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Cardiopulmonary Exercise Testing under Hyperoxia: Is the Haldane-Transformation the Correct Approach?

Hermann Eschenbacher
Marketing Department, CareFusion Germany,
Höchberg, Germany

With great interest, I read the study by Ulrich et al. [1] who investigated the mechanisms of improved exercise performance under hyperoxia. I completely agree with their main conclusion that in healthy subjects, hyperoxia increases the maximal power output and endurance. Furthermore, they found that minute ventilation and dyspnea perception were reduced. However, the measurement data also showed that for the same workload, $\dot{V}O_2$ is increased when breathing oxygen-enriched air ($FIO_2 = 50\%$) compared to ambient air breathing ($FIO_2 = 21\%$). The conclusion was that these findings suggest that hyperoxia enhances cycling performance through a more efficient pulmonary gas exchange and a greater availability of oxygen to muscles and the brain (cerebral motor and sensory neurons).

The publication does not mention in detail how $\dot{V}O_2$ and $\dot{V}CO_2$ were determined or calculated, but according to oral communication with the authors, the calculations are based on the traditional Haldane-transformation (HT) [2], which is still the “Golden Standard” for CPET calculations [3]. HT is extremely well-known and has been used for more than 100 years, but it is also known that above 40% FIO_2 , the measured (calculated) oxygen uptake is increased. Above 60%, data calculated with the HT are not reliable anymore and at 100% FIO_2 the $\dot{V}O_2$ (and if applied correctly also $\dot{V}CO_2$) cannot be calculated [4]. However, no detailed investigations have been published to date advising up to which FIO_2 value the HT can be applied [5], or even more importantly, if it should be applied at all? There are numerous publications showing a similarly increased $\dot{V}O_2$ at elevated FIO_2 when using the HT, but to a certain extent, they fail to find a reasonable explanation for this increase [6–9]. This false increased $\dot{V}O_2$ (when the HT is applied) is also supported by Stanek et al. [10] who found that in ponies the $\dot{V}O_2$ – calculated with the HT equation – is elevated in hyperoxia. However, when using the cardiovascular Fick (CVF) equation, $\dot{V}O_2$ remains unchanged between normoxia and hyperoxia.

As the HT mainly influences $\dot{V}O_2$, the data from Ulrich et al. [1] also indicate that the increase at elevated FIO_2 seems not to be a real increase in $\dot{V}O_2$, but a result of the transformation: while $\dot{V}O_2$ is increased, $\dot{V}CO_2$ does not increase, and it even seems to decrease somewhat. In addition, the RER_{max} is much lower under elevated

FIO_2 compared to air breathing ($RER_{max} [@ 50\%] = 1.0$ compared to $RER_{max} [@ 21\%] = 1.2$). Therefore, the $RER_{rest} [@ 21\%]$ compared to $RER_{rest} [@ 50\%]$ would be of great interest, mainly to see if – after the wash-in phase – the RER starts close to a value of 0.70 or even below. Since such low RER values are physiologically implausible and also would support the false too high $\dot{V}O_2$.

In addition, the publication does not clearly point out how the additional dead space of the 2-way low-resistance T valve is considered in the calculations and how the FIO_2 is determined. This dead space does not contain the FIO_2 delivered from the system, but the gas from the last expiration, which lowers the mean FIO_2 . This fact, if not considered correctly in the calculations, will result in an additional false increase in $\dot{V}O_2$.

There is a strong likelihood that the observed increase in $\dot{V}O_2$ at elevated FIO_2 is at least to a certain extent not the result of an increased oxygen uptake, but the consequence of the HT derived from the assumption that $VN_2 = 0$ and possibly also due to the additional dead space. Therefore, both the apparatus setup as well as the calculations via the HT should be carefully considered, especially with elevated FIO_2 .

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