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The paramount parameter

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EDITORIAL

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The paramount parameter: arterial oxygen tension versus arterial oxygen saturation as target in trials on oxygenation in intensive care

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Main text

Oxygenation targets in critically ill patients admitted to the intensive care unit (ICU), in particular in patients with acute hypoxaemic respiratory failure, are still a matter of debate. There is mounting evidence for potential harm through hyperoxia [1–3]. Nevertheless, the optimal oxygenation targets, which minimise hyperoxia while maintaining sufficient oxygenation to avoid harm through hypoxia, remain unclear. Therefore, larger randomised clinical trials on the subject are needed. Several observational studies [4] as well as interventional before-and-after trials [1, 5] and three small randomised controlled trials [2, 3, 6] have added valuable, although not definitive, evidence to the field. Arterial oxygen saturation (SaO₂) or pulse oximetry (SpO₂) has been the primary parameter defining the target range in most of the interventional studies conducted. We would like to dispute this preference of SaO₂ and SpO₂ over arterial oxygen tension (PaO₂) as the target parameter. Hence, this proposition for debate.

The general hypothesis of the studies on oxygen use in the ICU is that the dangers of oxygen toxicity are underestimated, and that the negative impact of hyperoxia is significant, even when compared to the risks of hypoxia following conservative oxygenation strategies [1, 2, 5, 6]. Hence, studies proposing more conservative oxygenation targets have been conducted primarily in the effort to

avoid hyperoxia. The parameters PaO₂ and SaO₂ are linked as visualised in the oxygen dissociation curve [7]. The interval of PaO₂ in ICU patients spans upwards from approximately 7.3 kPa (55 mmHg) [8–10]. In this area, the oxygen dissociation curve is rather flat [7] and covers only a small range of SaO₂ values. The SaO₂ range becomes even narrower with hyperoxaemic levels of PaO₂ depending on its definition, which varies from over 13.3 kPa (100 mmHg) to over 64.9 kPa (487 mmHg) [4], while the corresponding SaO₂ encompasses only four numeric values from 97% to 100%. This limits the control of hyperoxaemia if SaO₂ is used as the target parameter of oxygenation. Furthermore, when SaO₂ defines the oxygenation target in clinical trials, the narrow SaO₂ spectrum will likely result in a larger risk of an overlap of PaO₂ or SaO₂ between the conventional and interventional study groups.

One could argue that the use of SaO₂ over PaO₂ offers the possibility to use the non-invasive measurement of oxygenation, SpO₂. The correlation between SaO₂ and SpO₂ is generally high which makes SpO₂ invaluable in the continuous monitoring and titration of oxygen supplementation in the ICU [11]. Nevertheless, SpO₂ is unreliable as a measure of arterial oxygenation in patients with sepsis [12], in patients with use of vasopressors [13], in patients with high or low body temperature [11], and in patients with hypoxaemia [12, 13]. Therefore, SpO₂ cannot be used in the ICU without intermittent measurements of SaO₂ for comparison as remarkable differences above 4.4 percentage points [11] may occur. Furthermore, SpO₂ has been shown inadequate in identifying and in quantifying hyperoxaemia defined as PaO₂ above 16.7 kPa (125 mmHg) at SpO₂ levels

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above 96% [14]. Thus, targeting normoxaemic oxygenation levels in the upper part of the normal reference interval by using SpO₂ would inarguably lead to episodes of definitive hyperoxaemia. Moreover, at the steep slope of the oxygen dissociation curve [7], where the differentiation in SaO₂ is the highest, SpO₂ is also inadequate in correctly identifying the oxygenation level in the ICU as SpO₂ above 94% is necessary to avoid a risk of having SaO₂ below 90% [13]. This fact further narrows the spectrum of differentiation when using SpO₂.

An argument for using SaO₂ over PaO₂ is that under normal, healthy conditions more than 98% of the transported oxygen is bound to haemoglobin [7]. Therefore, SaO₂ in combination with the haematocrit or haemoglobin level represents the most direct parameter for expressing the amounts of oxygen actually carried in the arterial blood whereas PaO₂ is only a secondarily derived parameter. However, the oxygen dissociation curve [7] shows that SaO₂ and PaO₂ are mutually dependent, and so this point remains essentially theoretical. Additionally, with increasing hyperoxaemia SaO₂ loses its value due to the rigid ceiling of SaO₂ at 100%. Furthermore, since the formation of reactive oxygen species is closely linked to the free amounts of oxygen [15] and since the reactive oxygen species contribute importantly to the detrimental effects of hyperoxia [15], PaO₂ is probably the parameter with the tightest relationship to the toxic properties of oxygen. As these toxic properties are what trials on the subject strive to minimise, one could claim that this connection is just as important as the link between SaO₂ and the total oxygen content of the blood.

In clinical practice, both SaO₂ and PaO₂ are commonly used to guide oxygen therapy, particularly in the ICU setting, as the majority of acute critically ill ICU patients require arterial cannulation for haemodynamic monitoring. For evaluating arterial oxygenation, a recent survey of northern European ICU physicians has shown that PaO₂ was preferred to SaO₂ [16].

In summary, to define the oxygenation target levels precisely, to reduce the risk of unwanted hyperoxaemia, and to minimise overlap between conventional and interventional groups, in clinical trials of higher versus lower oxygenation targets in the ICU population, PaO₂ is in our opinion the superior target parameter as compared to SaO₂. This is also reflected in clinicians' self-reported preferences. Therefore, we advocate the use of PaO₂ as the primary target parameter of arterial oxygenation in future clinical trials that aim to establish the evidence of how to use medical oxygen in patients admitted to the ICU.

Abbreviations

HOT-ICU: Handling Oxygenation Targets in the Intensive Care Unit; ICU: Intensive care unit; PaO₂: Arterial oxygen tension; SaO₂: Arterial oxygen saturation; SpO₂: Pulse oximetry

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BSR conceived the idea for the editorial. OLS drafted the primary manuscript. OLS and BSR revised the manuscript together. Both authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Both authors are involved in an ongoing investigator-initiated randomised trial targeting oxygenation in acutely ill patients in the ICU, the Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU) trial (ClinicalTrials.gov NCT03174002), OLS as coordinating investigator and BSR as sponsor and primary investigator.

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