P_{aO_2}/F_{IO_2} ratio: the mismeasure of oxygenation in COVID-19

Reply to A. Tulaimat:

We read with interest A. Tulaimat's letter concerning our recent editorial in the *European Respiratory Journal* [1]. A. Tulaimat makes several insightful comments on problems with criteria used for entering patients into randomised controlled trials of noninvasive ventilation. Among these, he notes that arterial-to-inspired oxygen (P_{aO_2}/F_{IO_2}) ratio varied between 170 and 400 among enrollees [2].

Low arterial oxygenation is the fundamental problem in a severely ill patient with coronavirus disease 2019 (COVID-19). P_{aO_2} is directly related to the likelihood of dying and it also influences choice of therapy. Many hypoxaemic patients have been exposed unnecessarily to life-threatening therapy (intubation) when noninvasive modalities were likely to have been successful [3].

P_{aO_2} is the most precise and least ambiguous measurement of patient oxygenation. In many case series of COVID-19 patients, oxygenation is reported solely in terms of P_{aO_2}/F_{IO_2} and P_{aO_2} is not mentioned. No organ in the body detects P_{aO_2}/F_{IO_2} , whereas several respond to miniscule changes in P_{aO_2} (carotid bodies). P_{aO_2}/F_{IO_2} plays no role in any biological process, whereas arterial oxygen saturation directly determines oxygen delivery to the brain and myocardium.

Rules of thumb (heuristics) are commonly employed to estimate F_{IO_2} in patients receiving supplemental oxygen: 1 L equals 24%; 2 L equals 27% or 28%; 3 L equals 30% or 32% (depending on which formula is used). The resulting numbers are inherently untruthful. In truth, 2 L·min⁻¹ by nasal cannula generates F_{IO_2} anywhere between 24% and 35% [4]. More often than not, reporting P_{aO_2}/F_{IO_2} involves taking a precise and physiologically meaningful entity (P_{aO_2}) and rendering it untruthful by combining it with a notoriously unreliable estimate of F_{IO_2} . To paraphrase Protagoras of Abdera, P_{aO_2}/F_{IO_2} ratio is the mismeasure of all things oxygen.

Contemplating oxygenation in terms of P_{aO_2}/F_{IO_2} fosters a focus on acute respiratory distress syndrome (ARDS), as the ratio has been included in all definitions of ARDS since first incorporated into the Murray score [5]. Making a diagnosis of ARDS is important for researchers to ensure homogeneity of patients being recruited into studies. It is not important for bedside doctors because not even one therapeutic action is decided by the diagnosis [6].

As a method for quantifying abnormal gas exchange, P_{aO_2}/F_{IO_2} is fundamentally flawed. Modelling by WEST [7] and DANTZKER [8] demonstrates that P_{aO_2} has a curvilinear relationship with F_{IO_2} that varies with degree of ventilation-perfusion inequality and shunt. In patients with ARDS and a fixed shunt, alterations in F_{IO_2} caused P_{aO_2}/F_{IO_2} to fluctuate unpredictably by greater than 100 mmHg [9]. In patients who fulfil all ARDS criteria, administration of 100% oxygen for 30 min caused P_{aO_2}/F_{IO_2} to increase such that 58.5% were no longer categorised as ARDS [10]. (The other pillar of ARDS diagnosis, radiological infiltrates, is equally flawed because of poor interobserver agreement ($\kappa \leq 0.55$) [11].)

MURRAY *et al.* [5] opted for P_{aO_2}/F_{IO_2} as an exemplar of abnormal gas exchange because it "is more easily calculated from information routinely available in patients' charts". Seldom did an intention of not wanting to burden others backfire so spectacularly. Thousands of authors endeavouring to report patient oxygenation have debased a pristine measurement by encasing it in a specious carapace. The P_{aO_2}/F_{IO_2} ratio exemplifies one of the most glaring examples of Gresham's law in medicine.

A. Tulaimat notes that patients with P_{aO_2}/F_{IO_2} 400 (equivalent to P_{aO_2} 160 mmHg on F_{IO_2} 40%) were exposed to noninvasive ventilation for the purpose of conducting a randomised controlled trial [2]. This is

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P_{aO_2} is the most precise measurement of patient oxygenation in COVID-19, but its accuracy is corrupted when communicated as P_{aO_2}/F_{IO_2} ratio <https://bit.ly/3tNipTJ>

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disturbing. These patients should have had pulse oximetry checked while breathing room air, not viewed as candidates for a treatment that carries substantial risks. For P_{aO_2}/F_{IO_2} 300 (P_{aO_2} 120 mmHg on F_{IO_2} 40%), patients should be managed with noninvasive modalities and intubation not contemplated.

Consideration of F_{IO_2} has never been part of the definition of hypoxaemia [12]. Some physicians quantify severity of hypoxaemia in litres of oxygen supplied to a patient. Judging severity of hypoxaemia in terms of “oxygen requirements” is to engage in circular reasoning, with hazardous consequences for patients [13].

It is probably too much to expect that P_{aO_2}/F_{IO_2} be eliminated from the definition of ARDS, but authors could at least include P_{aO_2} and not solely present P_{aO_2}/F_{IO_2} in their articles. The reporting of P_{aO_2}/F_{IO_2} values should come with a health warning.

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