



ORIGINAL ARTICLE

Cardiorespiratory optimal point during exercise testing as a predictor of all-cause mortality



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KEYWORDS

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Abstract

Introduction and Aim: The cardiorespiratory optimal point (COP) is a novel index, calculated as the minimum oxygen ventilatory equivalent (VE/VO_2) obtained during cardiopulmonary exercise testing (CPET). In this study we demonstrate the prognostic value of COP both independently and in combination with maximum oxygen consumption (VO_{2max}) in community-dwelling adults.

Methods: Maximal cycle ergometer CPET was performed in 3331 adults (66% men) aged 40–85 years, healthy (18%) or with chronic disease (81%). COP cut-off values of <22, 22–30, and >30 were selected based on the log-rank test. Risk discrimination was assessed using COP as an independent predictor and combined with VO_{2max} .

Results: Median follow-up was 6.4 years (7.1% mortality). Subjects with COP >30 demonstrated increased mortality compared to those with COP <22 (hazard ratio [HR] 6.86, 95% confidence interval [CI] 3.69–12.75, $p < 0.001$). Multivariate analysis including gender, age, body mass index, and the forced expiratory volume in 1 s/vital capacity ratio showed adjusted HR for COP >30 of 3.72 (95% CI 1.98–6.98; $p < 0.001$) and for COP 22–30 of 2.15 (95% CI 1.15–4.03, $p < 0.001$). Combining COP and VO_{2max} data further enhanced risk discrimination.

Conclusions: COP >30, either independently or in combination with low VO_{2max} , is a good predictor of all-cause mortality in community-dwelling adults (healthy or with chronic disease). COP is a submaximal prognostic index that is simple to obtain and adds to CPET assessment, especially for adults unable or unwilling to achieve maximal exercise.

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PALAVRAS-CHAVE

Consumo de oxigênio;
Exercício;
Ventilação;
Teste cardiopulmonar
de exercício

Ponto ótimo cardiorrespiratório como preditor de mortalidade por todas as causas**Resumo**

Introdução e objetivos: O ponto ótimo cardiorrespiratório (POC) representa o menor valor do equivalente ventilatório de oxigênio (VE/VO₂), obtido durante um teste cardiopulmonar de exercício (TCPE). Neste estudo, demonstramos a utilidade prognóstica do POC de forma independente e associado ao VO₂max.

Métodos: Foram avaliados TCPE máximos em cicloergômetro de 3331 adultos (66% homens) com idades entre 40-85 anos, saudáveis (18%) e com doenças crônicas (81%). Ao POC foram atribuídos pontos de corte para a criação de grupos <22, 22-30 e >30, com base no teste *log-rank*. As associações de risco foram verificadas por meio de regressões de Cox, utilizando o POC como preditor independente e combinado com VO₂max.

Resultados: O seguimento médio foi de 6,4 anos (7,1% das mortes). Indivíduos com POC >30 demonstraram maior mortalidade, em comparação com POC <22; HR=6,86 (intervalo de confiança [IC] 95%=3,69-12,75, p<0,001). A análise multivariada ajustada, incluindo idade, sexo, índice de massa corporal, e a capacidade vital 1-s volume expiratório forçado mostraram HR POC >30 de 3,72 (IC 95%=1,98-6,98; p<0,001) e para a POC 22-30 de 2,15 (IC 95%=1,15-4,03, p<0,001). Combinando POC e VO₂max, aumentou-se a discriminação do risco.

Conclusões: O POC >30, de forma independente ou combinado com baixo VO₂max, é um bom preditor de mortalidade por todas as causas em adultos (saudáveis ou com doença crônica). Simples de se obter, o POC como índice prognóstico submáximo acrescenta ao TCPE uma nova possibilidade de avaliação de risco de mortalidade, especialmente para adultos incapazes ou não dispostos a alcançar o exercício máximo.

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List of abbreviations

COP	cardiorespiratory optimal point
CPET	cardiopulmonary exercise testing
FEV1	forced expiratory volume in 1 s
FVC	forced vital capacity
HR	heart rate
OUES	oxygen uptake efficiency slope
VAT	ventilatory anaerobic threshold
VE	ventilation
VE/VO ₂	oxygen ventilatory equivalent
VO ₂	oxygen uptake
VO ₂ max	maximum oxygen uptake

Introduction

Quantification of gas exchange during exercise with cardiopulmonary exercise testing (CPET) is used in healthy and diseased populations.¹⁻⁶ Previous studies have indicated the prognostic importance of several CPET ventilatory variables,⁷ including maximum oxygen uptake (VO₂max),⁸ ventilatory anaerobic threshold (VAT),⁹ oxygen uptake efficiency slope (OUES)^{10,11} and ventilatory equivalent for CO₂ (VE/VCO₂),^{12,13} as well as in the immediate recovery after CPET, such as the recently proposed O₂ kinetics.¹⁴ While a submaximal measure of exercise performance may be useful in adults who are physiologically unable to reach a peak

level of exercise, such theoretical utility is often offset by methodological limitations in the assessment of some of these variables.¹⁵

The cardiorespiratory optimal point (COP) constitutes a novel submaximal CPET index which provides an alternative approach to respiratory physiology.^{16,17} The COP represents the lowest value of the oxygen ventilatory equivalent (the ratio between ventilation [VE] in l/min and oxygen consumption [VO₂] in l/min, VE/VO₂) in a given minute during incremental exercise. As an index that quantifies the lowest ventilation required to extract 1 l of oxygen, COP characterizes the interplay between the circulatory and respiratory systems.¹⁷ COP is simple to identify and occurs at modest exercise levels (30-50% of VO₂max), much earlier than VAT.¹⁷ While COP has been shown to be reliable¹⁶ and reference values are available,¹⁷ its utility as a clinical prognostic indicator has not been evaluated. Therefore, our objective was to assess the ability of COP, as an independent prognostic index and in combination with VO₂max, to predict all-cause mortality in middle-aged and older adults with and without chronic disease.

Methods

In a retrospective observational study, clinical data from 5643 subjects assessed in an exercise medicine clinic between January 1996 and July 2013 were reviewed. A subset that had completed maximal CPET and were aged between 40-85 years old narrowed the study population to 3331 adults. Among these subjects, 2220 (66.6%) were male,

and all were censored until the date of death or September 30, 2013 by reviewing the State's official records. All subjects were unpaid volunteers and their assessments were typically requested by their attending physicians for different clinical reasons. All subjects read and signed an informed consent form before participating in the study. The consent form and retrospective data analysis were approved by the institutional research ethics committee (number 0166.0.000.399-11) in accordance with the Declaration of Helsinki and local regulations.

In the sample, 613 subjects (18.4%) were healthy (no known diseases) and were not taking regular medications that could affect exercise performance. Among the other 2718 individuals, 938 (28.2%) had coronary artery disease; of these, 456 (13.7%) were diagnosed with myocardial infarction; 534 (16.0%) had undergone angioplasty; and 396 (11.9%) had undergone coronary artery bypass graft surgery. The most prevalent risk factors were systemic hypertension (1374 [41.2%]) and diabetes (290 [8.7%]).

Assessment protocol

Initially, subjects underwent a detailed medical interview and physical examination. Subsequently, anthropometric measurements and a 12-lead resting electrocardiogram were obtained. In addition, an SP-1 spirometer (Schiller, Switzerland), periodically calibrated as recommended,¹⁸ was used to determine the flow-volume curve, forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁), and the FEV₁/FVC ratio was calculated.

Maximal cardiopulmonary exercise testing

All subjects underwent maximal CPET using a cycle ergometer (CatEye EC-1600, CatEye, Japan or Inbrasport CG-04, Inbrasport, Brazil), following an individualized ramp protocol, aiming to achieve exhaustion at about 8-12 min. An initial load of 25-50 watts was increased continuously in increments of 4-22 watts/min until exhaustion, defined as the inability to keep pedaling at ≥ 60 revolutions/min, despite strong verbal encouragement. Characterization of a true maximal physiological performance was based on a composite of three indicators: a respiratory exchange ratio of >1.05 , a U-shaped curve of the ventilatory equivalents, and a maximum score of 10 on the Borg exertion scale. These physiological criteria were further validated by the impression of the CPET supervising physician. The CPETs of subjects who terminated early due to clinical abnormalities or who did not simultaneously fulfill all of these three physiological criteria were considered submaximal and excluded from the study. Prior to, during, and within 5 min after CPET, blood pressure and arterial oxygen saturation were recorded minute-by-minute, as was heart rate, the latter obtained from a single-lead digital electrocardiogram (CC5 or CM5) (ErgoPC Elite, Micromed, Brazil).¹⁹

Expired gas analysis

During CPET, expired gases were collected with a preVent™ pneumotach (MedGraphics, USA) coupled to a mouthpiece

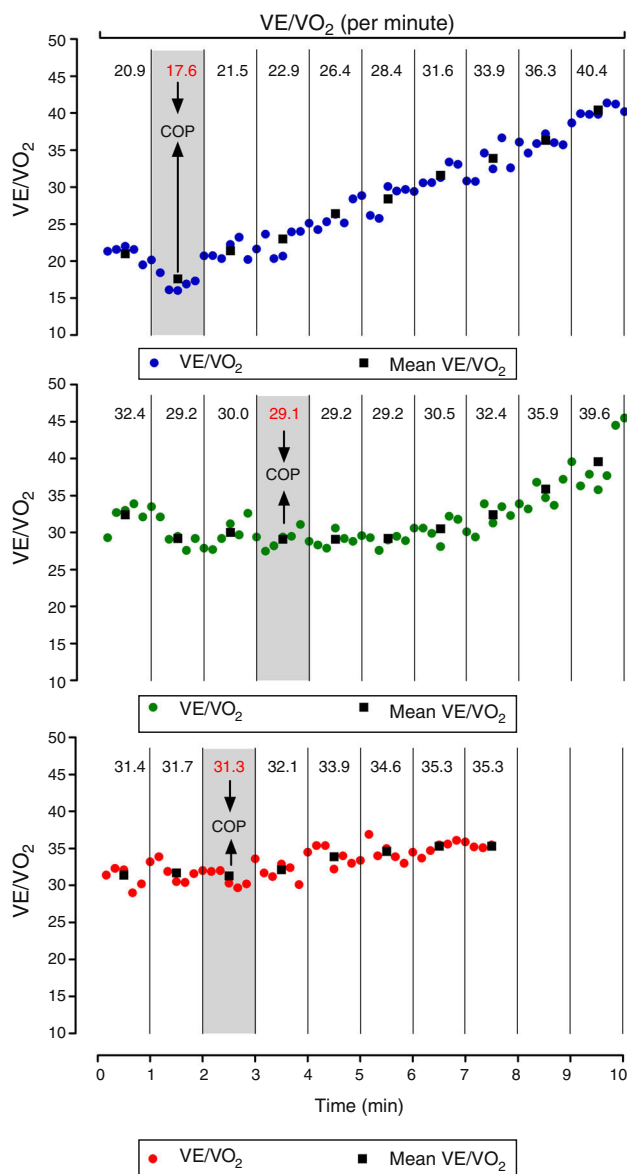


Figure 1 Identification of the cardiopulmonary optimal point in maximal CPET performed using a ramp protocol on a cycle ergometer. COP: cardiopulmonary optimal point; CPET: cardiopulmonary exercise testing; VE/VO₂: oxygen ventilatory equivalent (average of six 10-s samples in a given minute of maximal CPET).

with nasal occlusion and quantified by a VO2000 metabolic analyzer (MedGraphics, USA), enabling measurement of pulmonary ventilation and partial fractions of O₂ and CO₂. The output of all respiratory data was expressed as means at each minute during CPET.

Cardiorespiratory optimal point

COP is defined as the lowest value of VE/VO₂ obtained in a given minute during incremental maximal CPET (Figure 1) and is a dimensionless variable. It is thus a simple, practical and objective measurement. COP reference values for healthy male and female adults have been previously

reported and are available elsewhere.¹⁷ In addition, COP has shown excellent reliability, with an intraclass correlation coefficient of 0.87 (95% confidence interval [CI] 0.82-0.90),¹⁶ which is similar or superior to other CPET ventilatory variables.^{18,20}

Statistical analysis

A log-rank test was used to determine the cut-off COP values for all-cause mortality. COP data were initially divided into quartiles and then the second and third quartiles were combined due to the considerable overlap between the two survival curves. The data were then stratified into three ranges: <22, 22-30, and >30, basically corresponding to the first, second and third, and fourth quartiles, respectively. VO₂max was similarly stratified into three ranges: <15.75, 15.76-30, and >30, also corresponding to the first, second and third, and fourth quartiles, respectively. Additionally, in order to ascertain the contribution of COP when added to the most commonly used CPET variable, mean VO₂max was calculated for each of the three COP ranges and subjects were divided into two groups for each COP range as being in the upper or lower half of VO₂max for this particular range. This produced six subgroups: high COP-high VO₂max, high COP-low VO₂max, medium COP-high VO₂max, medium COP-low VO₂max, low COP-high VO₂max, and low COP-low VO₂max.

COP, VO₂max and the combination of COP-VO₂max results as described above were related to all-cause mortality by univariate and multivariate Cox regression. For multivariate analysis, the results were adjusted for age, gender, body mass index and FEV1/FVC ratio, and expressed as hazard ratios (HR). Survival curves were determined using the Kaplan-Meier method for the whole sample as well as for healthy and unhealthy subjects separately.

For other comparisons between the three COP ranges, one-way analysis of variance was calculated at a 5% significance level and a 95% confidence interval. The statistical analysis was performed using either SPSS version 17 (IBM, USA) or Prism version 5.01 (GraphPad, USA).

Results

Descriptive analysis for all subjects and the three COP ranges is shown in Table 1. Median follow-up was 6.4 years (0.23-17.70 years), with a total death rate of 7.1%. The all-cause mortality rate increased from 1.4% for COP <22 to 17.1% in subjects with COP >30 (chi-square=78.34, p<0.001) (Figure 2).

Univariate Cox regression analysis indicated that for COP >30, HR was 6.86 (95% CI 3.69-12.75, p<0.001). Furthermore, HR remained significant in multivariate analysis, confirming the predictive value of COP >30 (adjusted HR=3.72, 95% CI 1.98-6.98, p<0.001) and COP 22-30 (adjusted HR=2.15, 95% CI 1.15-4.03, p<0.001) compared to COP <22 (Table 2).

Combining the COP and VO₂max results, we found that for high COP-low VO₂max, i.e., COP >30 and VO₂max below the average for this COP range, there was a very high mortality of 30.9% and an HR of 28.19 (95% CI 6.92-114.71) (Table 3). On the other hand, for those in the low COP-high VO₂max subgroup, mortality was only 0.5% (Figure 3).

Table 1 Description and main results of maximal cardiopulmonary exercise testing (n=3331).

Rest variables	All (n=3331)			Cardiorespiratory optimal point			P
	<22 (n=803)	22-30 (n=1792)	>30 (n=736)	<22 (n=803)	22-30 (n=1792)	>30 (n=736)	
Age (years)	58±11.1 (58-59)	58.5±10.9 (58-59)	64±10.4 (63-65)	54±9.6 (53-55)	58.5±10.9 (58-59)	64±10.4 (63-65)	<0.001
Weight (kg)	79.0±16.7 (78.4-79.6)	80.0±17.5 (79.1-80.8)	76.2±15.6 (75.1-77.3)	79.5±15.7 (78.5-80.6)	80.0±17.5 (79.1-80.8)	76.2±15.6 (75.1-77.3)	<0.001
Height (cm)	169±9.2 (169-169)	169±9.2 (169-170)	167±9.3 (166-167)	171±8.9 (170-171)	169±9.2 (169-170)	167±9.3 (166-167)	<0.001
BMI (kg/m ²)	27.4±4.7 (27.3-27.6)	27.7±4.9 (27.5-27.9)	27.2±4.4 (26.8-27.5)	27.1±4.4 (26.8-27.4)	27.7±4.9 (27.5-27.9)	27.2±4.4 (26.8-27.5)	<0.001
Heart rate (bpm)	66±11.5 (65-66)	67±11.4 (66-67)	69±11.9 (68-70)	62±10.6 (61-63)	67±11.4 (66-67)	69±11.9 (68-70)	0.002
SBP (mmHg)	132±17.7 (132-133)	133±17.5 (132-133)	133±20.4 (131-134)	131±15.2 (130-132)	133±17.5 (132-133)	133±20.4 (131-134)	0.056
DBP (mmHg)	77±10.6 (77-78)	78±10.6 (77-78)	78±11.3 (77-78)	77±10.6 (76-78)	78±10.6 (77-78)	78±11.3 (77-78)	0.279
FEV1/FVC (%)	79.1±7.9 (78.8-79.4)	79.6±7.3 (79.3-79.9)	76.8±10.3 (76.0-77.5)	80.1±6.3 (79.6-80.5)	79.6±7.3 (79.3-79.9)	76.8±10.3 (76.0-77.5)	<0.001
CPET variables							
Total time (min)	9.4±2.6 (9.3-9.5)	9.4±2.5 (9.3-9.5)	8.1±2.4 (7.9-8.3)	10.6±2.6 (10.4-10.7)	9.4±2.5 (9.3-9.5)	8.1±2.4 (7.9-8.3)	<0.001
Maximum HR (bpm)	148±26.8 (147-149)	149±25.8 (147-150)	133±26.8 (131-135)	159±22.7 (157-160)	149±25.8 (147-150)	133±26.8 (131-135)	<0.001
Maximal oxygen uptake (ml/[kg.min])	23.9±10.1 (23.6-24.3)	23.6±8.9 (23.2-24.0)	17.5±7.1 (17.0-18.0)	30.5±10.7 (29.7-31.3)	23.6±8.9 (23.2-24.0)	17.5±7.1 (17.0-18.0)	<0.001
COP	26.3±5.9 (26.1-26.5)	25.7±2.3 (25.6-25.9)	34.8±4.6 (34.5-35.2)	19.7±1.7 (19.5-19.8)	25.7±2.3 (25.6-25.9)	34.8±4.6 (34.5-35.2)	<0.001

BMI: body mass index; CI: confidence interval; COP: cardiorespiratory optimal point; CPET: cardiopulmonary exercise testing; DBP: diastolic blood pressure; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; HR: heart rate; SBP: systolic blood pressure; VO₂: oxygen uptake. All values mean ± SD (95% CI).

Table 2 Univariate and multivariate Cox regression analysis for the cardiorespiratory optimal point and all-cause mortality (n=3331).

Hazard ratio (95% CI)	All (n=3331)	Cardiorespiratory optimal point			p
		<22 (n=803)	22-30 (n=1792)	>30 (n=736)	
Univariate regression	-	Ref.	2.80 (1.50-5.23)	6.86 (3.69-12.75)	-
Multivariate regression	-	Ref.	2.15 (1.15-4.03)	3.72 (1.98-6.98)	-
Follow-up (median, range)	6.4 (0.2-17.7)	9.6 (0.2-17.7)	6.6 (0.2-17.7)	4.2 (0.3-17.7)	<0.001
Events (n, %)	237 (7.1)	11 (1.4)	100 (5.6)	126 (17.1)	<0.001

CI: confidence interval; Ref.: reference tertile.

Table 3 Univariate and multivariate Cox regression analysis for the cardiorespiratory optimal point and maximum oxygen uptake and all-cause mortality (n=3331).

Variable	Description	Univariate regression		Multivariate regression	
		HR (95% CI)	p	HR (95% CI)	p
Low COP-High VO ₂ max	All normal	Reference	-	Reference	
Low COP-Low VO ₂ max	1 abnormal	4.21 (0.91-19.50)	0.066	2.38 (0.50-11.18)	0.271
Median COP-High VO ₂ max	1 abnormal	4.04 (0.96-16.97)	0.057	3.13 (0.74-13.21)	0.119
Median COP-Low VO ₂ max	1 abnormal	10.89 (2.67-44.42)	0.001	4.98 (1.19-20.80)	0.028
High COP-High VO ₂ max	1 abnormal	10.28 (2.48-42.60)	0.001	5.28 (1.26-22.18)	0.023
High COP-Low VO ₂ max	All abnormal	28.19 (6.92-114.71)	0.000	9.95 (2.36-41.91)	0.002

CI: confidence interval; COP: cardiorespiratory optimal point; HR: hazard ratio; VO₂max: maximum oxygen uptake.**Table 4** Univariate and multivariate Cox regression analysis for maximal oxygen uptake and all-cause mortality (n=3331).

Hazard ratio (95% CI)	All (n=3331)	Maximal oxygen uptake (ml/[kg.min])			p
		>30 (n=818)	30-15.75 (n=1775)	<15.75 (n=737)	
Univariate regression	-	Ref.	3.13 (1.78-5.49)	10.10 (5.82-17.54)	-
Multivariate regression	-	Ref.	1.75 (0.98-3.13)	3.26 (1.76-6.00)	-
Follow-up (median, range)	6.4 (0.1-17.7)	6.6 (0.3-17.7)	6.3 (0.1-17.7)	6.6 (0.1-17.7)	>0.05
Events (n, %)	237 (7.1)	14 (1.7)	94 (5.3)	129 (17.5)	<0.001

CI: confidence interval; Ref.: reference tertile.

Analyzing VO₂max results separately, univariate Cox regression indicated that for the lowest VO₂max tertile, HR was 10.10 (95% CI 5.82-17.54, p<0.001) (Table 4).

COP also performed well when the sample was separated into healthy subjects and those with chronic disease. For the latter (n=2718), univariate Cox regression analysis indicated that for COP >30, HR was 5.14 (95% CI 2.76-9.59, p<0.001) and for COP 22-30 HR was 2.18 (95% CI 1.16-4.08, p<0.001), compared to COP <22 (Figure 4). There were no deaths in healthy subjects presenting COP <22. On the other hand, 3.1% and 9.4%, respectively, of healthy subjects died with COP 22-30 and >30 (Figure 4).

Discussion

The clinical use of CPET for prognosis has gradually improved through the addition of several ventilatory and hemodynamic variables.^{2,8,21-23} In this context, the present retrospective study including data from 3331 subjects adds to the current state of knowledge by demonstrating the

prognostic value of COP, a variable that is easily identified at low submaximal levels of CPET.

The ease with which COP can be identified derives from the physiological profile of VE/VO₂ observed in the transition from rest to incremental exercise, typically a U-shaped curve with a clear lowest point. COP in fact has several advantages over other CPET variables, considering that it is obtained at relatively low-intensity exercise, i.e., at 30-50% of VO₂max,¹⁷ and much earlier than VAT, thereby considerably reducing the effort required for clinical assessment. It should also be emphasized that determination of COP is free from observer error, since it is simply obtained from identification of the lowest VE/VO₂ value in a listing of successive minute-by-minute CPET data. Additionally, COP is dimensionless, which makes it even simpler and easier to express and to compare. The use of COP to study prognosis using a large retrospective cohort with a broad clinical profile is thus both feasible and valuable.

Concerning our main objective, it was found that COP is a good predictor of all-cause mortality, by indicating that subjects with COP >30 exhibited an approximately six-fold

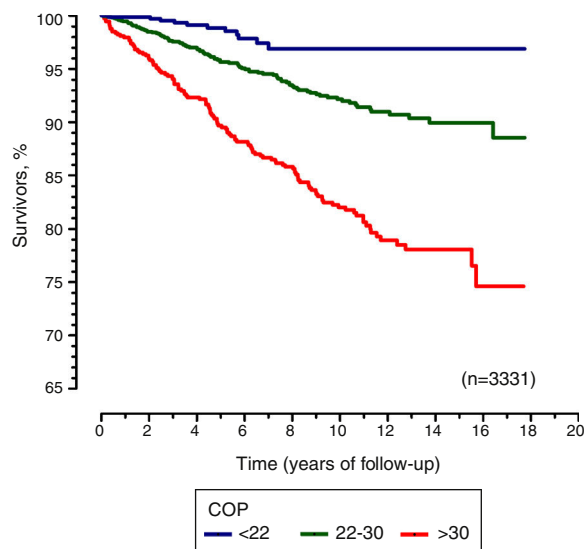


Figure 2 Kaplan-Meier survival estimates in subjects aged 40-85 years according to the three cardiopulmonary optimal point ranges. COP: cardiopulmonary optimal point.

higher mortality risk than those with COP <22. Interestingly, even after adjusting for age, gender, body mass index and FEV1/FVC ratio, the mortality risk of subjects with COP >30 remained significantly higher. The inclusion of these potential confounder variables in the adjusted model is theoretically justifiable. COP has been reported to be influenced by gender, with COP values in men tending to be lower than those for women in the same age-group,¹⁷ and by age, as values tends to increase proportionally with aging. Adjustment for body mass index was necessary because central adiposity and abnormalities in FEV1/FVC are known to affect ventilation,²⁴ and therefore this adjustment reduced the possible negative influences of respiratory dysfunction.²⁵

In a separate analysis stratified according to clinical condition (which was feasible due to the characteristics of our sample, in which both healthy and unhealthy

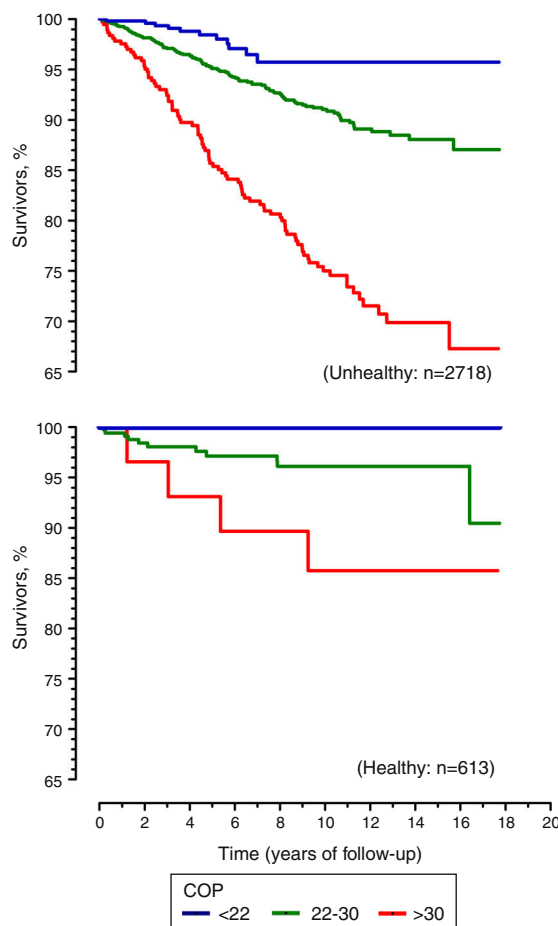


Figure 4 Kaplan-Meier survival estimates in subjects aged 40-85 years according to cardiopulmonary optimal point and clinical condition (unhealthy or healthy).

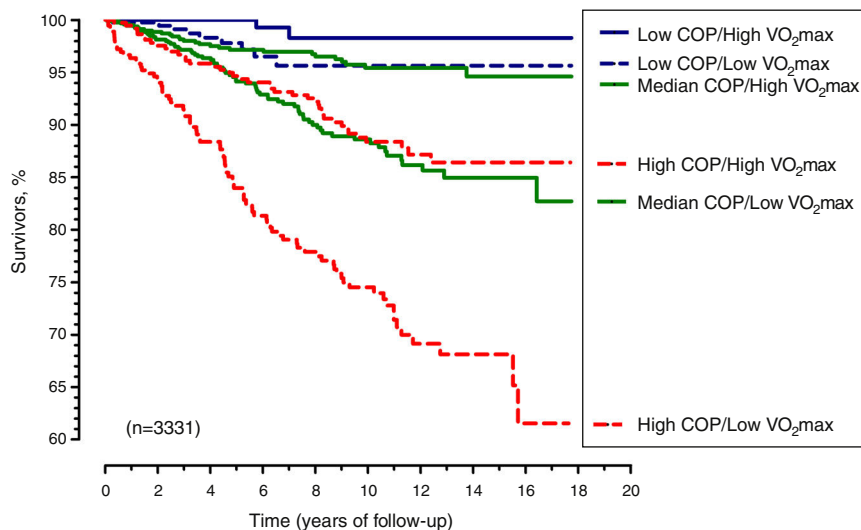


Figure 3 Kaplan-Meier survival estimates in subjects aged 40-85 years according to cardiopulmonary optimal point and maximum oxygen uptake. COP: cardiorespiratory optimal point; VO₂max: maximum oxygen uptake.

subjects were deliberately included in order to resemble the actual profile of patients undergoing CPET in an exercise medicine clinic), COP remained a good prognostic indicator for all-cause mortality in the median 6.4 years of follow-up. Specifically, for those presenting any disease, COP >30 had an unadjusted HR of 5.14. A unique feature of our study was its demonstration that COP could also provide valuable information on prognosis for all-cause mortality in healthy middle-aged adults. In healthy subjects with COP <22, no deaths occurred in the follow-up period, suggesting that the combination of being healthy and having a good circulation-respiration interaction is an excellent indicator of good prognosis and is accompanied by a very low probability of all-cause mortality in the following six years. Further studies are warranted to determine whether for subjects in whom a maximal test is unavailable or impossible to obtain, COP is a good prognostic indicator for all-cause mortality.

As mentioned above, several previous studies, especially those using selected samples, have shown that other ventilatory variables obtained during CPET are also prognostic indicators. These variables include the lowest VE/VCO₂ ratio²⁶ and the VE/VCO₂ slope,²⁷ the latter being particularly valuable for heart failure patients. A potential advantage of COP in relation to these CO₂-related variables is that physiological studies have clearly indicated that the rate of CO₂ production and the VE/VCO₂ ratio or minimum value, during both constant load¹¹ and incremental exercise,^{12,20} are strongly influenced by the composition of food intake and the amount of muscle glycogen available prior to CPET, in clear contrast to VE/VO₂, when considering the same effort intensity.¹⁵ In fact, these studies^{12,15} showed that a low-carbohydrate diet or a glycogen-depleted state contributed to an increase in VCO₂, resulting in higher VE/VCO₂ values, whereas ventilation and VO₂ curves remained basically unchanged and did not significantly depend on diet composition, a variable that is rarely controlled in CPET in clinical practice.

The prognostic value of exercise capacity and VO₂max are well established, as reported in several studies.^{8,14} For instance, Laukannen et al.²⁸ found a 2.76 and 3.09 higher risk, respectively, of all-cause and cardiovascular death in a cohort of Finnish men, on the basis of VO₂max measurements. However, obtaining a truly maximal exercise test can be difficult or undesirable. In this context, a recent study identified normal COP values, often accompanied by low VO₂max, in patients who have had panic attacks with or without cardiorespiratory symptoms, a typical situation in which maximal testing is particularly difficult to obtain.²⁹

It is worth noting that combinations of COP and VO₂max data were even more powerful in differentiating mortality rates (Figure 3), as exemplified by the two extreme subgroups, low COP-high VO₂max and high COP-low VO₂max. Even more interesting is the canceling effect of differences in COP and VO₂max, so that the survival curves of some opposite combinations – e.g. median COP-low VO₂max and low COP-low VO₂max – almost overlap. It can be seen by comparing the multivariate Cox regression results that COP showed slightly better prognostic discrimination than VO₂max.

Regarding the variables obtained during CPET that are used as prognostic indicators, another one that combines

VO₂ and ventilation data is OUES,^{11,27,30} which was first described in 1996.³¹ OUES is obtained from analysis of the VE/VO₂ curve during CPET, using multiple points rather than a single point, as is the case with COP. OUES has proved to be a good prognostic indicator in heart failure patients.²³ However, a recent meta-analysis found only three studies in which this variable had prognostic value.² To the best of our knowledge, the clinical or prognostic significance of OUES for healthy subjects is still unclear. As also pointed out for VE/VO₂ slope, there are difficulties in standardizing the determination of OUES. In addition to these limitations, OUES can be mathematically derived using several different approaches and at different percentages of maximal CPET.³² Additionally, genuinely maximal CPET will always be required to accurately determine the percentage of the curve for these calculations, reducing the number of patients that could benefit from determination of this variable.

It should be pointed out that our study has some limitations. First is the fact that the sample was mostly made up of Caucasians with high socioeconomic status, and so different results may be found in populations with different demographic characteristics. Furthermore, we were unable to control for the specific cause of mortality or for the influence of subjects' past history or current patterns of exercise, including sports. In addition, we chose VO₂max, the most common marker of cardiorespiratory fitness, to combine with COP for further analysis. There is a need to study combinations and direct comparisons between COP and other submaximal and maximal CPET ventilatory indices that have been proposed for prognostic purposes. Lastly, it was not possible to determine the specific causes of mortality in our sample.

To summarize, this study adds a new ventilatory variable to the CPET repertoire, either alone or combined with VO₂max, further extending its prognostic utility not only for specific clinical conditions such as heart failure, but in a much broader range of unhealthy and apparently healthy middle-aged adults. Unlike other CPET ventilatory variables (VAT, VE/VCO₂ and OUES), COP does not require sophisticated calculations or observer judgments, it is more likely to be precisely identified in submaximal or prematurely ended CPET, and its interpretation is supported by a large age-standardized dataset of healthy adults. Interestingly, if minute-by-minute ventilation and oxygen consumption data are available, virtually any laboratory performing CPET can retrospectively determine COP by simply reviewing their current CPET dataset, and therefore help to further validate its clinical relevance.

CPET is increasingly used in sports and clinical contexts. Several ventilatory variables have been proposed to reflect different physiological aspects of normal exercise physiology and some of them have been shown to have prognostic relevance for all-cause mortality. However, various methodological constraints remain that limit a broader and more useful incorporation of some of these variables, including the subjectivity of criteria for identification and selection of the data to be used for calculations, the need for sophisticated calculations, dependence on genuinely maximal CPET, and the influence of pre-test food intake.

Conclusion

COP, defined as the lowest VE/VO₂ value in a given minute of CPET and previously shown to be simple, practical, reliable and free from observer error, has now been characterized as an excellent indicator of all-cause mortality risk in six-year follow-up, either alone or strengthened by combination with VO₂max, not only for specific populations of cardiac patients, but in a much broader range of middle-aged subjects, including healthy and unhealthy individuals, a population that is frequently seen for routine clinical exercise testing.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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References

- Balady GJ, Arena R, Sietsema K, et al. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation*. 2010;122:191–225.
- Cahalin LP, Chase P, Arena R, et al. A meta-analysis of the prognostic significance of cardiopulmonary exercise testing in patients with heart failure. *Heart Fail Rev*. 2013;18:79–94.
- Grigioni F, Specchia S, Maietta P, et al. Changes in exercise capacity induced by heart transplantation: prognostic and therapeutic implications. *Scand J Med Sci Sports*. 2011;21:519–25.
- Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Joint Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Eur Heart J*. 2012;33:2917–27.
- Keteyian SJ, Patel M, Kraus WE, et al. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. *J Am Coll Cardiol*. 2016;67:780–9.
- Mezzani A, Hamm LF, Jones AM, et al. Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol*. 2013;20:442–67.
- Abreu A. Comment on "Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure". *Rev Port Cardiol*. 2016;35:317–8.
- Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*. 2002;346:793–801.
- Gitt AK, Wasserman K, Kilkowski C, et al. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation*. 2002;106:3079–84.
- Arena R, Myers J, Abella J, et al. Prognostic significance of the oxygen uptake efficiency slope: percent-predicted versus actual value. *Am J Cardiol*. 2010;105:757–8.
- Coeckelberghs E, Buys R, Goetschalckx K, et al. Prognostic value of the oxygen uptake efficiency slope and other exercise variables in patients with coronary artery disease. *Eur J Prev Cardiol*. 2016;23:237–44.
- Imamura T, Kinugawa K, Nitta D, et al. Novel scoring system using cardiopulmonary exercise testing predicts prognosis in heart failure patients receiving guideline-directed medical therapy. *Circ J*. 2015;79:1068–75.
- Ingle L, Goode K, Carroll S, et al. Prognostic value of the VE/VCO₂ slope calculated from different time intervals in patients with suspected heart failure. *Int J Cardiol*. 2007;118:350–5.
- Fortin M, Turgeon P-Y, Nadreau É, et al. Prognostic value of oxygen kinetics during recovery from cardiopulmonary exercise testing in patients with chronic heart failure. *Can J Cardiol*. 2015;31:1259–65.
- Hughson RL, Kowalchuk JM. Influence of diet on CO₂ production and ventilation in constant-load exercise. *Respir Physiol*. 1981;46:149–60.
- Ramos PS, Araújo CGS. Analysis of the stability of a submaximal variable in the cardiopulmonary exercise testing: cardiopulmonary optimal point. *Rev Bras Ativ Fis Saúde*. 2013;18:585–93.
- Ramos PS, Ricardo DR, Araújo CG. Cardiorespiratory optimal point: a submaximal variable of the cardiopulmonary exercise testing. *Arq Bras Cardiol*. 2012;99:988–96.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319–38.
- Ricardo DR, de Almeida MB, Franklin BA, Araújo CG. Initial and final exercise heart rate transients: influence of gender, aerobic fitness, and clinical status. *Chest*. 2005;127:318–27.
- Barron A, Dhutia N, Mayet J, et al. Test-retest repeatability of cardiopulmonary exercise test variables in patients with cardiac or respiratory disease. *Eur J Prev Cardiol*. 2014;21:445–53.
- Brunelli A, Belardinelli R, Pompili C, et al. Minute ventilation-to-carbon dioxide output (VE/VCO₂) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *Ann Thorac Surg*. 2012;93:1802–6.
- Jensen MT, Marott JL, Allin KH, et al. Resting heart rate is associated with cardiovascular and all-cause mortality after adjusting for inflammatory markers: the Copenhagen City Heart Study. *Eur J Prev Cardiol*. 2012;19:102–8.
- Toste A, Soares R, Feliciano J, et al. Prognostic value of a new cardiopulmonary exercise testing parameter in chronic heart failure: oxygen uptake efficiency at peak exercise – comparison with oxygen uptake efficiency slope. *Rev Port Cardiol*. 2011;30:781–7.
- Dreher M, Kabitz HJ, Burgardt V, et al. Proportional assist ventilation improves exercise capacity in patients with obesity. *Respiration*. 2010;80:106–11.
- Pekkarinen E, Vanninen E, Lansimies E, et al. Relation between body composition, abdominal obesity, and lung function. *Clin Physiol Funct Imaging*. 2012;32:83–8.
- Myers J, Arena R, Oliveira RB, et al. The lowest VE/VCO₂ ratio during exercise as a predictor of outcomes in patients with heart failure. *J Card Fail*. 2009;15:756–62.

27. Arena R, Myers J, Hsu L, et al. The minute ventilation/carbon dioxide production slope is prognostically superior to the oxygen uptake efficiency slope. *J Card Fail.* 2007;13:462–9.
28. Laukkanen JA, Kurl S, Salonen R, et al. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: a prospective population-based cohort study. *Eur Heart J.* 2004;25:1428–37.
29. Ramos PS, Sardinha A, Nardi AE, et al. Cardiorespiratory optimal point: a submaximal exercise variable to assess panic disorder patients. *PLOS ONE.* 2014;9:e104932.
30. Davies LC, Wensel R, Georgiadou P, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J.* 2006;27:684–90.
31. Baba R, Nagashima M, Goto M, et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol.* 1996;28:1567–72.
32. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol.* 2000;36:194–201.