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Usefulness of cardiopulmonary exercise testing to predict the development of arterial hypertension in adult patients with repaired isolated coarctation of the aorta ☆

Roselien Buys [a,*], Alexander Van De Bruaene [b], Jan Müller [c], Alfred Hager [c], Sachin Khambadkone [d,1], Alessandro Giardini [d,1], Véronique Cornelissen [a], Werner Budts [b,2], Luc Vanhees [a,2]

[a] Research Centre for Cardiovascular and Respiratory Rehabilitation, Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium
[b] Internal Medicine, Division of Cardiology, University Hospital Gasthuisberg, Leuven, Belgium
[c] Department of Pediatric Cardiology and Congenital Heart Disease, Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
[d] Cardiac Unit, Great Ormond Street Hospital for Children, London, United Kingdom

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A B S T R A C T

Background: Patients who underwent surgery for aortic coarctation (COA) have an increased risk of arterial hypertension. We aimed at evaluating (1) differences between hypertensive and non-hypertensive patients and (2) the value of cardiopulmonary exercise testing (CPET) to predict the development or progression of hypertension.

Methods: Between 1999 and 2010, CPET was performed in 223 COA-patients of whom 122 had resting blood pressures of <140/90 mm Hg without medication, and 101 were considered hypertensive. Comparative statistics were performed. Cox regression analysis was used to assess the relation between demographic, clinical and exercise variables and the development/progression of hypertension.

Results: At baseline, hypertensive patients were older (p = 0.007), were more often male (p = 0.004) and had repair at later age (p = 0.008) when compared to normotensive patients. After 3.6 ± 1.2 years, 29/120 (25%) normotensive patients developed hypertension. In normotensives, VE/VCO_2-slope (p = 0.0016) and peak systolic blood pressure (SBP; p = 0.049) were significantly related to the development of hypertension during follow-up. Cut-off points related to higher risk for hypertension, based on best sensitivity and specificity, were defined as VE/VCO_2-slope ≥ 27 and peak SBP ≥ 220 mm Hg. In the hypertensive group, antihypertensive medication was started/extended in 48/101 (48%) patients. Only age was associated with the need to start/extend antihypertensive therapy in this group (p = 0.042).

Conclusions: Higher VE/VCO_2-slope and higher peak SBP are risk factors for the development of hypertension in adults with COA. Cardiopulmonary exercise testing may guide clinical decision making regarding close blood pressure control and preventive lifestyle recommendations.

1. Introduction

Adults after surgery for aortic coarctation (COA) require lifelong follow-up because of increased late cardiovascular morbidity and mortality [1]. This is mainly due to the development of arterial hypertension and the occurrence of vascular complications [2–5]. It is estimated that up to 75% of patients with repaired COA develop hypertension within 20–30 years after surgery [2,6]. Repair with prosthetic material, late repair, male gender and older age were the most important predictors of late systemic hypertension [6].

In adult patients with congenital heart disease, cardiopulmonary exercise testing (CPET) is generally used to measure the degree of exercise intolerance [7,8] which has been related to cardiovascular morbidity and mortality [8–12]. Furthermore, decreased physical fitness has been related with the incidence of hypertension in the general population [13]. However, this has not yet been investigated in patients with repaired COA.

There is a relationship between exercise-induced hypertension and sustained hypertension in adults with aortic coarctation [14]. Recently, Luijendijk et al. demonstrated that peak exercise systolic blood pressure (SBP) is predictive for the development of chronic hypertension [1]. However, their findings are based on small groups and they did not include other exercise measures.

Early identification of patients at risk for developing arterial hypertension is important in order to intensify screening strategies in subjects at the highest risk with the possibility to intervene early in

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* Corresponding author at: KU Leuven, Department of Rehabilitation Sciences, Tervuursevest 101 — bus 01501 B-3001 Heverlee, Belgium. Tel.: +32 486 388176; fax: +32 16 329197.
E-mail address: Roselien.Buys@faber.kuleuven.be (R. Buys).

[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
[2] Contributed equally as last author.

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the treatment of hypertension [15]. This study aimed at (1) evaluating differences in exercise responses between hypertensive and non-hypertensive patients at baseline, and (2) to assess the value of CPET to predict the development or progression of arterial hypertension.

2. Methods

2.1. Subjects

This study was designed as a multicenter retrospective study. In three European institutions, all consecutive patients with COA who were referred for CPET as part of their routine clinical follow-up were included in the study. Patients, ≥16 years of age at the time of the exercise test, with repaired COA with or without other small cardiac defects, which did not require an intervention (like normally functioning bicuspid aortic valve) were included. Patients with any syndrome, aberrant subclavian arteries, Shone complex, hypoplastic or borderline left heart and other heart defects that needed treatment, were excluded. A control group of healthy adults with normal physical examination who performed CPET in one institution (University Hospitals Leuven) in the same time period was used as control group to outline the pathologic CPET findings in patients after coarctation surgery.

The study was approved by the Institutional Review board of the University Hospitals Leuven, Belgium. The authors of this manuscript have certified that they comply with the principles of ethical publishing in the International Journal of Cardiology.

2.2. Baseline data

Baseline characteristics, including resting blood pressure values, were obtained from the patients' medical records. Blood pressure was measured in sitting position, at the right arm, after 2 min of rest at the same day of the exercise test. Only one measurement was performed. Restenosis was defined as a brachial–ankle SBP gradient > 20 mm Hg.

Patients were stratified into a hypertensive patient group and a normotensive patient group according to their blood pressure and/or need for antihypertensive medication at baseline. Hypertension was defined as SBP ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg and/or the use of antihypertensive drugs [16].

2.3. Cardiopulmonary exercise testing (CPET)

All patients underwent symptom limited CPET on a bicycle ergometer in upright position, which is part of their regular medical check-up visit. All patients maintained their normal medication scheme on the day of the exercise test. Baseline parameters were recorded at rest. Workload was increased ramp wise until exhaustion, as defined by shortness of breath and/or fatigue of the legs. Systolic and diastolic blood pressures were measured at rest and every other minute during the exercise test at the right arm. Heart rate was calculated from the continuously registered 12-lead electrocardiogram. Breath-by-breath gas exchange analysis was used in order to obtain respiratory data. During the exercise test, oxygen uptake (VO_2) and carbon dioxide elimination (VCO_2) were determined from the continuous measurement of oxygen and carbon dioxide concentration in the inspired and expired air. Peak VO_2 was defined as the highest 30-second average of VO_2 at the end of the test. The percentage of predicted peak VO_2 (peak VO_2%) was calculated as peak VO_2 divided by the maximal predicted VO_2, using the values reported by Wasserman and colleagues [17]. VE/VCO_2-slope was calculated on the linear part of the curve, excluding values beyond the respiratory compensation point [7]. The first ventilatory anaerobic threshold was determined by the V-slope method according to Beaver [18] and corrected by the trough of the VE/VO_2-time curve as suggested by Wasserman [17].

2.4. Follow-up

Patients had a regular follow-up for hypertension at their tertiary care center. Patients' medical records were consulted in order to abstract the cardiovascular status and the need for cardiac medication. Patients with reinterventions for re-coarction were excluded from the analysis.

In the normotensive patient group, the endpoint was the development of hypertension during follow-up, as defined above. In the hypertensive group, the endpoint was defined as the start or an extension of antihypertensive therapy.

2.5. Statistical methods

SAS statistical software version 9.3 for windows (SAS Institute Inc., Cary, NC, USA) was used for all analyses. Data are presented as mean ± standard deviation (SD), median (range) or numbers (percentage). Comparisons between patients and controls and between subgroups were performed by unpaired Student's *t*-test, Wilcoxon rank sum test, or chi-square tests, as appropriate. Prognostic values were assessed using multivariable Cox regression analysis. The tested variables to predict hypertension-free survival were age at CPET, age at primary repair, gender, resting SBP, aortic valve gradient, the presence of restenosis and exercise variables (VE/VCO_2 slope, peak VO_2, peak oxygen pulse, peak SBP). Furthermore, receiver operator characteristic (ROC) curve analysis was performed to define the cut-off values of the statistically significant results. Cut-off values were chosen according to the highest sum of sensitivity and specificity. All statistical tests were two-sided at a significance level of ≤0.05.

3. Results

3.1. Patient characteristics

In total, 223 patients who underwent surgical COA repair between 1959 and 2007 were eligible for inclusion in the study. All baseline characteristics are summarized in Table 1, and compared to a group of healthy adults of similar age and gender.

In Table 2, normotensive patients are compared with hypertensive patients. At the time of CPET, 122 patients were normotensive and 101 patients were considered hypertensive of which 61 patients were treated with antihypertensive drugs. Hypertensive patients were significantly older, more often of male gender and underwent repair at older age. In addition, there was a trend towards higher systolic brachial–ankle blood pressure difference between patient groups ($p = 0.059$).

3.2. Exercise testing

As shown in Table 1, peak VO_2, peak heart rate, peak ventilation and peak oxygen pulse were significantly lower in patients compared to controls ($p < 0.001$).

Both resting and peak SBP were significantly higher in COA patients compared to healthy controls ($p < 0.0001$).

In comparison to normotensive patients (Table 2), hypertensive coarctation patients stopped cycling earlier with a lower peak respiratory exchange ratio ($p = 0.029$). They had a similar peak VO_2, contributed by a lower peak heart rate ($p < 0.0001$) and a higher peak oxygen pulse ($p = 0.007$). However, they had a significantly lower anaerobic threshold ($p = 0.027$). Furthermore, both resting and peak SBP (219 ± 34 versus 193 ± 29 mm Hg, $p < 0.0001$) were significantly

Table 1
Comparison between patients and healthy controls.

	All patients	Healthy controls	p
Demographic and clinical variables			
Number of subjects	223	176	
Male gender	162 (73)	112 (64)	ns
Age at surgery (years)	5.7 (0.01–32)		
Type of repair			
Resection and end-to-end	111 (50)		
Patch aortoplasty	61 (27)		
Subclavian flap aortoplasty	28 (13)		
Resection and tube graft	17 (7.5)		
Extra anatomic bypass	2 (0.8)		
Unknown	4 (1.7)		
Bicuspid aortic valve	90 (41)		
Resting variables			
Age at CPET (years)	29 ± 10	29 ± 10	ns
Body mass index (kg/m^2)	23.9 ± 4.06	23.0 ± 2.98	ns
Systolic blood pressure at rest (mm Hg)	135 ± 16	128 ± 21	p < 0.0001
Heart rate at rest (beats/min)	77 ± 16	78 ± 14	ns
Exercise variables			
Peak oxygen uptake (ml/min/kg)	31.8 ± 8.73	38.9 ± 8.42	p < 0.0001
Peak oxygen uptake (%)	77 ± 17	102 ± 17	p < 0.0001
Peak heart rate (beats/min)	173 ± 20	183 ± 18	p < 0.0001
Peak oxygen pulse (ml/beat)	13.4 ± 3.86	15.6 ± 7.13	p = 0.0002
Peak ventilation	76.3 ± 23.2	102 ± 28.6	p < 0.0001
Anaerobic threshold	20.1 ± 6.1	24.1 ± 6.1	p = 0.0002
Peak respiratory exchange ratio	1.14 ± 0.09	1.23 ± 0.12	p < 0.0001
Peak systolic blood pressure (mm Hg)	205 ± 34	183 ± 25	p < 0.0001
VE/VCO_2-slope	25.5 ± 4.38	24.9 ± 4.10	ns

Data are presented as number (percentage). Mean ± standard deviation or as median (range); p = p value for comparative statistics (student's *t*-test or Wilcoxon two-sample test); ns = not significant; CPET = cardiopulmonary exercise testing.