Oxygen Uptake Efficiency Slope at a Glance: A Fascinating Index Carrying Unsolved Questions

Since 1996, when it was first introduced by Baba et al,[1] oxygen uptake (VO_2) efficiency slope (OUES) has represented a controversial index of cardiopulmonary efficiency. This parameter was derived from the relation between VO_2 and the logarithmic transformation of ventilation (VE): given the equation $VO_2 = a \times \log VE + b$, they called OUES the "a," namely, the constant representing the rate of VO_2 increase in response to VE.[1] Therefore, a steeper slope represents a more efficient VO_2, meaning, less ventilatory requirement for a given VO_2. The log transformation of VE creates a high linearity in relation to VO_2, thus making the OUES theoretically effort-independent, enabling to calculate it also in case of a submaximal cardiopulmonary exercise testing (CPX).[2] Despite the interesting intuition, OUES has never entered the common clinical practice and has never been considered a necessary variable to be described in a CPX report.

This can be explained in primis by the uncertainties about mathematical assumption and physiological basis (is the VE vs VO_2 relation really exponential?)[3] and by the awareness that peak VO_2 cannot be predicted reliably from OUES[4] and that there are no universally accepted reference values normalized for anthropometric variables, although various limits have been proposed over the years in different subgroups.[5]

However, the greatest open question remains whether OUES can really have a prognostic utility in heart failure (HF), given that various studies reported conflicting results. Patients with HF have demonstrated significantly lower OUES values than healthy cohorts, with a lower OUES in accordance with disease severity,[6] but the ability of the index to remain a significant prognostic marker in a multivariate regression with the full panel of established CPX variables is uncertain.[2]

On the one hand, some studies reported that the OUES prognostic value seems to be stronger than the best available existing measures of exercise physiology,[7] also in patients with end-stage HF.[8]

In contrast, there is evidence that the strongest maximal and submaximal CPX predictors of events (i.e., mechanical circulatory support implantation, heart transplantation, or death) remain to be the VO_2 pulse and the minute VE/carbon dioxide production (VCO_2) slope, respectively.[9]

In this issue of the *American Journal of Cardiology,* Gordon et al[10] have attempted to address this gap, reporting the results of a post hoc analysis of HF-ACTION (The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) trial, with the aim of establishing the prognostic utility of OUES and determine whether it provides prognostic information beyond peak VO_2 and VE/VCO_2 slope in patients with HF with reduced ejection fraction and submaximal effort on CPX. The authors should be congratulated; indeed, the analysis assessed a large population (i.e., 2,074 patients included) with left ventricular ejection fraction ≤35% and New York Heart Association class II to IV. Of note, 17% of the patients performed a submaximal CPX (here defined as peak respiratory exchange ratio <1).

Several important lessons can be derived from this work. Although confirming a good correlation between peak VO_2 and OUES in patients with HF with reduced ejection fraction, in this analysis, the strength of the association appears lower than that previously reported.[6] This is not different from what recently described by Sheridan et al[11] in a cohort of healthy adults, in which the OUES exhibited a significant magnitude bias when used to predict peak VO_2, overpredicting at submaximal effort and underpredicting at high levels of effort. On this basis, the use of OUES as a replacement for peak VO_2 to assess cardiorespiratory fitness (CRF) in clinical practice should be cautious and thoughtful.

The authors also reported that even if lower OUES was associated with an increased risk of HF hospitalization or cardiovascular death, also in multivariable analyses, and independently of the VE/VCO_2 slope, peak VO_2 once again demonstrated a significantly higher capacity for discriminating each clinical outcome, remaining de facto a more consisting prognostic index. However, the most interesting finding of this article probably comes from the analysis of the subgroup with respiratory exchange ratio <1, given that OUES, with its relatively constant value throughout much of the exercise, has been described as a CRF index relatively independent of exercise intensity. Despite this premise, in this subgroup, peak VO_2 was associated with the outcome more robustly than OUES in the fully adjusted models.

In summary, despite the limitations of this study and, first of all, its nature as a post hoc analysis, it helps to better understand the value of OUES, confirming that even if correlated with peak VO_2, it appears to be not interchangeable with the peak VO_2 and VE/VCO_2 slope, the 2 parameters widely accepted as markers of risk in HF, currently used during consideration for heart transplantation or left ventricular assist device placement. Peak VO_2 remains the gold-standard measurement for assessing CRF and, together with the VE/VCO_2 slope, the best index in the assessment of the prognosis in patients with HF.

However, there is a challenging and new field of research in which the OUES can maintain a potential value: the development of CPX parameters based or integrated composite risk scores, which have already demonstrated to out-perform the traditional single variable binary approach in predicting the outcome in HF.[12–14] In the kaleidoscopic

world of HF, made of an increasing number of complex patients differing in age, co-morbidities, disease etiology, and trajectory, a prognostic assessment that is as accurate as possible represents an unmet need, which can no longer be overlooked. The development of a multiparametric risk model, analyzing a contemporary cohort on current guidelines−directed therapy and perhaps using artificial intelligence algorithms, has become increasingly important to optimally stratify these patients, allowing clinicians to better select the ones who would most likely benefit from certain therapeutic interventions. CPX variables, including OUES, combined with a measure of exercise capacity and a measure of ventilatory response to exercise and so providing incremental an independent information will have to be necessarily incorporated.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Maddalena Rossi, MD
Gianfranco Sinagra, MD
Marco Merlo, MD*
Cardiothoracovascular Department, Cardiology, Giuliano Isontina University Health Authority (ASUGI), European Reference Network for rare, low-prevalence, or complex diseases of the Heart (ERN GUARD-Heart), University of Trieste, Trieste, Italy
* Corresponding author
(marco.merlo79@gmail.com).

1. Baba R, Nagashima M, Goto M, Nagano Y, Yokota M, Tauchi N, Nishibata K. 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;28:1567–1572.
2. 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. *Eur Heart J* 2018;39:1144–1161.
3. Agostoni P, Gugliandolo P, Campodonico J. Inside OUES: fact or fiction? *Eur J Prev Cardiol* 2019;26:174–176.
4. Pichon A, Jonville S, Denjean A. Evaluation of the interchangeability of VO2MAX and oxygen uptake efficiency slope. *Can J Appl Physiol* 2002;27:589–601.
5. Hossri CA, de Souza IPA, de Oliveira JS, Mastrocola LE. Assessment of oxygen-uptake efficiency slope in healthy children and children with heart disease: generation of appropriate reference values for the OUES variable. *Eur J Prev Cardiol* 2019;26:177–184.
6. Van Laethem C, Bartunek J, Goethals M, Nellens P, Andries E, Vanderheyden M. Oxygen uptake efficiency slope, a new submaximal parameter in evaluating exercise capacity in chronic heart failure patients. *Am Heart J* 2005;149:175–180.
7. Davies LC, Wensel R, Georgiadou P, Cicoira M, Coats AJ, Piepoli MF, Francis DP. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J* 2006;27:684–690.
8. Lin YS, Huang HY, Lin WH, Wei J, Chen JC, Kuo LY, Hsu CL, Chen BY, Cheng FH. Oxygen uptake efficiency slope predicts major cardiac events in patients with end-stage heart failure. *Transplant Proc* 2016;48:956–958.
9. Lala A, Shah KB, Lanfear DE, Thibodeau JT, Palardy M, Ambardekar AV, McNamara DM, Taddei-Peters WC, Baldwin JT, Jeffries N, Khalatbari S, Spino C, Richards B, Mann DL, Stewart GC, Aaronson KD, Mancini DM, Investigators REVIVAL. Predictive value of cardiopulmonary exercise testing parameters in ambulatory advanced heart failure. *JACC Heart Fail* 2021;9:226–236.
10. Gordon J, Michelis KC, Pandey A, Ayers C, Thibodeau JT, Grodin JL, Drazner MH. Oxygen uptake efficiency slope and prognosis in heart failure with reduced ejection fraction. *Am J Cardiol* 2023;201:273–280.
11. Sheridan S, McCarren A, Gray C, Murphy RP, Harrison M, Wong SHS, Moyna NM. Maximal oxygen consumption and oxygen uptake efficiency in adolescent males. *J Exerc Sci Fit* 2021;19:75–80.
12. Myers J, Oliveira R, Dewey F, Arena R, Guazzi M, Chase P, Bensimhon D, Peberdy MA, Ashley E, West E, Cahalin LP, Forman DE. Validation of a cardiopulmonary exercise test score in heart failure. *Circ Heart Fail* 2013;6:211–218.
13. Ingle L, Rigby AS, Sloan R, Carroll S, Goode KM, Cleland JG, Clark AL. Development of a composite model derived from cardiopulmonary exercise tests to predict mortality risk in patients with mild-to-moderate heart failure. *Heart* 2014;100:781–786.
14. Agostoni P, Corrà U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magrì D, Fiorentini C, Mezzani A, Salvioni E, Scrutinio D, Ricci R, Bettari L, Di Lenarda A, Pastormerlo LE, Pacileo G, Vaninetti R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Confalonieri M, Giannuzzi P, Passantino A, Cas LD, Piepoli MF, Passino C, MECKI Score Research Group. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013;167:2710–2718.