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Comparison between Two VO2 Peak Prediction Models in a Cohort of Children and Adolescents with and without Diseases

Albane Bertha Rosa Maggio[1]*, Xavier Eric Martin[1], Julie Wacker[2] and Maurice Beghetti[2]

[1]*Department of Pediatrics, Gynecology and Obstetrics, Health and Movement Consultation, Division of Pediatric Specialties, University Hospitals of Geneva and University of Geneva, 26 Boulevard De La Cluse, 1211 Geneva 14, Switzerland*

[2]*Department of Pediatrics, Gynecology and Obstetrics, Pediatric Cardiology Unit, Division of Pediatric Specialties, University Hospitals of Geneva and University of Geneva, 6 rue Willy-Donzé, 1211 Geneva 14, Switzerland*

Abstract

Scope: Currently there are several reference values for evaluating cardiorespiratory fitness in children. However, one of the most commonly used reference model seems to overestimate normal exercise capacity. We aimed to compare the reference values of peak VO2 between the Bongers model and the newly published Z-score model on a population of children and adolescents referred for CPET.

Methodology: This is a cohort study including 195 healthy young people with exercise symptoms as well as children with different pathologies. All included subjects completed CPET on a bicycle according to a standard protocol. Their exercise values were recorded and the predicted peak VO2 values were compared using the two methods using Bland-Altman, one-sample t-test, linear regression, Welch's t-test and Chi-2.

Findings: Subjects were aged 14.1 ± 0.6 years. The predicted values between Bongers and the z-score model were not consistent. The Z-score model seems to better estimate the predicted value of our population, since the difference between observed and predicted VO2 was smaller than according to the Bongers model, whether in the entire cohort (-258.2 ± 402.2 *vs.* -559.7 ± 536.7 mL/min) or in healthy children (-393.6 ± 337.5 *vs.* -685.3 ± 415.8 mL/min).

Conclusions: The new Z-score model seems to better predict normal CRF in our population of healthy children and in children with various conditions than the Bongers model. This new equation was developed from three populations from different countries and with a wide diversity of ages and BMI, making it applicable to a more heterogeneous population.

Limitations: Our subjects without known condition were referred to us for exercise symptoms. We cannot therefore consider them as healthy in "strictu sensu". However, as they all had a normal cardiological examination, we had considered them as healthy.

Keywords: Cardiorespiratory fitness • Cardiorespiratory exercise test • Peak oxygen consumption • Children • Reference values

Abbreviations: BMI: Body Mass Index; BMIzs: Body Mass Index z-score; BR: Breathing Reserve; CHD: Congenital Heart Disease; COVID: Corona Virus Disease; CPET: Cardiopulmonary Exercise Test; CRF: Cardiorespiratory Fitness; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; HR: Heart Rate; PaO_2: Partial Pressure of Oxygen; $P(A\text{-}a)O_2$: Alveolar-Arterial Gradient; RER: Respiratory Exchange Ratio; RR: Respiratory Rate; SpO_2: Partial Oxygen Saturation; VE/VCO_2: Minute Ventilation/Carbon Dioxide Production; VO2: Oxygen Consumption; VT: Ventilatory Threshold; W: Watt

Introduction

Cardiorespiratory Fitness (CRF) has been recognized as a marker of future morbidity and mortality in children and adolescents with chronic conditions, such as Congenital Heart Diseases (CHD) and cystic fibrosis [1-4]. Therefore, reference values are of prime interest to evaluate and compare those patients. As reported in a recent extensive review [5], many reference values for Cardiopulmonary Exercise Testing (CPET) have been published with a wide diversity of protocols and studied population. Authors highlight the fact that each center should adopt reference values reflecting at best their clinical practice and population. Until now, Bongers BC, et al. reference values [6] were used in our center to evaluate children with chronic conditions and healthy children complaining of symptoms during exercise, as we used similar cycle protocols. Yet, based on their predicted value, many otherwise healthy children were surprisingly categorized has having low CRF, which made us hypothesize that our population was different from the Bongers cohort. Very recently, other reference values have been proposed using z-scores models elaborated on similar population and CPET protocol than ours [7,8].

This study aimed at comparing CRF prediction obtained from Bongers BC, et al. references value to the new Z-score model, to find the one that fitted the best our CPET protocol and population of symptomatic but healthy children, as well as young with chronic diseases.

***Address for Correspondence:** Albane Bertha Rosa Maggio, Department of Pediatrics, Gynecology and Obstetrics, Health and Movement Consultation, Division of Pediatric Specialties, University Hospitals of Geneva and University of Geneva, 26 Boulevard De La Cluse, 1211 Geneva 14, Switzerland, Tel: +41795533222, E-mail: albane.maggio@hcuge.ch*

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Materials and Methods

Study design and subjects

This is a cohort study held at the Geneva University Hospitals between February 2015 and February 2023. We recruited children and adolescents addressed for a CPET at our clinic for one of the following indications: 1) evaluation of children complaining of symptoms during exercise after a complete cardiological examination; 2) normal follow up of children or adolescents known to have a chronic heart or pulmonary disease: Congenital Heart Disease (CHD), cystic fibrosis, pulmonary hypoplasia, asthma; etc. 3) evaluation of children with other conditions: suspected or known heart rhythm disturbances, cancer, sickle cell disease, long COVID, etc.

Children who were included in the study met the same criteria as those published in Gavotto A, et al.'s article [7]: 1) aged <18 years; 2) a peak heart rate ≥ 80% of maximal age-predicted heart rate (220-age); 3) inability to maintain a pedalling rate above 60, despite verbal encouragements. Furthermore, we included only subjects for whom the test was performed on a cycle ergometer with a similar protocol as the one used in the proposed VO2max Z-score model.

The Cantonal Ethics Committee (CCER) approved the study (CCER 2020-00414). Our cohort study was composed of retrospective and prospective parts. Parental and child written informed consent was obtained for the prospective part of the study and non-opposition consent was used for the retrospective part.

Measures

Anthropometrics: We assessed body weight (kg) in light clothes (underwear and tee-shirt) and height (cm) without shoes. Body Mass Index (BMI) was calculated as weight/height squared (kg/m^2) and z-scores were derived using the World Health Organization references [9].

Cardiopulmonary Exercise Test (CPET): CPET was performed on a pediatric cycle ergometer and oxygen consumption was measured by direct gas analysis (MetaLyzer® 3B/II, Cortex, Leipzig, Germany).

MetaLyzer® 3B is a breath-by-breath device, whereas MetaLyzer® II uses the mixing chamber technique. Data were analyzed using ABRM on the manufacturer software (MetaSoft®, Cortex, Leipzig, Germany). For most of the subjects (181/195), blood gases were obtained by capillary blood sampling of the fingertip before the start of the test and once the test was completed. Hemoglobin level, pH, Partial Pressure of Oxygen (PaO_2) and lactate were recorded.

Before the test, we performed a spirometry with measurements of the Forced Expiratory Volume in One Second (FEV1), the Forced Vital Capacity (FVC) and the FEV1/FVC ratio (FEV1/FVC%). The results were expressed as Z-scores from the spirometry reference equations [10].

Subjects performed a ramp protocol consisting of baseline measurements at rest for 1 minute; warm-up (at 10, 20 or 25 Watts) for 3 minutes; incremental exercise with fixed increments of 10, 15, 20 or 25 W per minute at a pedalling rate of 60 to 80 revolutions per minute; 3-minute recovery phase at 20 W and 2 minutes without pedalling.

Peak Oxygen Consumption (peak VO2), Peak Heart Rate (peakHR), Respiratory Rate (RR), Respiratory Exchange Ratio (RER), Breathing Reserve (BR), Partial Oxygen Saturation (SpO2), minute ventilation/carbon dioxide production (VE/VCO2) slope, Alveolar-Arterial Gradient P(A-a)O2 and peak work level were recorded.

Statistical analysis

Statistical analyses were performed using the SPSS software 25.0 (Chicago, IL). Descriptive analyses were performed using frequency distributions for the qualitative variables and mean and Standard Deviation (SD) for the quantitative ones.

Bland-Altman, one-sample t-test and linear regression were used on the whole cohort to compare the concordance between the two predicted VO2 values (in ml/min) obtained from the Bongers and z-score models.

Then, to find the best reference value model for our population, we separated our population into two groups: 1) children evaluated for symptoms, but with normal cardiac evaluation and no other health conditions, named "Healthy group"; and 2) children with chronic condition known to have a negative impact on CRF, named "Disease group". We calculated the difference between observed and predicted VO2 for the two models and analysed their distributions and their Normality (Shapiro-Wilk tests) in the whole cohort and both groups.

Finally, to define impaired aerobic fitness, we used the following cut off values: peak VO2<80% of predicted values using the Bongers equation; and <-2 z-score use the VO2max Z-score model. We looked at the predicted VO2max in each group, as well as the number of subjects with abnormal CRF according to the Bongers and the Z-score models. Welch's t-test and Chi-2 were used to compare differences between groups. Differences were considered significant if p<0.05.

Results

Patients' characteristics

From the entire cohort of 294 performed tests, 195 subjects, between 7 and 18 years of age, met the inclusion criteria and were included in the analyses. Patients' characteristics and anthropometrics are presented in Table 1.

Table 1. Subjects' characteristics and CPET results.

	Whole Cohort	Healthy Group	Disease Group	P value
	N=195	N=57	N=66	
Female (n, %)	85 (43.6%)	18 (31.6%)	46 (69.7%)	<0.001*
Age (years)	14.1 ± 0.6	14.3 ± 1.9	14.6 ± 2.3	0.495
Haemoglobin (g/dL) (n=181/195)	14.2 ± 1.9	14.7 ± 1.4	13.4 ± 2.6	0.002*
Anthropometrics				
Weight (kg)	54.0 ± 13.4	54.3 ± 14.6	52.7 ± 9.6	0.486
Height (cm)	164.4 ± 12.8	167.6 ± 12.5	163.0 ± 10.3	0.032*
BMI (kg.cm^{-2})	19.8 ± 3.4	19.2 ± 3.7	19.8 ± 2.6	0.291
BMI z-score	-0.07 ± 1.16	-0.36 ± 1.3	-0.09 ± 1.0	0.181
Underweight (%)	19.5	31.6	15.2	-
Normal weight (%)	64.6	52.6	72.7	-
Overweight (%)	10.8	12.3	10.6	-
With obesity (%)	5.1	3.5	1.5	-
Spirometry at Rest				
FEV_1 (%)	94.4 ± 19.7	98.5 ± 15.2	89.2 ± 18.4	0.003*
FEV_1 z-score	-0.28 ± 1.3	-0.06 ± 1.2	-0.67 ± 1.3	0.014*
FEV_1/FVC ratio (%)	89.3 ± 7.3	90.0 ± 6.9	88.3 ± 5.1	0.148
CRF at Peak Exercise				
Peak VO_2 (mL/kg/min)	35.8 ± 9.5	38.7 ± 7.6	30.6 ± 7.8	<0.001*
Workload (W)	147.1 ± 50.4	159.9 ± 45.9	126.1 ± 45.2	<0.001*
Peak HR (beat (min)	181.9 ± 9.3	184.1 ± 9.0	180.0 ± 8.9	0.014*
% of predicted max HR (220-age)	88.5 ± 4.6	89.5 ± 4.4	87.6 ± 4.4	0.023*
O_2 pulse (mL/beat)	10.5 ± 3.4	11.2 ± 3.0	8.9 ± 2.9	<0.001*
RR (per min)	45.2 ± 9.3	44.4 ± 9.9	46.2 ± 8.9	0.298
BR (%)	34.3 ± 16.6	33.0 ± 15.9	34.7 ± 16.1	0.568
VE/VCO_2 slope	30.8 ± 5.5	30.1 ± 5.3	32.2 ± 5.8	0.044*
SpO_2 (%)	95.9 ± 2.8	96.1 ± 2.0	94.9 ± 3.4	0.013*

PaO_2 mmHg (n=181/195)	87.4 ± 12.8	91.2 ± 13.0	83.4 ± 11.5	0.001*
$P(A\text{-}a)O_2$ mmHg (n=181/195)	28.0 ± 11.9	24.4 ± 12.3	30.6 ± 9.5	0.004*
RER	1.14 ± 0.08	1.13 ± 0.07	1.15 ± 0.07	0.185
pH (n=181/195)	7.29 ± 0.05	7.29 ± 0.04	7.30 ± 0.05	0.401
Lactate (mmol/l) (n=181/195)	8.3 ± 2.5	8.6 ± 2.4	7.9 ± 2.4	0.132

Results are expressed as mean and SD

*p< .05 between groups

Abbreviations: BMI: Body Mass Index; BR: Breathing Reserve; CRF: Cardiorespiratory Fitness; FEV_1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; PaO_2: Partial Pressure of Oxygen; $P(A\text{-}a)O_2$: Alveolar-Arterial Gradient; RER: Respiratory Exchange Ratio; RR: Respiratory Rate; SpO_2: Partial Oxygen Saturation; VE/VCO_2: Minute Ventilation/Carbon Dioxide Production; VO_2: Oxygen Consumption

Almost half (49.7%) were addressed for evaluation of symptoms during exercise. For the other subjects, CPET was performed as part of their usual follow-up, or to address pharmacological or surgical treatment outcome. Complete description of our cohort (symptoms and pathologies) is presented in Appendix 1. In total, 138/195 (70.8%) subjects suffered from at least one disease and 57/195 (29.2%) had no known medical condition with normal cardiological check-up (physical examination, electrocardiogram and echocardiography).

CPET results

To match criteria of Gavotto A, et al., we included in our study subjects with a peak heart rate of at least 80% of the predicted heart rate (220-age) and with an inability to continue pedalling [7]. When looking at other commonly used criteria [11,12], 72.3% of our subjects reached at least an 8/10 on the Borg scale, 32% reached a VO2 plateau; 96.9% a RER of at least 1.00 and 72.8% a lactate level of at least 6 mmol/l.

Furthermore, 82.6% of them decreased their pH of more than 0.4 from baseline value and 22.8% had a BR under 20%.

Globally, mean peak HR, RER, lactate level and pH value of our cohort were compatible with maximal test.

We present the CPET results for the whole cohort in Table 1.

Comparison of the two predicted models on the whole cohort

The mean peak VO2 of our cohort was lower than the 80% peak VO2 predicted by Bongers, with only 87/195 (44.6%) subjects with normal VO2 peak. The mean z-score, however, was within the Z-score model norms and as much as 149 (76.4%) subjects had normal VO2 peak when using the Z-score formula (Table 2).

To evaluate the correlation between the two prediction models, a Bland-Altman plot was performed (Figure 1). There was no agreement between them as the mean difference between the predicted peak VO2 from Bongers and the Z-score models was significantly different (mean diff: 301.8 ± 377.4 ml/min; 95%CI = 248.5–355.1; p<0.001). Linear regression confirmed a systematic proportional bias between the two methods (B=0.360; t=9.341, p=0.001).

Furthermore, the distribution of the difference between the observed and measured peak VO2 was normal for the Z-score model, but not for the Bongers (Shapiro-Wilk test: p<0.001; Figure 2).

Application of the two models on two distinct groups

To determine whether the new equation was applicable to any type of patient, we decided to create two distinct and "extreme" groups: healthy-looking children ("Healthy group", n=57) and subjects with diseases known to influence CRF ("Disease group", n=66; subjects' description in Appendix 2). Their characteristics and CPET results are presented in Table 1.

When comparing the groups, there were significantly more girls and the height was lower in the Disease group, but the other characteristics were similar. Furthermore, there were no differences among BMI categories (p=0.105).

As expected, CPET values were significantly different between groups, but indicators of maximal test (RER, pH and lactate level) were similar.

Predicted VO2 and consequently the difference between observed and predicted peak VO2 were lower for the Z-score model in both groups (Table 2). The distribution of the difference between observed and predicted peak VO2 for each group is presented in Figure 3. The difference was normally distributed in both groups for the Z-score model (Shapiro-Wilk in Healthy: p=0.901; in Disease: p=0.751), but not for the Bongers model, in the Disease group (Shapiro-Wilk: p<0.001; in Healthy: p=0.070).

Table 2 presents the proportion of subjects with abnormal CRF for each model. For the Healthy group, the Z-score model seems to better reflect a normal group of children as 81.4% of them were categorized as having normal

Table 2. Predicted and observed peak VO2.

	Whole Cohort	Healthy Group	Diseases Group
	N=195	N=57	N=66
Predicted Peak VO2			
Bongers model (mL/kg/min)	45.5 ± 4.0	46.4 ± 3.8	43.7 ± 3.5
Bongers model (mL/min)	2469.6 ± 708.4	2538.0 ± 763.6	2306 ± 488.0
Z-score model (mL/kg/min)	40.8 ± 6.5	43.2 ± 6.9	38.6 ± 6.0
Z-score model (mL/min)	2167.8 ± 505.2	2294.7 ± 520.8	2014.6 ± 406.4
Observed Peak VO2			
Peak VO_2 (mL/kg/min)	35.8 ± 9.5	38.7 ± 7.6	30.6 ± 7.8
Peak VO_2 (mL/min)	1909.6 ± 626.6	2070.3 ± 582.8	1621.1 ± 550.6
% of predicted Bongers	78.4 ± 18.7	83.5 ± 16.0	69.8 ± 15.5
Peak VO_2 z-score model	-0.98 ± 1.8	-0.71 ± 1.2	-1.65 ± 1.5
Difference between Observed and Predicted Peak VO_2			
Diff. VO_2 Bongers (mL/min)	-559.7 ± 536.7	-467.7 ± 499.9	-685.3 ± 415.8
Diff.VO_2 Z-score model (mL/min)	-258.2 ± 402.2	-224.4 ± 381.8	-393.6 ± 337.5
Impaired CRF			
Nbr<80% pred Bongers (n, %)	108 (55.4%)	26 (45.6%)	50 (75.8%)
Nbr< -2 z-score (n, %)	46 (23.6%)	10 (17.5%)	25 (37.9%)

Results are expressed as mean and SD

Abbreviations: CRF: Cardiorespiratory Fitness; VO_2: Oxygen Consumption

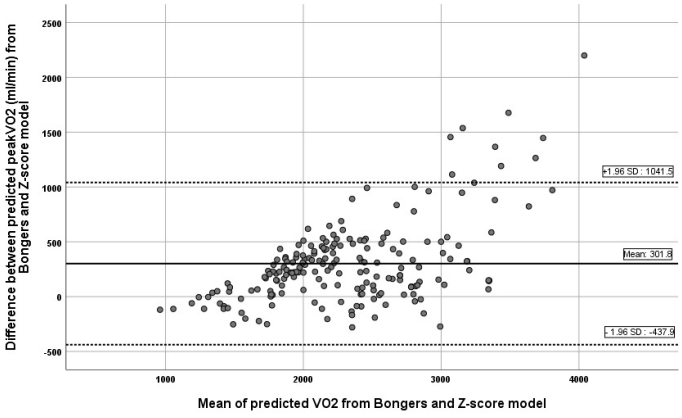

Figure 1. Bland-Altman for predicted VO2 from Bongers and Z-score model in the whole cohort.

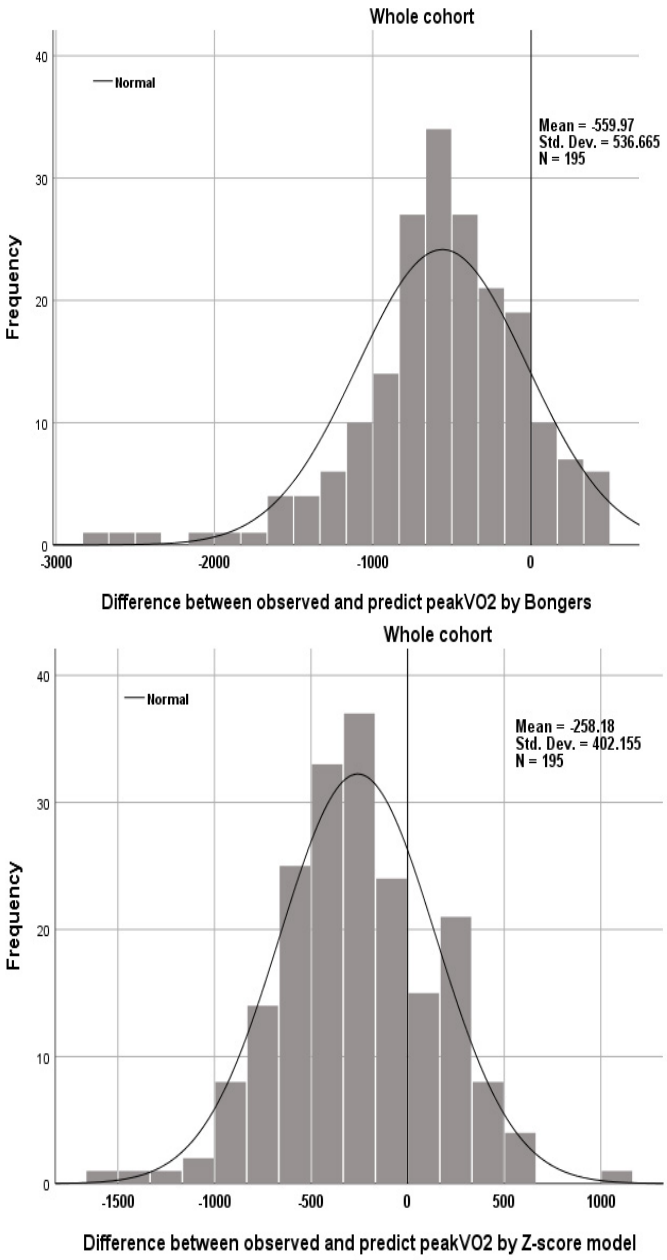

Figure 2. Distribution of the difference between observed and measured peak VO2 (mL/min) for the two model in the whole cohort; **a)** Bongers model and **b)** Z-score model.

CRF, while they were only 54.1% in the Bongers model. In the "Diseased group", as much as 77.8% of the subjects had abnormal CRF according to Bongers normative values, but only 38% when using the Z-score model.

Discussion

This study aimed to find the best prediction model to assess cardiorespiratory fitness in our population of children and adolescent addressed to our clinic for evaluation. Our population was composed of healthy children complaining of symptoms during exercise and children known to have a chronic disease.

We therefore compared two different models: the Bongers and the Z-score models [6,7]. First, our study demonstrated that there was little agreement between them, with a systematic bias, the Bongers model proposing higher normal peak VO2. Secondly, the distribution of the difference between the observed and predicted peak VO2 on the whole cohort or per groups was not normal for the Bongers model. Finally, this difference was lower with the Z-score model in healthy children, but also in the disease one, suggesting a better concordance between the prediction model and the clinical reality of our population.

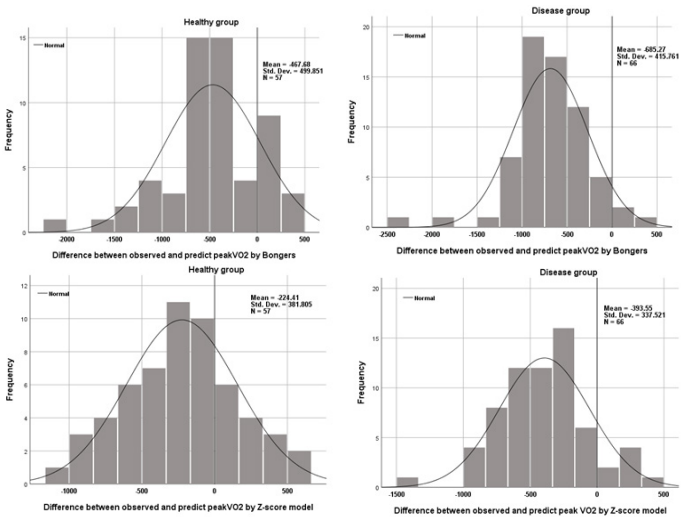

Figure 3. Distribution of the difference between observed and measured peak VO2 (mL/min) for the two model in each group; **a)** Bongers model and **b)** Z-score model.

In order to explain the difference between both models, we had to look at their prediction equations. In Bongers, only gender and age are included, while in the Z-score model gender, height but also BMI were selected making it applicable to any body type. This model seems to suit our population better as almost 20% of the subjects were underweight and 16% of them suffered from being overweight or obese, reflecting the prevalence in our country [13]. Consequently, with the Z-score model, the proportion of healthy children with a normal CRF seems closer to reality than with the Bongers model (81 *vs.* 54%). In addition, the Bongers equation was constructed on the basis of a single cohort of 214 subjects, whereas the Z-score was developed from a cohort of 909 children and then externally validated on 232 subjects coming from two separate countries. This model is therefore also applicable to a larger population.

Conclusion

In conclusion, we demonstrated that the Z-score model seemed to better predict normal CRF in our population of healthy and with various conditions children and adolescents than the Bongers model. This new equation was developed from three populations from different countries and with a wide diversity of ages and BMI, making it applicable to a more heterogeneous population. Finally, experts recommend using z-scores instead of percentage of normal values [5].

Limitations

However, our study has some limitations. First, our subjects without known condition were referred to us for exercise symptoms. We cannot therefore consider them as healthy in "strictu sensu". However, as they all had a normal cardiological examination, we had considered them as healthy. In addition, our whole cohort is quite large, but the number of healthy children may have been too small. We must point out that even with this number; we were able to demonstrate a large difference between the two prediction models.

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None.

Conflict of Interest

All the authors declare that he/she has no conflict of interest.

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