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Inside OUES: fact or fiction?

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The 'efficiency of the peripheral oxygen uptake' or 'oxygen uptake efficiency slope', the so-called OUES, is defined by the logarithmic regression curve between oxygen uptake (VO_2) and ventilation (V_E). In other words, it is the 'a' in the $VO_2 = a \times \log V_E + b$ equation. In Figure 1, the VO_2 versus V_E relationship of a normal subject and of a patient with pulmonary hypertension is reported in the upper panel, and the OUES of the same subjects is shown in the lower panel. Steeper slopes represent a more efficient oxygen uptake.[1] However, it seems to us that the physiological meaning of 'efficiency of the peripheral oxygen uptake' is undefined. This term needs at least some clarification and some physiology background. Indeed, efficiency of V_E is how well or poorly V_E performs. The main duty of V_E is gas exchange for both oxygen and carbon dioxide. Therefore, V_E efficiency is the highest when V_E is the lowest for a given carbon dioxide uptake (VCO_2) or VO_2, provided that arterial carbon dioxide tension ($PaCO_2$) or arterial oxygen tension (PaO_2) are still. V_E efficiency can be assessed for carbon dioxide as the slope of the relationship between V_E and VCO_2 measured from the beginning of loaded exercise up to the respiratory compensation point, when the slope is linear. Alternatively, V_E efficiency can be assessed as the ratio of V_E/VCO_2 during exercise, usually at the anaerobic threshold or when it is at its lowest. And what about oxygen? Notably, the V_E/VCO_2 and V_E/VO_2 ratios are usually plotted in combination, and their changes are similar with a similar nadir, although the V_E/VO_2 ratio increases at the anaerobic threshold, while the V_E/VCO_2 ratio increases at the respiratory compensation point. Indeed, as opposed to a linear increase of VO_2 during a progressively increasing workload exercise, the V_E versus VO_2 relationship is linear only up to the anaerobic threshold, i.e. for a small part of the exercise. Therefore, the slope of the V_E versus VO_2 relationship can be calculated as a linear equation only at the beginning of exercise, when V_E is more erratic and more affected by psychological stress. In the late 1990s, Baba et al.[2] suggested that the equation be linearised by applying the logarithmic regression, but this implies that the curve is exponential. Is that true? Probably not, because V_E in an exercise ramp protocol from rest to peak is progressively under different domains – VO_2, VCO_2, PH and temperature, respectively. Notably, all of these domains are characterised by specific V_E kinetics. Indeed, we identify thresholds on V_E, such as the anaerobic threshold and the respiratory compensation point, both undefinable in an exponential equation.[3] However, the true question is: does OUES tell something different from V_E versus VCO_2? Indeed, VO_2 includes three major independent diffusion steps limiting oxygen transport: lungs, blood, and capillary to mitochondria. But almost the same applies to carbon dioxide, albeit in a reverse order: muscles to capillary, blood and lungs. However, the pressure gradients of oxygen and carbon dioxide between upper airways and mitochondria are different, as are their degrees of resistance to gas flow. Figure 2 shows that pO_2 decreases from 160 mmHg in inspired air to 100 mmHg in the alveoli and almost to zero in the mitochondria, where it may even become negative in some circumstances, such as during heavy exercise.[4] The pressure gradient for carbon dioxide is much lower, from approximately 45 mmHg in the muscles to 40 mmHg at the end of expiration. The reduction of pO_2 has two quantitatively different steps, the smallest inside the lung and the largest from the capillary to the mitochondria. It is different for pCO_2 changes, which are almost negligible, from the muscles, where carbon dioxide is stored, to venous blood, and from venous blood to expired air. As a matter of fact, end-tidal carbon dioxide is mainly an index of dead space V_E, and therefore of V_E efficiency. In conclusion, V_E versus VCO_2 is mainly lung efficiency, while V_E versus VO_2 is a composite of lung, circulation and capillary-to-mitochondria resistance to oxygen flow, i.e. total body efficiency, and not only peripheral

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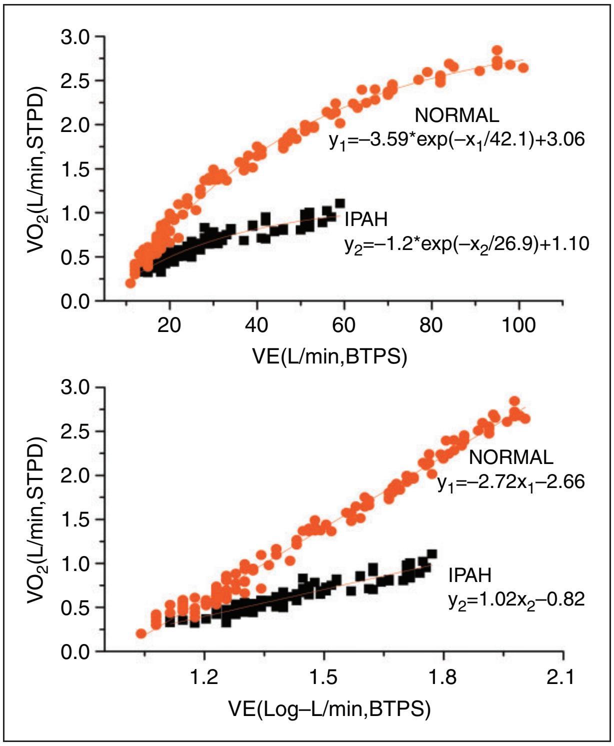

Figure 1. Difference in oxygen uptake efficiency slope (OUES) between a typical idiopathic pulmonary arterial hypertension (IPAH) patient and a control subject. Linear (upper panel) and single-segment logarithmic (lower panel) relation between oxygen uptake (VO_2) (ml/min) and ventilation (V_E) (ml/min) for two different subjects. Steeper slopes represent more efficient oxygen uptake. The control subject (steeper slopes, aged 24 years, height 158 cm; weight 45 kg) has a OUES of 2.72 whereas the IPAH patient (shallower slopes, aged 21 years, height 161 cm; weight 47 kg) has an OUES of 1.02. Reproduced from Tan et al.[1] (under the terms of the Creative Commons Attribution Licence).

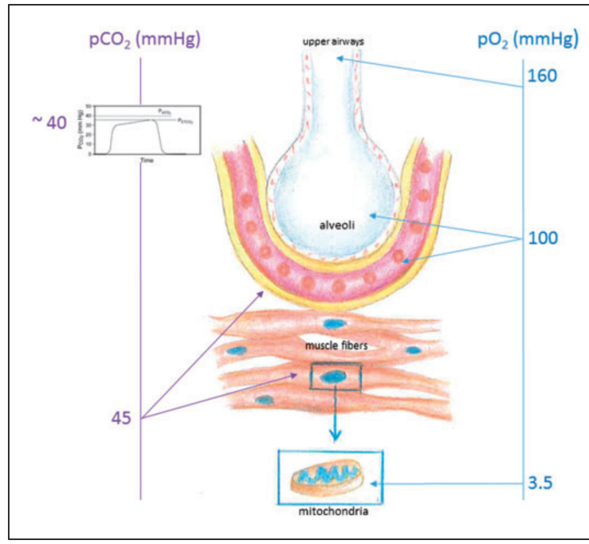

Figure 2. Gradient of the partial pressure of oxygen and carbon dioxide in the body.

efficiency as stated in one of the OUES definitions reported above. Moreover, if OUES is an index of total body VO_2 efficiency, it is unclear to us why we should plot VO_2 versus V_E and not versus workload, as in the VO_2 versus workload relationship, because V_E is only one of the diffusing limiting steps for VO_2.

Another major issue is how to 'normalise' efficiency. Indeed, the slope of the V_E versus VCO_2 relationship is considered normal below 34, and this cut-off is reported in several guidelines and expert consensus documents.[1,3,5–9] Indeed, the value of 34 has been found in a population of healthy individuals as the average +2 standard deviations (SD). Nobody, as far as we know, uses any sort of predicted value for the V_E versus VCO_2 slope. However, the V_E versus VCO_2 relationship is higher in women than in men, and it increases slowly but progressively with age.[10] Notably, in the present issue of the *European Journal of Preventive Cardiology*, Hossri[11] proposed OUES reference values for children and adolescents, and a sort of 'normalisation' considering OUES/kg or body surface area (BSA). This is one of the first efforts in the process of V_E efficiency normalisation, but are kg or BSA enough? In other words, are any gender differences or any kind of differences related to the development of sexual hormones? And what about V_E versus VCO_2 in this young population? Do OUES and the V_E versus VCO_2 slope have similar behaviours with age increase in children and adolescents? In our opinion, the paper by Hossri is the first effort in the direction of a normalisation of efficiency, but a more comprehensive assessment including gender, height, race, abdominal circumference, etc. is needed for a proper evaluation.

Regardless of this, Hossri et al.[11] showed that ventilatory requirements are increased in children and adolescents with congenital heart disease either in absolute values or normalised for weight or BSA, this information is clinically relevant and helps to understand the exercise limitation in these patients.

In conclusion, it is important to normalise every measurement, so that we can compare subjects of different age, gender, race, height and weight, but before normalising OUES we need to know what OUES really means. In other words: efficiency of what?

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References

1. Tan X, Yang W, Guo J, et al. Usefulness of decrease in oxygen uptake efficiency to identify gas exchange abnormality in patients with idiopathic pulmonary arterial hypertension. *PloS One* 2014; 9: e98889.
2. Baba R, Nagashima M, Goto M, et al. 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.
3. Wasserman KHJ, Sue DY, Stringer WW, et al. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia, USA: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2005.
4. Severinghaus JW. Paradoxical relation of mitochondrial PO_2 to VO_2. *Adv Exp Med Biol* 1999; 471: 595–604.
5. Guazzi M, Arena R, Halle M, et al. 2016 Focused Update: clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation* 2016; 133: e694–e711.
6. Wagner J, Agostoni P, Arena R, et al. The role of gas exchange variables in cardiopulmonary exercise testing for risk stratification and management of heart failure with reduced ejection fraction. *Am Heart J* 2018; 202: 116–126.
7. Corra 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.
8. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; 136: e137–e161.
10. Sun XG, Hansen JE, Garatachea N, et al. Ventilatory efficiency during exercise in healthy subjects. *Am J Resp Crit Care Med* 2002; 166: 1443–1448.
11. Hossri CA, Souza IPA, de Oliveira JS, et al. 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*. Epub ahead of print 2018. Doi: 20474873 18807977.