Supplemental oxygen administration was first noted to correct signs and symptoms of hypoxic respiratory failure more than a century ago. Since that time, oxygen has become one of the most widely administered therapeutic interventions in medicine. The prevention or reversal of hypoxia can be lifesaving, but excessive oxygen supplementation and resulting hyperoxia promotes resorption atelectasis and free radical formation leading to oxidative damage to tissues, endothelial dysfunction, and other deleterious effects. The optimal dose of supplemental oxygen has been explored in several randomized clinical trials. A single-center trial that included 434 patients in a general intensive care unit (ICU) population and compared oxygen titration to a partial pressure of arterial oxygen (PaO₂) of 70 to 100 mm Hg (arterial oxygen saturation [SpO₂] of 94%-98%) vs titration to a PaO₂ up to 150 mm Hg (SpO₂ of 97%-100%) found that the lower oxygenation goals reduced mortality. By contrast, subsequent multicenter trials that included general ICU patients (sample sizes of 965, 400, and 2928 patients), as well as patients with acute respiratory distress syndrome (n = 205) or myocardial infarction (n = 6629) found no benefit from lower oxygen targets.

It is uncertain whether data from ICU-based trials in other patient populations generalize to the out-of-hospital and emergency department treatment of patients resuscitated from cardiac arrest. The pathophysiological sequelae of pulselessness and cardiopulmonary resuscitation may increase susceptibility to and potential harm from both hypoxia and hyperoxia in a manner that changes rapidly in the minutes after return of spontaneous circulation (ROSC). Respiratory failure is a common antecedent cause of cardiac arrest, whereas aspiration, pulmonary contusions, atelectasis, and hypotension develop in most patients who are resuscitated and contribute to ventilation-perfusion mismatch and hypoxemia. Even when SpO₂ and PaO₂ values are within normal range, perivascular edema in the brain can cause tissue hypoxia that may contribute to secondary brain injury after ROSC. Conversely, reperfusion injury is a major contributor to organ dysfunction after ROSC that is worsened by hyperoxia. Postarrest hyperoxia may also reduce cerebral blood flow and cardiac output by increasing vascular resistance.

In this issue of JAMA, Bernard et al report a multicenter clinical trial that randomized adult patients with ROSC after out-of-hospital cardiac arrest and advanced airway placement to receive rapid reduction in supplemental oxygen delivery targeting an SpO₂ of 90% to 94% or high-flow supplemental oxygen targeting an SpO₂ of 98% to 100%. Paramedics randomized eligible patients and initiated the study intervention in the out-of-hospital setting with oxygen titration continued through the emergency department until the first arterial blood gas measure was obtained in the ICU. The primary outcome was survival to hospital discharge, with key secondary outcomes including rates of reaerest, hypoxia (SpO₂ <90%), and Cerebral Performance Category score at 12 months. By design, the investigators planned to enroll 1416 adults with ROSC after cardiac arrest, but the study was halted because of the COVID-19 pandemic after 428 patients were enrolled.

Of 428 enrolled patients, 214 randomized to receive conservative supplemental oxygen (intervention; SpO₂ of 90%-94%) and 211 randomized to receive standard care (SpO₂ of 98%-100%) were included in the primary analysis, with 3 patients excluded for lack of consent or withdrawal from the study. The primary outcome of survival to hospital discharge was lower among patients receiving the conservative oxygen intervention compared with those receiving standard care (82/214 [38%] vs 101/211 [48%; difference, −9.6% [95% CI, −18.9% to −0.2%]). Hypoxia was twice as common in the intervention group compared with the standard care group (67/214 [31%] vs 34/211 [16%]; difference, 15% [95% CI, 7%-23%]), with no differences in other secondary outcomes between the groups.

The findings of this study by Bernard et al, showing possible harm with conservative oxygen titration in the out-of-hospital and emergency department setting, differ from the recently published and neutral Blood Pressure and Oxygen (BOX) trial. The BOX trial randomized 789 adults with previous cardiac arrest who survived to hospital admission to receive conservative (PaO₂ of 68-75 mm Hg) vs liberal (PaO₂ of 98-105 mm Hg) oxygen targets during ICU care and found no significant difference in functionally independent survival to hospital discharge or any prespecified secondary outcome between study groups. Compared with the ICU setting, adverse events including hypoxemia are common during out-of-hospital care of patients following cardiac arrest. Indeed, even in the pilot study that preceded the study by Bernard et al, titrating supplemental oxygen delivery down to 2 L/min resulted in a significant number of hypoxic episodes, particularly if the patient was receiving a larger minute ventilation. Rapid changes in cardiopulmonary physiology early after ROSC, aspiration, and treatment factors including airway obstruction or malpositioning, as well as mechanical failures, may increase the chance of hypoxemia in the out-of-hospital setting. Even brief exposures to hypoxia can have deleterious effects on the injured brain.

How do the findings from the clinical trial by Bernard et al apply to other out-of-hospital systems of care? Implementation of emergency medical services is highly variable even among well-developed and resourced systems. After
out-of-hospital cardiac arrest, survival to discharge varies among North American emergency medical services systems from 0% to 29%.\textsuperscript{22,23} In comparison, survival to hospital discharge in the trial by Bernard et al exceeded 40%.\textsuperscript{17} Emergency medical services in Victoria and South Australia involve highly skilled, professional clinicians with 3 to 4 years of university training and evidence-based protocols. Following survival from cardiac arrest, patients are attended to by 3 clinicians and continuously monitored with pulse oximetry, electrocardiography, noninvasive blood pressure, and end-tidal carbon dioxide. These emergency medical services perform rigorous quality improvement, frequently participate in cardiac arrest research, and are comparable to or more advanced than nonphysician systems in North America, Europe, and Asia.\textsuperscript{24} Given these strengths, the challenge of preventing hypoxemia when titrating FIO2 observed in this robust emergency medical services system may be particularly relevant to other emergency medical services systems with more variable outcomes.

The study by Bernard et al\textsuperscript{17} also has several limitations that should be considered. The trial compared 2 strategies for oxygen supplementation at a population level. This approach is insufficient to define a more complex (eg, U-shaped) dose-response curve or identify an inflection point that represents an optimal dose or delivery strategy.\textsuperscript{25} Moreover, it is biologically plausible that there is between-patient variability in risk of hypoxemia or harm from hyperoxia. For example, a patient who has significant antecedent lung disease or experiences cardiac arrest from pulmonary embolism may benefit from a different strategy than a patient with cardiac arrest from myocardial infarction. Elucidating these factors will require larger trials with multiple treatment intervention groups and more sophisticated designs to maximize efficiency. Although continuous $\text{SpO}_2$ monitoring is standard care in the out-of-hospital environment, $\text{SpO}_2$ is a surrogate measure several steps removed from adequate brain and cardiac tissue oxygen delivery. Directly quantifying arterial or tissue oxygen is difficult and typically provides only intermittent data. Thus, this limitation is unlikely to be addressed until better monitoring tools become available.

When interpreted in the context of other related studies, the clinical trial reported by Bernard and colleagues\textsuperscript{27} in this issue of JAMA provides convincing evidence that harm from hypoxia during conservative oxygen supplementation outweighs any benefit of hyperoxia avoidance during out-of-hospital care of unselected patients after cardiac arrest. The out-of-hospital environment has unique limitations and complexity that require rigorous study to extrapolate interventions primarily tested during intensive care. To be successful, future studies that aim to optimize oxygen delivery after cardiac arrest will require better tools for direct end-organ monitoring and improved approaches to identify those patients most likely to derive benefit from a particular oxygen delivery strategy.