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Editorial

Cardiopulmonary Exercise Testing in Patients With Heart Failure and a Preserved Ejection Fraction: Filling the Prognostic Knowledge Gap

Prueba de esfuerzo cardiopulmonar en pacientes con insuficiencia cardiaca y fracción de eyección conservada: colmando las lagunas sobre el pronóstico

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Given the sobering rise of heart failure (HF) with a preserved ejection fraction (HFpEF) and the increasing financial burden of HF-related hospital readmissions, it is imperative to identify patients at increased risk of rehospitalization in order to initiate aggressive medical and healthy living interventions.[1,2] Cardiopulmonary exercise testing (CPX) has gained much scientific traction, showcasing its usefulness for predicting rehospitalizations, adverse events, and mortality.[3–5] Although the evidence demonstrating the prognostic strength of CPX in HFpEF patients lags behind the mounting evidence collected in HF patients with a reduced ejection fraction (HFrEF), the few studies that exist reveal similar observations between the 2 phenotypes. The study by Palau et al., published in *Revista Española de Cardiología*,[6] demonstrates for the first time the power of percent-predicted peak oxygen consumption (VO_2) in identifying HFpEF patients that were at an increased risk of recurrent hospital admissions over a 3-month period. Their findings contribute valuable data that extend the evidence supporting the application of CPX in clinical settings and encourage the use of percent-predicted peak VO_2 in patients with HFpEF, which has been established as a powerful prognosticator in HFrEF.[3,5,7] Of note, Palau et al. identified an independent, linear association with recurrent all-cause and cardiovascular mortality as well as acute HF admissions in an elderly, highly symptomatic HFpEF cohort. A 10% reduction in percent-predicted peak VO_2 was associated with a 32% increased risk of recurrent hospitalization, which remained significant when the minute ventilation/carbon dioxide production (VE/VCO_2) slope was added to the multivariate model. However, the VE/VCO_2 slope on its own was not predictive of recurrent hospitalizations. Globally, these findings are a valuable contribution to the limited HFpEF literature showcasing the value of CPX in predicting recurrent hospital readmissions.

Many of the initial investigations related to the exploration of CPX markers have been conducted in patients with HFrEF. Since the initial landmark studies highlighting the strength of mortality prediction using peak VO_2,[8–10] many efforts have been made to identify stronger predictive measures. Assessment of ventilatory efficiency (ie, the VE/VCO_2 slope) has emerged as a more telling predictor of events, hospitalizations, morbidity, and mortality in patients with HFrEF, compared with peak VO_2.[11,12] Similarly, identification of a cyclic or oscillatory breathing pattern[13–15] in roughly 30% of HFrEF patients[16,17] in response to increasing exercise intensity (ie, exercise oscillatory ventilation [EOV]) has also emerged as an equally–if not more–predictive marker of cardiac events compared with VE/VCO_2 slope in HFrEF.[11,12] In contrast, a clear ranking of the most powerful event predictors has not emerged in the HFpEF population. Guazzi et al. reported the superior prognostic power of EOV compared with VE/VCO_2 and peak VO_2, while VE/VCO_2 outperformed peak VO_2 in predicting cardiac events in patients with HFpEF.[18] Yan et al. confirmed the stronger predictive power of VE/VCO_2 compared with peak VO_2, but did not assess EOV.[19] It is worth mentioning that neither of these studies calculated percent-predicted peak VO_2, a robust predictor–more so than peak VO_2 alone–in a cohort with a wide age range. Indeed, the severity of a person's disease state greatly impairs oxidative capacity; however, the inevitable decline in peak VO_2 with age confounds comparisons of peak VO_2 across various ages (ie, 50-year-old and 70-year-old HF patients). It may therefore be more accurate to calculate a patient's percentage of predicted peak VO_2 to establish prognostic significance in a cohort of varying ages. Furthermore, percent-predicted peak VO_2 has been shown to be equally–if not more–predictive of adverse events than VE/VCO_2 when the Wasserman/Hansen[20] prediction equation is used in patients with HFrEF.[21] Shafiq et al. were the first to evaluate the predictive power of percent-predicted peak VO_2 in patients with HFpEF.[22] Their comprehensive, retrospective analysis tested the strength to predict mortality and cardiac transplants in 173 HFpEF patients and the findings partly contradicted previous findings in patients with HFrEF or HFpEF. Percent-predicted peak VO_2 (chi-square = 15.0, hazard ratio per 10%, $P < .001$) was found to be the strongest predictor of events, followed by peak VO_2 (chi-square = 11.8, $P = .001$). However, the VE/VCO_2 slope (chi-square = 0.4, $P = .54$) and EOV (chi-square = 0.15, $P = .70$) were not significant predictors. Although the current study by Palau et al. did not evaluate EOV, their observation of percent-predicted peak VO_2 outperforming the VE/VCO_2 slope (which was not a significant predictor on its own) in predicting recurrent hospitalizations was

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similar to the observations by Shafiq et al. With few studies evaluating the prognostic usefulness of CPX in HFpEF patients, and only 1 study including all measures (peak VO_2, VE/VCO_2, percent-predicted peak VO_2, EOV), it is difficult to make objective comparisons among the available reports. The conflicting outcomes among the existing HFpEF studies regarding the VE/VCO_2 slope may certainly be due to differences in cohort characteristics.

Notable differences among the HFpEF studies discussed include disease state, age, and sex distribution of the HF cohorts. Patients in the studies by Guazzi et al. and Yan et al., demonstrating the VE/VCO_2 slope as a powerful prognostic marker, had an average slope of $\sim$35 and $\sim$36, respectively, compared with $\sim$30 in the cohort reported by Shafiq et al. Additionally, EOV was only prevalent in 7% of the group described by Shafiq et al., whereas average prevalence rates have previously been reported to be closer to 30%, suggesting that the disease state of the cohort studied by Shafiq et al. may not have been as advanced as that of the patients in the studies by Guazzi et al. and Yan et al. Despite the reported average peak VO_2 of 10 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ and VE/VCO_2 slope of $\sim$36 in the study by Palau et al., the latter was not found to be a significant predictor of multiple hospital readmissions in a 3-month period ($P = .08$). While previous studies have endorsed the use of the VE/VCO_2 slope to identify patients at risk for time-to-first cardiac hospitalization, the same studies did not assess its ability to predict recurrent hospital visits, as done in the study by Palau et al. Moreover, an observation period longer than 3 months may be needed to establish VE/VCO_2 as a significant predictor of recurrent hospitalizations. There have also been differences in the age and sex distributions of patients with HFpEF among the available studies. The sample of HFpEF patients in the current study were older (72.5 $\pm$ 9.1 years) and had a higher percentage of women (53%) than the other patient samples from previous studies. This is in line with epidemiologic characterization studies of HFpEF patients, who have been identified to be older and to consist of a higher proportion of women than patients with HFrEF. In contrast, participants in the study by Shafiq et al.[22] were on average younger (54 $\pm$ 14 years), mostly male (65%), similar to patients in the study by Guazzi et al.,[23] in which more than 80% were men and the mean age was 58 years, while participants in the study by Yan et al.[19] were also composed of a greater proportion of men (71.4%) but were older (68.8 $\pm$ 9.0 years). The wide variance in participant characteristics has been thought to be associated with practitioner biases favoring CPX referrals for relatively younger HFpEF men in clinical settings. Although it is currently difficult to make direct comparisons among studies with differing HFpEF cohorts, it is encouraging that agreements exist between contrasting cohorts on the strongest prognostic measures (ie, Guazzi et al.[18,23] and Yan et al.[19]).

As our understanding of the clinical and prognostic implications of CPX outcomes continues to evolve, an area worth exploring relates to the 3-dimensional characterization of response to exercise, including cardiopulmonary, electrocardiographic, hemodynamic, and subjective symptom responses. Each of the CPX measures discussed in this editorial comment (peak VO_2, percent-predicted peak VO_2, VE/VCO_2 slope, EOV) and other studies (ie, heart rate recovery, blood pressure response, symptoms) have been recognized to identify patients with an increased risk of recurrent hospitalizations, cardiac events, and/or death in one or more investigations. With much of the current scientific effort placed on highlighting the measure with the greatest predictive power, opportunities to better guide medical treatment by developing either a composite CPX score or a comprehensive outcome table may have been overlooked. Arena et al.[21] identified the presence or absence of unfavorable CPX measures (ie, VE/VCO_2 slope $\geq$ 36, percent-predicted peak VO_2 < 47%, left ventricular ejection fraction $\leq$ 25%, New York Heart Association class III/IV) and compared adverse event rates among those that had 0, 1, 2, 3, or 4 abnormal values in HFrEF patients; they found a significant increase in adverse event rates with the increased number of abnormal characteristics.[21] While additional investigative inquiry is required to support the implementation of this model, it is still attractive, particularly when considering the number of studies that are in disagreement regarding the single most powerful event predictor. The lack of agreement on the single most powerful prognosticator may also partly contribute to practitioners' hesitant adoption of CPX over traditional symptom-limited tests. A more attractive, comprehensive model using color-coded tables to facilitate the interpretation of CPX outcomes has been proposed and presented in a number of guideline statements and reviews.[4,5,24] These tables present each CPX measure (ie, the VE/VCO_2 slope, percent-predicted peak VO_2, EOV, hemodynamic response, heart rate recovery, etc) stratified into their respective level of abnormality by evidence-based classification schemes. Normal responses are identified by green, while intensifying abnormalities are highlighted in yellow, orange, and red. In theory, a greater proportion of CPX variables highlighted in orange and red would indicate the need for aggressive medical intervention. The clinical application of this method has not currently been investigated and therefore future efforts are required to explore its efficacy.

The novel observations by Palau et al. are timely considering the increased diagnosis and rehospitalization rates of patients with HFpEF, which have placed a high financial burden on health care systems.[25] This study further establishes the clinical significance of expressing peak VO_2 as a percentage of age- and sex-predicted peak VO_2 equations. While there are still many gaps in the literature regarding CPX as a prognostic tool in the HFpEF population, valuable advances are being made in shorter time periods. The next line of investigations should consider evaluating CPX outcomes in a comprehensive manner in patients with HFpEF.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Arena R, Lavie CJ. Preventing Bad and Expensive Things From Happening by Taking the Healthy Living Polypill: Everyone Needs This Medicine. *Mayo Clin Proc.* 2017;92:483–487.
2. Arena R, McNeil A, Sagner M, Lavie CJ. Healthy Living: The Universal and Timeless Medicine for Healthspan. *Prog Cardiovasc Dis.* 2017;59:419–421.
3. 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;67:780–789.
4. Guazzi M, Arena R, Halle M, Piepoli MF, Myers J, Lavie CJ. 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation.* 2016;133:e694–e711.
5. Arena R, Guazzi M, Cahalin LP, Myers J. Revisiting cardiopulmonary exercise testing applications in heart failure: aligning evidence with clinical practice. *Exerc Sport Sci Rev.* 2014;42:153–160.
6. Palau P, Domínguez E, Núñez E, et al. Peak Exercise Oxygen Uptake Predicts Recurrent Admissions in Heart Failure With Preserved Ejection Fraction. *Rev Esp Cardiol.* 2018;71:250–256.
7. 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.
8. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. *Am J Cardiol.* 1985;55:1037–1042.
9. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds Jr LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation.* 1991;83:778–786.
10. Willens HJ, Blevins RD, Wrisley D, Antonishen D, Reinstein D, Rubenfire M. The prognostic value of functional capacity in patients with mild to moderate heart failure. *Am Heart J.* 1987;114:377–382.
11. Leite JJ, Mansur AJ, de Freitas HF, et al. Periodic breathing during incremental exercise predicts mortality in patients with chronic heart failure evaluated for cardiac transplantation. *J Am Coll Cardiol.* 2003;41:2175–2181.

12. Guazzi M, Myers J, Peberdy MA, Bensimhon D, Chase P, Arena R. Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. *Eur Heart J.* 2008;29:2751–2759.
13. Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. *Am Rev Respir Dis.* 1992;145:776–781.
14. Francis DP, Davies LC, Piepoli M, Rauchhaus M, Ponikowski P, Coats AJ. Origin of oscillatory kinetics of respiratory gas exchange in chronic heart failure. *Circulation.* 1999;100:1065–1070.
15. Francis DP, Willson K, Davies LC, Coats AJ, Piepoli M. Quantitative general theory for periodic breathing in chronic heart failure and its clinical implications. *Circulation.* 2000;102:2214–2221.
16. Guazzi M, Arena R, Ascione A, Piepoli M, Guazzi MD; Gruppo di Studio Fisiologia dell'Esercizio CdSeRCotISoC.. Exercise oscillatory breathing and increased ventilation to carbon dioxide production slope in heart failure: an unfavorable combination with high prognostic value. *Am Heart J.* 2007;153:859–867.
17. Guazzi M, Raimondo R, Vicenzi M, et al. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. *J Am Coll Cardiol.* 2007;50:299–308.
18. Guazzi M, Myers J, Abella J, et al. The added prognostic value of ventilatory efficiency to the Weber classification system in patients with heart failure. *Int J Cardiol.* 2008;129:86–92.
19. Yan J, Gong SJ, Li L, et al. Combination of B-type natriuretic peptide and minute ventilation/carbon dioxide production slope improves risk stratification in patients with diastolic heart failure. *Int J Cardiol.* 2013;162:193–198.
20. Wasserman KHJ, Sue DY, Stringer W, Whipp BJ. *Principles of Exercise Testing and Interpretation*. Philadelphia, PA: Lippincott Williams and Wilkins; 2005.
21. Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail.* 2009;2:113–120.
22. Shafiq A, Brawner CA, Aldred HA, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction. The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J.* 2016;174:167–172.
23. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol.* 2005;46:1883–1890.
24. 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;126:2261–2274.
25. Kilgore M, Patel HK, Kielhorn A, Maya JF, Sharma P. Economic burden of hospitalizations of Medicare beneficiaries with heart failure. *Risk Manag Healthc Policy.* 2017;10:63–70.