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EDITORIAL COMMENT

Cardiopulmonary exercise testing for heart failure prognosis: What to prioritize – maximal aerobic power or submaximal efficiency parameters?

Prova de esforço cardiopulmonar para prognóstico de insuficiência cardíaca - O que privilegiar: potência aeróbia máxima ou parâmetros de eficiência submáxima?

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Cardiopulmonary exercise testing (CPET) provides a thorough assessment of integrative exercise physiology involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems.[1] It is well established that expired gas data obtained during CPET can be used in the diagnosis and prognosis of heart failure (HF), especially if combined with other key clinical parameters that help optimize risk stratification and the selection of management options in HF patients.[2] Many parameters are known to be independent markers of severity and predictors of morbidity and mortality in this patient group, but most cut-off values require the effort obtained in the CPET to be maximal. Many HF patients cannot attain maximal effort during CPET and in the presence of a submaximal CPET (respiratory exchange ratio [RER] >1.05) the ventilation equivalent of carbon dioxide (VE/VCO_2) slope of >35 has been used as a criterion in listing for transplantation, but with a low level of evidence (class IIb, level of evidence C).[3]

The study presented in the current issue of the *Journal* by Reis et al.[4] is relevant, particularly in terms of prognosis in clinical practice, enabling the better use of variables that are collected routinely but not properly interpreted. Physical exertion is complex and requires an integrated interpretation that is often not compatible with recommendations or cut-off values. Due to the considerable individual variability of response in this patient group, rather than looking at maximum values, an integrated interpretation of different submaximal ventilation parameters will help make sense of the mechanisms behind the initiation and progression of fatigue that determines functional capacity.

Reis et al.[4] analyzed the prognostic power of various exercise parameters in submaximal CPET for risk stratification in patients with HF with reduced ejection fraction (HFrEF), particularly the cardiorespiratory optimal point (COP), which represents the minimum ventilation (VE)/oxygen uptake (VO_2) value and reflects the best circulatory-respiratory interaction.[5] In practice, the COP corresponds to the point during incremental exercise when there is least VE for a liter of VO_2; the lower the equivalent values the more effective is gas exchange or work of breathing. COP is a submaximal variable that increases with age and is slightly higher in women. As it is moderately associated with other ventilation measures, it seems

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to make an independent contribution to the interpretation of the cardiorespiratory response to CPET.[6]

The authors performed a prospective follow-up of 12 months from the initial assessment, which included etiology of HF (ischemic vs. non-ischemic), implanted cardiac devices, medication, comorbidities, New York Heart Association (NYHA) class, laboratory, electrocardiographic, echocardiographic and CPET data, and Heart Failure Survival Score. The primary endpoint was a composite of cardiac death and urgent heart transplantation (HT) occurring during an unplanned hospitalization for worsening inotrope-dependent HF. CPET was performed on a treadmill, in accordance with the Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations,[7] and patients were encouraged to exercise until the RER was >1.10, a submaximal CPET being defined as one with a peak RER $\leq$1.10. The authors used an appropriate statistical analysis: the predictive power of all CPET parameters regarding the primary outcome was analyzed for the greatest area under the curve (AUC) in the follow-up period, the cut-off values for variables were determined from receiver operating characteristic (ROC) curves, the Hanley-McNeil test was used to compare two correlated ROC curves, and survival curves were determined using the Kaplan-Meier method for subjects with submaximal CPET.

The study analyzed 442 consecutive HF patients with left ventricular ejection fraction (LVEF) $\leq$40% and NYHA class II or III referred for assessment by the HF team and possible indication for HT or mechanical circulatory support (MCS). The overall population had a mean age of 56.2$\pm$12.5 years, 80% were male and mean LVEF was 28.6$\pm$6.9%. A submaximal CPET (peak RER $\leq$1.10) was recorded in 66% of cases (290 patients). A similar proportion of patients reached the primary endpoint in both groups (submaximal CPET 5.9% vs. maximal CPET 8.6%, p=0.285), which also applied to the individual components of the primary endpoint: cardiac mortality 3.1% vs. 5.9%, p=0.155, and urgent HT 2.8% vs. 2.6%, p=0.872. No patients required urgent MCS.

In the submaximal CPET group, COP had the highest AUC value (0.989) and its predictive power was significantly higher than that of other variables, including peak oxygen uptake, anaerobic threshold (AT), VE/VCO_2 slope, oxygen uptake efficiency slope, circulatory power, ventilatory power, peak oxygen pulse, partial pressure of end-tidal carbon dioxide at rest and at AT, and $PetCO_2$ increase until the AT is achieved (p<0.05 for all). The COP retained a high predictive ability for the study's primary endpoint, irrespective of patient age ($\leq$50 vs. >50 years) and gender, HF etiology (ischemic vs. non-ischemic), heart rhythm (sinus rhythm vs. atrial fibrillation) or the presence of chronic kidney disease.

Interestingly, Reis et al.'s results determined cut-off values for variables from the ROC curves, showing that patients with peak RER $\leq$1.10 presenting a COP of less than 36 had a significantly lower 12-month survival free of events (p<0.001); a COP of 36 had a sensitivity of 100% and a specificity of 89% for the primary outcome. These findings highlight the importance of analyzing ventilatory rates and provide information that can improve the ability of the HF team to identify HF patients at high risk, which is a goal of considerable clinical relevance.

Regarding the limitations of the study, the authors point out that HF may have been less severe in their sample than in other studies that assessed the performance of submaximal CPET parameters, which may compromise the reproducibility of their results,[8] and consider that a long-term follow-up will be necessary for effective validation of their results.

Despite these limitations, in my view their article should be read, as it presents an excellent and promising use of submaximal ventilatory parameters, particularly the cardiorespiratory optimal point, in the prognosis and treatment of heart failure with reduced ejection fraction.

Conflicts of interest

The author has no conflicts of interest to declare.

References

1. Guazzi M, Bandera F, Ozemek C, et al. Cardiopulmonary exercise testing: what is its value? J Am Coll Cardiol. 2017;70:1618–36.
2. Corrà U, Agostoni PG, Anker SD, et al. Role of cardiopulmonary exercise testing in clinical stratification in heart failure. A position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20:3–15.
3. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35:1–23.
4. Reis JF, Gonçalves A, Brás P, et al. The prognostic value of the cardiorespiratory optimal point during submaximal exercise testing in heart failure. Rev Port Cardiol. 2022;41:751–8.
5. Ramos PS, Sardinha A, Nardi AE, Araújo CG. Cardiorespiratory optimal point: a submaximal exercise variable to assess panic disorder patients. PLoS ONE. 2014;9:e104932.
6. Ramos PS, Ricardo DR, Araújo CG. Cardiorespiratory optimal point: a submaximal variable of the cardiopulmonary exercise testing. Arq Bras Cardiol. 2012;99:988–96.
7. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation. 2012;126:2261–74.
8. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. Circulation. 2007;115:2410–7.