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EDITORIAL COMMENT

"Recovering" the Recognition for VO_2 Kinetics During Exercise Recovery in Heart Failure

A Good Practice in Need of More Exercise*

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For many years, the advantage of using exercise gas exchange analysis by cardiopulmonary exercise testing (CPET) in heart failure (HF) has been confined to the measure of peak oxygen uptake (VO_2) as a reference indicator of exercise performance with remarkable diagnostic and prognostic value (1). Clinicians have, thus, relied on these undisputed strengths without caring as much, except for isolated cases (2,3), about what physiologists have been practicing for a long time, that is, to examine the entire exercise VO_2 kinetics to better understand the mechanisms limiting functional capacity focusing on their implications rather than catalyzing the interest on a single variable (4).

The ideal approach for studying the kinetics of exercise VO_2 is based on the use of submaximal test protocols at constant workloads of different, prespecified intensities to dissect the dynamic phases of O_2 delivery and use from external to cellular respiration. Briefly, at the beginning of the imposed load, the increase in VO_2 is due to enhanced circulatory time and pulmonary blood flow (phase I or cardiodynamic), followed by a slower and monoexponential increase (phase II) that reflects O_2 muscular extraction, and then by a subsequent plateau in oxygen uptake (phase III or steady state), if exercise level is maintained below the anaerobic threshold. The lag in VO_2 seen from phase I to the steady state is termed O_2 credit and the recovery delay from steady state to baseline represents the debt for repaying O_2. Calculation of VO_2 kinetics in the early and recovery phases is performed by measuring the VO_2 time constant (τ) by fitting the curve through a monoexponential equation, or the $T_{1/2}$, the time for VO_2 to decrease to the 50% of the peak value adjusted for VO_2 at rest.

Whereas examination of these variables may yield to a bulk of relevant clinical information, because, for the most part, daily activities are submaximal in nature, this approach has never become standard practice in clinics due to the requirement of post-processing mathematical elaborations, rendering the calculation of these metrics potentially impractical and time consuming. Some authors have proposed to limit the analysis at the recovery phase after a maximal exercise test to partially overcome these drawbacks (2,3). This measure is relevant in terms of pathophysiological insights, given that the recovery VO_2 kinetics correlates with the recovery of energy stores in active muscles, reflecting the rate of phosphocreatine's supply and the extent of blood and tissue O_2 stores after exercise (5). Indeed, landmark physiological studies performed in the gastrocnemius muscle of the dog have documented a close relationship between the time required for the resynthesis of high-energy phosphates and VO_2 kinetics after exercise (6).

Overall, given the relevance of these physiological aspects, whatever approach is used, a phenotype of prolonged kinetics in VO_2, although not specific, is highly sensitive to HF-mediated impairment in O_2

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delivery (cardiac output) and diffusion (O_2 transit from capillaries to mitochondria) and becomes a target for our interventions (1).

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In this issue of *JACC: Heart Failure*, Bailey et al. (7) provide a reappraisal of the clinical implications of measuring VO_2 kinetics in the recovery phase of a maximal CPET, by introducing a new parameter, the VO_2 delay recovery (VO_2DR), defined as the time from the end of exercise until VO_2 permanently decreased below peak. They studied 30 patients with HF with preserved ejection fraction (HFpEF), 20 with HF with reduced ejection fraction (HFrEF), and 22 controls with invasive CPET. A group of 106 patients with HFrEF undergoing noninvasive CPET was additionally studied to test the prognostic validity of the new indicator. The VO_2DR was significantly prolonged in either HFrEF (28 s) and HFpEF (25 s) compared with a median value of 5 s in controls. A cutoff of 25 s predicted transplant-free survival after adjustments for other landmark CPET-derived prognostic variables, peak VO_2% predicted, oxygen uptake efficiency slope, minute ventilation carbon dioxide production relationship slope heart rate recovery at 2 min. A correlation of VO_2DR was found with the rate of increase in VO_2 over the work rate and exercise changes in cardiac output and not with augmentation in C(a-v)O_2. Of note, patients with a VO_2DR of >25 s exhibited severe ventilation inefficiency with impressively high slopes in the minute ventilation carbon dioxide production relationship.

The strength of this paper is the ease of methodology, the potential to improve the iteration process of patients' phenotyping (especially for HFpEF), and the accuracy in predicting the outcome. Remarkably, observations confirm, under a different approach, that we are going to expand our knowledge of hemodynamic contributory factors of exercise limitation in HFpEF patients. This study is the first to document an impaired VO_2 kinetic recovery in this category, supporting the mounting evidence for a mixed contribution to exercise limitation of impaired cardiac reserve combined with a delayed O_2 diffusion and quite preserved O_2 extraction (8).

Along with these merits, the methodology should have been strengthened by testing the reproducibility of the VO_2DR, and criteria for calculating the VO_2DR in the presence of a blunted VO_2 increase due to a flattening or downsloping pattern have yet to be defined. In addition, descriptive and prognostic subanalyses on VO_2DR in the presence of oscillatory ventilation and postexercise VO_2 overshooting would have been useful to understand how this approach may really apply to the entire spectrum of gas exchange phenotypes. Although this is the first study that combines the assessment of systemic and pulmonary hemodynamics with VO_2 recovery kinetics, some information is missing. It is actually tempting to speculate that patients with a VO_2DR of >25 s developed some degree of exercise-induced mitral regurgitation as an additional hemodynamic mechanism in limiting cardiac output delivery not only during exercise, but also during recovery.

It is also noteworthy that in both HFpEF and HFrEF a VO_2DR of >25 s did not result in any differences in pulmonary hemodynamics as far as average pulmonary capillary wedge pressure and mean pulmonary arterial pressure values are concerned. However, a set of additional basic measurements, such as pulmonary arterial compliance, pulmonary vascular resistance, and a calculation of the diastolic pressure gradient would have clarified the likely key role of a vascular precapillary component in a delayed recovery phase.

In conclusion, although peak VO_2 will continue to be an endurance indicator of disease severity and clinical outcome, a simplified analysis of VO_2 kinetics during the recovery phase from a maximal exercise test seems to be an appealing step forward for looking, in a more confident way, at the complex pathways implicated in the impaired VO_2 kinetics, helping to improve sensitivity in risk definition and clinical decision-making in HF syndrome. Due to the relevance that exercise limitation has in the context of HF stages, "recovering" exercise physiology into daily clinical activities seems to be a good practice in need of more exercise.

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