

## COVID-19 CORRESPONDENCE

## Haemodynamic impact of positive end-expiratory pressure in SARS-CoV-2 acute respiratory distress syndrome: oxygenation versus oxygen delivery

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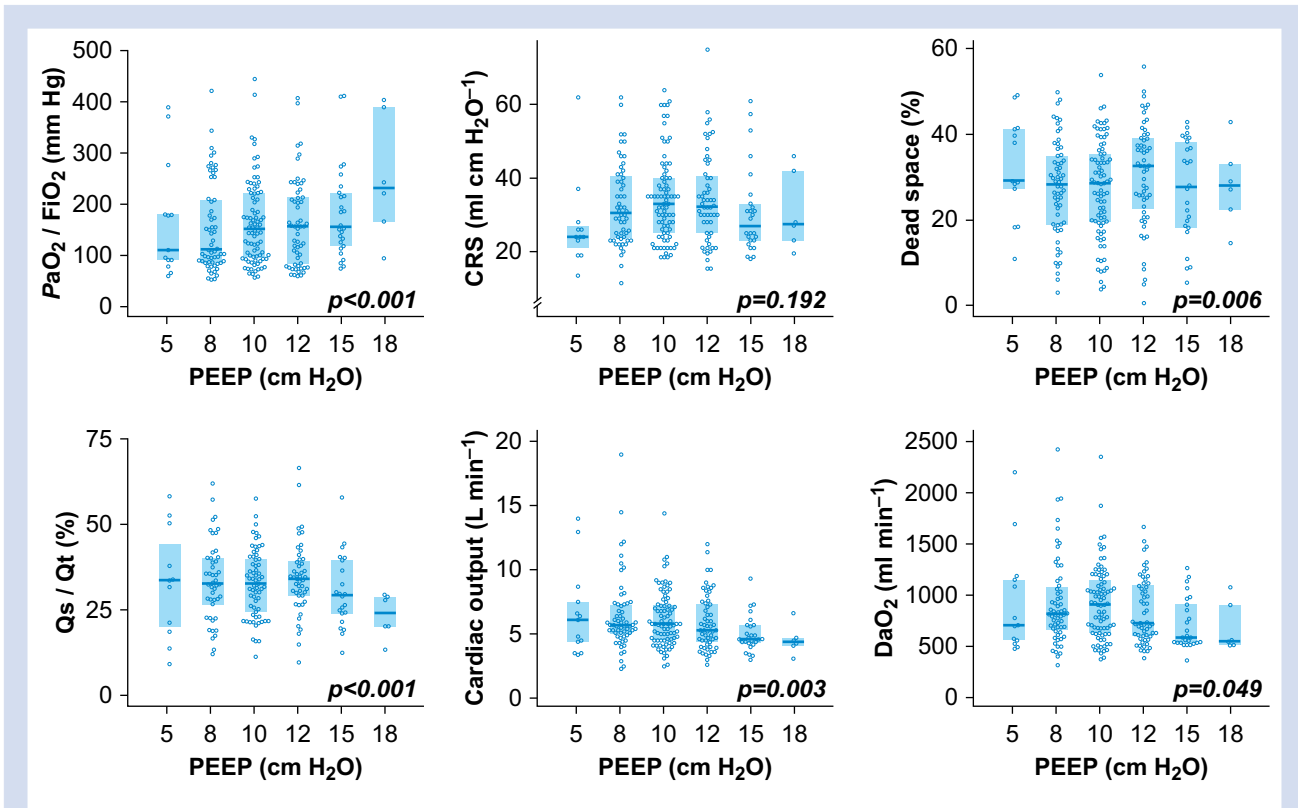
Editor—Several recommendations have been written for the management of acute respiratory distress syndrome (ARDS) over the last decade. The latest ones issued from a French group<sup>1</sup> suggest individualising positive end-expiratory pressure (PEEP) settings, reserving higher PEEP for patients in whom oxygenation improves without deterioration of respiratory system compliance ( $C_{RS}$ ) or haemodynamic status. In contrast, coronavirus 2019 (COVID-19) guidelines<sup>2</sup> suggest using higher PEEP (>10 cm H<sub>2</sub>O), although the risk of haemodynamic deterioration is not mentioned. However, it has been suggested that a significant proportion of intubated COVID-19 patients respond poorly to recruitment,<sup>3</sup> and some experts have pointed out the risks of haemodynamic deterioration and congestion from the beginning of the pandemic in these patients.<sup>4</sup> COVID-19 ARDS can be associated with an increase in intrapulmonary shunt fraction ( $Q_s/Q_t$ ) related to abnormal pulmonary vasodilation and increased perfusion in some lung areas<sup>5</sup> that might be related to endothelial and vascular dysfunction.<sup>6</sup> Thus, although arterial oxygenation may improve through alveolar recruitment,  $Q_s/Q_t$  reduction as a result of the decrease in cardiac output caused by higher PEEP<sup>7</sup> may be another mechanism to consider. Some studies have suggested that haemodynamic deterioration may occur when higher PEEP is used in COVID-19 ARDS,<sup>8,9</sup> but the consequences on cardiac output and thus oxygen delivery (DaO<sub>2</sub>) have not been evaluated.

This single-centre retrospective study aimed to evaluate the haemodynamic impact of PEEP increase in COVID-19 ARDS and

its consequences on DaO<sub>2</sub>. The study was conducted in a 36-bed ICU (Hôpital Lariboisière, Paris, France). Medical records of patients admitted between March 14, 2020 and April 22, 2020 were reviewed. Inclusion criteria were: ICU admission for respiratory failure, diagnosis of ARDS according to the Berlin criteria, laboratory confirmed SARS-CoV-2 infection, and at least one PEEP trial with cardiac output monitoring. The primary endpoints were the consequences of increasing PEEP on oxygenation, haemodynamics and oxygen delivery, and respiratory mechanics. The secondary endpoint was the association between higher PEEP (>10 cm H<sub>2</sub>O) and improvement of oxygenation and oxygen delivery. This study was approved by the Institutional Review Board (IRB-00006477) of HUPNVS, Paris 7 University.

Patients were managed according to our previously described local protocol<sup>10</sup> based on the latest guidelines.<sup>1</sup> The PEEP trial protocol is described in the Supplementary data. The effect of PEEP level on the dependent variables was tested in linear mixed-models with PEEP as a fixed effect and PEEP trial nested by patient as random effects to deal with the fact that a patient may have had multiple PEEP trials, and that a PEEP trial includes more than one PEEP level. The proportions of patients who benefited from higher PEEP (>10 cm H<sub>2</sub>O) were compared with a  $\chi^2$  test. Statistical analyses were performed using R statistical software version 3.6.1 (R Core Team, 2019, R Foundation for Statistical Computing, Vienna, Austria, <https://www.R-project.org>). A p-value <0.05 was considered significant.

Of 89 patients admitted to our ICU during the study period with a diagnosis of COVID-19 ARDS, 30 patients met inclusion



**Fig 1.** Effect of PEEP level on oxygenation, respiratory system compliance, dead space, intrapulmonary shunt, cardiac output, and oxygen delivery.  $C_{RS}$ , respiratory system compliance;  $DaO_2$ , arterial oxygen delivery;  $PaO_2/FiO_2$ , arterial oxygen partial pressure ( $PaO_2$ ) to fraction of inspired oxygen ( $FiO_2$ ) ratio with  $FiO_2=1$ ;  $Qs/Qt$ , intrapulmonary shunt. The values are presented in [Supplementary Table S1](#).

criteria and were analysed (age 61 [54–59] yr, sex ratio M/F 2.3, BMI 28 [26–31] kg m<sup>-2</sup>). The median number of PEEP trials performed per patient was two (one to five). The median time from ICU admission was 6 (3–9) days.

The effects of increasing PEEP levels on respiratory mechanics, oxygenation, haemodynamic status, and oxygen delivery are presented in [Figure 1](#). Increased PEEP was associated with an increase in  $PaO_2/FiO_2$  ( $P<0.001$ ) and a decrease in  $Qs/Qt$  ( $P<0.001$ ), without changes in  $C_{RS}$  ( $P=0.192$ ) but with decreases in cardiac output ( $P=0.003$ ) and  $DaO_2$  ( $P=0.049$ ). For each cm H<sub>2</sub>O of PEEP increase,  $PaO_2/FiO_2$  increased by 10 mm Hg (95% confidence interval [CI] 8–13) and  $Qs/Qt$  decreased by –1% (95% CI –1 to –2), but cardiac output and  $DaO_2$  decreased by –92 ml min<sup>-1</sup> (95% CI –152 to –33) and –8.5 ml min<sup>-1</sup> (95% CI –17.1 to 0.1), respectively (results for all variables in [Supplementary Table S2](#)). In our cohort, 43% of PEEP trials were associated with a positive response to higher PEEP (10 cm H<sub>2</sub>O) for  $PaO_2/FiO_2$ . For  $DaO_2$ , the positive response to higher PEEP decreased to 27% ( $P=0.031$ ).

We showed that higher PEEP was associated with an increase in  $PaO_2/FiO_2$  ratio without improvement in oxygen delivery because of a decrease in cardiac output. When haemodynamic status and oxygen delivery were considered, most patients did not benefit from higher PEEP (>10 cm H<sub>2</sub>O). Interestingly, higher PEEP had a poor impact on  $C_{RS}$ , and therefore was unlikely to have prevented ventilation-induced lung injury.

Higher  $PaO_2/FiO_2$  ratio associated with higher PEEP does not only rely on alveolar recruitment and improvement of lung

mechanics. The correction of the ventilation-perfusion mismatch, which may result partly from reduced  $Qs/Qt$  associated with reduced cardiac output, may contribute to the improvement of arterial oxygenation.<sup>7</sup> This observation is in line with a report of high interindividual variability of potential for lung recruitment,<sup>3</sup> and ventilation-perfusion mismatch likely related to blood flow redistribution rather than non-ventilated units.<sup>9</sup> The relative contribution of increased pleural pressure and increased transpulmonary pressure with PEEP increase, resulting from decreased right ventricle preload and increased right ventricular afterload (eventually leading to the decrease in cardiac output), were not specifically evaluated in this study. Their co-existence has been suggested by others as well.<sup>8</sup>

Even though this is a small study with potential selection bias, our data suggest that interpretation of results of PEEP titration in COVID-19 ARDS should not rely only on  $PaO_2/FiO_2$ .  $C_{RS}$  and cardiac output should be considered simultaneously to identify the patient-centred effect of PEEP level on alveolar recruitment and haemodynamic effect. When haemodynamic effect is preeminent, the apparent increase in  $PaO_2/FiO_2$  may not be associated with more oxygen delivery to the patient.

In COVID-19 ARDS, higher PEEP may lead to a decrease in cardiac output without increases in  $DaO_2$ , despite an increase in  $PaO_2/FiO_2$ . Higher PEEP could be unbeneficial to a significant proportion of patients. These results require a cautious and multimodal approach including cardiac output monitoring when using higher PEEP.

## Authors' contributions

Designed the study: RBa, VB, RBo, BGC

Participated in the collection of data: RBa, VB, RBo, BGC, MC, ALG, AH

Performed the statistics: RBa, VB, RBo, BGC

Participated in interpretation of the data: RBa, VB, RBo, BGC, EG, AM

Participated in drafting of the manuscript: RBa, VB, RBo, BGC, MC, ALG, AH, EG, AM

Read and approved the final manuscript: all authors

## Declarations of interest

RBa reports non-financial support from Vygon and from Getinge France. EG received lecture fees from Edwards Life-science and research grants from Philips and Radiometer. AM received speaker's honoraria from Novartis, Orion, and Servier and fees as a member of the advisory board, steering committee, or both from Adrenomed, Sanofi, Roche, Abbott, and 4TEEN4. BGC received fees as a member of an advisory board from Roche Diagnostics. The other authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2020.10.026>.

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# Potential for personalised application of inhaled nitric oxide in COVID-19 pneumonia

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