



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

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ARTICLE INFO

Article history:

Received 18 October 2012

Received in revised form 20 December 2012

Accepted 13 January 2013

Available online 27 February 2013

Keywords:

Aortic coarctation

Hypertension

Cardiopulmonary exercise testing

ABSTRACT

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.

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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

[☆] No grant support.

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¹ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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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 $\text{VO}_2\%$) 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-coarctation 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 \pm 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 \pm 10	29 \pm 10	ns
Body mass index (kg/m^2)	23.9 \pm 4.06	23.0 \pm 2.98	ns
Systolic blood pressure at rest (mm Hg)	135 \pm 16	128 \pm 21	$p < 0.0001$
Heart rate at rest (beats/min)	77 \pm 16	78 \pm 14	ns
Exercise variables			
Peak oxygen uptake ($\text{ml}/\text{min}/\text{kg}$)	31.8 \pm 8.73	38.9 \pm 8.42	$p < 0.0001$
Peak oxygen uptake (%)	77 \pm 17	102 \pm 17	$p < 0.0001$
Peak heart rate (beats/min)	173 \pm 20	183 \pm 18	$p < 0.0001$
Peak oxygen pulse (ml/beat)	13.4 \pm 3.86	15.6 \pm 7.13	$p = 0.0002$
Peak ventilation	76.3 \pm 23.2	102 \pm 28.6	$p < 0.0001$
Anaerobic threshold	20.1 \pm 6.1	24.1 \pm 6.1	$p = 0.0002$
Peak respiratory exchange ratio	1.14 \pm 0.09	1.23 \pm 0.12	$p < 0.0001$
Peak systolic blood pressure (mm Hg)	205 \pm 34	183 \pm 25	$p < 0.0001$
VE/VCO_2 -slope	25.5 \pm 4.38	24.9 \pm 4.10	ns

Data are presented as number (percentage). Mean \pm 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.

Table 2
Comparison between patient groups.

	Normotensive	Hypertensive	p
Number of patients	122	101	
Male gender	79 (65)	83 (83)	0.004
Age at surgery (years)	5.4 (0.01–28)	8.2 (0.01–32)	0.008
Type of repair			
Resection and end-to-end	61 (50)	50 (50)	ns
Patch aortoplasty	35 (29)	26 (26)	ns
Subclavian flap aortoplasty	21 (17)	7 (7)	0.031
Resection and tube graft	3 (3)	14 (14)	0.001
Extra anatomic bypass	0	2 (2)	ns
Unknown	2 (1)	2 (2)	ns
Bicuspid aortic valve	52 (43)	38 (38)	ns
Basic variables			
Age at CPET (years)	27 ± 9	31 ± 11	0.007
Body mass index (kg/m ²)	23.5 ± 3.93	24 ± 4.16	ns
Systolic blood pressure at rest (mm Hg)	127 ± 11	143 ± 17	<0.0001
Heart rate at rest (beats/min)	77 ± 19	76 ± 13	ns
Systolic brachial–ankle difference (mm Hg)	0 (–45–41)	5 (–37–60)	ns (0.059)
Restenosis	9 (7)	13 (13)	ns
Echocardiography			
LV ejection fraction (%)	70 ± 9	69 ± 11	ns
Aortic valve gradient (mm Hg)	14.7 (2.7–95)	14.0 (3–75)	ns
LV end-diastolic diameter (mm)	49 ± 5.6	51.2 ± 7.06	0.023
LV posterior wall (mm)	10 ± 5.2	10.3 ± 2.22	ns
LV interventricular septum (mm)	10.4 ± 2.37	10.6 ± 2.37	ns
Antihypertensive therapy	0	61 (60)	
Betablocker	0	38 (38)	
ACE inhibitor	0	34 (34)	
Calcium antagonist	0	6 (6)	
Diureticum	0	19 (18)	
Exercise variables			
Peak oxygen uptake (ml/min/kg)	32.2 ± 8.59	31.3 ± 8.93	ns
Peak oxygen uptake (%)	78 ± 16*	76 ± 17*	ns
Peak heart rate (beats/min)	178 ± 15	166 ± 22.6	<0.0001
Peak oxygen pulse (ml/beat)	12.8 ± 3.9	14.2 ± 3.69	0.007
Peak ventilation	76.2 ± 24.3	76.5 ± 22.0	ns
Anaerobic threshold	20.9 ± 6.57	19.6 ± 5.31	0.027
Peak respiratory exchange ratio	1.16 ± 0.08	1.13 ± 0.09	0.029
Peak systolic blood pressure (mm Hg)	193 ± 29	219 ± 34	<0.0001
VE/VCO ₂ -slope	25.6 ± 4.61	25.4 ± 4.10	ns
Follow-up (years)	3.7 ± 1.2	4.1 ± 1.9	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; LV = left ventricle; ACE = angiotensin converting enzyme.

* Significantly different from the normal population, *p* < 0.0001.

higher in hypertensive patients compared to normotensive patients (Fig. 1).

3.3. Outcome

Patients were followed up for a mean period of 3.9 ± 1.6 years during which 3 patients died and 9 patients underwent reoperation or intervention for restenosis, 7 of them where hypertensive at baseline.

In the normotensive group, 2 patients underwent intervention for re-coarctation and were therefore excluded from the follow-up analysis. Of the 120 remaining patients who were normotensive at baseline, 29 (24%) developed arterial hypertension. When resting SBP was higher, a larger proportion of patients developed hypertension: 5% of patients with resting SBP between 100 and 120 mm Hg, 23% of patients with resting SBP between 121 and 130 mm Hg and 41% of patients with resting SBP between 131 and 140 mm Hg developed hypertension during follow-up.

At multivariable analysis, only VE/VCO₂-slope (HR 1.151; 95% CI 1.026–1.290; *p* = 0.016) and peak SBP (HR 1.018; 95% CI 1.001–1.036; *p* = 0.049) were significantly related to the development of arterial hypertension, independent of age, gender, age at primary

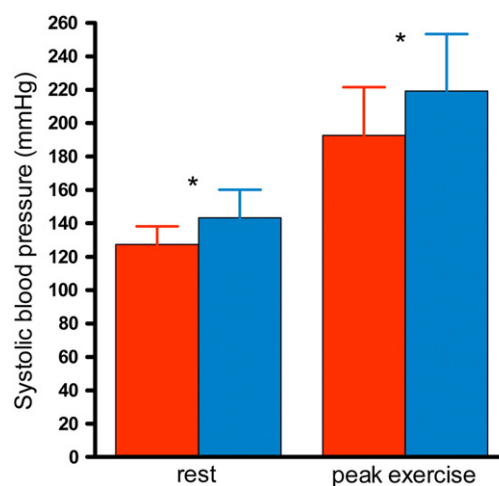


Fig. 1. Comparison of resting and peak systolic blood pressure between normotensive (red) and hypertensive (blue) patients with repaired aortic coarctation. *Comparison between normotensive and hypertensive patients, *p* < 0.0001.

repair and resting SBP. The association between peak SBP and the development of hypertension is further documented in Fig. 2. When peak SBP is higher, a larger proportion of patients develop hypertension at rest.

Receiver operating curve analysis revealed that VE/VCO₂-slope ≥ 27 (sensitivity 66%, specificity 34%) and peak SBP ≥ 220 mm Hg (sensitivity 45%, specificity 88%) were optimal cut-off values for the development of hypertension. Furthermore, the risk for the development of hypertension increased if both risk factors were present. Kaplan–Meier curves based on the number of present risk factors are shown in Fig. 3. In addition, the significance of VE/VCO₂-slope and peak SBP did not change, even when baseline systolic blood pressure was included in the multivariable regression model.

In the hypertensive group, anti hypertensive drug treatment was started or extended in 48 (48%) patients. Only older age at assessment was independently associated with the need to start or extend antihypertensive drug therapy (HR 1.054; 95% CI 1.002–1.110; *p* = 0.042). The residual SBP gradient at the former coarctation site was not related with starting or escalation of the drug therapy.

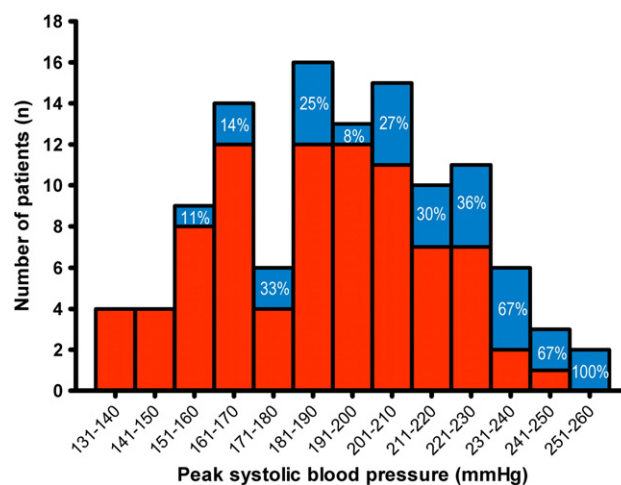


Fig. 2. Distribution of peak systolic blood pressure in normotensive patients with repaired aortic coarctation. The red parts represent patients who remain normotensive during follow-up, the blue parts represent the percentage of patients that become hypertensive during follow-up.

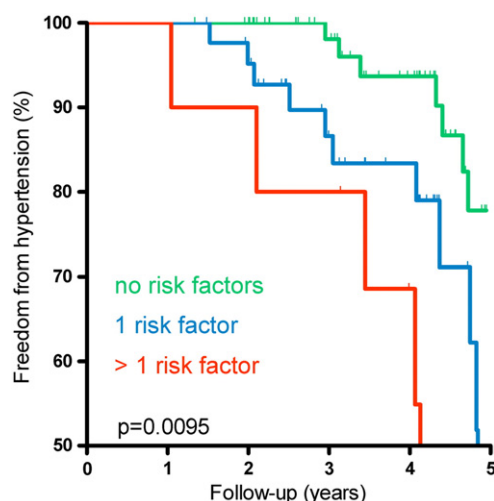


Fig. 3. Percentage freedom from hypertension according to the number of risk factors of VE/VCO₂-slope or peak SBP.

4. Discussion

This study showed that hypertensive patients with repaired isolated COA are older, more often male and underwent repair at older age compared to normotensive COA patients. In non-hypertensive patients with COA, a steeper VE/VCO₂-slope and higher peak SBP are associated with an increased risk for the development of arterial hypertension.

4.1. Patients with normal blood pressure in comparison with hypertensive patients

A first aim of this study was to compare COA-patients with and without hypertension and we found that hypertensive patients were older, more often male and underwent surgical repair at older age. We confirm the parameters that have been described earlier as risk factors for the development of hypertension [2,19–21].

4.2. Predictors of the development of chronic hypertension

Almost a quarter of the investigated patients who were normotensive at baseline, developed arterial hypertension during our short follow-up period. This is a substantial amount, but seems not abnormal since virtually all patients with aortic coarctation will become hypertensive [2]. Our results are in line with Luyendijk et al., who reported that 14 of the 47 patients that were normotensive at rest, with or without exercise hypertension, developed arterial hypertension during a follow-up of 6.3 years [1].

In order to be able to early detect hypertension, the second aim of this study was to identify predictors of the development of chronic hypertension in adult patients with repaired COA among CPET parameters. Our results show that exercise variables can predict the development of arterial hypertension independently from baseline SBP.

4.2.1. VE/VCO₂-slope

Even though VE/VCO₂-slope in our patient group was not significantly different from the control group or between patient groups, our results indicate that COA-patients who present with steeper slopes more often develop hypertension. Rhodes et al. described that COA patients display an early and excessive reliance on anaerobic metabolism during exercise [22]. A similar pattern is seen among patients with peripheral vascular disease and it seems that COA patients, like patients with peripheral vascular disease, often cannot augment the blood flow to their muscles appropriately during exercise. In patients with chronic heart failure, metabolic abnormalities in the skeletal muscles with early acidosis and accumulation of catabolites during exercise may be responsible

for enhanced ergoreflex activity [23]. In turn, this results in increased ventilation and a steeper VE/VCO₂-slope during exercise and may be responsible for persistent sympathetic activation. Eventually, this constitutes a possible pathway for the development of hypertension [24,25].

Also endothelial dysfunction can cause increased ventilatory response to exercise and abnormal blood flow distribution. Patients with COA often have endothelial dysfunction which has been shown to be related to a hypertensive response to exercise and resting hypertension [26,27]. In this light, a steeper VE/VCO₂ slope might be an indicator of endothelial dysfunction and therefore be related to the development of hypertension.

4.2.2. Exercise blood pressure

Even after correcting for resting SBP, peak SBP remained a strong predictor for the development of hypertension. Normally, exercise causes an immediate vasodilatation in the active skeletal muscles and an increase in peripheral vascular resistance in tissue that is not involved. The total result is a decrease in overall systemic vascular resistance. When the involved mechanisms are inadequately functioning, an abnormal blood pressure response to exercise will occur. Exercise hypertension is often present in adults with COA, even when they have normal blood pressures at rest and has been the subject of many previous studies. Occult coarctation, alterations in baroreceptor function, hyper responsiveness of the renin-angiotensin system, abnormal response to sympathomimetic agents, increased aortic stiffness and reduced vascular reactivity may all be responsible for the exaggerated blood pressure response to exercise [3,28–31]. Thanassoulis suggested that a greater increase in blood pressure during exercise seems to be caused by the combination of a stiffer aorta and impaired endothelial function [27]. Guenthard et al. and Ross et al. previously demonstrated evidence for an enhanced sympathetic nervous system output at peak exercise in patients who underwent coarctectomy and had exercise-induced hypertension [32,33]. Furthermore, Tantengco et al. found evidence for increased left ventricular peak filling rates in patients with systolic arm hypertension at peak exercise [34].

It has been previously reported that an exaggerated blood pressure response to exercise is related to a higher risk of developing systemic hypertension and cardiovascular events in the general population, which has been attributed to a dysregulation of the vascular function [27–31]. Our study supports the results of Luyendijk et al. who recently showed that maximum exercise SBP was a predictor for the development of chronic hypertension in a small group of patients with COA [1]. Impairment of vascular mechanisms that contribute to an abnormal blood pressure regulation seem also in COA patients to be first demonstrated during exercise, and to contribute on the longer term to the development of arterial hypertension at rest.

4.3. Progression of hypertension

In the hypertensive group, only age remained a significant predictor for the progression of hypertension. It seems therefore warranted to actively and aggressively search for the first signs of hypertension in this patient cohort and to emphasize on primary prevention measures in order to delay/prevent the onset of hypertension as much as possible.

4.4. Physical activity and hypertension

It has been clearly shown that physical activity has an important role in the prevention, treatment and management of hypertension in the general population [35]. Furthermore, recent research has shown that exercise training can improve endothelial function in patients with cardiovascular risk factors [36–39]. In this light, it is not unlikely that exercise could ameliorate endothelial function and the quality of the vascular bed in patients with COA and therefore reduce blood pressure response to exercise and eventually reduce the incidence of high blood pressure. However, this remains to be determined in future studies.

4.5. Limitations

Patients with COA are often only seen on an annual basis by their specialist cardiologist, this might explain the fact that on Fig. 3, no events are shown on the Kaplan–Meier curves in the first year of follow-up.

The patients in the hypertensive group were not all on anti-hypertensive drug therapy at baseline, but many of them were started on medications after that assessment. It is possible that in some patients CPET was requested as the final step before planning ambulatory blood pressure measurement and, based on the latter, starting treatment in a patient with borderline/high blood pressure.

4.6. Conclusion

Cardiopulmonary exercise testing can provide important information for the future risk of hypertension. Higher VE/VCO₂-slope and higher peak SBP are associated with the risk 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 including diet, weight and exercise.

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