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EDITORIAL

Cardiorespiratory Optimal Point: A New Kid in the Block or an Established Star?

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Editorial referring to the article: High Cardiorespiratory Optimal Point Values Are Related to Cardiovascular Mortality in Men Aged 46 to 70 Years: a Prospective Cohort Study

The article by Araújo et al.[1] published in this issue of the *International Journal of Cardiovascular Sciences* studied the association of cardiorespiratory optimal point (COP), a parameter obtained from a cardiopulmonary exercise test (CPET), and cardiovascular mortality in 2201 consecutive male patients, aged 46 to 70 years (mean age 57 ± 6 years), from the CLINIMEX Exercise Open Cohort. The patients underwent a CPET, assessed between January 1994 and February 2023, under an individualized ramp protocol, on a cycle ergometer, and they were followed for 4688 ± 2416 days.

A cardiovascular death rate of 5.6% was found in the study population, increasing from 3.2% to 9.6% and 18.7%, according to 3 levels of COP: lower (< 28), high (28 to 30), or very high (> 30). After adjustment for age, history of myocardial infarction or coronary artery disease, and diabetes mellitus, cardiovascular mortality increased from 2.76% in the group with the lowest COP (< 28) to 4.07% in the group with the highest COP (> 30). Importantly, when the COP value was below 28 in a group of individuals aged 66 to 70, they had the same survival as the group of subjects aged 46 to 50 years with COP superior to 30.

COP is the lowest value of the ventilatory equivalent for oxygen, the ratio between ventilation and oxygen consumption (oxygen equivalent), which designs a U shape curve during a CPET, starting high, declining around the middle of a maximal test, and returning to a high value at the end of the exercise period. The lowest point of this curve, before it starts to increase, obtained by average values over 1 minute of breath-by-breath achieved data, corresponds to the first ventilatory threshold formerly called the anaerobic threshold, but COP is, in fact, the value of the oxygen equivalent and not the oxygen consumption at the level of the first ventilatory threshold.

COP can be considered a measure of aerobic efficiency, since it represents the minimal amount of ventilation required to consume one liter of oxygen at a submaximal level and may reflect the best equilibrium between oxygen transport (circulation: heart and arteries) and oxygen uptake (lungs and cellular respiration), during an incremental exercise test.

As written before, COP is a submaximal parameter, and it does not depend on the operator or the patient's performance. It is easy to determine by the operator; it is practically free of observer error, and it does not require the performance of a true maximal CPET.

In the first paper by Ramos et al. about this topic,[2] published in 2012, moderate inverse correlations were found with maximum oxygen consumption (VO_2max) ($r = -0.47$; $p < 0.001$), oxygen consumption (VO_2) at the anaerobic threshold ($r = -0.42$; $p < 0.001$), and oxygen uptake efficiency slope (OUES) ($r = -0.34$; $p < 0.001$), which was confirmed by Charitonidis et al.[3] and Silva et al.,[4] who also did not find a correlation between COP and VO_2max in the assessment of 11 male (15.18 ± 0.75 years old) and 13 female (14.77 ± 0.44 years old) adolescent volleyball players or in 198 soccer players, respectively.

The authors' scientific hypothesis was that COP, as it is related to cardiorespiratory fitness, obtained at a submaximal level of exercise, easy to identify, and almost free of interobserver variability, could become an alternative parameter or obtain an added value to oxygen consumption at peak exercise (pVO_2), which is the gold

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standard for cardiorespiratory fitness and is inversely related to cardiovascular mortality in many populations, for example, apparently healthy subjects or in the setting of several diseases like heart failure (HF).

After these preliminary papers, several groups around the world started to assess the prognostic value of COP in different populations, some mixed (healthy subjects and patients with diseases) or involving specific groups, such as HF or congenital heart disease, with different endpoints, including cardiovascular death, all-cause death, or sudden cardiac death. Peterman et al.[5] found that COP was related to all-cause mortality in apparently healthy males but not in females, which was unexpected considering other previously published papers. Female patients seem to have naturally higher levels of COP than men.

Table 1 summarizes the published articles where the prognostic value of COP was studied according to the different endpoints mentioned above.

In all of these studies, it is clear that COP proved to be useful for prognostic assessment in several middle-aged populations, mostly male, for example, a mixed population of community-dwelling adults, including mainly people with unspecified chronic disease (n = 3331),[6] healthy adults (n = 2190; n = 2205; n = 3160),[5,7,8] HF (n = 442; n = 277)[9,10] and congenital heart disease (n = 30),[11] in terms of identifying subjects or patients with higher risk of cardiovascular death,[9] all-cause mortality,[5,6,8] sudden cardiac death,[7] or clinical severity.[11]

Considering the seven published papers, only Reis[9] compared the relative value of COP regarding the most recognized CPET parameters, for example, pVO_2, VO_2max, VE/VCO_2 slope, or OUES, for prognostic assessment of the different populations. They found that, at the submaximal level, COP demonstrated to have a higher prognostic value than pVO_2, VE/VCO_2 slope, and OUES, but at maximal exercise, it was overtaken by these variables showing an area under the curve (AUC) of 0.632, while pVO_2 and VE/VCO_2 slope showed an AUC of 0.749 and 0.750, respectively, for the primary combined endpoint (cardiac death or urgent heart transplant) during 12 months follow-up.

These authors' work pointed out what eventually needs to be done to consecrate COP, a submaximal CPET parameter, as a major variable for prognostic assessment of several populations, including apparently healthy subjects and patients with several types of cardiovascular diseases, cardiovascular risk factors, coronary artery disease, different HF phenotypes, and other chronic diseases, such as COPD , in addition to frail individuals.

It will be necessary to identify the value of COP in more populations, with more robust samples, in patients who can perform a maximal CPET, to identify which is the net added value of COP versus pVO_2, VE/VCO_2 slope, OUES, or other CPET parameters at maximal exercise level. In other words, is it enough to perform a submaximal test, or is it necessary to perform a maximal CPET in order to obtain the highest risk prognostic assessment in every clinical setting?

Future research must include patients with ethnic diversity, more female patients, and patients from different socioeconomic and educational strata.

In terms of different cardiovascular entities, it is advisable to identify New York Heart Association and Canadian Cardiovascular Society functional classes, NT-proBNP or BNP level, left ventricular ejection, ventricle volumes, presence of valvular heart disease, HF, HF phenotype, clinical stability, and type of medication.

It also seems necessary to define better the cutoff values for risk stratification for COP in specific populations, in terms of age, sex, and type of disease.

Summary

COP researchers have already conducted very important research that must be expanded, including larger and more diverse and better defined populations, with patients around the world, different cardiovascular and non-cardiovascular diseases, tests using a treadmill (more experience with treadmill CPET is needed), and evaluation of the prognostic values of sub-maximal parameters, such as COP and eventually VO_2 at VT1, versus the maximal parameters, such as pVO_2, VE/VCO_2 slope, and OUES.

A clear answer is needed: Is the information obtained from a submaximal CPET enough, or should it be considered only as an alternative when it is not possible to perform a maximal CPET or when peak VO_2 was not reached?

The new research providing a response to those questions will make a great difference concerning how COP is considered among the scientific community involved in research with cardiorespiratory fitness: the difference between an interesting promise, “a new kid in the block,” or a fundamental parameter, “an established star.”

Table 1 – Summary of the published papers correlating COP and cardiovascular mortality, all-cause death, or sudden cardiac death

Published paper	Study population Population type and size and age	Main results	Value of COP to predict mortality versus other CPET parameters
Ramos PS[6] Rev Port Cardiol. 2017; 36(4):261-9.	3331 community-dwelling adults (66% men), healthy (18%) or with chronic disease (81%). Age: 40-85 years	COP > 30, either alone or in combination with low VO_2max, is a good predictor of all-cause mortality.	Not tested
Laukkanen JA[7] Prog Cardiovasc Dis. 2021; 68:12-8.	2190 healthy middle-aged men. Age: 52.8 ± 5.1 (42 to 61) years	COP is strongly, inversely, and independently associated with SCD in a graded fashion.	Not tested
Laukkanen JA[8] Scand J Med Sci Sports. 2021;31(10):1949-61	2205 healthy middle-aged men. Age: 53 ± 5 years	COP is associated with fatal CV and all-cause mortality in a positive dose-response.	Not tested
Peterman JE[5] J Cardiopulm Rehabil Prev. 2022; 42(6):E90-E6	3.160 healthy adults (46% female). Age: 44.0 ± 12.5 years	COP is related to all-cause mortality in males, but not females.	Not tested
Reis J[9] Rev Port Cardiol. 2022; 41(9):751-8	442 patients with HFrEF (80% male), of whom 290 (66%) had a submaximal CPET. Age: 56 ± 12 years	COP had the highest prognostic power of all parameters analyzed in a submaximal CPET.	**Submaximal level**: COP had the highest AUC at submaximal level versus pVO_2; VE/VCO_2 slope and OUES; **Maximal level**: OUES had the highest AUC (0.853), closely followed by VE/VCO_2 slope and pVO_2 (0.750 and 0.749, respectively). COP had an AUC of 0.632.
Kroesen SH[10] Med Sci Sports Exerc. 2023 May. PMID: 37192340	277 patients with HF, (72% with HFrEF; 30% female). Age: 67 (58 to 74) years	Low COP is associated with lower risk for adverse outcomes. Participation in CR lowers COP.	Not tested
Wernhart S[11] J Sports Med Phys Fitness. 2023. 63(8):941-8	30 patients with congenital heart disease with moderate (n = 13) and severe lesions (n = 17). Age: 39.7 ± 16.2	COP discriminated between moderate and severe lesions.	COP was a better between group discriminator than O_2 pulse max, but not than OUES.

AUC: area under the curve; COP: cardiorespiratory optimal point; CR: cardiac rehabilitation; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; OUES: oxygen uptake efficiency slope; SCD: sudden cardiac death.

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