Bram Rochwerg, MD, MSc (Epi), FRCPC, Series Editor

Oxygenation During Venoarterial Extracorporeal Membrane Oxygenation: Physiology, Current Evidence, and a Pragmatic Approach to Oxygen Titration

Lavienraj Premraj, BMSc[1–3]
Alastair Brown, MBChB[4–6]
John F. Fraser, MBchB, PhD[2,7–9]
Vincent Pellegrino, MBBS[4]
David Pilcher, MD[4,6,10,11]
Aidan Burrell, MBBS, PhD[4,6]

OBJECTIVES: This review aims to: 1) identify the key circuit and patient factors affecting systemic oxygenation, 2) summarize the literature reporting the association between hyperoxia and patient outcomes, and 3) provide a pragmatic approach to oxygen titration, in patients undergoing peripheral venoarterial extracorporeal membrane oxygenation (ECMO).

DATA SOURCES: Searches were performed using PubMed, SCOPUS, Medline, and Google Scholar.

STUDY SELECTION: All observational and interventional studies investigating the association between hyperoxia, and clinical outcomes were included, as well as guidelines from the Extracorporeal Life Support Organization.

DATA EXTRACTION: Data from relevant literature was extracted, summarized, and integrated into a concise narrative review. For ease of reference a summary of relevant studies was also produced.

DATA SYNTHESIS: The extracorporeal circuit and the native cardiorespiratory circuit both contribute to systemic oxygenation during venoarterial ECMO. The ECMO circuit's contribution to systemic oxygenation is, in practice, largely determined by the ECMO blood flow, whereas the native component of systemic oxygenation derives from native cardiac output and residual respiratory function. Interactions between ECMO outflow and native cardiac output (as in differential hypoxia), the presence of respiratory support, and physiologic parameters affecting blood oxygen carriage also modulate overall oxygen exposure during venoarterial ECMO. Physiologically those requiring venoarterial ECMO are prone to hyperoxia. Hyperoxia has a variety of definitions, most commonly Pao_2 greater than 150 mm Hg. Severe hypoxia ($Pao_2 > 300$ mm Hg) is common, seen in 20%. Early severe hyperoxia, as well as cumulative hyperoxia exposure was associated with in-hospital mortality, even after adjustment for disease severity in both venoarterial ECMO and extracorporeal cardiopulmonary resuscitation. A pragmatic approach to oxygenation during peripheral venoarterial ECMO involves targeting a right radial oxygen saturation target of 94–98%, and in selected patients, titration of the fraction of oxygen in the mixture via the air-oxygen blender to target postoxygenator Pao_2 of 150–300 mm Hg.

CONCLUSIONS: Hyperoxia results from a range of ECMO circuit and patient-related factors. It is common during peripheral venoarterial ECMO, and its presence is associated with poor outcome. A pragmatic approach that avoids hyperoxia, while also preventing hypoxia has been described for patients receiving peripheral venoarterial ECMO.

KEYWORDS: brain injury; cardiogenic shock; extracorporeal membrane oxygenation; hyperoxemia

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Venoarterial extracorporeal membrane oxygenation (ECMO) provides both temporary mechanical circulatory support and extracorporeal gas exchange via a membrane oxygenator. Venoarterial ECMO is used as a rescue therapy for patients with cardiogenic shock as a bridge to recovery or advanced therapy (1, 2). Venoarterial ECMO may also be used as a rescue therapy in selected patients with refractory cardiac arrest, termed extracorporeal cardiopulmonary resuscitation (ECPR) (3, 4).

Although venoarterial ECMO and ECPR are deployed to prevent organ ischemia, patients also frequently experience arterial hyperoxia (above normal partial pressures of oxygen Pao_2 > 100 mm Hg) (5–7). Exposure to supraphysiologic Pao_2 can result in organ damage due to increased mitochondrial generation of reactive oxygen species. Early randomized controlled trials (RCTs) and meta-analyses of critically ill patients suggested that conservative oxygen targets (Pao_2 70–100 mm Hg, oxygen saturation [Spo_2] 90–94%), compared with liberal targets (Pao_2 up to 150 mm Hg, Spo_2 97–100%), may reduce in-hospital mortality (8). Since then results have been discordant: other thresholds for hyperoxia have been associated with harm (9), no difference (10) or even benefit in subgroups of critically ill patients, including those with cardiac arrest (11), acute respiratory distress syndrome (9, 12), sepsis (13, 14), and trauma and brain injury (11, 15–17).

However, such thresholds provide little guidance for the titration of oxygen in venoarterial ECMO or ECPR patients. First, patients requiring venoarterial ECMO or ECPR may be especially vulnerable to the effects of hyperoxia due to severe ischemia-reperfusion injury (18, 19). Second, the previous RCTs conducted in ICU patients do not reflect the magnitude of oxygen exposure experienced by venoarterial ECMO/ECPR patients (9). Third, systemic oxygenation during ECMO is achieved via the titration of circuit parameters in addition to ventilatory parameters (Fio_2). Thus, it may not be appropriate to apply the findings of RCTs in the general ICU population to ECMO patients.

Currently, observational studies provide the best evidence base to evaluate effect of hyperoxia on patient outcomes. Definitions of hyperoxia (Pao_2 > 400, > 300, > 200, > 150) and normoxia (Pao_2 < 300, < 200, < 150, and 60–100 mm Hg) have varied. These definitions were initially derived from cardiac arrest (11, 20) and cardiopulmonary bypass literature (21), which, in turn, relied on expert consensus and animal studies (22, 23). Normoxia was generally defined by practice at the time. Interpretation of findings in these studies is hampered by differences in the frequency and timing of arterial blood gas (ABG) sampling (first 24 hr, mean Pao_2 over ICU course, maximum Pao_2). Regardless, hyperoxia remains prevalent and the association between Pao_2 greater than 300 mm Hg and mortality (5, 24–26) is relatively consistent.

The extent to which this association is driven by consequences of direct hyperoxic injury rather than disease severity is heavily debated (26–28). Mechanistically, hyperoxia during venoarterial ECMO/ECPR may potentiate mortality and poor neurologic outcome by: 1) exacerbating reperfusion injury and neurometabolic failure (3, 29, 30), 2) worsening pulmonary injury via pulmonary neutrophil sequestration (31–33), and 3) propagating systemic inflammation in patients with underlying sepsis or acute respiratory distress syndrome (19, 33–36). Equally, hyperoxia may simply indicate low cardiac output states in which the patient is dependent on high ECMO blood flows (27). ABG samples in these patients necessarily express Pao_2 values well above normal.

Current Extracorporeal Life Support Organization (ELSO) guidelines caution against excessively high Pao_2 levels, recommending "slight hyperoxemia after the oxygenator (150 mm Hg)" (1). However, achieving this is complicated by the numerous circuit parameters and patient factors that influence oxygenation during venoarterial ECMO (37).

This review aims to: 1) examine the circuit and patient factors affecting oxygenation during peripheral venoarterial ECMO, 2) synthesize literature reporting the association between hyperoxia and patient outcomes, and 3) describe a pragmatic approach for oxygen titration during peripheral venoarterial ECMO support.

THE DETERMINANTS OF OXYGENATION AND CIRCUIT PHYSIOLOGY

Circuit Factors

Peripheral venoarterial ECMO (wherein ECMO blood is returned peripherally into the femoral artery; **Fig. 1**) is the most commonly deployed circuit configuration (1) and thus forms the primary subject of this review. In this configuration, venous blood is drained from the inferior vena cava and right atrium via large access cannula. Blood is then circulated through a centrifugal pump and passed through a membrane oxygenator (Fig. 1). In the membrane oxygenator, an air-oxygen

mixture flows through an array of hollow microporous tubes (38); the fraction of oxygen in the mixture is determined by the gas blender (Fbo_2). Simultaneously, blood flows around these tubular fibers. Oxygen diffuses into the venous blood across the walls of the tube (the opposite is true for Co_2; Fig. 1). Using this arrangement membrane oxygenators raise arterial oxygen saturation (Sao_2) from 50% to 80–100% (38, 39). The oxygenated blood is then returned into the iliofemoral junction or distal aorta via return cannula (Fig. 1). In this way, blood bypasses the native pulmonary circulation and perfuses the arterial tree directly via retrograde ECMO blood flow.

Systemic oxygenation, as supplied by ECMO (oxygen delivery [Do_2], mL/min), can be expressed as the product of ECMO blood flow (L/min) and arterial oxygen content (Cao_2, ml/L) (40):

$$DO_2\left(\frac{mL}{min}\right) = \text{ECMO flow}\left(\frac{L}{min}\right) \times CaO_2\left(\frac{mL}{L}\right) \quad [1]$$

$$CaO_2 = 1.34 \times (Hb) \times SaO_2 + (0.003 \times PaO_2) \quad [2]$$

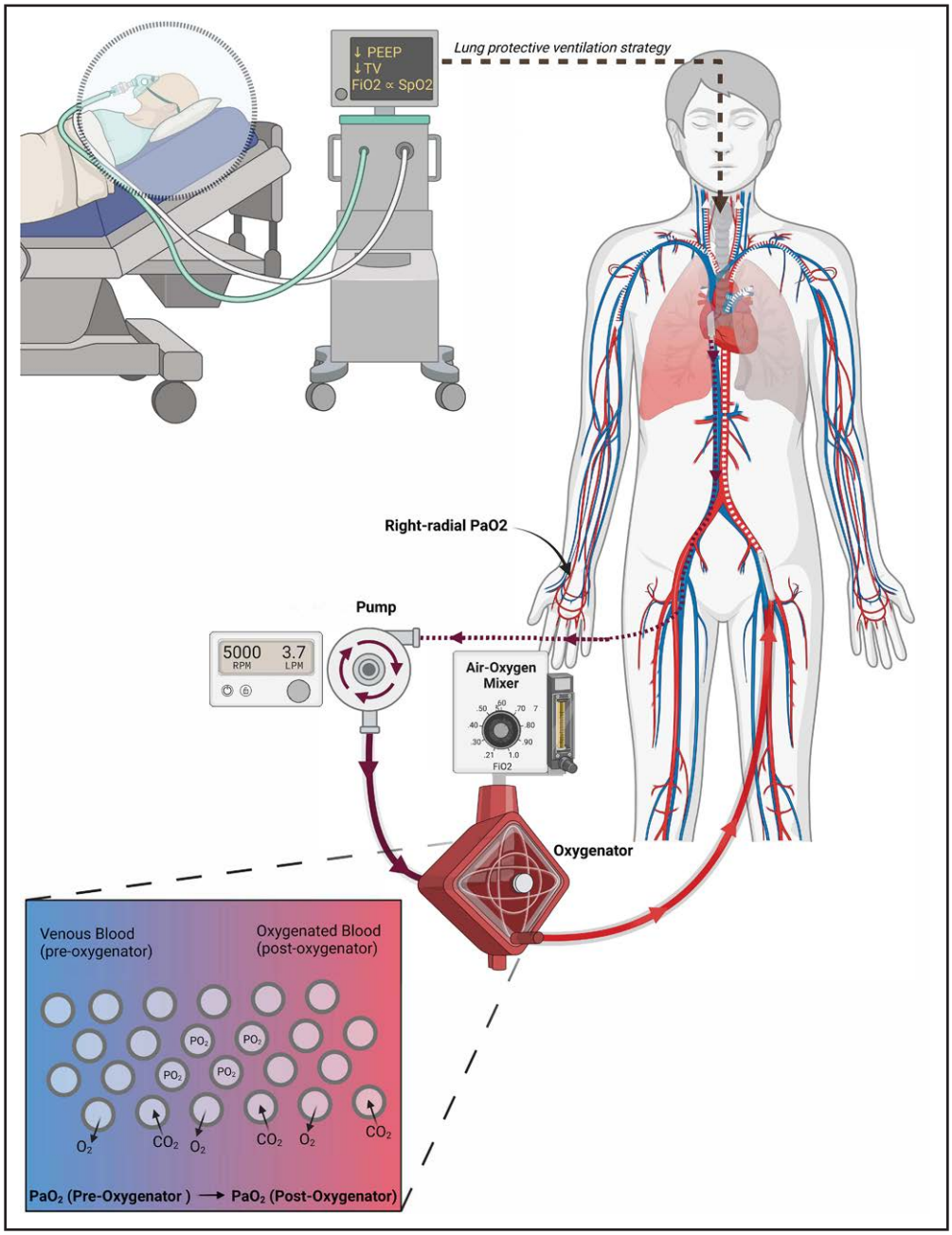

Figure 1. Peripheral venoarterial extracorporeal membrane oxygenation cannulation configuration. LMP = liters/min, O_2 = oxygen, PEEP = positive end-expiratory pressure, RMP = revolutions/min, Spo_2 = oxygen saturation.

Likewise, native circulation also contributes to systemic oxygenation, and this is also governed by the same variables in Equations 1 and 2. Therefore, net systemic oxygenation during venoarterial ECMO can be thought of as the combined contributions of the ECMO circuit and the native cardiopulmonary circuit.

Per Equation 2, the oxygen content of blood (Cao_2) is modulated by several factors; concentration of hemoglobin, the degree to which this hemoglobin is saturated (Sao_2), and the amount of oxygen dissolved in the blood (Pao_2). Raising the hemoglobin content of blood via transfusion may be considered in hypoxic patients with anemia. However, transfusion also increases blood viscosity, which may impair flow through the ECMO circuit and also increases the risk of transfusion-related complications, such as infection, transfusion-related acute lung injury, and transfusion-associated circulatory overload (41, 42). ELSO

recommends maintaining a hematocrit of greater than 40% (to achieve arterial saturations above 95% with "low" F_{IO_2}); hemoglobin is amply saturated (Sa_{O_2} > 95%) at Pa_{O_2} levels greater than 80–100 mm Hg (1, 43). The results from several RCTs investigating the optimal hemoglobin transfusion threshold are awaited (44, 45).

Increasing the Fb_{O_2} increases the oxygen gradient across the membrane, promoting the movement of oxygen into the blood (Fig. 1) (46). This manifests supraphysiologic postoxygenator Pa_{O_2} levels far in excess of 500 mm Hg (38). Fb_{O_2} is a key determinant of Pa_{O_2}. Pa_{O_2} itself has a proportionally small effect on Ca_{O_2} (Equation 2). It follows that high postoxygenator Pa_{O_2} values only have a marginal impact on ECMO D_{O_2}, as per Equation 2.

Therefore, the primary determinant of D_{O_2} (via ECMO circuit) is the ECMO blood flow rate (27, 38, 39, 47, 48). When ECMO blood flow (L/min) is increased, D_{O_2} increases proportionately (Equation 1). However, above a blood flow threshold, transit time through the oxygenator may be so reduced that RBCs are not fully oxygenated. Consequently, outlet saturation falls from 100%. This is the "rated flow": the flow rate beyond which venous blood (Sa_{O_2} 75%, hemoglobin 12 mg%) fails to attain 95% saturation at the outlet. The rated flow is specific to the membrane lung used and is not exceeded in practice (38, 49–51).

Patient Factors

Systemic oxygenation is also influenced by patient factors, including native respiratory function and cardiac output, which can vary throughout the ECMO run and disease course. The contribution of respiratory function to systemic oxygenation is augmented by ventilatory parameters; F_{IO_2} and positive end-expiratory pressure (PEEP) (38, 39). Organ specific perfusion and oxygenation is additionally modified by the interaction between anterograde native cardiac output and retrograde ECMO blood flow in the aorta (1, 37).

Respiratory Failure. Respiratory failure in patients with cardiogenic shock requiring venoarterial ECMO is common and has numerous etiologies. Etiologies of pulmonary complications in patients with cardiogenic shock frequently include ischemia-reperfusion injury; lung contusion arising from chest compressions (52); and, aspiration of gastric contents leading to pneumonitis and pneumonia (53). It may also result from venoarterial ECMO support itself. Left ventricular (LV) distension (54) results from the imbalance between a relatively overactive right ventricle and a poor (or nonejecting) left ventricle (which may be exacerbated by the increased afterload on the left ventricle create by the retrograde venoarterial ECMO blood flow). Stasis of blood in the pulmonary circulation can result in severe pulmonary edema and thus, respiratory impairment.

Management of patients with cardiorespiratory failure generally involves: 1) treatment of the primary pulmonary pathology where possible; 2) lung-protective ventilation to limit ventilator-induced lung injury, tidal volume 4–6 mL/Kg, and careful PEEP titration (to prevent atelectasis and maintain lung recruitment) and low F_{IO_2} (titrated to appropriate Sp_{O_2}); and 3) consideration of adjunctive therapies such as LV venting.

Interactions Between ECMO and the Failing Heart. *The failing heart and hyperoxia*. Competition between ECMO blood flow and native cardiac output also modulates systemic D_{O_2}. In early and/or severe cardiogenic shock, native cardiac output is typically low and occasionally absent. Systemic perfusion is sustained predominantly by retrograde aortic ECMO blood flow and systemic oxygenation comes almost entirely from the membrane oxygenator. In this scenario, perfusion of the cerebral circulation may be entirely by hyperoxic retrograde venoarterial ECMO blood flow, exposing the brain to harmful Pa_{O_2} levels (up to 500 mm Hg) (55–57). Additionally, lack of LV ejection (and thus aortic valve opening) in those with severe cardiogenic shock may predispose to intracardiac or aortic root thrombosis and other associated thromboembolic complications (4, 57, 58).

Clinical observations support the above physiologic understanding that peripheral venoarterial ECMO increases oxygen exposure, especially in the setting of severe circulatory failure. A retrospective study of cardiac arrest patients (n = 169) requiring either ECPR or conventional cardiopulmonary resuscitation (CCPR) showed higher mean Pa_{O_2} levels (211 ± 58.4 vs. 119 ± 18.1 mm Hg; p < 0.0001) and higher proportion of hyperoxic episodes (> 300 mm Hg; 74.7% vs. 16.7 mm Hg; p < 0.001) in the ECPR (vs. CCPR) group. The INCEPTION trial randomized patients with refractory out-of-hospital cardiac arrest (OHCA) and an initial ventricular arrhythmia to either ECPR

or CCPR. Despite similar baseline characteristics, severity of OHCA and circulatory failure, in-hospital median Pao_2 was significantly greater in the ECPR group (60 mm Hg; interquartile range [IQR], 22–135 vs. 45 mm Hg; IQR, 22–67 mm Hg; $p < 0.001$ [4, 59]). Furthermore, in ECPR patients, higher mean 24 hours Pao_2 was correlated with lower mean blood pressure recordings (during first 24 hr of ECPR) (25).

Differential hypoxia. Upon partial recovery of cardiac function, native (anterograde) cardiac ejection competes with retrograde aortic ECMO blood flow (57). The mixing zone may subsequently move distally in the aorta (**Fig. 2**). If there is concomitant respiratory failure or a failure to increase the minute ventilation by clinicians this can result in poorly oxygenated blood from the native circulation being delivered to the upper body (including the coronary and carotid circulations) while highly oxygenated blood from the ECMO circuit perfuses the lower body. This is termed differential hypoxia (60). A variety of strategies can be used to manage this, including treatment of underlying lung pathology, increasing ventilatory support (Fio_2, PEEP), reducing native cardiac output by reducing inotrope doses, removing venoarterial ECMO, or moving to alternative cannulation configurations, such as veno-venoarterial ECMO (61–63).

HYPEROXIA AND PATIENT OUTCOMES

Venoarterial Extracorporeal Membrane Oxygenation

Hyperoxia occurs in a substantial proportion of venoarterial ECMO patients: 30.2% and 19.8% of patients included in the ELSO registry (2010–2020) experienced mild hyperoxia (151–300 mm Hg) and severe hyperoxia (> 300 mm Hg), respectively, within the first 24 hours of ECMO cannulation (64). This is corroborated by recent observational studies using similar definitions (26, 64–67). Longitudinal data provides added insight: 1) cannulation configuration (central, peripheral, femoro-axillary) appears not to drastically affect early hyperoxia exposure (26, 64); 2) single Pao_2 obtained via ABG within 24 hours of cannulation does not appropriately categorize early and long-term oxygen exposure (6, 7, 26); and 3) prevalence of hyperoxia has generally decreased with time (64).

The association between hyperoxia and mortality is most consistent among patients exposed to severe hyperoxia (**Fig. 3**). An analysis of 4 hourly blood gases taken within 24 hours of venoarterial ECMO initiation ($n = 132$; where venoarterial ECMO was initiated for postcardiotomy shock [38.6%], cardiogenic shock [25.8%], and ECPR [31.8%]) found that duration (hr) of severe (> 300 mm Hg) and moderate hyperoxia (> 200 mm Hg) was significantly associated with mortality. This was despite adjustment for illness severity (Sequential Organ Failure Assessment score, venoarterial ECMO indication) and complications (brain injury during ECMO) (65). Alternative definitions of early Pao_2 (first Pao_2, mean 24 hr Pao_2, maximum Pao_2) showed no or weak association with ICU mortality (65). Moussa et al (26) collected Pao_2 up to 48 hours postadmission and used the air-oxygen blender as the primary controller of Pao_2. In a propensity weighted analysis of 143 venoarterial ECMO patients (considering variables related to 28-d mortality for patients who did/did not experience Pao_2 > 150 mm Hg), both peak and overall mean Pao_2 were significantly associated with 28-day mortality (adjusted odds ratio [aOR], 2.65; 95% CI, 1.79–6.07 and aOR, 2.85; 95% CI, 1.12–7.37; respectively, per 10 mm Hg) (26). Survival analysis showed that mild hyperoxia (200–300 mm Hg) was associated with greater 28-day survival compared with moderate (< 200 mm Hg) and severe hyperoxia (> 300 mm Hg; $p = 0.005$) (26). Analyses of the ELSO registry (64) and external single centers (67) demonstrated that patients who experienced early severe (> 300 mm Hg; hazard ratio [HR], 1.78; 95% CI, 1.63–1.94) or mild (151–300 mm Hg; HR, 1.32; 95% CI, 1.22–1.42) hyperoxia had greater overall risk of death compared with normoxic patients (60–150 mm Hg). This was despite adjustment for ECMO circuit flow and Fio_2 among other variables indicative of illness severity (64).

Neurologic outcome is seldom investigated. Thus, far poor functional outcome (Modified Rankin Scale 4–6) has been weakly associated with mean 24 hours Pao_2 (aOR, 1.01; 95% CI, 1.01–1.02) (65).

Extracorporeal Cardiopulmonary Resuscitation

Analysis of ECPR patients in the ELSO registry showed that moderate (200–299 mm Hg; aOR, 1.42; 95% CI, 1.02–1.97) and severe hyperoxia (> 300 mm Hg; aOR, 1.59; 95% CI, 1.20–2.10) were associated with acute brain injury and in-hospital mortality (56). These

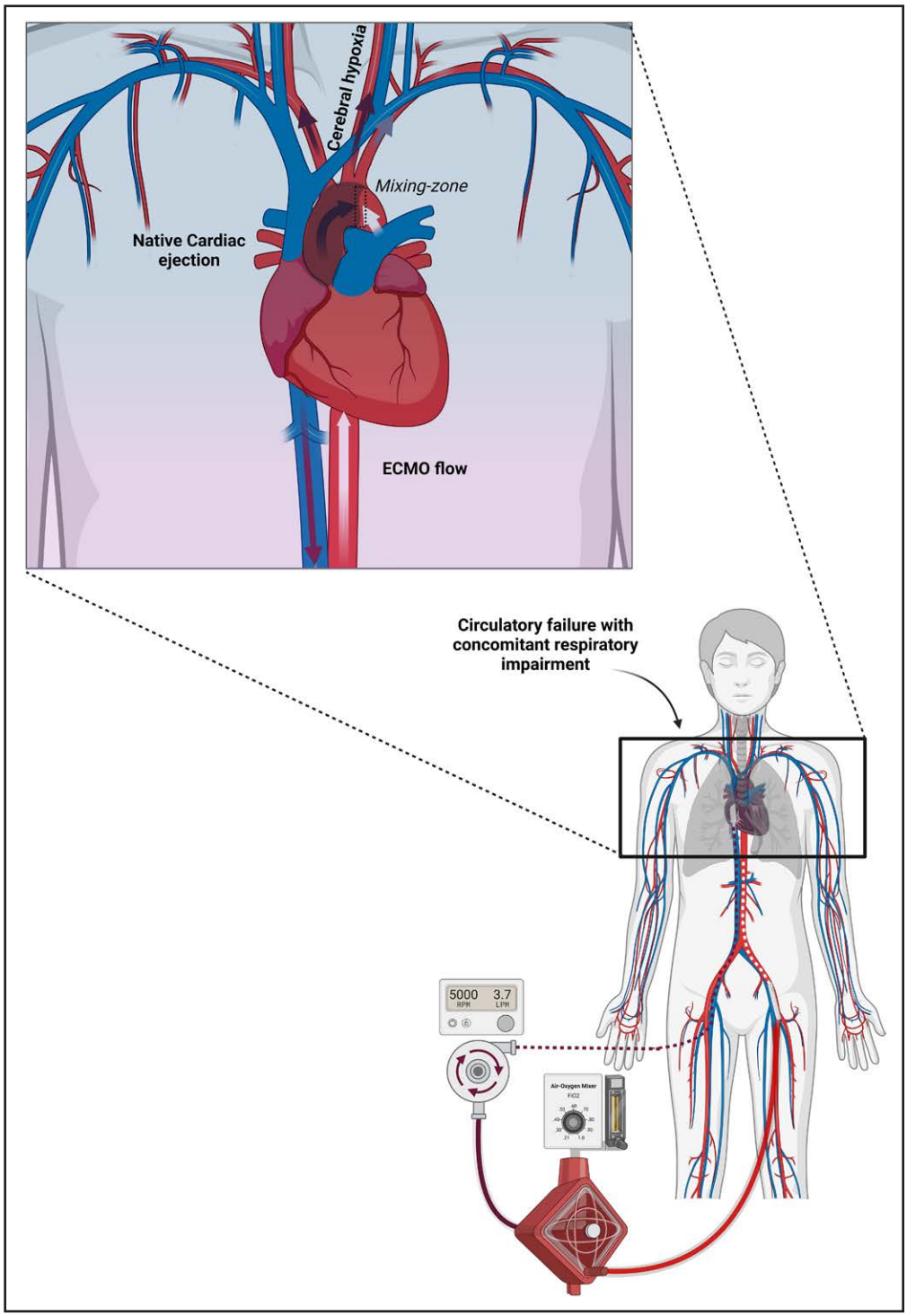

Figure 2. Differential hypoxia. ECMO = extracorporeal membrane oxygenation, LMP = liters/min, RMP = revolutions/min.

findings are consistent among observational studies and persist regardless of disease severity and ventilatory parameters (5, 24, 25, 56, 68, 69) (Fig. 3). Bonnemain et al (25) found mean Pao_2 (n = 44, first 24 hr) was associated with increased mortality independent of arterial line position. This suggests the association between hyperoxia and mortality in ECPR patients cannot be explained by differences in native cardiac function alone (25): nonsurvivors had significantly higher mean 24 hours Pao_2 than survivors (306 ± 121 vs. 164 ± 53 mm Hg; $p < 0.001$) but similar pulse pressure (within the first 24 hr).

Severe hyperoxia during ECPR (Pao_2 > 400 mm Hg) substantially decreased likelihood of discharge with good neurologic outcome (Cerebral Performance Category [CPC] score ≤ 2 at 30 d; aOR, 0.48; 95% CI, 0.29–0.82); adjustment was carried out for propensity score (which comprised patient demographics, nature of cardiac arrest, prehospital interventions, time to ECMO initiation), $Paco_2$, and lactate (70). Further observational studies have consistently demonstrated that hyperoxia, at various thresholds (> 160, > 200, > 300 mm Hg), significantly decreases likelihood of good neurologic outcome (CPC score) (65, 68–71). It is useful to note that analysis of a mixed cohort of venoarterial ECMO and ECPR patients (n = 42, 31.8%) did not reproduce the same level of association as above when using functional outcome (modified Rankin score 4–6, at discharge) as the indicator neurologic recovery (odds ratio, 1.01; 95% CI, 1.01–1.02; p = 0.001; per mm Hg of mean 24 hr Pao_2) (65).

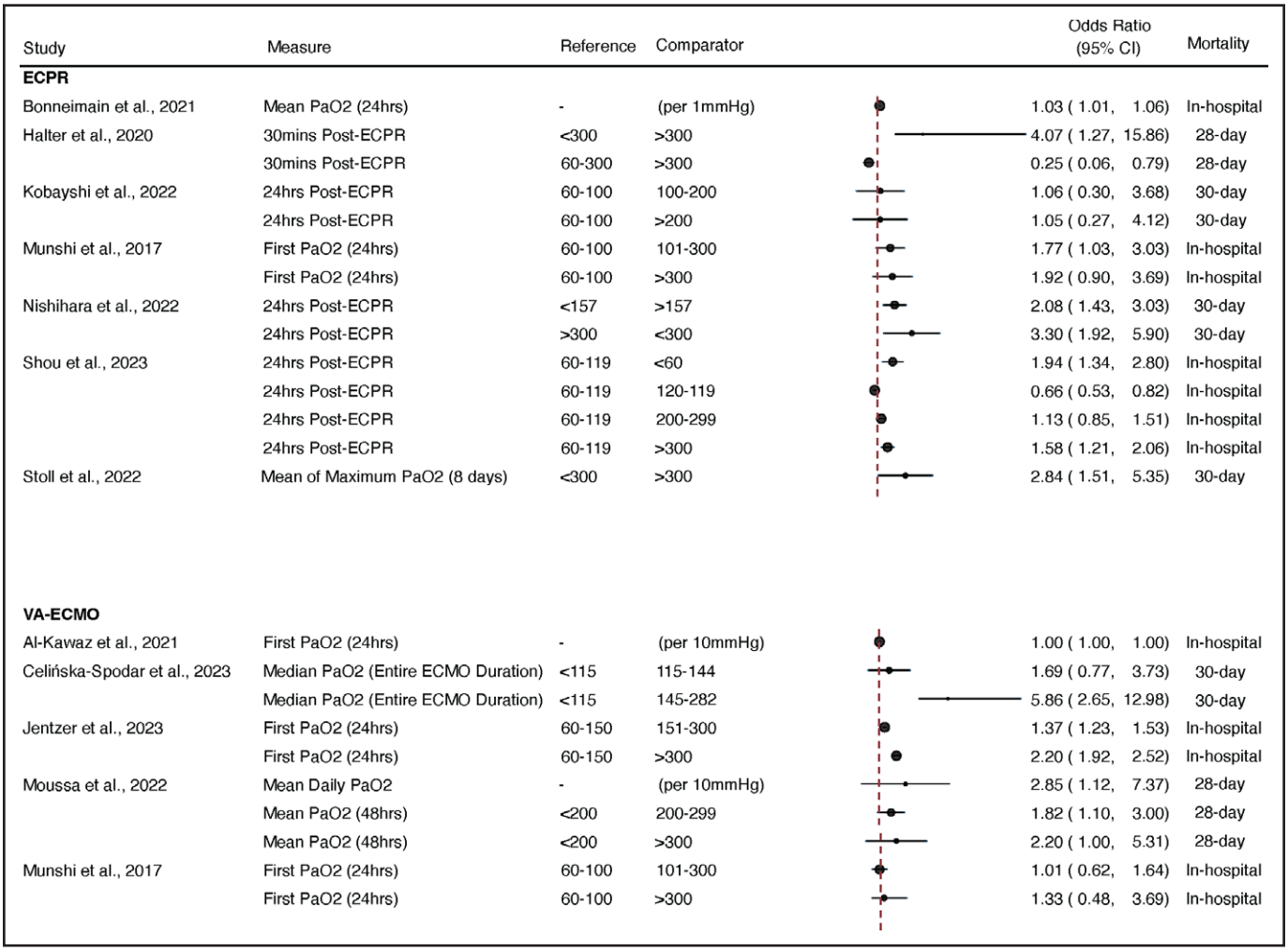

Figure 3. Summary of reported effect sizes among key studies in venoarterial (VA) extracorporeal membrane oxygenation (ECMO) and extracorporeal cardiopulmonary resuscitation (ECPR) patients investigating hyperoxia and mortality. Where odds ratio (OR), compares odds of mortality (in-hospital, 28- or 30-d) in the comparator vs. reference group. Therefore, OR greater than 1 indicates patients in the comparator group had higher risk of death than those in the reference group.

However, in all of the above studies, native cardiac output has not been directly measured. Therefore, whether or not hyperoxia causes direct damage or is a marker of poor native cardiac output remains to be determined. Prospectively designed RCTs are eagerly awaited to resolve such questions (NCT03841084).

A SUGGESTED APPROACH

The determinants of oxygenation during venoarterial ECMO are complex, largely due to the interaction between the circuit physiology and dynamic patient factors described above (48, 60). As such, the assessment and interpretation of oxygen exposure is challenging given that it may vary across body regions, and varies with different phases of the patients' illness (25). Although hyperoxia during venoarterial ECMO or ECPR is common and has been consistently associated with poor outcome and survival (26), the ideal targets for oxygenation during venoarterial ECMO are not known (1, 72). Above, we identified ECMO circuit parameters as a key determinant of patient oxygenation, and the control of Fbo_2 is a clinically appealing (73) method to modulate oxygenation. The advantages and disadvantages of this approach are discussed below and summarized in **Table 1**.

Blending

Titration of Fbo_2 is readily achieved through the addition of an oxygen air blender to the sweep gas flow meter (**Fig. 4**). This system typically requires both an oxygen and air outlet, which may not be available during interhospital or intrahospital transport.

TABLE 1.
Advantages and Disadvantages of Reducing Oxygen Targets in Venoarterial Extracorporeal Membrane Oxygenation and Extracorporeal Cardiopulmonary Resuscitation Patients

Advantages	Disadvantages
Limits exposure to high oxygen levels	May be associated with hypoxic episodes
Possible less oxygen injury/ischemic reperfusion injury	Blending requires the addition of an air tank which can complicate transportation
Easily achieved with air oxygen blender	Need to monitor postoxygenator blood gases
	Additional staff training
	Will have less influence on the oxygenation of blood from native circulation

While Fbo_2 can be manipulated using the blender, this strategy introduces the risk of causing hypoxemia if introduced without adequate monitoring of postoxygenator oxygen levels. Oxygenator function declines over time and as such postoxygenator outlet Pao_2 cannot be assumed to be stable over long periods.

Continuous oxygen titration is an important consideration due to the dynamic nature of patient and circuit oxygenation, and for the need to intervene quickly when hypoxia occurs. However, the measurement of postoxygenator saturations is not routinely performed by many commercially available circuits. Thus, monitoring is often best achieved by direct blood sampling from the postoxygenator port (Fig. 4). While not technically demanding this adds to nursing workload and repeatedly accessing the circuit may increase the risk of infection (74) (Table 1). An alternative strategy is to measure Spo_2 in two body locations.

Targets

Current ELSO interim guidelines recommend "slight hyperoxemia after the oxygenator (150 mm Hg)" (1), while also cautioning against hyperoxia (although there is no specified upper target). The goal is to strike a balance between the risks of hyperoxia on the one hand, and a buffer against the potential for hypoxia on the other.

Although unvalidated by RCTs, the Pao_2 target of 150 mm Hg appears to fall within the hypothetical safety zone (5, 24, 25, 56, 65, 70, 72). As previously noted, studies that describe associations between hyperoxia and outcome differ in methodology and may unknowingly attribute mortality to hyperoxia rather than more severe disease (27, 37). Still, taken together the evidence suggests that targeting a Pao_2 of less than 300 mm Hg avoids sequelae of hyperoxia.

During venoarterial ECMO, lower targets (< 150 mm Hg) may increase risks of hypoxemia: subclinical membrane dysfunction, clot formation, changes in native cardiopulmonary function or ventilation may all contribute to this risk. Continuous and accurate monitoring of postoxygenator arterial saturations and tensions is therefore vital (Fig. 4).

RCTs in OHCA patients not requiring ECMO support may lend some insight into management of ECPR patients: the EXACT trial concluded that among patients achieving return of spontaneous circulation after OHCA, targeting an oxygen saturation of 90–94%, compared with 98–100% offered no benefit (pre-ICU admission) (75). In ECPR patients who are hemodynamically stable with no respiratory failure or complications, risk of hypoxia is low and targeting Spo_2/Sao_2 between 92% and 98% may be beneficial, as per cardiac arrest guidelines (76–79). In such patients, blending may be considered by experienced centers to achieve optimal oxygenation.

The effect of a routine conservative oxygen target (targeting right radial and postoxygenator saturations of 92–96%) vs. a liberal oxygen target (right radial artery and postoxygenator saturations target of 97–100%) is currently being investigated in the 300 patients, multicenter Blend to Limit Oxygen in ECMO: A RanDomised ControllEd Registry trial (NCT03841084). This study will enroll both venoarterial ECMO and ECPR patients who are normoxic at baseline—patients that have concomitant hypoxic respiratory failure will be excluded as they require careful, individualized titration of ventilatory parameters (80). In the interim, an approach that avoids hypoxia while preventing severe hyperoxia seems prudent and has been outlined in Figure 4.

CONCLUSIONS

The determinants of oxygenation during venoarterial ECMO are complex and involve both ECMO and

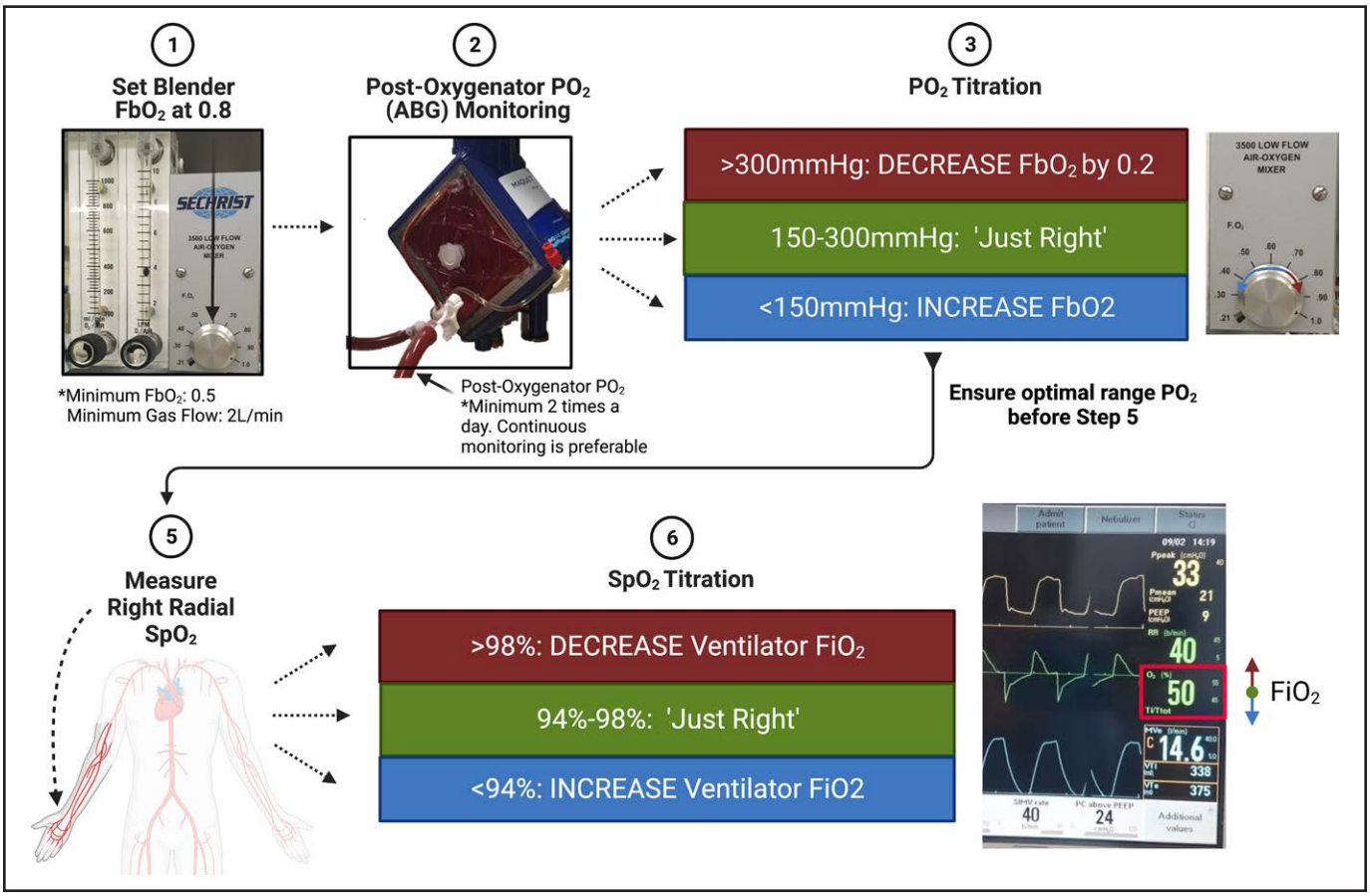

Figure 4. Potential algorithm for appropriate oxygen control during venoarterial extracorporeal membrane oxygenation cannulation. ABG = arterial blood gas, b/min = breaths/min, Fbo_2 = fraction of oxygen in the mixture is determined by the gas blender, O_2 = oxygen, PEEP = positive end-expiratory pressure, RR = respiratory rate, Spo_2 = oxygen saturation.

patient related factors. There is a growing body of observational data that suggest hyperoxia is associated with harm, however, reducing oxygenation targets may also increase the risk of hypoxia. An approach that balances these risks is outlined in this article. We await further evidence to identify an optimal strategy.

1 *Griffith University School of Medicine and Dentistry, Brisbane, QLD, Australia.*

2 *Critical Care Research Group, The Prince Charles Hospital, Brisbane, QLD, Australia.*

3 *Hopkins Education, Research, and Advancement in Life Support Devices (HERALD) Group, Division of Cardiac Surgery, Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD.*

4 *Department of Intensive Care, The Alfred Hospital, Melbourne, VIC, Australia.*

5 *Department of Critical Care Medicine, St Vincent's Hospital Melbourne, Melbourne, VIC, Australia.*

6 *Australian and New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health, Monash University, Melbourne, VIC, Australia.*

7 *The University of Queensland, Faculty of Medicine, Brisbane, QLD, Australia.*

8 *Australian Centre for Health Services Innovation (AusHSI) and Centre for Healthcare Transformation, School of Public Health & Social Work, Queensland University of Technology (QUT), Brisbane, QLD, Australia.*

9 *St Andrew's War Memorial Hospital, UnitingCare, Brisbane, QLD, Australia.*

10 *Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, VIC, Australia.*

11 *The Australian and New Zealand Intensive Care Society (ANZICS), Centre for Outcome and Resources Evaluation, Melbourne, VIC, Australia.*

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For information regarding this article, E-mail: lavienraj.premraj@griffithuni.edu.au

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