distress syndrome (PHARLAP): a phase II, multicenter randomized controlled clinical trial. *Am J Respir Crit Care Med* 2019;200: 1363–1372.

12. Goligher EC, Kavanagh BP, Rubenfeld GD, Adhikari NK, Pinto R, Fan E, *et al*. Oxygenation response to positive end-expiratory pressure predicts mortality in acute respiratory distress syndrome: a secondary analysis of the LOVS and ExPress trials. *Am J Respir Crit Care Med* 2014;190:70–76.

13. Jonson B, Richard JC, Straus C, Mancebo J, Lemaire F, Brochard L. Pressure-volume curves and compliance in acute lung injury: evidence of recruitment above the lower inflection point. *Am J Respir Crit Care Med* 1999;159:1172–1178.

14. Yoshida T, Piraino T, Lima CAS, Kavanagh BP, Amato MBP, Brochard L. Regional ventilation displayed by electrical impedance tomography as an incentive to decrease positive end-expiratory pressure [letter]. *Am J Respir Crit Care Med* 2019;200:933–937.

15. Katira BH, Engelberts D, Otulakowski G, Giesinger RE, Yoshida T, Post M, *et al*. Abrupt deflation after sustained inflation causes lung injury. *Am J Respir Crit Care Med* 2018;198:1165–1176.

16. Chen L, Chen GQ, Shore K, Shklar O, Martins C, Devenyi B, *et al*. Implementing a bedside assessment of respiratory mechanics in patients with acute respiratory distress syndrome. *Crit Care* 2017;21: 84.

17. Chen L, Del Sorbo L, Grieco DL, Shklar O, Junhasavasdikul D, Telias I, *et al*. Airway closure in acute respiratory distress syndrome: an underestimated and misinterpreted phenomenon. *Am J Respir Crit Care Med* 2018;197:132–136.

18. Mojoli F, Bouhemad B, Mongodi S, Lichtenstein D. Lung ultrasound for critically Ill patients. *Am J Respir Crit Care Med* 2019;199: 701–714.

19. Franchineau G, Bréchot N, Lebreton G, Hekimian G, Nieszkowska A, Trouillet JL, *et al*. Bedside contribution of electrical impedance tomography to setting positive end-expiratory pressure for extracorporeal membrane oxygenation-treated patients with severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;196:447–457.

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∂ The Risk of Hyperoxemia in ICU Patients
Much Ado About O_2

The provision of supplemental oxygen is perhaps the most ubiquitous therapeutic intervention in critical care medicine. To prevent and treat hypoxemia, oxygen is typically administered liberally in the ICU, and patients are often exposed to a high F_{IO_2} and higher than normal Pa_{O_2} (1–3). The association between exposure to hyperoxemia and mortality risk in critical illness has been reported in a number of studies (4–6). However, these studies did not allow for a robust assessment of any dose–response relationship. If such a dose–response relationship were demonstrable, this would increase the probability of a causal relationship between exposure to hyperoxemia and mortality risk.

In this issue of the *Journal*, Palmer and colleagues (pp. 1373–1380) report the findings of an observational study conducted in five university hospitals in the United Kingdom in which they examined the association between longitudinal exposure to hyperoxemia and ICU mortality (7). Hyperoxemia was defined as a $Pa_{O_2} > 13.3$ kPa (100 mm Hg), on the basis that values exceeding this threshold can only be achieved with supplemental oxygen. Patients who stayed in the ICU for 24 hours or less were not included in the analysis. Another important exclusion was patients who had received cardiopulmonary resuscitation in the 24 hours preceding ICU admission. This exclusion is important because the basic science that supports the notion that exposure to hyperoxemia is harmful in hypoxic ischemic encephalopathy is comparatively strong (8) and is supported by prospective observational data (9). The aim of the study was to examine the association between longitudinal exposure to hyperoxemia, defined

as time-weighted mean exposure to supraphysiologic Pa_{O_2}, and mortality.

Regrettably, as outlined by the investigators, modeling exposure to hyperoxemia is inherently complicated for several reasons. First, patients can recover and leave the ICU or die and stop contributing data in a nonrandom fashion. Second, to measure the effect of longitudinal exposure to hyperoxemia, a window of time to observe exposure and subsequent effect is needed. Third, patients receiving more vigorous supplemental oxygen therapy are more likely both to be more severely ill and to develop hyperoxemia. Fourth, such patients are also more likely to have arterial blood gas measurements performed (surveillance bias), thus linking the probability of detecting exposure with the likelihood of being both sicker and more frequently monitored at the time of identified exposure and, probably, both before and thereafter. In an effort to account for these complexities, the investigators divided their cohort into groups with different time windows for potential exposure to hyperoxemia. A total of 77.5% of patients were exposed to hyperoxemia by Day 1, increasing to 90.6% by Day 7.

The authors found that exposure to any hyperoxemia was statistically significantly associated with increased mortality risk in patients with 3, 5, and 7 days of potential exposure, but the dose of hyperoxemia was not. In this regard, when considering the data from this study and whether they reflect a "causative pathway" or yet another association between one of the innumerable variables measured in ICU and outcome, one might want to reflect on the canonical Sir Bradford Hill criteria, which can be applied to assess the "functional relationship" between exposure and outcome (10).

In this regard, when relating hyperoxemia to mortality, the strength of association is weak, the consistency of association is limited and the specificity of association is low, the temporality is complex, the biological gradient is absent, the plausibility is unclear, the coherence is uncertain, the experimental data (outside of cardiac arrest models) are lacking, and the presence of an analogy for a

similar gas-related physiological variable is absent. Thus, given the above consideration, and after acknowledging that this study provides the most detailed epidemiological data available (7), much doubt remains. Moreover, there is one more shortcoming: For clinicians considering the most appropriate dose of oxygen to administer to their patients, the risk associated with hyperoxemia is not the only salient risk. Attempting to minimize the risk for exposure to hyperoxemia with conservative oxygen therapy regimens can inadvertently increase exposure to hypoxemia (11); thus, the risks of hyperoxemia and of hypoxemia need to be considered together, not in isolation.

Despite these concerns, these doubts about hyperoxemia as a possible causative contributor to unfavorable outcomes, and the lack of a demonstrated dose–response relationship between hyperoxemia and mortality, the current study suggests that this issue is important. It also implies that clinicians should wait for data from high-quality randomized controlled trials before implementing conservative oxygen regimens in the ICU. In this regard, although a recent systematic review and meta-analysis reported reduced mortality in acutely ill adults when oxygen use was comparatively restrictive, this included relatively few studies of critically ill patients (12). Moreover, the majority of the critically ill patients included were from a single-center trial, which was stopped early at an unplanned interim analysis (13).

Two comparatively large randomized controlled trials comparing liberal versus conservative oxygen regimens in ICU adults will be reported in the near future (14, 15). These trials promise to substantially advance our understanding of the most appropriate dose of oxygen to use in ICU patients. However, given that the primary outcome for one trial is ventilator-free days (14) and that the other trial focuses on patients with hypoxic respiratory failure (15), further high-quality randomized controlled trials will be needed to establish whether conservative oxygen therapy regimens that seek to limit exposure to hyperoxemia reduce mortality risk.

The provision of supplemental oxygen is such a fundamental treatment for critically ill patients that we consider that future trials should be powered to detect a true minimally important difference in mortality. We submit that an absolute effect on mortality of 1.5 percentage points represents such a difference. A treatment effect of this magnitude would have profound global public health importance because for every 100,000 patients treated, such a difference would equate to 1,500 lives saved or lost. Moreover, in the event of a zero percentage point absolute mortality difference between treatment groups, 95% confidence intervals would be expected to exclude the possibility of an absolute increase or decrease in mortality of well under 1 percentage point. In this situation, the possibility of a clinically important effect of conservative oxygen therapy on in-hospital mortality would effectively be excluded. Until the data from such studies become available, a course of action that prudently avoids unnecessary hyperoxemia while monitoring for and protecting against hypoxemia remains the most sensible approach. ∎

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References

1. Young PJ, Beasley RW, Capellier G, Eastwood GM, Webb SA; ANZICS Clinical Trials Group and the George Institute for Global Health. Oxygenation targets, monitoring in the critically ill: a point prevalence study of clinical practice in Australia and New Zealand. *Crit Care Resusc* 2015;17:202–207.
2. Helmerhorst HJ, Schultz MJ, van der Voort PH, Bosman RJ, Juffermans NP, de Jonge E, et al. Self-reported attitudes versus actual practice of oxygen therapy by ICU physicians and nurses. *Ann Intensive Care* 2014;4:23.
3. Panwar R, Capellier G, Schmutz N, Davies A, Cooper DJ, Bailey M, et al. Current oxygenation practice in ventilated patients-an observational cohort study. *Anaesth Intensive Care* 2013;41:505–514.
4. de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 2008;12:R156.
5. Helmerhorst HJ, Arts DL, Schultz MJ, van der Voort PH, Abu-Hanna A, de Jonge E, et al. Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med* 2017;45:187–195.
6. Eastwood G, Bellomo R, Bailey M, Taori G, Pilcher D, Young P, et al. Arterial oxygen tension and mortality in mechanically ventilated patients. *Intensive Care Med* 2012;38:91–98.
7. Palmer E, Post B, Klapaukh R, Marra G, MacCallum NS, Brealey D, et al. The association between supraphysiologic arterial oxygen levels and mortality in critically ill patients: a multicenter observational cohort study. *Am J Respir Crit Care Med* 2019;200:1373–1380.
8. Pilcher J, Weatherall M, Shirtcliffe P, Bellomo R, Young P, Beasley R. The effect of hyperoxia following cardiac arrest: a systematic review and meta-analysis of animal trials. *Resuscitation* 2012;83:417–422.
9. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability: prospective multicenter protocol-directed cohort study. *Circulation* 2018;137:2114–2124.
10. Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.
11. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al.; CLOSE Study Investigators; ANZICS Clinical Trials Group. Conservative versus liberal oxygenation targets for mechanically ventilated patients: a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med* 2016;193:43–51.

12. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391:1693–1705.

13. Girardis M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA* 2016;316:1583–1589.

14. Mackle DM, Bailey MJ, Beasley RW, Bellomo R, Bennett VL, Deane AM, et al.; Australian and New Zealand Intensive Care Society Clinical Trials Group. Protocol summary and statistical analysis plan for the intensive care unit randomised trial comparing two approaches to oxygen therapy (ICU-ROX). *Crit Care Resusc* 2018;20: 22–32.

15. Schjørring OL, Perner A, Wetterslev J, Lange T, Keus F, Laake JH, et al.; HOT-ICU Investigators. Handling Oxygenation Targets in the Intensive Care Unit (HOT-ICU)-protocol for a randomised clinical trial comparing a lower vs a higher oxygenation target in adults with acute hypoxaemic respiratory failure. *Acta Anaesthesiol Scand* 2019; 63:956–965.

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Cystic Fibrosis Lung Disease and Immunometabolism
Targeting the NLRP3 Inflammasome

The CFTR (cystic fibrosis transmembrane conductance regulator) protein regulates airway mucus viscosity and surface fluid pH (1). Defective CFTR leads to severe chronic airway infection and inflammation that destroys the structural support of bronchi. Correction of the basic defect by highly effective modulators of CFTR function is fueling the hope of a cure or effective control for people with cystic fibrosis (CF) (2). However, structural damage to CF airways is likely to persist even in those individuals whose CFTR function is restored. Furthermore, inflammatory mediators such as oxidants and proteases can suppress CFTR function (3, 4). If all individuals are to fully benefit from CFTR modulator therapies, we will need a better understanding of chronic inflammatory pathways associated with CF lung disease.

Chronic lung disease remains the leading cause of morbidity and mortality in CF (5). The cardinal feature of CF lung disease is the presence of bronchiectasis: floppy cystic airways bearing abundant purulent secretions. The appearance and severity of bronchiectasis is strongly associated with the abundance of airway secretion neutrophil elastase (6). One of the key cytokines driving neutrophilic inflammation in the CF lung is IL-1β (7).

The regulation of IL-1β synthesis and its activation involves a complex interplay of cellular danger sensors, metabolic reprogramming, and post-transcriptional protein processing (8). The study published in this issue of the *Journal* by McElvaney and colleagues (pp. 1381–1391) documents these interactions in CF lung and peripheral blood neutrophils and provides key information pointing to potential new antiinflammatory strategies (9). These immunometabolic changes in neutrophils are independent of CFTR function.

Neutrophil immunometabolism is altered by the CF airway environmental signals known as damage-associated molecular patterns and pathogen-associated molecular patterns, particularly bacterial LPS (Figure 1). Once engaged by LPS, the neutrophil increases transcription of the key metabolic protein, PKM2 (pyruvate kinase M2 isoform). PKM2 undergoes post-translational modification, forming a transcriptional complex with PHD3 (prolyl hydroxylase-3), P300, and HIF1 (hypoxia inducible factor-1) to induce several glycolytic proteins (10). Neutrophil metabolism of glucose is thus reprogrammed toward glycolysis (known as the Warburg effect), rather than oxidative phosphorylation through the Krebs cycle (tricarboxylic acid cycle and citric acid cycle). The HIF1 complex binds to the HRE (HIF1-responsive element) and increases neutrophil PKM2, HIF1, and pro–IL-1β synthesis. Increased glycolysis was confirmed in the CF neutrophil cytosol by high PKM2, lactate, and succinate as well as low pH.

The current study reveals that the amount of circulating LPS in CF blood is sufficient to increase neutrophil PKM2 and pro–IL-1β but not to activate pro–IL-1β. In contrast, the amount of LPS in the CF lung is sufficient to assemble the NLRP3 inflammasome and initiate caspase-1–dependent cleavage and activation of pro–IL-1β. Interestingly, the levels of IL-1β in CF airway secretions strongly correlate with neutrophil burden and patient outcomes. The addition of an NLRP3 inflammasome diarylsulfonylurea-containing inhibitor (MCC950), blocked the LPS-dependent IL-1β production both *in vitro* and in animal models of LPS exposure and *Pseudomonas aeruginosa* airway infection.

The NLRP3 inflammasome is a protein complex comprising an intracellular sensor (Nod-1–like receptor), procaspase-1, and the inflammasome adaptor protein ASC, an activating adaptor for procaspase-1 (11). Oligomerization of the NLRP3 inflammasome into a functional complex activating IL-1β occurs in the presence of mitochondria-derived reactive oxygen species, phagolysosomal destabilization, or bacterial cytotoxins that induce potassium efflux (12). Although the exact mechanism(s) by which the NLRP3 inflammasome is assembled remains unknown, the importance of this complex and its effects on IL-1β activation in CF lung disease is strongly supported by the results of this study as well as the work of previous investigators (13).

Inhibition of the IL-1β and/or the NLRP3 inflammasome represents an attractive goal in the quest to find new efficient strategies to control CF inflammation and possibly improve pathogen clearance. Several molecules capable of preventing the