

## O<sub>2</sub>, DO WE KNOW WHAT TO DO?

Paul J Young<sup>1,2</sup>, Michael Bailey<sup>3,4</sup>, Rinaldo Bellomo<sup>3,4,5</sup>, Diane Mackle<sup>2</sup>, David Pilcher<sup>6</sup>, Giovanni Landoni<sup>7,8</sup>, Alistair Nichol<sup>3,6,9</sup>, Daniel Martin, Paul Mouncey, Kathy Rowan.

<sup>1</sup> Intensive Care Unit, Wellington Hospital, Wellington, New Zealand

<sup>2</sup> Medical Research Institute of New Zealand, Wellington, New Zealand

<sup>3</sup> Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia

<sup>4</sup> University of Melbourne, Parkville, Victoria, Australia

<sup>5</sup> Intensive Care Unit, Austin Hospital, Heidelberg, Victoria, Australia

<sup>6</sup> The Alfred Hospital Intensive Care Unit, Melbourne, Australia

<sup>7</sup> IRCCS San Raffaele Scientific Institute, Milan, Italy

<sup>8</sup> Vita-Salute San Raffaele, Milan, Italy

<sup>9</sup> University College Dublin- Clinical Research Centre at St Vincent's University Hospital Dublin, Ireland

<sup>10</sup> University College London Division of Surgery and Interventional Science, 9th Floor, Royal Free Hospital, London, NW3 2QG, United Kingdom

Correspondence: [paul.young@ccdhb.org.nz](mailto:paul.young@ccdhb.org.nz)

The human body has adapted to breathe air, which contains 21% oxygen. In normal circumstances, the arterial partial pressure of oxygen ( $\text{PaO}_2$ ) is 80-100mmHg. This  $\text{PaO}_2$  range normally corresponds to an oxygen saturation of 95-99% when measured by arterial blood gas sampling ( $\text{SaO}_2$ ) or via pulse oximetry ( $\text{SpO}_2$ ). Oxygen is required to convert biochemical energy from nutrients into adenosine triphosphate (ATP) via aerobic cellular respiration and is fundamental to sustaining human life<sup>1</sup>. As well as producing ATP, aerobic cellular respiration produces reactive oxygen species. Although reactive oxygen species have important roles in cellular signalling and homeostasis<sup>2</sup>, they can also damage nucleic acids, proteins, and lipid membranes resulting in cell death<sup>3</sup>. In normal physiology, a number of antioxidant enzymes prevent the cellular damage from reactive oxygen species. However, hyperoxia increases generation of reactive oxygen species and, when production of reactive oxygen species exceeds the capacity of the antioxidant enzymes, an imbalance known as “oxidative stress” results<sup>4</sup>.

In particular, in the lungs, in addition to the damaging effects of “oxidative stress”, provision of supplemental oxygen has potentially adverse effects on physiology<sup>4</sup>. Specifically, supplemental oxygen causes washout of alveolar nitrogen (i.e. oxygen replaces nitrogen in the alveolus). Oxygen dissolves in the blood more easily than nitrogen and, if oxygen diffuses from the alveoli more rapidly than it is replenished by inhaled oxygen, areas of lung collapse (atelectasis) develop<sup>5</sup>. An additional pathophysiological consequence of liberal oxygen administration is that it increases the risk of arterial

hypercapnia<sup>6-9</sup> and may worsen ventilation/ perfusion mismatch by blunting hypoxic pulmonary vasoconstriction.

The *Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen therapy (ICU-ROX)* trial, which was published recently<sup>10</sup>, is the largest oxygen therapy trial so far undertaken in ICU patients. ICU-ROX included 1000 mechanically ventilated adults from 21 Australian and New Zealand ICUs who were randomly assigned to conservative oxygen therapy or usual oxygen therapy. Compared to patients allocated to usual oxygen, those allocated to conservative oxygen spent more time in the ICU receiving an inspired oxygen concentration (FiO<sub>2</sub>) of 0.21 and less time with an SpO<sub>2</sub> of  $\geq 97\%$  or higher. The PaO<sub>2</sub> in conservative oxygen therapy patients was also correspondingly lower than in usual oxygen therapy patients. Despite a substantial reduction in oxygen exposure, which was achieved without an increase in episodes of low SpO<sub>2</sub>, conservative oxygen therapy neither increased nor decreased the primary end point of ventilator-free days to day 28<sup>10</sup>.

While these findings provide a degree of reassurance that the apparent increased mortality risk associated with liberal oxygen therapy in a previous single centre Italian RCT<sup>11</sup> might represent type 1 error, they are not definitive. In the ICU-ROX trial, day 180 mortality was 35.7% in patients allocated to conservative oxygen therapy and 34.5% in patients allocated to usual oxygen therapy<sup>10</sup>. This corresponds to an absolute treatment effect on mortality of 1.2% (95%CI, -4.9% to 7.3%). Based on this distribution of data,

compared with usual oxygen therapy, there is a 46% chance that conservative oxygen therapy increases absolute mortality by more than 1.5% and a 19.3% chance that conservative oxygen therapy decreases absolute mortality by more than 1.5%. These probabilities are supported by simulation data. In 100,000 trial simulations, which reflect random sampling from the ICU-ROX trial database, the absolute mortality of conservative oxygen therapy patients was more than 1.5% higher than the absolute mortality of usual oxygen therapy patients 45.9% of the time; the absolute mortality of conservative oxygen therapy patients was more than 1.5% less than the absolute mortality of usual oxygen therapy patients 19.25% of the time. In other words, based on the ICU-ROX data, there is an almost 66% chance that conservative oxygen either increases or decreases absolute mortality in mechanically ventilated adults in the ICU by more than 1.5%.

Given that a recent high impact publication in the Lancet highlighted the potential harms associated with liberal oxygen regimens<sup>12</sup>, conservative oxygen therapy may continue to be used by some clinicians. Clearly, either an increase or decrease in absolute mortality of 1.5% with conservative oxygen therapy would have profound implications for global public health because oxygen is given to the millions of people around the world requiring life support in ICU every year. Accordingly, we now plan to conduct a multicentre, multinational, randomized clinical trial to compare conservative oxygen therapy with usual oxygen therapy in mechanically ventilated patients who are either admitted to ICU emergently or intubated in ICU.

Assuming a control group mortality rate of 29%, a sample size of 37,860 provides 90% power to detect an absolute mortality difference of 1.5% using a two tailed hypothesis at an alpha of 0.05. An ICU trial of this size has never been attempted and will require a novel approach. Rather than collecting study data using case report forms, we plan to use existing national ICU data registries in respective participating countries. Central randomisation will be performed by clinical staff using a purpose-built study website. At the time of randomisation we will collect a basic dataset consisting of: 1) the date and time of randomisation and the study centre (these will be recorded automatically by the study website); 2) the date of ICU admission; 3) the date of hospital admission; 4) the patient's gender; and 5) the patient's age. These data, along with the ICU discharge date, will be used to match study patients to patient records in respective participating countries' ICU registries. Registry data will be used to obtain baseline data and outcome data; the primary outcome will be in-hospital mortality.

One common criticism of prior multicentre RCTs in ICU patients has been failure to account sufficiently for potential heterogeneity of treatment responses<sup>13</sup>. Whether or not conservative oxygen therapy affects mortality overall, it is plausible that conservative use of oxygen benefits some patient groups and harms others. For example, in ICU-ROX patients with suspected hypoxic ischaemic encephalopathy appeared to benefit from conservative oxygen therapy<sup>10</sup>. In the Mega Randomised Registry-embedded OXYgen (Mega-ROX) trial, subgroups of significant numerical size where a differential effect of oxygen therapy is plausible will be investigated in nested trials that

will be conducted within the overall participant sample. Moreover, we plan to adjust randomisation ratios so that patients within such subgroups receive the oxygen therapy regimen associated with the lowest risk of death based on accumulated trial data. In a sense this means that every patient in the Mega-ROX trial will benefit from the information gained from previous patients.

We are already embarking on the vanguard phase of the Mega-ROX trial. If this vanguard phase demonstrates feasibility, the Mega-ROX global collaborative initiative could further this design to investigate other ubiquitous ICU therapies. This would allow us to conduct the largest ICU trials to date, at a fraction of the cost and time usually required, to detect small but clinically important effects of these ubiquitous therapies.

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