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LETTER TO THE EDITOR

Fraction of inspired oxygen (FiO_2) to modulate respiratory drive in a mechanically ventilated patient

A. Osinski, J. van Rosmalen, R.P.J. Baltussen

Department for Critical Care, Máxima Medical Centre, Veldhoven, the Netherlands

Correspondence

J. van Rosmalen - jeroen.van.rosmalen@mmc.nl

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Dear editor,

With great interest we read the review by Jonkman, de Vries and Heunks, extensively explaining the physiology of respiratory drive in ICU patients, published recently in Critical Care.[1] We would like to present a recent clinical observation of a patient's respiratory drive that was possibly influenced by subtle differences in arterial oxygen content.

A 71-year-old male was admitted to our ICU in the spring of 2020 with respiratory insufficiency due to COVID-19. He had no relevant medical history, especially no pulmonary diseases or tobacco use. According to our local protocol, he was treated with selective digestive tract decontamination and (after his approval) chloroquine. His admission was complicated by subsegmental pulmonary emboli, infection with *Aspergillus fumigatus*, a pneumothorax and a central line-associated bloodstream infection. Chronic lymphocytic leukaemia without secondary complications or indications for therapeutic intervention was diagnosed during his ICU stay. He was ventilated mainly in the prone position. After tracheotomising him, our patient was weaned from mechanical ventilation and discharged to the pulmonology ward after 51 days in the ICU.

When we observed bradypnoea during pre-oxygenation for bronchial suctioning, we hypothesised our patient's respiratory drive might be influenced by the arterial oxygen content (CaO_2). Secondly, we hypothesised that we might be able to use this characteristic (instead of sedatives and/or neuromuscular blocking agents) to maintain a supposedly, safe manner of mechanical ventilation. Our observations and measurements were obtained in the fourth week of his ICU admission. At that moment, he was being mechanically ventilated (PEEP 5 cmH_2O, 12 cmH_2O pressure support), in a supine position and haemodynamically stable without vasopressors or inotropes (blood pressure 138/53 mmHg, heart rate 96 beats/min). His PaO_2/FiO_2 ratio was 139. He was sedated with midazolam (9 mg/hour), propofol (70 mg/hour), fentanyl (125 µg/hour) to a Richmond Agitation-Sedation Scale (RASS) of -5. Neuromuscular blocking agents were ceased and his core temperature was 37.2 °C. The haemoglobin level was 6.1 mmol/l.

We performed three sets of measurements (*table 1*) in which we gradually decreased the FiO_2 to obtain different oxygen saturation levels, as measured by pulse oximetry (SpO_2). Apart from the FiO_2, all of the ventilator settings and the sedatives remained unchanged. Each arterial blood gas analysis was performed after five minutes of stable SpO_2. Directly after obtaining the arterial blood sample we performed advanced respiratory measurements (*figure 1*) as recently described by Bertoni et al.[2] Our first set of measurements was obtained at five levels of SpO_2 in order to find a threshold of SpO_2 above which our patient's mechanical ventilation would remain

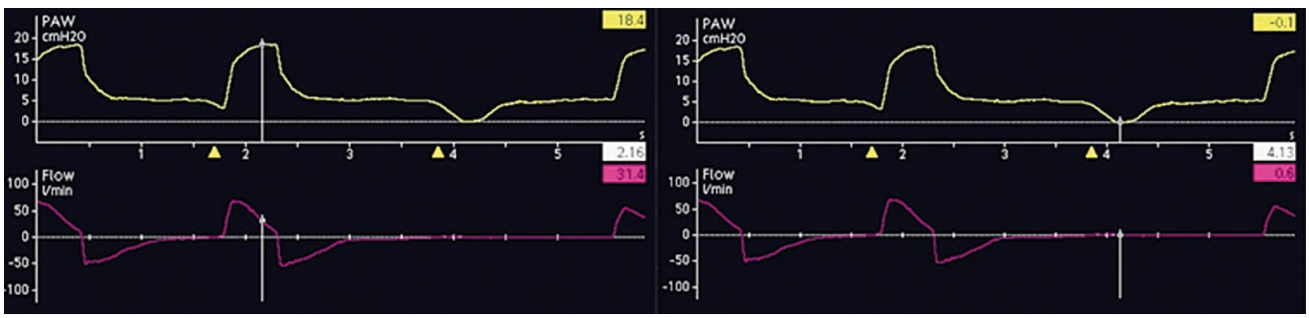

Figure 1. Measurements of peak airway pressure (P_{peak}, left) and delta occlusion pressure (ΔP_{occ}, right) through an expiratory hold. Predicted dynamic transpulmonary driving pressure ($P_{L,dyn}$) is derived from the formula (P_{peak} – PEEP) – 2/3 x ΔP_{occ}. Predicted respiratory muscle pressure (P_{mus}) is derived from the formula -3/4 x ΔP_{occ}. These formulas and methods were recently described by Bertoni et al. [2]

Table 1. Three decremental FiO_2 trials with their accompanying clinical parameters, arterial blood gas values and mechanical ventilation measurements, showing lower predicted dynamic transpulmonary driving pressure and predicted respiratory muscle pressure with higher FiO_2

	First trial					Second trial			Third trial		
Time	16:41h	16:54h	17:09h	17:15h	17:26h	17:49h	18:09h	18:15h	18:20h	18:34h	18:43h
Clinical parameters											
Targeted SpO_2 (%)	98-100	96-97	95-94	92-93	90-91	98-100	96-97	94-95	98-100	96-97	94-95
Actual SpO_2 (%)	99	97	95	93	90	99	97	94	99	97	94
Respiratory rate (breaths/min)	24	24	24	24	28	24	23	25	16	25	17
Tidal volume (ml)	352	372	418	452	421	384	376	426	414	431	477
Arterial blood pressure (mmHg)	138/53	145/56	145/57	146/56	153/57	151/53	146/51	152/53	165/51	119/50	121/50
Heart frequency (beats/min)	96	95	95	96	97	98	99	98	97	103	96
Arterial blood gas values											
pH	7.40	7.42	7.43	7.47	7.48	7.42	7.46	7.47	7.43	7.45	7.46
$PaCO_2$ (mmHg)	73	68	66	61	59	68	62	59	66	63	62
PaO_2 (mmHg)	97	76	65	52	48	89	69	60	110	69	61
Bicarbonate (mmol/l)	45	44	44	44	44	44	43	43	44	44	44
SaO_2 (%)	98	96	94	89	86	97	95	93	99	95	93
Arterial oxygen content (CaO_2, ml/dl)	13.4	13.1	12.8	12.1	11.6	13.2	12.9	12.6	13.6	12.9	12.6
Mechanical ventilator measurements											
FiO_2	0.70	0.60	0.50	0.40	0.38	0.70	0.48	0.40	0.65	0.45	0.40
$EtCO_2$	55	50	47	45	43	50	47	46	55	48	43
Peak (cmH_2O)	17.6	15.8	16.5	18	17.7	18	17.6	18.4	17.8	17.9	17.9
PEEPtotal (cmH_2O)	5	5	5	5	5	5	5	5	5	5	5
Predicted dynamic transpulmonary driving pressure ($P_{L,dyn}$, cmH_2O)	15.9	17.2	18.4	20.1	22.1	14.2	15.5	16.8	14.9	15.8	18.1
Predicted respiratory muscle pressure (P_{mus}, cmH_2O)	3.8	7.2	7.8	8.0	10.6	1.4	3.3	3.8	2.4	3.2	7.9

Arterial oxygen content was derived from the formula (SaO_2 x haemoglobin concentration) x 1.34 + (0.003 x PaO_2). Haemoglobin concentration was 6.1 mmol/l

(predicted) lung-protective. We found this to be at an SpO_2 of 96-97% and repeated our measurements twice. In all three sets of measurements, with decreasing FiO_2 (and thus CaO_2) we observed an increasing respiratory drive, measured as predicted respiratory muscle pressure (P_{mus}, an indicator of load-induced diaphragm trauma). We also found an increasing predicted dynamic transpulmonary driving pressure ($P_{L,dyn}$, an indicator of lung stress) with decreasing FiO_2. Average percentage changes in P_{mus} and $P_{L,dyn}$ (SpO_2 targets 98-100% compared with 94-95%) were 168.3% and 18.3%. More interestingly, $P_{L,dyn}$ consequently shifted from values regarded as safe to unsafe (≥16-17 cmH_2O), as stated by Bertoni et al.[2] Theoretically, this might increase lung stress and the risk of patient self-inflicted lung injury (P-SILI). As a result of - and not the cause of - the increasing respiratory drive, $PaCO_2$ levels decreased with lower CaO_2. Our measurements suggest that the respiratory drive in our patient was influenced by CaO_2, even if the changes were small. More remarkably, this relationship was seen even when SpO_2 values remained in the normal range (≥94%).

Since excessive respiratory drive is regarded to possibly cause patient self-inflicted lung injury (P-SILI) in selected patients, strategies to modulate respiratory drive have gained recent interest. Modulation of ventilator support is proposed, but also more invasive procedures such as administration of sedation, neuromuscular blocking agents or even extracorporeal CO_2 removal.

We appreciate the ongoing debate about oxygen dosing in mechanical ventilation[3] and we are aware of the drawbacks of hyperoxia. In treating ARDS patients, we target oxygenation goals as suggested in the ARDS network trial, i.e. SpO_2 88-95.[4] In this patient however, aiming for a higher SpO_2 seemed to effectively reduce respiratory drive. A little bit more oxygen supported our

lung-protective strategy, probably with less risk and/or adverse effects then the above-mentioned alternatives.

We found no studies elaborating on the influence of arterial oxygen content on the respiratory drive in ICU patients. We do not know whether our findings are applicable to a larger population and if the reaction to oxygen might be a temporary phenomenon in this patient. More research is needed to answer these questions.

Disclosures

Written informed consent was obtained from the patient for this publication.

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References

1. Jonkman AH, de Vries HJ, Heunks LMA. Physiology of the Respiratory Drive in ICU Patients: Implications for Diagnosis and Treatment. Crit Care. 2020;24:104.
2. Bertoni M, Telias I, Urner M, et al. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. Crit Care. 2019;23:346.
3. Angus DC. Oxygen Therapy for the Critically Ill. N Engl J Med. 2020;382:1054-6.
4. Acute Respiratory Distress Syndrome Network; Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. N Engl J Med. 2000;342:1301-8.