To the Editor: We read with great interest the recently published pilot phase of the ICU-ROX trial by Young and colleagues, who are trying to answer a question from daily practice: what is the best oxygenation target during mechanical ventilation? In this pilot trial enrolling adults requiring invasive mechanical ventilation, the authors found that conservative oxygen strategy was feasible, and resulted in a shorter time spent with an oxygen saturation measured by pulse oximetry (SpO₂) above 97% than standard care.

A pragmatic and simple protocol is necessary to complete a large trial such as ICU-ROX. In line with that, the positive end-expiratory pressure (PEEP) setting was let to the clinician’s discretion, in both intervention and control groups. Despite this, there was no significant difference in mean PEEP level between the two groups, which was 7–8 cmH₂O for the first 10 days. Although this result seems to validate the choice of the authors to not standardise PEEP setting, it might be discussed depending of the enrolled population. As more than 20% of enrolled patients had a predominantly respiratory failure, it might be useful to know which proportion of them fulfilled acute respiratory distress syndrome (ARDS) criteria. Indeed, in our opinion, enrolment of a large number of patients with ARDS might induce a systematic bias due to differences in PEEP settings. Because there is currently no optimal strategy to set the PEEP, PEEP/fraction of inspired oxygen (FiO₂) tables are frequently used. As a consequence, one could argue that, in this trial, patients with ARDS in the experimental group will be systematically treated with lower PEEP levels than those in the control group, according to a lower FiO₂. There are some conflicting data about the beneficial effect on mortality of higher versus lower PEEP level in ARDS. However, it is likely that if a high proportion of enrolled patients have ARDS, heterogeneous management of PEEP level will make it difficult to conclude about the real impact of FiO₂ management on patient outcomes.

Apart from difference in PEEP level, ARDS might also be a confounder through its own severity. Because randomisation was only stratified by treating centre, it is possible that the two groups would be imbalanced regarding the arterial partial pressure of oxygen (PaO₂)/FiO₂ ratio. According to the Berlin definition, mild, moderate and severe ARDS are distinguished by differences in ventilator-free days, which constitute the primary outcome of the ICU-ROX trial. Therefore, ARDS baseline severity might be an important confounding factor, and, while imperfect, stratification by an early PaO₂/FiO₂ ratio performed with standardised ventilator settings might be useful.

As in the recent Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, in which 23% of all the patients requiring mechanical ventilation had ARDS, it is probable that a significant proportion of the patients enrolled in the ICU-ROX trial will have ARDS.

Apart from potential number of patients with ARDS, a high proportion of patients (20%) were included after having cardiac arrest. Recent guidelines recommend avoiding hyperoxia as soon as reliable oxygen measurements are provided. The authors need to discuss such an issue and provide at least a separate analysis for this subgroup of patients.

Young and colleagues provide data on PaO₂ and FiO₂ levels (mean, lowest and highest). While FiO₂ is always lower in the conservative arm compared with the standard arm, highest PaO₂ shows large variations in the conservative arm. Moreover, the SpO₂ values are not provided; they would be useful to explain such discrepancies as they might reflect higher workload for the nurses to adjust the ventilator setting in the conservative arm. Furthermore, these values might indicate a risk of alarm fatigue and an increase in the withdrawal of arterial blood gases to prevent hypoxaemia. Such information could be valuable to address the feasibility aspects of the protocol in daily life.

To conclude, the results of the ICU-ROX trial are highly anticipated to confirm the beneficial effect of a restrictive oxygenation strategy in a mixed critically ill population. However, because of the potential confounding effect of PEEP level and baseline PaO₂/FiO₂ ratio, enrolment of a large number of patients with ARDS might not be ideal to adequately answer the study question. Evaluating the nurses’ workload may also add valuable information.

Competing interests
None declared.

Author details
Hadrien Winiszewski
Loïc Barrot
Gaël Piton
Gilles Capellier

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LETTER

In their letter, Winiszewski and colleagues raise a number of important points regarding the pilot phase of the ICU-ROX trial\(^1\) which require clarification. One of the pre-specified subgroups for the ICU-ROX trial comprises patients with an arterial partial pressure of oxygen/inspired oxygen (Pa\(_{\text{O}_2}/\text{Fi}_\text{O}_2\)) ratio of < 300 mmHg at baseline.\(^2\) While patients with acute respiratory distress syndrome (ARDS) represent an important subset of such population, there is no evidence that patients with ARDS are more prone to oxygen toxicity than patients with pulmonary pathologies who do not have ARDS. Accordingly, we have not defined patients with ARDS as a separate subgroup in our trial. Our experience is that positive end-expiratory pressure (PEEP)/Fi\(_{\text{O}_2}\) tables are not commonly used in patients with ARDS in Australian and New Zealand intensive care units, and, indeed, recent data from the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) suggest that they are probably not used frequently elsewhere either.\(^3\)

Stratification of patients by ARDS severity in a multicentre trial such as ICU-ROX would require patients to be correctly diagnosed with ARDS and categorised into one of the severity groups before randomisation. Given that diagnosis of ARDS is difficult,\(^4\) such stratification would be challenging in a multicentre randomised controlled trial with a 2-hour enrolment window. The mean ± standard deviation (SD) PEEP levels in the patients with a Pa\(_{\text{O}_2}/\text{Fi}_\text{O}_2\) ratio < 300 mmHg assigned to the conservative and standard oxygen groups in the pilot phase of ICU-ROX were 8.4 ± 3.0 cmH\(_2\)O and 8.9 ± 3.0 cmH\(_2\)O respectively \((P = 0.21)\). Thus, while we acknowledge that there is a one in 20 chance of statistically significant baseline imbalance in the number of patients with ARDS between treatment groups, we submit that that heterogeneous PEEP management is unlikely to be a major confounding factor.

The number of arterial blood gas tests performed, and a range of oxygen saturation measured by pulse oximetry (Sp\(_{\text{O}_2}\))-related metrics that provide insight into nursing workload, will be reported in the main study.\(^2\) Recommendations in relation to oxygen management in patients with cardiac arrest are based on low quality evidence.\(^5\) Among patients with cardiac arrest enrolled in the ICU-ROX pilot phase, the mean ± SD Fi\(_{\text{O}_2}\) was 0.31 ± 0.14 for conservative oxygen therapy and 0.36 ± 0.10 for standard oxygen therapy \((P = 0.007)\). The mean ± SD Pa\(_{\text{O}_2}\) was 85 ± 28 mmHg for those allocated to conservative oxygen

Paul Young, on behalf of the ICU-ROX Investigators

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1 Medical Intensive Care Unit, University Hospital of Besançon, Besançon, France.  
2 Adult Intensive Care and Burn Unit, Lausanne University Hospital, Lausanne, Switzerland.  
3 Research Unit EA 3920 and SFR FED 4234, University of Franche Comté, Besançon, France.  
4 Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, Vic, Australia.

Correspondence: hwiniszewski@chu-besancon.fr

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therapy and 100 ± 26 mmHg for those allocated to standard oxygen therapy (P < 0.001). The results from the pilot phase of ICU-ROX suggest that the proportion of patients with cardiac arrest in the main study will be relatively high.\(^1\) The ICU-ROX trial will thus provide some randomised controlled data to support or refute existing recommendations for oxygen management in this population of patients.

**Competing interests**
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**Author details**
Paul Young on behalf of the ICU-ROX Investigators
Medical Research Institute of New Zealand, Wellington, New Zealand.

**Correspondence:** Paul.Young@ccdhb.org.nz

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