular velocity; SBP = systolic blood pressure; SD = standard deviation; VO_2 = oxygen consumption

https://doi.org/10.1017/S1047951112001114 Published online by Cambridge University Press

Vascular results

The mean pulse wave velocity value in this cohort of coarctation patients (4.8 metres per second) was within normal reference values when compared to healthy children and teenagers.[23] No significant correlations were observed between resting arm–leg systolic blood pressure gradient and pulse wave velocity nor between maximum exercise arm–leg systolic blood pressure gradient and pulse wave velocity. When pulse wave velocity was compared with maximum exercise systolic blood pressure index, the observed correlation was in the negative direction (r equal to −0.3, p equal to 0.1) and did not reach statistical significance.

Determinants of maximal exercise blood pressure

Resting systolic blood pressure was a significant predictor of maximum systolic blood pressure index during exercise with univariate analysis (r equal to 0.36, p equal to 0.05). When cut-points corresponding to the 95th percentile for maximum exercise systolic blood pressure index and the 90th percentile for resting systolic blood pressure were applied, a predictive model for the development of elevated exercise systolic blood pressures was not observed (Fig 2). Multivariate analysis demonstrated that the predictive determinants of maximal exercise systolic blood pressure index (Table 3) were body mass index, pulse wave velocity, aortic valve annulus, shortening fraction, and age (exercise systolic blood pressure index = $0.71 - 0.16 \times$ annulus $- 0.07 \times$ pulse wave velocity $+ 0.08 \times$ body mass index z-score $+ 0.02 \times$ shortening fraction $+ 0.02 \times$ age; $R^2 = 0.79$, model $p = 0.0009$ and all parameter estimate p-values ≤ 0.05).

Discussion

The significant finding of this study is that an exaggerated systolic blood pressure response to exercise can occur despite normal resting systolic blood pressure. In our study, nearly 17% of patients developed elevated systolic blood pressure during exercise. Prior studies have demonstrated a prevalence ranging from 10–28%.[6,24] The echocardiographic and ambulatory blood pressure monitoring results appear to advocate for more frequent testing in patients with exercise hypertension, despite resting normotension. Further studies to establish post-operative coarctation-specific reference values for acceptable resting, exercise, and ambulatory blood pressure values may be necessary to provide the needed data for more informed and aggressive management in this population.

Role of ambulatory blood pressure monitoring

Ambulatory blood pressure monitoring, specifically night-time systolic blood pressure correlated significantly with the primary outcome of maximum exercise systolic blood pressure index. Daytime systolic blood pressure did not correlate and this may be secondary to inherent challenges with obtaining accurate ambulatory measurements in children. Arm–leg systolic blood pressure cuff gradients at rest and at peak exercise did not demonstrate any significant correlations. This suggests that the absence of a significant resting arm–leg gradient should not be a reassuring sign and that an abnormal systolic blood pressure response to exercise can still be manifested.

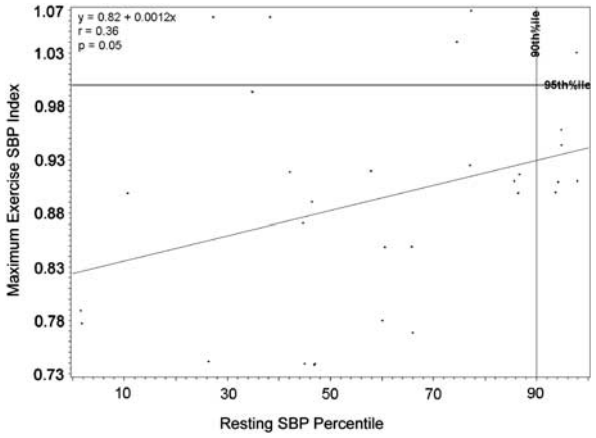

Figure 2.
Maximum exercise systolic blood pressure (SBP) index versus resting systolic blood pressure percentile. The horizontal line corresponds to a maximum exercise systolic blood pressure index cut-point of the 95th percentile and demonstrates the five patients with exaggerated systolic blood pressures responses to exercise. The vertical line corresponds to a resting blood pressure at the 90th percentile.

Table 3. Determinants of maximum exercise systolic blood pressure.

Aortic valve annulus (mm)	$p \leq 0.05$
Pulse wave velocity (m/s)	$p \leq 0.05$
Body mass index z-score	$p \leq 0.05$
Shortening fraction (%)	$p \leq 0.05$
Age (years)	$p \leq 0.05$

Evaluation of function

Shortening fraction and indexed left ventricular mass in our cohort were higher than normal values referenced in our laboratory.[21] Elevated indexed left ventricular mass in this patient population may be a secondary compensatory mechanism to overcome the greater afterload. This has previously been demonstrated by Kimball et al,[25] who postulated that persistent hypertension in the post-operative coarctation population may be due to a hypercontractile state. Left ventricular filling pressures were not predictive and may represent a later finding not

https://doi.org/10.1017/S1047951112001114 Published online by Cambridge University Press

yet manifested in our young cohort. However, when compared with normal data published by Eidem et al[22] in healthy children, our mean values for left ventricular filling pressures were elevated and suggest some degree of diastolic dysfunction that was not yet clinically evident. These results lend support to the need for continued echocardiographic assessment in these patients to evaluate for the development of left ventricular hypertrophy due to increased blood pressure with activity.

Role of aortic arch diameters

Smaller aortic arch diameters are associated with elevated systolic blood pressures during exercise. The strongest correlation was observed at the level of the transverse aortic arch. Patients with small transverse arch diameters also had small aortic annular diameters and this may explain the association of annulus diameter with hypertension as it relates to increased afterload and elevated systolic blood pressures during exercise. Although the isthmus was not a significant univariate correlate as we had hypothesised, the inherent difficulties in accurately measuring the complex three-dimensional anatomy of this area with two-dimensional echocardiography may have limited our ability to show significant associations.

Role of arterial stiffness

Pulse wave velocity has been previously studied and has been shown to be abnormal in patients with aortic coarctation.[26–28] Those studies used the photo-plethysmographic technique and magnetic resonance imaging to demonstrate an association with post-operative *resting* hypertension in normotensive and hypertensive patients.[26,27] In our study, the pulse wave velocity values were normal when compared with published normal tables, suggesting that their arteries were not stiffer at baseline when measured under resting conditions.[23] When we compared pulse wave velocity with maximum exercise systolic blood pressure index, a negative correlation was observed, which remained significant with multivariate analysis. The precise explanation for the negative correlation is not clear. It is possible that no identifiable relationship exists between pulse wave velocity and exercise systolic blood pressure in patients who are normotensive at rest. It is also possible that peripheral stiffness, not measured in this study, is a more important determinant of exercise blood pressure than central stiffness.

Limitations

The population available to us was relatively small, which led to reduced statistical power during multivariate analysis. A case–control design with a control population might identify other important differences. Comparison of different surgical- and catheter-based techniques may also be revealing. Finally, there were missing data associated with some subjects, especially with the acquisition of the ambulatory blood pressure data. These were accounted for statistically, but also reduced the power in this study.

Conclusion

In conclusion, simple blood pressure measurements including resting, exercise, and ambulatory remain powerful tools for evaluation of the cardiovascular health of post-operative coarctation patients. Patients may require annual exercise testing during the growth of adolescence to identify those at risk for developing additional long-term secondary findings. Clinicians should not forego important additional testing to comprehensively evaluate each individual. The use of all available tools can help establish new paradigms for periodic evaluation of post-operative coarctation patients.

Acknowledgements

Many thanks to the Heart Institute Research Core for financial and personnel support, which allowed the completion of this study. Research supported by the Heart Institute Research Core at the Cincinnati Children's Hospital Medical Center.

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