Original Article

Cardiorespiratory Optimal Point: a Submaximal Variable of the Cardiopulmonary Exercise Testing

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Abstract

Background: At the maximal Cardiopulmonary Exercise Testing (CPET), several ventilatory variables are analyzed, including the ventilatory equivalent for oxygen (VE/VO2). The minimum VE/VO2 value reflects the best integration between the respiratory and cardiovascular systems and may be called "Cardiorespiratory Optimal Point (COP)".

Objective: To determine the behavior of the COP according to gender and age in healthy adults and verify its association with other CPET variables.

Methods: Of 2,237 individuals, 624 were selected (62% men and 48 ± 12 years), non-athletes, healthy, who were submitted to maximal CPET. COP or minimum VE/VO2 was obtained from the analysis of ventilation and oxygen consumption in every minute of CPET. We investigated the association between age and COP for both genders, as well as associations with: VO_2max, VO_2 at anaerobic threshold (VO_2AT), oxygen uptake efficiency slope (OUES) and with maximum VE. We also compared the intensity of exertion (MET) at the COP, AT and VO_2max.

Results: COP increases with age, being 23.2 ± 4.48 and 25.0 ± 5.14, respectively, in men and women = ($p < 0.001$). There are moderate and inverse associations with VO_2max ($r = -0.47$; $p < 0.001$), with VO_2AT ($r = -0.42$; $p < 0.001$) and with OUES ($r = -0.34$; $p < 0.001$). COP occurred, on average, at 44% do VO_2max and before AT (67% of VO_2max) ($p < 0.001$).

Conclusion: COP, a submaximal variable, increases with age and is slightly higher in women. Being modestly associated with other ventilation measures, there seems to be an independent contribution to the interpretation of the cardiorespiratory response to CPET. (Arq Bras Cardiol 2012;99(5):988-996)

Keywords: Exercise, cardiopulmonary exercise testing, spirometry, oxygen consumption, ventilation-perfusion ratio.

Introduction

During a maximum Cardiopulmonary Exercise Testing (CPET), different ventilatory data are obtained with clinical, diagnostic and/or prognostic implications[1], such as maximum oxygen consumption (VO_2max) - an objective measure of cardiorespiratory function[2,3] - the maximum oxygen pulse, both absolute and relative to body weight[4,5], the anaerobic threshold (AT)[6], the ventilatory equivalent for carbon dioxide (VE/VCO2)[7] and the curve generated by the oxygen uptake efficiency slope (OUES)[8]. However, there are several limitations with the measurement of these variables, such as low reproducibility[9], different manners of calculation or identification[10], and the fact that to obtain most of these, it is necessary to perform a truly maximum test[11,12], which usually depends the motivations of the evaluator and the evaluated.

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The typical behavior of the ventilatory equivalents in an incremental exercise has a U-shape, characterized by suboptimal levels of efficiency at rest and very intensive efforts and improved efficiency at submaximal levels of exercise. Among the ventilatory measures obtained during an incremental exercise, the minimum value of the ventilatory equivalent for oxygen (VE/VO2 minimum), i.e., the lowest value of this variable at any given minute of CPET performed in a ramp protocol, remains to be better explored. In theory, the moment at which VE/VO2 minimum occurs represents the best association or integration between the respiratory and cardiovascular systems or ventilation-perfusion, which may be called Cardiorespiratory Optimal Point (COP). In practice, the COP corresponds to the moment during the incremental exercise in which there is less ventilation (VE) for a liter of oxygen to be consumed (VO2).

An important characteristic of COP is that - unlike most of other ventilatory indices or variables obtained or calculated at CPET – in order to obtain it, it is not necessary to perform a maximum effort. Hypothetically, the COP is much less dependent on the evaluator and, most likely, on the choice of protocol or the incremental effort ratio, thus being easier to measure, with greater accuracy. Thus, it seems appropriate to investigate the behavior of the COP in a large sample of healthy individuals, providing objective conditions for the clinical and physiological interpretation of this variable. Therefore, the aim of this study was to determine the COP related to gender and age for adults with no cardiopulmonary diseases. In addition, the associations between COP and other ventilatory variables commonly obtained in a maximum CPET were also determined.

Methods

Sample

We retrospectively analyzed data from 2,237 medical and functional evaluations performed at a private clinic specialized in Exercise Medicine between 2006 and March 2012, and identified 624 adults (62% men) non-athletes, aged 48 ± 12 years (mean ± standard deviation), who concomitantly met the following inclusion criteria: 1) no history of cardiorespiratory disease or mitral valve prolapse, 2) no regular use of cardiorespiratory medication, 3) absence of obesity (body mass index < 30 kg/m^2), 4) present a result of FEV1/FVC > 70% of the value measured[13] at resting spirometry, 5) absence of electrocardiographic alterations suggestive of significant myocardial ischemia at the CPET, 6) no locomotor limitation that could affect performance at the CPET, 7) performing the CPET on a lower-limb cycle ergometer and 8) having completed a truly maximum CPET, i.e., one that was not stopped early due to heart rate and/or blood pressure thresholds.

Protocol

The evaluation consisted of a clinical examination, comprising detailed history and physical examination. Data on anthropometrics, spirometry and electrocardiogram at rest were obtained prior to the performance of the maximum CPET. Subjects voluntarily submitted to the assessment, typically done at their own request and by indication of their attending physicians. All subjects read and signed a specific informed consent form, before the performance of the procedures, formally authorizing the use of data in scientific research, whereas preserving individual privacy. The consent form and retrospective analysis of data were previously approved by the institutional ethics committee in research, according to Resolution 196/96 of the National Health Council and the Declaration of Helsinki.

Resting Spirometry

At least three maneuvers were carried out to determine the flow-volume curve using a periodically calibrated pneumotachograph (Cardiovit AT-10, Schiller, Switzerland), using the protocol specified in the guidelines of the American Thoracic Society and European Respiratory Society[14].

Maximum Cardiopulmonary Exercise Testing (CPET)

All subjects were submitted to a maximum CPET in a lower-limb cycle ergometer (Cateye EC-1600, Cateye, Japan or Inbrasport CG-04, Inbrasport, Brazil), following an individualized ramp protocol targeting a duration between 8 and 12 minutes. The load in watts was increased gradually until the patient reached exhaustion, represented by the incapacity to continue to ride at the previously established cycling frequency. Subjects were strongly encouraged by verbal stimuli to reach the maximum effort during the CPET, and this only stopped when individuals reached the maximum voluntary exhaustion. As mentioned in the inclusion criteria, the CPETs were only considered in the analysis when they were not interrupted by clinical reasons, such as exaggerated BP response and/or the occurrence of an incompetent chronotropic response, or even due to electrocardiographic, hemodynamic and ventilatory alterations[15].

Analysis of Exhaled Gases

During the CPET, the exhaled gases were collected by a Prevent pneumotachograph (MedGraphics, USA) coupled to a mouthpiece, with concomitant nasal occlusion, and quantified by a VO2000 metabolic analyzer (MedGraphics, USA), calibrated periodically by a 2-L syringe and gases of known concentration. The metabolic analyzer enabled the quantification of pulmonary ventilation and partial fractions of oxygen and carbon dioxide, expressed and analyzed every 10 s. Following a standardization pattern[16], VO2 values were reported every minute during the CPET, through the mean of six readings obtained during this period. Thus, the value of the largest mean obtained referring to a given minute was considered the VO_2max.

Determination of Anaerobic Threshold (AT)

The AT was determined based on the graphical inspection of data on VO2 and VE, at which point there was a decrease in the linearity of VE, whereas VO2 continued to increase linearly with the work load[17].

Determination of Oxygen Uptake Efficiency Slope (OUES)

OUES was determined by linear regression related to the log transformation of VE and VO2 obtained every minute of CPET using the following equation (VO2 = a log VE + b). In this equation, the constant 'a' represents the regression coefficient (called OUES), and 'b' represents the intercept[8,18].

Determination of COP

COP, a dimensionless result, was obtained by identifying the lowest value of the ratio between the data ventilation (VE) and oxygen uptake (VO2) obtained at every minute during the maximum CPET, regardless of when it occurred.

Statistical Analysis

Initially, the normality (Kolmogorov-Smirnov) and homogeneity of data distribution were tested, validating the use of parametric statistics. To describe the sample, the central tendency and variability of the data were expressed as mean ± standard deviation (2.5 and 97.5 percentiles), while for the data used in inferential statistics, the results were presented as mean ± standard error of mean. An analysis of variance for repeated measures was used to compare the values of exercise intensity in MET in three occasions: COP, AT and VO2max. Pearson's correlation was used to test the association between COP and other ventilatory variables. The influence of age on the COP, separately by gender, was analyzed by linear regression. Statistical calculations were performed using SPSS (IBM, USA), release 17 and Prism release 5.01 (GraphPad, USA), considering a significance level of 5%.

Results

The demographic characteristics, as well as the results of resting spirometry and CPET regarding gender are shown in Table 1.

The associations between COP and VO_2max as well as with OUES and the VO_2AT were significant, but only moderate, whereas the correlation coefficient between the COP and maximum VE was weak (Table 2).

In all tested subjects, the COP always occurred before AT, being identified at 4.1 ± 0.05 metabolic equivalents (MET) (44% of VO_2max), quite lower than the value of AT 6.4 ± 0.09 MET (67% of VO_2max), and maximum effort 9.7 ± 0.12 MET ($p < 0.001$) (Figure 1).

COP increases progressively with age in both men and women, with no difference between the regression slope ($p = 0.76$); however, women have a slightly higher COP, two points for the same age, with a difference in the intercept of the linear regression ($p = 0.001$) (Figure 2). The linear regression equations that explain the association between COP and age for each gender are shown in Table 3. Figure 3 shows the behavior of the COP related to age range and gender, and for its use in clinical practice, we present in Table 4 the COP percentiles by age range and gender.

Discussion

Our study makes an original contribution to the body of knowledge, being the first to address the behavior of the COP during CPET in a large and carefully selected cohort, determining the regression equations of this variable related to age for healthy adults of both genders. Our sample selection was carried out with a stringent control to include only distinctly healthy individuals, where several criteria had to be met simultaneously, including specifically, to have never been diagnosed or treated for cardiovascular and/or respiratory diseases and obesity and not having any musculoskeletal abnormalities that could impair the performance at the CPET on a lower-limb cycle ergometer.

We also suggest in our study that the COP can be directly related to a probably optimal point of cardiorespiratory and metabolic integration, reflecting a more efficient and less expensive use of inspired VE, which is particularly important when one knows that there is a considerable energy expenditure to maintain a high pulmonary ventilation, which can reach up to 15% of the observed VO_2max[19]. Particularly, this variable has some advantages when compared to others obtained during a CPET, such as VO_2max, the oxygen pulse curve and AT, which are often addressed in other studies related to ergospirometry and presented as good prognostic indicators[3,6]. However, we must emphasize that to obtain VO_2max and other such indices it is necessary to perform a truly maximum effort[1,12] and that the determination of AT time can be influenced by the protocol used, the choice of method of detection[10] and the experience and knowledge of the evaluator[20]. As for the determination of the COP, it is not necessary to perform a truly maximum exercise considering that this variable has always been identified at relatively low levels of exercise intensity and well before the AT, and that its determination does not depend on the evaluator's interpretation, as it is easily obtained by identifying the lowest numerical ratio between the VE and VO2 values for each minute of the CPET, thus being a dimensionless ratio, simple to express and compare.

There are other ventilatory indices in the CPET that tend to express the association between the respiratory and cardiovascular systems. In 1996, Baba et al.[8] proposed an index associated to the cardiorespiratory functional reserve, related to an equation that determines the oxygen uptake efficiency slope (OUES), using the ventilatory equivalent for oxygen (VE/VO2). This variable has a strong association with VO_2max ($r = 0.94$, $p < 0.001$) in pediatric ($r = 0.78$, $p < 0.001$) and adult patients; however, these authors took into consideration several points of the VE/VO2 curve[18,21] and adjusted it as if it had a linear behavior, a fact that does not reflect the physiological behavior of this variable. Furthermore, the calculation of the equation for OUES determination is mathematically more complex and less practical than the identification of only one value, such as with the COP proposed by our study.

Our results demonstrate that the COP has a modest association with VO_2max (-0.47, $p < 0.001$) and a low association with maximum VE (-0.14, $p < 0.001$), as well as OUES (-0.34, $p < 0.001$), thus suggesting that it is a possible independent variable with potential complementary contribution to the interpretation of cardiorespiratory integration during the CPET. Another equally important aspect is that the COP (Figure 1) occurs between approximately 30% and 50% of the VO_2max, i.e., at a relatively low intensity effort, being considerably less intense than the AT in a CPET performed using an individualized ramp protocol, which can be useful when thinking about the evaluation of patients with severe coronary artery disease or even in patients with advanced heart failure. In our results of healthy individuals, the COP occurred on average at 4.1 MET, compatible with the concept of cardiorespiratory optimal point, considering that most situations of everyday movements and physical activities, exercises and sports are performed between 2 and 6 MET[22], rather than at truly maximum effort.

The aging process results in several structural and physiological alterations, such as muscle strength decrease[23], loss of flexibility[24] and VO_2max reduction[25], so we might expect that this would occur with the COP. Regarding the ventilatory variables, it is known that, over the years, there is also a reduction in respiratory muscle strength[26] and some ventilatory indicators, such as forced expiratory volume in one second (FEV1)[27] and forced vital capacity (FVC)[28], as well as a less effective response to the increase in PaCO2 at rest[29].

More specifically, in our study we observed that with increasing age, there is an increase in the COP value, a fact that can probably be explained by changes that occur in

Table 1 – Demographic characteristics and main results of resting spirometry and CPET (n = 624)

Variables	All (n = 624)	Female (n = 237)	Male (n = 387)
Characteristics			
Age (years)	48.0 ± 12.2* (23.0 - 73.0)	48.8 ± 12.6 (22.8 - 73.0)	47.6 ± 11.9 (24.0 - 73.0)
BMI (kg/m²)	24.7 ± 2.7 (19.0 - 29.4)	23.4 ± 2.7 (18.6 - 28.8)	25.6 ± 2.4 (20.5 - 29.5)
HR at rest (bpm)	65 ± 11.30 (45 - 91)	67 ± 11.30 (46 - 94)	65 ± 11.30 (48 – 89)
SBP at rest (mmHg)	126 ± 15.0 (99 - 158)	120 ± 15.80 (96 - 152)	130 ± 13.3 (108 -160)
DBP at rest (mmHg)	75 ± 9.9 (58 - 96)	73 ± 10.2 (58 - 96)	77 ± 9.3 (61 - 96)
Spirometry			
FEV_1 (L)	3.1 ± 0.78 (1.7 - 4.6)	2.4 ± 0.49 (1.5 - 3.4)	3.5 ± 0.67 (2.3 - 4.7)
FVC (L)	3.8 ± 0.95 (2.1 - 5.7)	3.0 ± 0.60 (2.0 - 4.2)	4.3 ± 0.78 (2.8 - 5.8)
FEV_1/FVC (%)	81.9 ± 5.02 (72.2 - 90.9)	81.9 ± 5.09 (72.8 - 92.0)	81.8 ± 4.99 (72.1 - 90.6)
CPET			
VO_2max (mL.(kg.min)$^{-1}$)	33.8 ± 10.60 (16.1 - 56.0)	27.5 ± 8.52 (16.8 - 35.4)	37.6 ± 9.93 (20.5 - 58.2)
Maximum MET	9.7 ± 3.03 (4.6 - 16.00)	7.9 ± 2.44 (4.1 - 13.2)	10.76 ± 2.84 (5.9 - 16.6)
VEmax (L.min^{-1})	89.0 ± 30.1 (34.9 - 149.1)	63.7 ± 16.5 (32.5 - 97.4)	104.0 ± 25.9 (49.3 -155.3)
COP	23.9 ± 4.81 (16.1 - 34.3)	25.0 ± 5.14 (16.8 - 35.4)	23.2 ± 4.48 (15.6 - 32.3)
OUES	2521.9 ± 1000.71 (1006.7 - 4725.5)	1749.4 ± 616.41 (790.1 - 3485.0)	2994.9 ± 903.29 (1398.9 – 5024.8)
Total time (min)	10.8 ± 2.23 (6.6 - 16.0)	10.0 ± 2.24 (6.0 - 15.0)	11.2 ± 2.10 (8.0 - 16.0)
Time to AT (min)	6.3 ± 2.07 (2.0 - 11.0)	5.7 ± 2.02 (2.0 - 10.1)	6.7 ± 2.00 (2.0 - 11.0)
Time to COP (min)	2.8 ± 1.28 (1.0 - 6.0)	2.9 ± 1.38 (1.9 - 6.0)	2.7 ± 1.20 (1.0 - 6.0)

**values expressed as mean ± standard deviation (2.5 and 97.5 percentiles).*
CPET: cardiopulmonary exercise testing; BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; VO_2 max: maximum oxygen uptake; MET: metabolic equivalent; OUES: oxygen uptake efficiency slope; AT: anaerobic threshold; COP: cardiorespiratory optimal point.

Table 2 - Coefficients of correlation between COP and the selected ventilatory variables obtained at CPET

Variable	r	p
Maximum VO2	-0.47	0.0001
VO2 AT	-0.42	0.0001
OUES	-0.34	0.0001
Maximum VE	-0.14	0.0001

COP: cardiorespiratory optimal point; CPET: cardiopulmonary exercise testing; OUES: oxygen uptake efficiency slope; VO2 max: maximum oxygen uptake.

the respiratory system[28,30]. Evidence has shown a reduction in alveolar surface, increase in the alveolar dead space, conditions that are associated with pulmonary hyperinflation and a reduction in the alveolar-capillary diffusion capacity[30,31], in addition to a lower VE[29], which, together with the stiffening of blood vessels[32] contributes to a worst ratio or increase in the V/Q[28,30-32]. In younger individuals, the pulmonary capillary recruitment probably occurs with greater efficiency, allowing an expansion of the so-called West zone III to the region of zones I and II, maintaining a more appropriate V/Q ratio[33]. It should be noted that the increased ventilation in exercise is not only related to the CO2 concentration, but also with

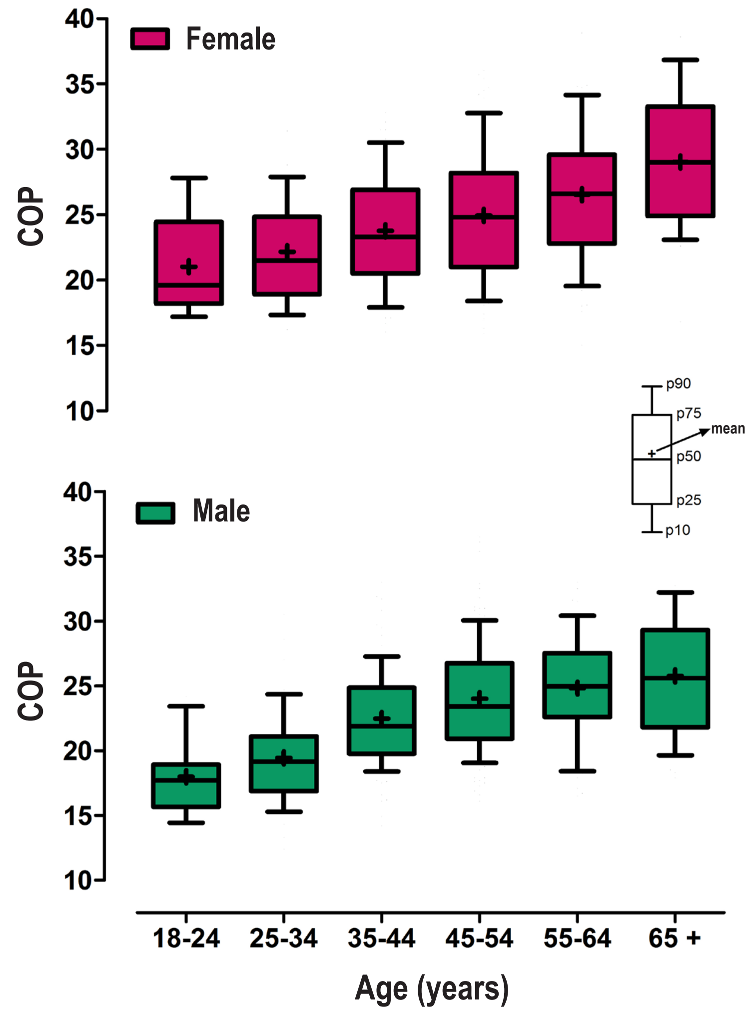

Figure 1 - *All groups differed among them (p < 0.001); COP: cardiorespiratory optimal point.*

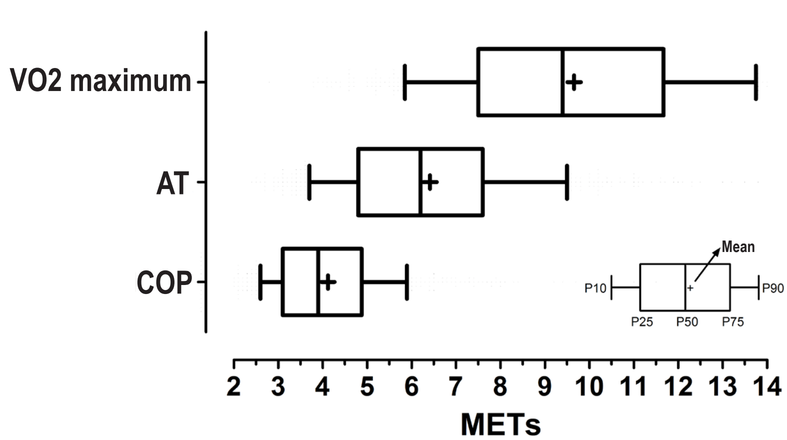

Figure 2 - *Exercise intensity values (MET) for COP, AT and maximal exertion. AT: anaerobic threshold; COP: cardiorespiratory optimal point; MET: Metabolic Equivalent.*

Table 3 – Linear regression equations between COP and age for female and male genders

Gender	COP prediction by age	Standard error of estimate
Female	COP = 0.149 x age (years) + 17.7	4.79
Male	COP = 0.158 x age (years) + 15.7	4.06

COP: cardiorespiratory optimal point.

Table 4 – Cardiorespiratory optimal point (COP) percentiles for the male and female genders

Female		Percentile				
Age (years)	n	10th	25th	50th	75th	90th
18 – 24	9	17.2	18.2	19.6	24.5	27.8
24 – 34	26	17.3	18.9	21.5	24.9	27.9
35 – 44	51	17.9	20.5	23.3	26.9	30.5
45 – 54	76	18.4	21.0	24.8	28.2	32.8
55 – 64	51	19.5	22.8	26.6	29.6	34.2
≥ 65	24	23.1	24.9	29.0	33.3	36.9
Male		**Percentile**				
Age (years)	n	10th	25th	50th	75th	90th
18 – 24	12	14.4	15.6	17.7	18.9	23.4
24 – 34	42	15.2	16.8	19.1	21.1	24.3
35 – 44	97	18.3	19.7	21.9	24.8	27.2
45 – 54	133	19.0	20.9	23.4	26.7	30.0
55 – 64	68	18.3	22.5	24.9	27.5	30.4
≥ 65	35	19.6	21.8	25.6	29.3	32.2

afferent stimuli from the mechanoreceptors[34,35]. Evidence of that is data from Araujo and Monteiro[36] indicating that there are substantial differences in the VE and also in VE/VO2, with probably different afferent stimuli, when an individual walks or runs for the same velocity on the treadmill.

The behavior of COP seems to be slightly different according to gender, while there is a similar increase in the COP with age for men and women. Over the years, one can consider that there is a worsening in VE[31] and a reduction in VO_2max[25], i.e. variables directly involved in the calculation of the COP; it seems, however, that the decline in ventilation is less significant or numerically important than the reduction in VO2, thereby explaining the higher COP values in older individuals.

Regarding gender, the slightly higher COP values found in women are probably related to the fact that they have lower values of VO_2max[37] and ventilation, when compared to men, remembering that, as with the equations[26,38,39] that predict ventilatory variables at resting spirometry, body size is taken into account and typically women are smaller than men.

Notwithstanding all the methodological steps involved in this study, we can point out some possible limitations to greater clinical application and external validity of our data, such as the characterization of the COP for CPET performed only in lower-limb cycle ergometer. However, this may also represent a strong point, as, by avoiding gait transitions when walking and running, which are normally observed in treadmill protocols, perhaps it was possible to better characterize the physiological behavior of the COP. Another potential limitation is the fact that it has not been objectively tested whether the COP values were distinct between individuals habitually active and sedentary, in spite of some evidence demonstrating differences in certain variables obtained at the CPET[40]. However, the modest association with the VO_2max and the VO_2AT suggests that there should be a marked overlap in COP values between active and sedentary individuals. Perhaps the most appropriate way to study the influence of the regular pattern of physical exercise on the COP is to evaluate the behavior of this variable before and after participating in an exercise program. Further studies will compare different ergometers that might produce different assessments and therefore, other results. Another important aspect is to test the potential clinical and epidemiological contribution of COP, either by measuring its response to interventions such as exercise programs, or by its prognostic impact on mortality.

Conclusion

In conclusion, this study proposes the analysis of a new submaximal variable in a CPET, which is easy to obtain, shows observer-independent quantification, is physiologically plausible and well-grounded, able to add relevant clinical information. The value of COP increases with age and is slightly higher in women, with associations being modest with other ventilation measures, suggesting an independent and potential contribution in the interpretation of the cardiorespiratory response at the CPET. The study also contributes by showing a comprehensive database of healthy individuals of both genders within a broad age spectrum, which will allow the analysis and interpretation of results obtained from patients suffering from cardiopulmonary diseases.

Potential Conflict of Interest

The author Claudio Gil Soares de Araújo declares to have conflict of interest with INBRAMED and MICROMED for cession of some of the equipments used in the study.

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Study Association

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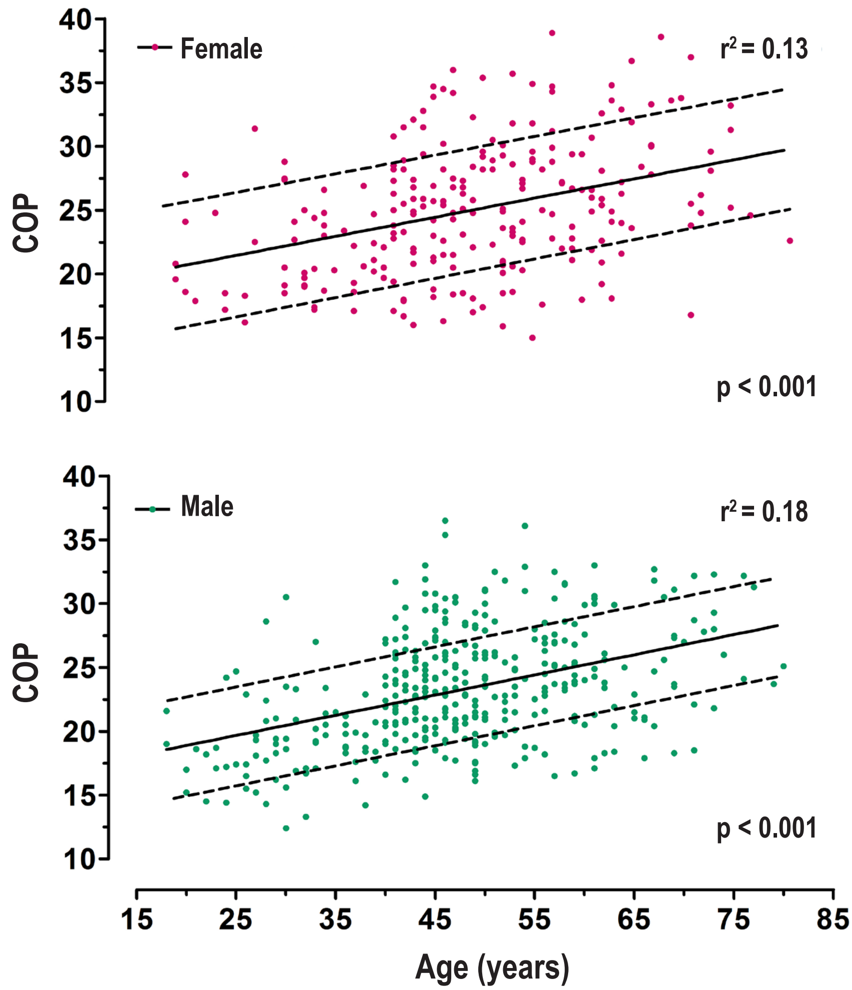

Figure 3 - *COP as a function of age for men (lower panel) and women (upper panel),(------) ± 1 standard error of estimate; COP: cardiorespiratory optimal point.*

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