Cardiac arrest (CA) is a devastating condition resulting in a high mortality rate. Even when a return of spontaneous circulation (ROSC) has been obtained, the vast majority of patients who remain comatose after a CA will subsequently die in the following days or weeks, mostly from brain injury (1,2). Of importance, it has been shown that this brain injury continues even after ROSC, due to the “reperfusion injury” process. Over the recent years, intense research aiming to limit this phenomenon was performed in order to decrease the risk of brain damage after CA. However, despite encouraging preclinical results, no drug was shown to be efficient in humans (3,4). To date, targeted temperature management (TTM) is the only treatment firmly recommended in comatose patients resuscitated from a CA (5).

In parallel with TTM, guidelines also suggest to prevent reperfusion injuries resulting from systemic insults, such as exposure to hyperoxia. Indeed, oxygen plays a pivotal role during cardiopulmonary resuscitation (CPR) and oxygen-enriched ventilation is highly recommended during the CPR sequence. However, hyperoxia is commonly observed in resuscitated patients as a consequence of an excessive oxygen supply continued after ROSC. Over the recent years, the hypothesis of a potential deleterious effect of this post-resuscitation hyperoxia has progressively emerged, based on the assumption that the increased oxygen partial pressure (PaO₂) results in overproduction of reactive oxygen species (ROS). Being highly unstable and reactive molecules, these ROS may provoke a large panel of toxic events such as DNA damages, lipid peroxidation, protein oxidation. In experimental studies, a worse neurological, histological and neurochemical outcome was reported in animals exposed to high concentration of oxygen after resuscitation (6-10). In humans, the effects of hyperoxia after CA were assessed in a randomized trial in which CA patients were randomized to either 30% or 100% inspired oxygen fraction (FiO₂) after ROSC (11). The main endpoint was the blood level of neuron-specific enolase (NSE) measured 24 h after resuscitation as a marker of neuronal injury. The main result was a significant increase in NSE in patients submitted to hyperoxia and not treated with therapeutic hypothermia. As an interpretation, authors hypothesized hyperoxia was probably deleterious and that therapeutic hypothermia may protect the brain from detrimental effects of hyperoxia. However, only 28 patients were included in the study, precluding from any firm conclusion. Another randomized clinical study was designed to evaluate the risk-benefit of hyperoxia in these patients, but investigators failed to safely titrate oxygen in the pre-hospital period (12). Thus, most of the available data come from retrospective studies and meta-analysis. On the whole, these human studies, which assessed the associations between hyperoxia and clinical outcomes, reported conflicting results (13-19). Evidence does not permit to know if exposure to hyperoxia contributes by itself to a worsening of reperfusion injuries or if it is only a marker of severity. At that time, current post-resuscitation guidelines recommend titrating the FiO₂ in patients after CA to avoid hypoxia and prolonged exposure to hyperoxia, which is commonly defined as arterial pressure in oxygen (PaO₂) above 300 mmHg (5) on arterial blood gas (ABG). Experts also highlighted the urgent need for well-designed prospective studies examining the effect of hyperoxia on the outcome after CA.
In a recent issue of Circulation, Roberts et al. reported the results of a prospective multicenter cohort study evaluating the association between high oxygen tension exposure after resuscitation from CA and neurological function or death at hospital discharge, defined as a modified Rankin Scale higher than 3 (20). From July 2013 to March 2017, all adult patients successfully resuscitated from in-hospital or out-of-hospital CA and subsequently admitted within one of the 6 participating hospitals in the United States were prospectively included. All these 280 post-cardiac arrest patients underwent therapeutic hypothermia during the first 24-hour. ABG was performed one hour (+2 hours) and 6 hours (+2 hours) and hyperoxia was defined as a PaO$_2$ higher than 300 mmHg on one or more ABG. Regarding initial rhythm, 55% of patients had an asystole or pulseless electrical activity and 37% had ventricular fibrillation or ventricular tachycardia (VF/VT). Percutaneous coronary intervention was performed in 26% of patients with OHCA with VF/VT. Hyperoxia during early hours was observed in 38% of the cohort. After adjusting for potential usual baseline and post-CA confounders, hyperoxia exposure was found to be an independent predictor of poor neurological function at hospital discharge (RR =1.23, 95% CI: 1.11–1.35) using a multivariate linear regression. This finding was confirmed in multiple sensitivity analyses. In addition, authors found an association between the duration of hyperoxia exposure and neurological injury. Assuming that the PaO$_2$ remained constant between two ABG measurements, the authors estimate the duration of exposure to hyperoxia and reported that a one-hour longer duration of hyperoxia exposure was associated with a 3% increase in the risk of poor neurological outcome (RR =1.03, 95% CI: 1.02–1.05). The main conclusion was that early hyperoxia exposure after resuscitation from CA was independently associated with death and poor neurological function at hospital discharge.

Authors should be congratulated for this well-conducted study that reinforced the hypothesis of hyperoxia toxicity in post-CA patients. As compared with previous clinical studies, strengths of the Robert study are multiple, including the prospective and multicentric design that allowed a powerful multivariate analysis, in addition with the multiple sensitivity analyses that confirmed the main result. Nevertheless, there are also some limitations. In addition to its purely observational design, the study suffers from the lack of mechanistic assessment that would have help to appreciate the effect of hyperoxia. In this way, it is regrettable to not have collected biomarkers of oxidative stress and antioxidant defences in order to assess the balance. Even if these biomarkers are difficult to manage ex vivo, showing that the imbalance was more pronounced in patients exposed to hyperoxia would have been an elegant way to explain the main result. In the same way, showing a higher release of brain injury biomarkers (such as NSE) in hyperoxic patients would have been useful to nourish and enhance the hypothesis. Finally, hyperoxic patients were also those with the lowest arterial pressure in CO$_2$ (even if the difference was not significant). Considering that hypercapnia was recently shown to be associated with a better outcome in post-CA patients, one may wonder if this may or not have been associated with the difference in outcome (21).

The study from Roberts et al. highlights the necessity of well-designed randomized studies. In this way, the recently published EXACT study is illustrative of the difficulties in performing an intervention (22). In this Australian phase 2 trial, 61 patients CA patients were randomized to receive either a titrated or a liberal oxygenation through bag-valve reservoir just after ROSC. The titration of oxygen started 35 minutes after ROSC and importantly, there was only a small difference in mean oxygen saturation on arrival at emergency department between the intervention and controls (97% vs. 99%). No difference was observed between the 2 groups regarding outcome. Based on this feasibility trial and considering the large body of evidence coming from observational studies, the same investigators recently started a phase 3 randomised control trial (NCT3138005), aiming to compare the outcome in patients managed with two different targets of oxygen saturations (90–94% or 98–100%) just after CPR. Performed in several Australian cities, investigators wish to enroll nearly 1,400 OHCA patients. Survival to hospital discharge will be the primary outcome by many important secondary outcomes will be assessed such as survival at different time points, quality of life and neurological recovery, oxygen saturation values over time, and adverse events. We are eager to discover the results of this major trial that may considerably influence future guidelines and practices.

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Footnote

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