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EDITORIAL FOCUS

Go West: translational physiology for noninvasive measurement of pulmonary gas exchange in patients with hypoxemic lung disease

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Assurance of adequate gas exchange is the primordial physiological function of the respiratory system. Accordingly, precise, continuous, and, ideally, noninvasive monitoring of gas exchange is of paramount importance in respirology and in particular in critical care. With classic pulse oximetry as a surrogate parameter with major limitations at supranormal inspiratory oxygen fractions ($F_{I_{O_2}}$), and arterial puncture being invasive and uncomfortable for the patient, a significant medical need for state-of-the-art monitoring of gas exchange remains.

In a recent series of publications, West and colleagues (9–11) developed an elegant physiological approach which allows for noninvasive quantification of abnormal pulmonary gas exchange. This technique uses pulse oximetry to calculate the arterial P_{O_2} from the oxygen dissociation curve in conjunction with measurements of end-expiratory P_{O_2} and P_{CO_2} in the expired gas. From these data, West and colleagues calculate the difference between the end-tidal P_{O_2} and the computed arterial P_{O_2} and define it as the so-called "oxygen deficit." In a study published in a recent issue of *American Journal of Physiology-Lung Cellular and Molecular Physiology*, the authors now tested this novel approach in a cohort of 34 patients with hypoxemic lung disease at sea level and compared the oxygen deficit against the classic, invasively measured alveolar-arterial oxygen difference ($AaDO_2$) (12). The oxygen deficit in this group of patients was 42.7 ± 4.0 mmHg and thus, markedly higher compared with healthy young (2 ± 0.8 mmHg) and older (7.5 ± 1.6 mmHg) subjects previously analyzed by this technique (10). The calculated arterial P_{O_2} correlated with the results from invasive Pa_{O_2} measurements with an r^2 of 0.76 and a mean bias of +2.7 mmHg as determined by Bland-Altman analysis. As such, the oxygen deficit may present a sensitive indicator of impaired pulmonary gas exchange that could easily be implemented into routine clinical use.

Importantly, the way the oxygen deficit is calculated overcomes several limitations of the classic Riley analysis of the $AaDO_2$. First, it also includes lung units with high ventilation-to-perfusion ratios (V/Q) into the analysis rather than only units with abnormally low V/Q (9). Second, calculation of the arterial P_{O_2} from the oximetric analysis of the expirate allows the continuous bedside monitoring of the Pa_{O_2}. Many intensivists still reminisce about the times when fiberoptic sensors allowed for continuous (intra-)arterial measurements of P_{O_2} in the intensive care unit (ICU), directly visualizing the prominent breathing- and cardiac cycle-dependent oscillations in Pa_{O_2} and thus providing for instantaneous feedback on the therapeutic effects of positive end-expiratory pressure, patient positioning, or inhaled gaseous therapeutics (e.g., nitric oxide) in the critically ill (2). Unfortunately, these devices required meticulous and repeated calibration procedures and were easily damaged during routine patient care and highly expensive. The third clinical advantage of the oxygen deficit is that it is fully noninvasive. This is important not only to reduce the risk of infections and vascular or nerve damage with invasive sampling, it also helps to reduce the amount of blood collected for biochemical analyses. This is relevant as ~30% of blood transfusions in the ICU are caused by iatrogenic blood sampling (3). Noninvasive monitoring of pulmonary gas exchange may thus aid to save human blood products, which are a scarce resource, and increase patient safety by avoiding the deleterious negative association of blood transfusion with short-term (survival) and long-term (tumor frequencies) outcome.

For these possible advantages to materialize, however, several problems remain to be solved. First, the accuracy of the sensors used for measurement of end-tidal P_{O_2} decreases at higher inspiratory oxygen concentrations. At present, this poses a relevant technical limitation, as the majority of critically ill patients can be expected to be ventilated at $F_{I_{O_2}} > 0.21$. Potential sensor drift also necessitates careful and repeated calibrations. Second, a stable alveolar plateau phase has to be reached to allow for a valid measurement of alveolar P_{O_2} from the end-tidal expirate. Considering the existence of different alveolar time constants, V/Q mismatches, and high respiratory rates in the critically ill, this may be challenging to achieve during respiratory therapy. Third, changes in both hemoglobin concentration and cardiac output impact on the classical $AaDO_2$ and will most probably also affect the calculated oxygen deficit. Fourth, the current P_{O_2} calculations are based on the subroutines developed by Kelman to correct for the allosteric effect of changes in P_{CO_2} on the oxygen affinity of hemoglobin, known as the Bohr effect. Notably, Kelman's solutions are based on the assumption that the change in P_{CO_2} moves the arterial P_{O_2} along the normal buffer line. Hence,

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P_{CO_2}-independent nonrespiratory changes in acid-base status, specifically changes in base excess, will affect these calculations in that P_{O_2} will be overestimated in nonrespiratory alkalosis yet underestimated in corresponding acidosis (4, 6). Given that the majority of critically ill patients have combined respiratory and metabolic acid base disturbances (chronic P_{CO_2} and bicarbonate elevations aggravated by acute and often severe lactic acidosis), the extent to which these changes affect the calculation of the arterial P_{O_2} remains to be addressed. The same holds true for the effects of temperature on the calculation of arterial P_{O_2}, in particular since the applied corrections originally introduced by Severinghaus (6) remain to be comprehensively validated.

One further notion arises from this elegant application of respiratory physiology to medicine that must not go unrecognized: When Dr. John B. West was born, the Scottish physiologist John S. Haldane still believed that the lungs used active transport to take up oxygen into the blood (7), although Marie Krogh had already proved him wrong in her impressive PhD thesis in 1915 (5). With more than six decades of outstanding contributions to respiratory physiology (including scientific milestones such as the gravitational ventilation-perfusion relationship, the first physiological expedition to Everest, capillary stress failure, and the comparative physiology of the mammalian and avian lungs, to name a few) and his brilliant lectures (8), it seems Dr. West himself has never ceased to wonder WHY and HOW. Today, with the promises of digitization, automation, big data, and artificial intelligence at hand, researchers and physicians frequently focus more on the WHAT of clinical outcomes, quality insurance, or systems medicine, and less on the HOW of the underlying (patho-) physiological mechanisms or, in the words of Julius Comroe, "what makes the sky blue" (1). Yet, thankfully for the present and hopefully also for the future, scientific discovery and clinical translation still stands on the shoulders of the lifelong work of an eminent physiologist like John B. West.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.A.P. and W.M.K. drafted manuscript; P.A.P. and W.M.K. edited and revised manuscript; P.A.P. and W.M.K. approved final version of manuscript.

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