Deborah J. Culley, M.D., Editor

Perioperative Management of the Adult Patient on Venovenous Extracorporeal Membrane Oxygenation Requiring Noncardiac Surgery

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ABSTRACT

The use of venovenous extracorporeal membrane oxygenation is increasing worldwide. These patients often require noncardiac surgery. In the perioperative period, preoperative assessment, patient transport, choice of anesthetic type, drug dosing, patient monitoring, and intraoperative and postoperative management of common patient problems will be impacted. Furthermore, common monitoring techniques will have unique limitations. Importantly, patients on venovenous extracorporeal membrane oxygenation remain subject to hypoxemia, hypercarbia, and acidemia in the perioperative setting despite extracorporeal support. Treatments of these conditions often require both manipulation of extracorporeal membrane oxygenation settings and physiologic interventions. Perioperative management of anticoagulation, as well as thresholds to transfuse blood products, remain highly controversial and must take into account the specific procedure, extracorporeal membrane oxygenation circuit function, and patient comorbidities. We will review the physiologic management of the patient requiring surgery while on venovenous extracorporeal membrane oxygenation. **(ANESTHESIOLOGY 2018; 128:181-201)**

VENOVENOUS (VV) extracorporeal membrane oxygenation (ECMO) is a system that externally oxygenates and decarboxylates central venous blood through an artificial membrane lung. The basic components of a VV ECMO circuit are an inflow cannula that drains deoxygenated blood from the patient and an outflow cannula that returns oxygenated blood to the patient, a centrifugal pump that circulates blood to and from the patient, and a semipermeable membrane (also referred to as "membrane lung" or "oxygenator"), in which oxygenation and decarboxylation occur (fig. 1). VV ECMO has no intrinsic curative effects; however, it facilitates low tidal volume (V_T) lung protective ventilation; reduces systemic hypercarbia and hypoxemia, providing time to allow patients' lungs to heal; and, in some cases, facilitates physical therapy in patients with respiratory failure (table 1).[1–9] Also referred to as "open lung" ventilation, low V_T ventilation purportedly limits ventilator-induced lung injury (VILI) through reductions in alveolar strain and overdistention and atelectotrauma (table 1).[2,9] Understanding VV ECMO physiology and its potential complications helps the anesthesiologist troubleshoot intraoperative challenges and provides insight as to when VV ECMO should be considered for the severely hypoxemic or hypercarbic patient.

The rapid growth of VV ECMO utilization in adults continues,[10] fueled by promising efficacy data generated in acute respiratory distress syndrome (ARDS) and H1N1 influenza patients.[11,12] A corresponding increase in the number of VV ECMO patients presenting to the operating room is anticipated, given up to 48% of patients on VV or venoarterial (VA) ECMO require noncardiac surgery, most commonly tracheostomy, laparotomy, vascular procedures, and thoracotomy or video-assisted thoracic surgery.[13,14] Two recent retrospective studies demonstrated a potential survival benefit when VV ECMO is utilized in polytrauma patients with severe lung injury, which may lead to an increase in both the frequency of ECMO utilization, as well as the number of ECMO patients requiring noncardiac surgery.[15,16] The data also suggest a potential role for VV ECMO in the management of intraoperative and postoperative severe ARDS.[17]

In a series of 563 VA and VV ECMO patients, 269 required noncardiac surgery, with associated increases in hospital length of stay, bleeding complications, wound infections, and cost of care ($487,975 *vs.* $371,245); however, there were no differences in mortality between the group that required surgical procedures and those who did not.[14]

In the vast majority of VV ECMO patients, one of three cannulation strategies is utilized: a single, dual-lumen catheter is inserted into the right internal jugular vein; separate inflow and outflow cannulas inserted into the femoral veins; and an

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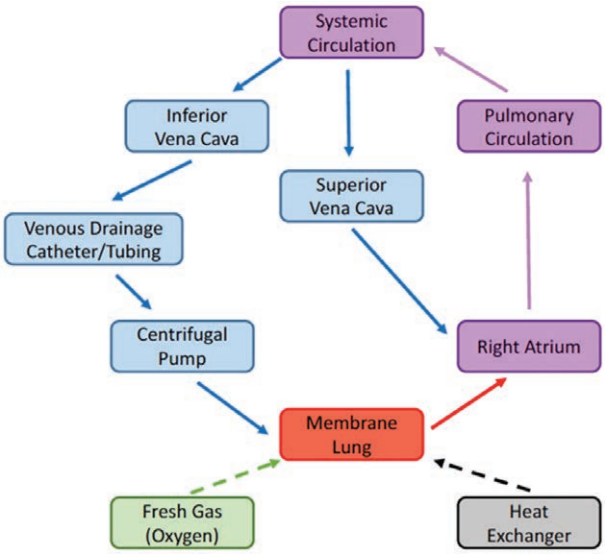

Fig. 1. Schematic flowsheet for femoral–internal jugular venovenous (VV) extracorporeal membrane oxygenation (ECMO). This flowsheet represents the course of blood flow in femoral–internal jugular VV ECMO. The *blue boxes* and *lines* represent mixed venous blood, *red* represents oxygenated blood, and *purple* represents admixture of oxygenated post–ECMO blood and mixed venous blood, which first occurs in the right atrium. Blood entering the systemic circulation from the pulmonary circulation remains admixed in oxygen content based on the assumption that native lung gas exchange is negligible. The addition of oxygen (or fresh gas) and heat exchange occurs as blood traverses the membrane lung (oxygenator).

outflow cannula inserted into the femoral vein combine with an inflow cannula inserted into the right internal jugular vein (figs. 2–5).[18,19] The cannulation strategy is ultimately based upon patient factors and specific circumstances leading to the need for ECMO, as well as the practitioner's or center's preference and skill sets.[19] The differences in the VV ECMO cannula configurations, when the system is functioning properly, have minimal impact on perioperative physiology (table 2).[20–25]

Discussion

The perioperative management of VV ECMO patients requires vigilant assessment for hypoxemia and hypercarbia, with interventions that take into account the ECMO system performance and patient physiology, adaptation of the anesthetic plan and monitoring techniques to both the patient's underlying critical illness and drug interactions related to mechanical support, and appreciation of situation-specific risks and benefits to systemic anticoagulation.

Ventilator Management

Most patients on VV ECMO require sustained mechanical ventilation to support blood oxygenation and to a lesser extent decarboxylation, despite maximization of blood flow and gas exchange, which are limited by cannula size.[26,27] Membrane surface area does not clinically limit oxygenation in properly functioning oxygenators but can be a limiting factor for decarboxylation when CO_2 production is excessive or during laparoscopy.[26] For example, a multicenter series of 168 patients on ECMO demonstrated 82% of patients developed plateau pressures (P_{plat}) of 24 cm H_2O or greater during days 1 to 3 and 13% required pressures greater than 30 cm H_2O, which is outside of lung-protective V_T thresholds.[1] More recently, "ultra protective ventilation," which maintains V_T of less than 4 ml/kg predicted body weight and P_{plat} less than 25 cm H_2O, has been proposed to reduce pulmonary edema, the presence of inflammatory markers, and VILI in patients supported with ECMO (table 1).[1,2,9,28] Such open lung strategies, which conceptually decrease the cyclic opening and closure of alveoli through the application of low V_T and high positive end-expiratory pressure (PEEP), have not yet been scientifically compared to ARDSNet lung protective ventilation protocols. However, ECMO consensus statements typically recommend utilization of 10 to 15 cm H_2O PEEP, whereas a retrospective analysis linked PEEP levels greater than 12 cm H_2O to improved survival.[1,9]

Intraoperative ventilator management should generally focus on maintenance of existing settings, when possible. The acute need for ventilator changes should be an uncommon event in the operating room and should prompt investigation of the cause for a change in patient condition. For example, surgical positioning or manipulation can result in changes to V_T or P_{Plat}, which are outside of the patient's goal range (table 1). Bleeding or evaporative fluid loss during surgery can reduce ECMO flows, resulting in hypoxemia. Anesthesia will alter a patient's respiratory drive, whereas utilization of paralytics may eliminate both respiratory effort and alter compliance affecting $Paco_2$ and Pao_2. When alterations in gas exchange persist despite optimization of the ECMO settings in the form of altering blood flow and sweep gas, the mechanical ventilator parameters P_{Plat} and inspired concentration of oxygen (Fio_2) should be raised by the lowest fraction possible to achieve the desired physiologic effect discussed below.

Blood Oxygenation

While on VV ECMO, a patient's Pao_2 is primarily governed by the blood flow through the ECMO circuit relative to the patient's cardiac output, the percentage of recirculation in the ECMO circuit, and the degree of pulmonary injury, transpulmonary shunting, and mechanical ventilator settings (table 3).[26,29] In addition to Pao_2, oxygen delivery (DO_2) is also dependent on hemoglobin concentration and cardiac output, with indirect contributions from mixed venous oxygen saturation ($Scvo_2$) and oxygen demand.

ECMO membranes are highly efficient, and when functioning with a Fio_2 of 1.0, in the absence of fibrous membranes or clots on the membrane surface, the postmembrane Pao_2 will be 300 to 500 mmHg.[27,30] Progressive fibrin or clot deposition within the membrane lung will decrease efficiency, resulting in a reduced postmembrane Pao_2, impaired decarboxylation, and ultimately systemic hypoxemia or hypercarbia.[30]

Table 1. Glossary of Respiratory, Gas Exchange, and ECMO Abbreviations and Terminology

ARDS	Adult Respiratory Distress Syndrome: a syndrome of acute respiratory illness after a trigger (such as sepsis, pneumonia, or influenza), categorized by a Pa_{O_2}:F_{IO_2} ratio of < 300 on > 5 cm H_2O PEEP combined with bilateral radiographic chest opacities in the absence of heart failure-mediated pulmonary edema. Based on the Berlin Criteria, ARDS can be further categorized as mild, moderate, or severe based on Pa_{O_2}:F_{IO_2} ratio.[4]
ARDSNet (ARDS Network)	A collaboration of researchers and institutions organized by the National Heart, Lung, and Blood Institute and National Institutes of Health (Bethesda, Maryland) that organizes multicenter trials relating to ARDS.[5]
Ca_{O_2}	Arterial oxygen content (of blood): the volume of oxygen bound to hemoglobin plus the volume of oxygen dissolved in plasma expressed in ml/dl. It can be calculated by the equation: (1.34 × hemoglobin (g/dl) × Sa_{O_2}) + (0.0031 × Pa_{O_2})
DO_2	Oxygen delivery: the volume of oxygen delivered systematically per minute expressed in ml/min or ml · kg^{-1} · min^{-1}. It can be calculated by the equation: DO_2 = cardiac output × [(1.34 × hemoglobin × Sa_{O_2}) + (0.0031 × Pa_{O_2})].
ECMO flow	The volume of blood that passes through the ECMO circuit per minute. This value includes "recirculated blood," or blood that passes through the ECMO circuit in a closed loop, without entering systemic circulation.
(ARDSNet) LPV	Lung protective ventilation: a system of low tidal volume ventilation used to improve outcomes in patients with ARDS. Parameters include: tidal volumes of 4–8 ml/kg predicted body weight, plateau pressure of < 30 cm H_2O, utilization of ARDSNet table for matching PEEP to F_{IO_2} to maintain Pa_{O_2} 55–80 mmHg or Sp_{O_2} 88–95%, respiratory rate of < 35, and pH goal of 7.30–7.45.[6]
Open lung ventilation	A low-volume, high-PEEP ventilation strategy designed to maximize alveolar recruitment. Classically, a PEEP level based on the patient's static pressure–volume curve is used to reduce atelectotrauma from cyclic closure and reopening of alveoli.[7] ARDSNet LPV uses concepts of open lung ventilation.
Pa_{O_2}	The partial pressure of oxygen dissolved in arterial blood expressed in mmHg
P_{Plat}	Plateau pressure: the pressure applied to the small airways and alveoli during mechanical ventilation, measured as an end-inspiratory pause.
PBW	Predicted body weight: body weight based on height and gender used for ARDSNet ventilator protocols.[8]
PEEP	Positive end-expiratory pressure: the alveolar pressure, above atmospheric pressure, that is present at the end of expiration
Postmembrane PO_2	The partial pressure of oxygen dissolved in blood immediately downstream of the membrane lung, before its admixture with circulating blood that bypasses the ECMO circuit.
Sa_{O_2}	Arterial oxygen saturation: the percentage of available hemoglobin that is saturated by oxygen.
Scv_{O_2}	Mixed venous oxygen saturation: the percentage of available hemoglobin that is saturated by oxygen in the superior or inferior vena cava. This value is synonymous with the pre-VV ECMO oxygen saturation.
Sp_{O_2}	Peripheral capillary oxygen saturation: an indirect measurement of Sa_{O_2} as measured by noninvasive pulse oximetry.
Sv_{O_2}	Central venous oxygen saturation: the percentage of available hemoglobin that is saturated by oxygen in blood in the pulmonary artery. This measurement assesses an admixture of the blood that is oxygenated by the membrane lung, as well as circulating blood that bypasses the ECMO circuit, before gas exchange by the native lungs. Accordingly, this value cannot be used as a surrogate for cardiac output in VV ECMO patients.
Sweep gas flow (ECMO)	The rate at which fresh gas is added to the ECMO circuit. Increasing sweep gas flow leads to an increase in decarboxylation analogous to an increase in minute ventilation, with minimal impact on oxygenation.
ULPV	Lung rest or ultra protective lung ventilation: a ventilation strategy used in some ECMO patients that generally targets tidal volumes of < 4 ml/kg PBW, peak inspiratory pressures of < 20–25 cm H_2O, and PEEP of > 10 cm H_2O.
V_E	(Expired) minute ventilation: calculated as $V_{T\,x}$ respiratory rate
V_T	Tidal volume
VO_2	Oxygen uptake: the volume of oxygen utilized by the body/min expressed in ml/min or ml · kg^{-1} · min^{-1}.
VILI	Ventilator-induced lung injury: iatrogenic ventilator injury stemming from overdistention of alveoli (volutrauma), high peak alveolar pressures (barotrauma), cyclic opening and closing of alveoli (atelectotrauma), or supraphysiologic F_{IO_2} (oxygen toxicity).

ECMO = extracorporeal membrane oxygenation; F_{IO_2} = inspired concentration of oxygen; VV = venovenous.

Assuming normal oxygenator function, systemic Pa_{O_2} is primarily dependent on the ratio of blood flow through the ECMO circuit to overall cardiac output. Notably, when ECMO flows are less than 60% of cardiac output, the arterial oxygen saturation will be less than 90% in patients with severely injured lungs.[26,27] The patient's underlying pulmonary disease prevents effective oxygenation by the lungs, limiting the ability of increasing ventilator F_{IO_2} and PEEP to increase Pa_{O_2}.

Assessment of Oxygen Delivery in VV ECMO

The minimum requisite Sp_{O_2} or Pa_{O_2} that facilitates an adequate DO_2 to prevent end-organ injury in VV ECMO patients and in hypoxemic respiratory failure in general is highly controversial. In critically ill patients, the basis of assessment of hemodynamic variables, serum lactate, hematocrit, Pa_{O_2}, and Scv_{O_2} is in the utilization of surrogate markers to determine the adequacy of DO_2 to organs and tissues.[31,32] Combining hemodynamic monitoring,

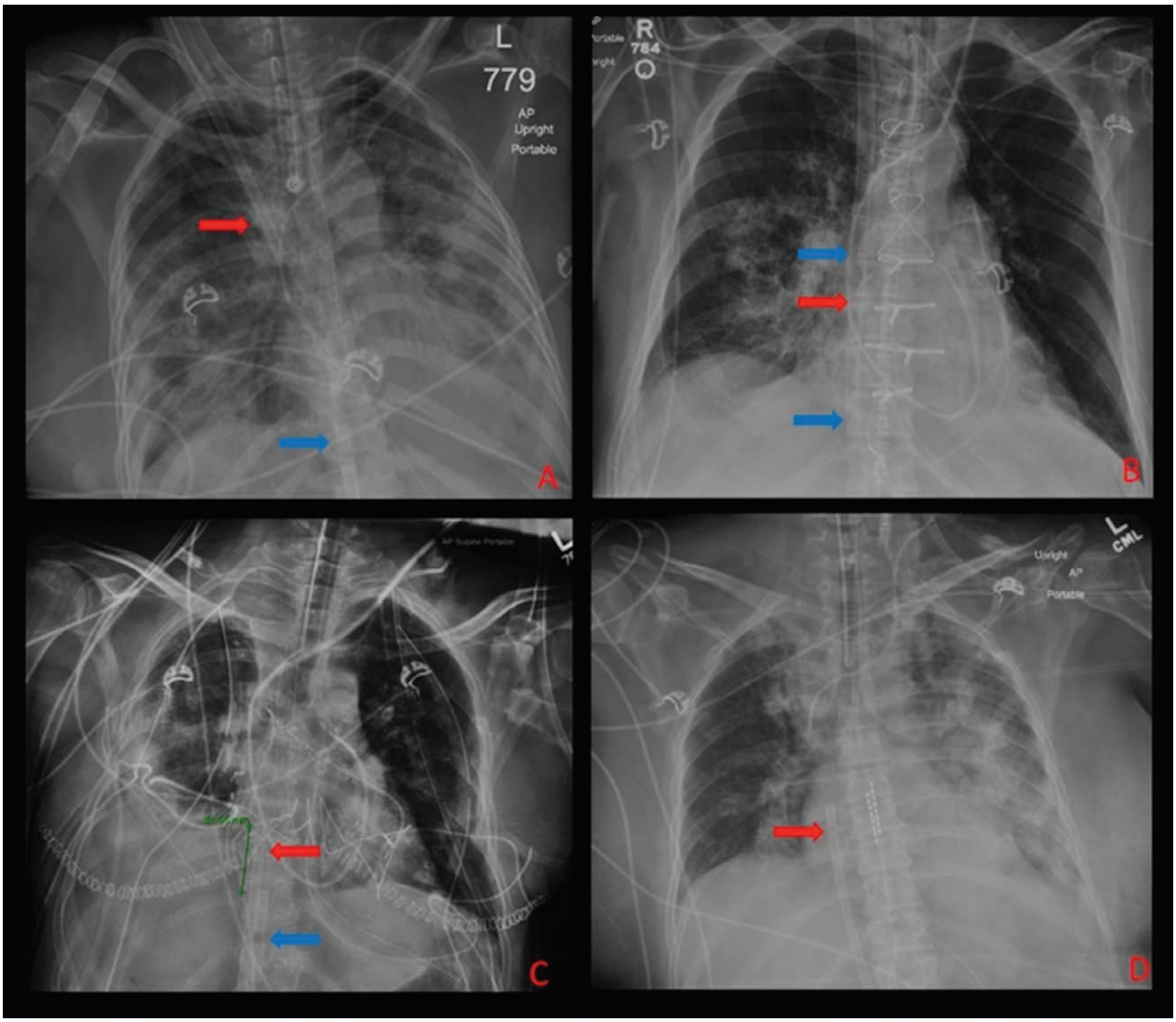

Fig. 2. Chest x-rays of patients with common venovenous extracorporeal membrane oxygenation cannulation strategies. *Red arrows* represent return sites of oxygenated blood to the patient. *Blue arrows* represent drainage of venous blood from the patient. (*A*) Femoral–right internal jugular cannulation. (*B*) Dual-lumen right internal jugular cannulation with Avalon Elite cannula. (*C*) Femoral–femoral cannulation with return cannula at the junction of the inferior vena cava (IVC) and right atrium and drainage in the IVC. (*D*) Femoral–femoral cannulation with the return cannula in the right atrium. The drainage cannula (not pictured) is in the femoral vein or distal IVC.

interpretation of serum markers for tissue perfusion, and clinical evaluation of end-organ function through assessments of mental status, urine output, serum creatinine, cardiac function, and liver function are essential to determining whether adequate DO_2 is being achieved. Until monitors that can directly measure oxygen delivery at the level of tissue beds are clinically available, practitioners will need to perform global assessments, because each individual marker has inherent limitations. For example, lactic acidosis may reflect either reduced hepatic clearance or CO, whereas normal or elevated Scv_{O_2} neither precludes volume responsiveness or ensures adequate DO_2 in all tissue beds.[31,33] Interpretation may be further confounded by the potential presence of microcirculatory dysfunction in critical illness, especially sepsis, where tissue-level capillary perfusion and oxygen extraction is inadequate despite "correction" of systemic hemodynamic variables that leads to organ dysfunction.[34] Optimal therapeutic management of decreased DO_2 is controversial, with variable responses elicited with treatments such as fluids, blood, and vasoactive drugs.[34] Although systemic hypoxemia often occurs in VV ECMO patients, with resulting oxygen saturations of 70 to 90% and Pa_{O_2} values of 40 to 60 mmHg, some patients will have adequate DO_2 at these levels.[26] It has been suggested that maintenance of DO_2 at a level of twice oxygen uptake ($\dot{V}O_2$), which has been measured at 265 ± 59 ml/

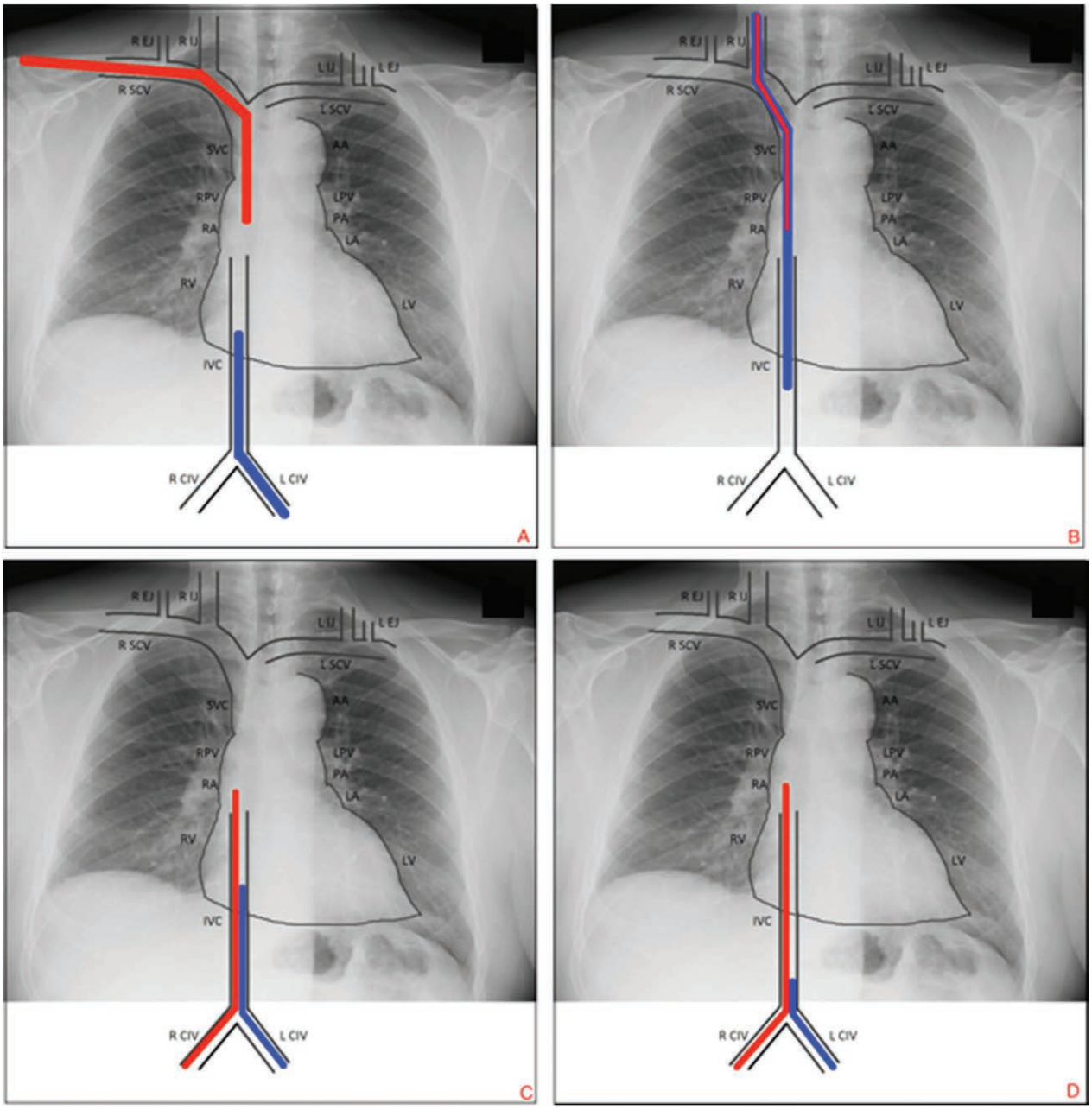

Fig. 3. Illustrated diagrams of common venovenous extracorporeal membrane oxygenation cannulation strategies corresponding with the x-rays in fig. 2. *Blue lines* represent drainage cannulas which deliver mixed venous blood from the patient to the membrane lung. *Red lines* represent return cannulas, which deliver oxygenated and decarboxylated blood from the membrane lung to the patient. (*A*) Femoral–right internal jugular cannulation. (*B*) Dual-lumen right internal jugular cannulation with Avalon Elite cannula. With this cannula, drainage occurs in the subclavian vein (SVC) and inferior vena cava (IVC), and blood is returned to the right atrium (RA). (*C*) Femoral–femoral cannulation with return cannula at the junction of the IVC and RA and drainage in the IVC. (*D*) Femoral–femoral cannulation with the return cannula in the RA. The drainage cannula (not pictured) is in the femoral vein or distal IVC. Femoral cannulas are often inserted into the femoral vein, which drains into the common iliac vein. AA = aortic arch; CIV = common iliac vein; EJ = external jugular vein; IJ = internal jugular vein; L = left; LA = left atrium; LV = left ventricle; PA = pulmonary artery; PV = pulmonary vein; R = right; RA = right atrium; RV = right ventricle.

min in critically ill, mechanically ventilated patients, is a minimum level necessary to prevent tissue hypoxemia.[26,35] Reassuringly, in two recent extreme altitude studies, healthy acclimated volunteers have demonstrated the ability to both sustain exercise with Spo_2 values of 46 to 61% and maintain serum lactate levels between 1.8 and 2.8 mM despite a mean Spo_2 of 54%.[36,37] Whether this translates to the critically ill patient has yet to be established.

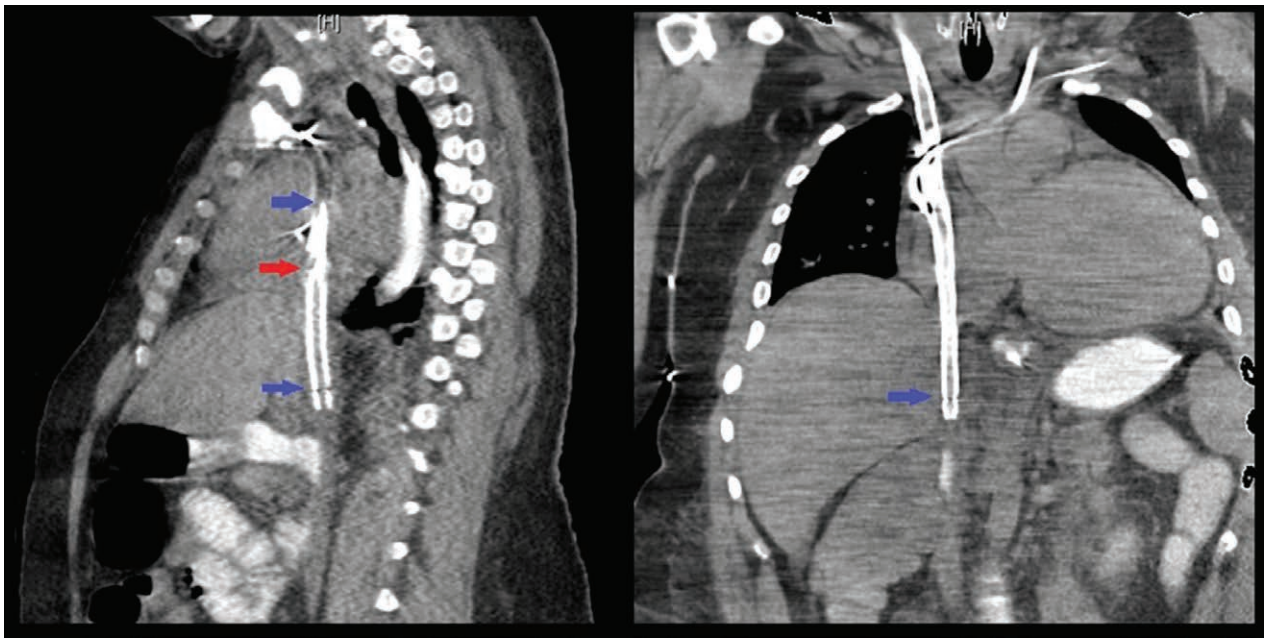

Fig. 4. Computed tomography (CT) imaging of right internal jugular cannulation with a dual lumen Avalon Elite cannula. *Red arrows* represent return sites of oxygenated blood to the patient. *Blue arrows* represent drainage of venous blood from the patient The outflow of oxygenated blood is directed across the tricuspid valve from a lumen in the right atrium. Venous drainage occurs through multiple cannula lumens in the superior vena cava and inferior vena cava . The tip of the cannula is in the intrahepatic IVC. A pulmonary artery catheter is also present. (*Left*) Sagittal chest CT view. (*Right*) Coronal chest CT view.

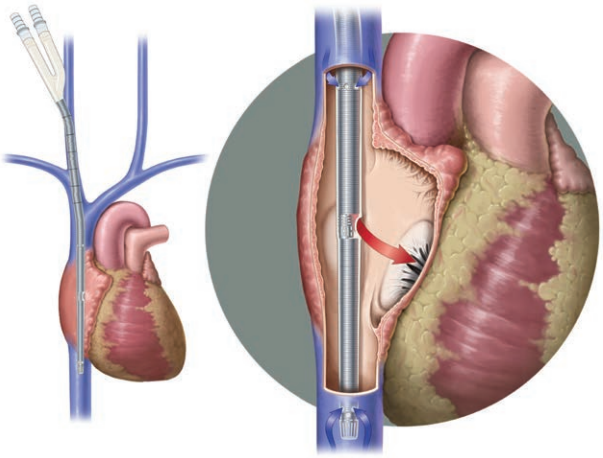

Fig. 5. Avalon Elite bi-caval dual lumen catheter. The *red arrow* represents outflow of oxygenated blood across the tricuspid valve. The *blue arrows* represent bicaval inflow of mixed venous blood. Reproduced from Maquet Cardiopulmonary GmbH, with permission.

Although mathematical equations can be used to calculate theoretical DO_2 based on CO, hemoglobin, Pa_{O_2}, and Sp_{O_2}, the influence of each of these variables on an individual patient's oxygen extraction is far more complex (table 1). For example, in a prospective randomized study of 100 critically ill patients, the use of the inotrope dobutamine increased DO_2, but did not increase in $\dot{V}O_2$, and actually increased mortality in the treatment group.[38] Similarly, the use of liberal blood transfusion strategies to boost DO_2 in critically ill (non-ECMO) patients has failed to demonstrate improved outcomes,[39,40] whereas restrictive transfusion practices have been shown to be feasible in VV ECMO patients.[41] Additional insight on the impact of Pa_{O_2} on patient outcomes may be gleaned from the ongoing Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial, which is randomizing patients with severe ARDS to either VV ECMO or conventional therapy and only allowing for crossover to ECMO in the control group when Sp_{O_2} remains less than 80% for more than 6 h.[42]

Ultimately, VV ECMO promotes a substantial improvement in a patient's capacity for DO_2 in respiratory failure, but assessment of a patient's ability to utilize the O_2 substrate is far more complex. This has led to variable practices regarding Sp_{O_2} management, where some institutions maintain values more than 88%, whereas others recognize Sp_{O_2} values as low as 70% as circumstantially capable of providing adequate DO_2.[18,26]

Management of Hypoxemia and Impaired Oxygen Delivery

The differential diagnosis for new or progressive hypoxemia in the VV ECMO patient should include: reduction of flow relative to the patient's cardiac output, impaired oxygenator function, worsening native lung function, or increased recirculation.[30] Assuming an ECMO F_{IO_2} of 1.0 and proper function of the membrane oxygenator, the most reliable way to increase Pa_{O_2} in patients on VV ECMO is to increase the blood flow through the membrane lung, by increasing pump revolutions/min (RPM) (fig. 6, table 3). Acutely, attempts at increasing flow may result in a relative lack of pump preload,

Table 2. Comparison of the Three Most Common VV ECMO Cannulation Strategies

Cannulation Strategy	Strengths	Weaknesses
Right internal jugular dual lumen cannula (currently only available as the Avalon Elite from Avalon Labs, USA)	- Ambulation feasible - Facilitates prone positioning[20] - May decrease transport risks[21] - Minimal recirculation unless tip migrates to hepatic vein or right atrium[21]	- Flow rates limited to 4.2 and 5.3 LPM in 27 and 31F models, respectively[21] - Risk of cardiac (RA or RV) or hepatic injury during placement[22] - Complex placement, which requires fluoroscopy or TEE[20,23]
Femoral–jugular* (femoral cannula will terminate in distal IVC at the level of the diaphragm, jugular cannula will terminate in RA, directed at the tricuspid valve)	- Allows for highest degree blood flow, especially in obese patients - A femoral drainage cannula (tip in the IVC) can be added to further increase flows	- Inflow and outflow cannulas having opposing lumens; recirculation is inversely related to the distance between the cannula tips
Femoral–femoral* (cannulas may be placed in a single or both femoral veins, with the tip of the drainage cannula terminating at the distal IVC at the level of the diaphragm and return cannula in the RA)[24]	- Least complex technically	- Prevents ambulation - Limits elevation of head of bed

*The configuration in which the tip of the drainage catheter is in IVC or SVC and blood is returned to the RA (femoroatrial) results in decreased recirculation, increased Pa_{O_2}, and increased total ECMO flow compared to atrial–femoral cannulation, in which blood is drained from the RA and returned to the IVC or SVC.[25]

ECMO = extracorporeal membrane oxygenation; IVC = inferior vena cava; LPM = liters per minute; RA = right atrium; RV = right ventricle; SVC = superior vena cava; TEE = transesophageal echocardiogram; VV = venovenous.

Table 3. Management Strategies for Hypoxemia

Intervention	Increases Sp_{O_2}	Increases DO_2	Decreases $\dot{V}o_2$
Blood transfusion	No	Yes	No
Muscle relaxation, sedation, cooling, controlled ventilation	Yes, indirectly	Yes, indirectly	Yes
Increasing ventilator FIO_2	Yes	Yes	No
Increasing ventilator PEEP	Yes	Yes	No
Increasing cardiac output	No	Yes	No
Increasing oxygen flow to membrane lung	Yes	Yes	No

DO_2 = systemic delivery of oxygen; FIO_2 = inspired concentration of oxygen; PEEP = Positive end-expiratory pressure; Sp_{O_2} = peripheral oxygen saturation; $\dot{V}O_2$ = metabolic uptake of oxygen.

evidenced by a partial collapse and vibration of the ECMO inflow tubing ("chatter"), which demonstrates an upper limit of pump blood flow. Subacutely, hemolysis and platelet damage, which are caused by shear stress, increase with increasing pump speed; therefore intensive care unit (ICU) management of ECMO includes maintaining the lowest blood flow required to achieve a target oxygen saturation. Conversely, reduction in pump flow increases contact time between circulating blood and the artificial surfaces within the circuit, which can increase the risk of thrombus formation.[43] Anecdotally, the maintenance of a minimum blood flow of 1.5 to 2.0 liters per minute (LPM; compared to typical maximum VV ECMO flows of 4 to 6 LPM, depending on cannula diameter) is employed regardless of saturation to offset the risk of thrombotic complications.

Evaluation of membrane lung function is important to the workup of hypoxemia, especially if increases in ECMO flow fail to clinically improve oxygenation. The first step is the visual assessment of the oxygenator through inspection for fibrin and clot deposition using a flashlight (fig. 7). Clinical impact of impaired function will typically only be recognized when postoxygenator Pa_{O_2} values result in an Sp_{O_2} of less than 100% and can be offset by high ECMO blood flows relative to cardiac output, recovering pulmonary function, or high mixed venous oxygen saturations. Alternatively, a high pressure drop across the oxygenator, which represents elevated resistance to blood flow across the membrane lung due to fibrin and clot, should also prompt consideration for oxygenator exchange. However, this represents a subacute process, unless a large thrombus was suddenly entrained. A gradient of 70 mmHg at 3 LPM blood flow, which can be measured with advanced systems, has been cited as a pressure drop threshold that should prompt oxygenator exchange.[44] Ultimately, the only way to rule out oxygenator dysfunction, which can occur despite a normal visual inspection, is to compare a premembrane blood gas with a postmembrane blood gas to quantitatively define the degree of oxygenation and decarboxylation occurring.

When ECMO flow is constant, Pa_{O_2} decreases as CO increases, whereas Pa_{O_2} increases after an acute decrease in CO. A series of three patients demonstrated that esmolol infusion can increase Pa_{O_2} in VV ECMO patients with high CO; however, this practice has the potential to ultimately decrease DO_2 due to its CO reduction.[45] Conversely, administration of an inotrope such as dobutamine can increase DO_2, whereas Sp_{O_2} may paradoxically decrease.[38]

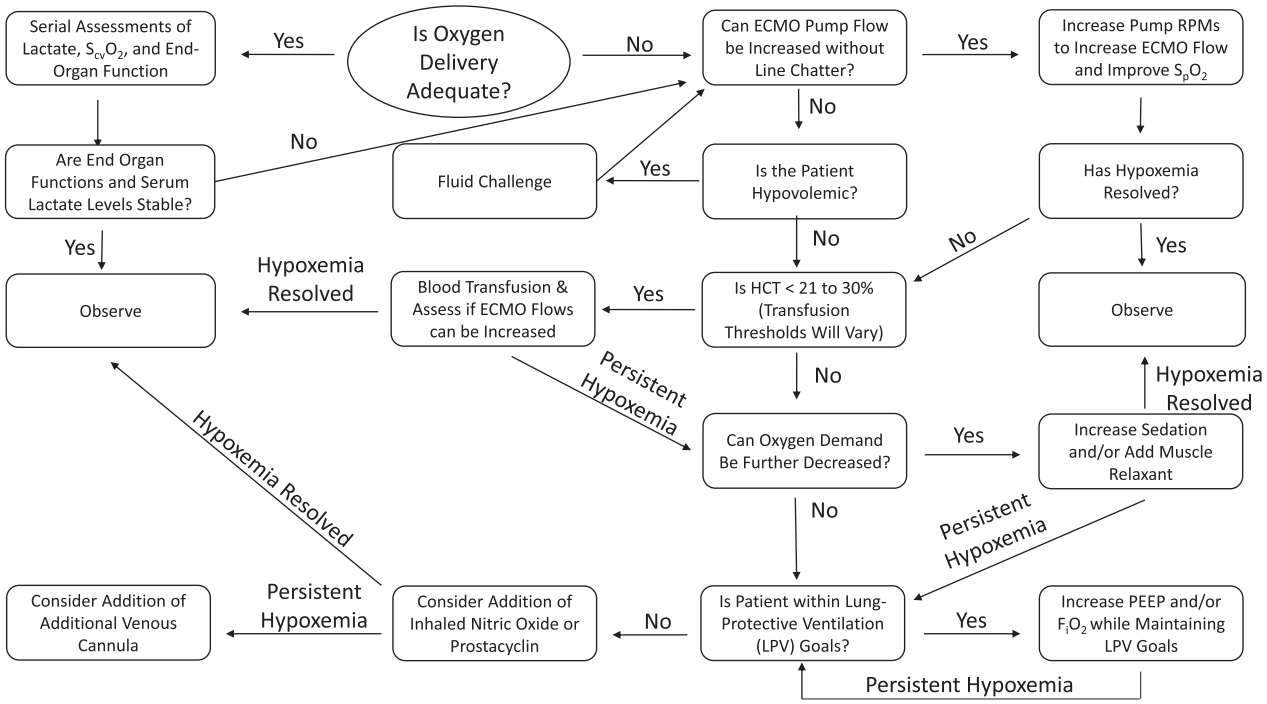

Fig. 6. Flowsheet for the management of perioperative hypoxemia in the venovenous extracorporeal membrane oxygenation cannulation patient. Assessment begins with the determination of the adequacy of systemic oxygen delivery. ECMO = extracorporeal membrane oxygenation; HCT = hematocrit; LPV = lung protective ventilation; PEEP = positive end-expiratory pressure; RPM = revolutions/min.

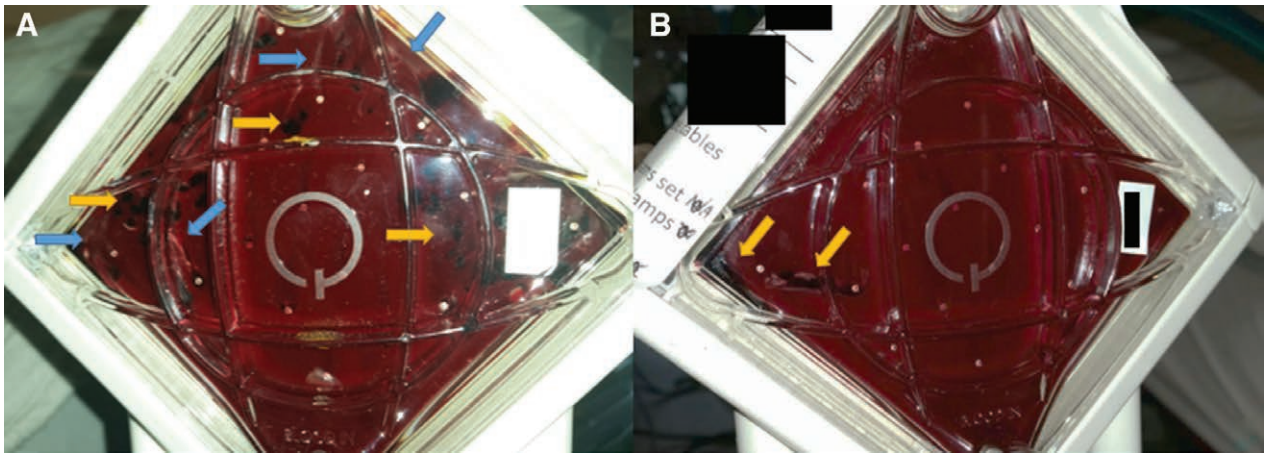

Fig. 7. Fibrin and clot deposition within extracorporeal membrane oxygenation cannulation oxygenators. (*A*) A poorly functioning oxygenator with a heavy burden of both thrombus (*yellow arrows*) and fibrin deposition (*blue arrows*). (*B*) An oxygenator with a lesser degree of thrombus formation (*yellow arrows*).

Blood transfusion increases oxygen carrying capacity and DO_2 without directly impacting Pa_{O_2} and can be considered when hypoxemia is present despite maximization of pump flows (table 3). Some specific organizational and study-based transfusion guidelines for VV ECMO patients vary widely from the Extracorporeal Life Support Organization (ELSO) recommendation to maintain hematocrits at 35 to 40%,[46] whereas two recent studies achieved success utilizing transfusion to maintain hemoglobin more than 7 mg/dl.[41,47] In these studies, the authors found that the mortality outcomes in restrictive transfusion practices were equivalent to those in liberal strategies but result in less product transfusion.[41,47] Given the discrepancies in recommendations and practice, blood administration should be individualized to the patient and considered when DO_2 appears clinically inadequate. Unfortunately, the specific situations in which liberal blood transfusion improves outcome in critically ill patients—including ECMO patients, if any—remain poorly defined.[39,40]

In situations in which DO_2 is determined to be inadequate and ECMO flows have been optimized, increasing ventilator F_{IO_2} and PEEP will improve oxygenation relative

to the extent of lung injury but should be done with consideration of preventing VILI (table 3). Although uncommonly necessary, the benefits of transient ventilator changes during the perioperative setting will likely exceed the risks of VILI when used to manage refractory hypoxemia or acidemia but should be made cautiously.

Adjuncts to Oxygenation

Inhaled nitric oxide may improve Pa_{O_2} in severe respiratory failure by decreasing ventilation–perfusion mismatch; however, both a mortality benefit in patients with ARDS and ECMO–specific literature are lacking.[48] A similar improvement in oxygenation can be expected with utilization of an inhaled prostacyclin but also without supportive ECMO or survival literature.[49,50] Given the high cost without clear patient benefit, these drugs should be reserved for situations in which refractory hypoxemia is resulting in impaired DO_2. A last resort to improve persistent hypoxemia is the addition of an additional ECMO cannula, which will support increased ECMO blood flow, allowing for additional oxygenation.

An alternative to increasing DO_2 is decreasing the patient's oxygen uptake ($\dot{V}O_2$), which will increase Scv_{O_2}. This can be achieved through deep sedation, controlled mechanical ventilation, hypothermia, and neuromuscular blockade.[51]

Recirculation

Recirculation is a phenomenon unique to VV ECMO patients, where blood leaving the ECMO outflow cannula immediately returns to the ECMO circuit through the inflow cannula, bypassing systemic circulation, generating a closed loop that does not contribute to oxygenation, while effectively reducing systemic ECMO blood flow. Recirculation is inherent and expected, with levels of at least a few percent of total flow with dual-lumen cannulas,[23,52] ranging to up to 15 to 20% of total flow with two-cannula configurations.[53] Exacerbation of recirculation, associated with reduced arterial oxygen saturation (Sa_{O_2}), can be triggered by increasing ECMO pump speeds or flows, decreasing CO, position changes and migration of cannulas during transport (identifiable by x-ray), and changes in intraabdominal pressures, such as during laparoscopy.[53] Increasing brightness of the blood in the inflow cannula or a lack of difference in blood color in the inflow and outflow cannula, increased inflow oxygen saturations, or a decreasing Sp_{O_2} after known triggers should prompt evaluation for recirculation.

Decarboxylation

CO_2 clearance (decarboxylation) occurs as a result of a partial pressure gradient between blood circulating through the membrane lung and the fresh gas added to the ECMO circuit *via* the membrane, referred to as "sweep gas," which is devoid of carbon dioxide. At clinically relevant ECMO blood flows, the amount of decarboxylation is almost exclusively dependent on sweep gas flow, with increasing flow rates resulting in increased carbon dioxide removal.[3,26,27] While on ECMO, the patient's Pa_{CO_2} is also dependent on alveolar ventilation and carbon dioxide production.

Management of Hypercarbia and Acidemia

The first response to hypercarbia or metabolic acidemia should be an increase in the sweep gas flow to normalize pH (table 4). Importantly, the relationship between gas flow and carbon dioxide removal is nonlinear, with decreasing incremental benefit with increasing flow rates above 2 LPM.[27] Once sweep gas flow has reached a threshold of 6 to 8 LPM, decarboxylation will become limited by the surface area of the membrane lung, and incremental increases in flow may have minimal clinical significance.[3,27] When adequate decarboxylation cannot be achieved, membrane dysfunction should be considered and can be confirmed by comparing pre- and postmembrane PCO_2 measurements. In uncommon situations where decarboxylation is inadequate at a sweep gas flow of more than 10 LPM despite therapies to reduce production, the addition of a second membrane will increase the limits of decarboxylation by doubling the surface area for gas exchange. Alternatively, increasing the patient's alveolar minute ventilation to manage hypercapnia may be required but should be reserved to uncommon situations in which there is clinically significant acidemia. It is advisable to use the slightest possible ventilator change required to meet the clinical goal, because increasing V_T or P_{Plat} will increase the risk of VILI.

In patients with metabolic acidosis, infusion of the buffer solution sodium bicarbonate can provide a temporary improvement in pH, but its effect will be limited due to the generation of CO_2 as a byproduct of metabolism, which will pose a challenge to lung protective ventilation. Alternatively,

Table 4. Management Strategies for Hypercarbia

Intervention	Increases CO_2 Elimination	Decreases CO_2 Production	Decreases Pa_{CO_2}
Increasing fresh gas flow (sweep flow rate)	Yes	No	Yes
Increasing ECMO blood flow	No	No	No
Muscle relaxation, sedation, cooling, controlled ventilation	No	Yes	Yes
Increasing alveolar ventilation (increased mechanical ventilator minute ventilation)	Yes	No	Yes
Increasing ventilator PEEP	No	No	No

ECMO = extracorporeal membrane oxygenation; PEEP = positive end-expiratory pressure.

utilization of deep sedation at general anesthetic doses, muscle relaxants, controlled ventilation with prevention of dyssynchrony, prevention of auto-PEEP, aggressive treatment of fever, and therapeutic hypothermia will decrease CO_2 production.

ECMO and the Anesthetic Plan

Preoperative Evaluation. Preoperative assessment of VV ECMO patients should be focused on evaluating frequent VV ECMO complications, such as arrhythmias, anemia, bleeding (gastrointestinal, cannula site, and intracerebral), pneumothorax, coagulopathies including platelet dysfunction and disseminated intravascular coagulation, and venous thrombosis, as well as determining the type of general anesthetic to be used (table 5).[54] ECMO blood flow and circuit inflow pressure should be documented, given that they will be important makers of perioperative volume status; sweep gas flow requirement is an important indicator of the severity of hypercapnia, and the premembrane oxygen saturation trend can be an indicator of oxygen delivery.

The ECMO circuit should also be evaluated before going to the operating room. A flashlight inspection of the membrane oxygenator may demonstrate fibrin deposition or thrombus presence before the surgery and stopping anticoagulation (fig. 7). If a significant deposition is present and results in hypoxemia or hypercarbia, consideration for oxygenator exchange should occur before the surgical procedure, because withholding anticoagulation in the perioperative setting can precipitate increasing membrane clot formation and decline in membrane functionality.

Unless already facing significant hemorrhagic complications, VV ECMO patients will be anticoagulated, primarily *via* heparin infusion. Assessment of coagulation studies will be useful in determining a patient's risk of intraoperative bleeding beyond the effect of administered anticoagulation. For selected patients and procedures, it may be favorable to hold systemic anticoagulation if a high risk of bleeding exists. Additionally, red blood cells should be cross-matched and available before procedures, in a quantity commensurate with bleeding risks.

Table 5. Summary of Anesthetic Implications for VV ECMO Patients Undergoing Surgery

Preoperative evaluation	- Assess and document ECMO settings and blood flow - Asses for coagulopathy, consider risks of platelet dysfunction and DIC - Type and cross for red blood cells, consider preparation of FFP - Assess ECMO–specific complications (arrhythmias, anemia, bleeding, pneumothorax, thrombosis) - Pause anticoagulation, if feasible and indicated
Transport to the OR	- Utilize standard ICU monitors - Utilize transport ventilator or portable ICU ventilator with alarms - Include a practitioner dedicated to ECMO and capable of troubleshooting
Induction and maintenance of anesthesia	- Patients may require little or no additional anesthetic depending on baseline degree of sedation - TIVA is preferred - Titrate anesthetics to clinical effect/depth monitor
Monitoring	- Arterial line can be at any site with VV ECMO - Anesthetic depth monitoring is useful - Echocardiography is a reliable measure of cardiac output; all other techniques have limitations - $ETco_2$ remains reliable, but value also reflects decarboxylation done by ECMO
Volume assessment and management	- Negative fluid balance is general goal in VV ECMO patients - Decreases in ECMO flows, venous pressure, and development of "chatter" can reflect low preload - Consider volume challenge if ECMO flows are decreasing during period of acute blood loss (especially if associated with decreased Spo_2)
RBC transfusion: indications/triggers	- Blood can be used to increase DO_2, regardless of hemoglobin level - Guidelines are widely variable; transfusion to Hb > 7 g/dl acceptable in selected patients
Management of anticoagulation for ECMO	- Acceptable to hold anticoagulation in perioperative period for most VV ECMO patients (unless they have had thromboembolic events) - Generally, aPTT goals are 40–60 s and ACT goals are 180–220 s in VV ECMO patients
Assessment and treatment of coagulopathy	- Utilize traditional coagulation labs and or thromboelastometry to direct management of surgical bleeding; aPTT elevations may be artificial due to critical illness - Platelet dysfunction and acquired von Willenbrand's disease common with prolonged ECMO durations - Prothrombin complex concentrate may be considered for patients with bleeding and prolonged INR or clotting time who cannot tolerate volume - Consider cryoprecipitate for hypofibrinogenemia

ACT = activated clotting time; aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation; $ETco_2$ = end-tidal carbon dioxide partial pressure; FFP = fresh-frozen plasma; ICU = intensive care unit; INR = international normalized ratio; OR = operating room; PT = prothrombin time; RBC = red blood cell; TIVA = total intravenous anesthesia; VV = venovenous.

Preoperative transthoracic or transesophageal echocardiography or intraoperative transesophageal echocardiography can be used to identify myocardial dysfunction, which is common in critical illness, as well as identify ECMO–specific complications such as cannula malposition and the presence of thrombus.[55,56]

Patient Transport. Transport of patients on VV ECMO represents a high-risk period. ELSO recommendations emphasize practitioner experience and the presence of a perfusionist or capable provider dedicated to the circuit management during transport (table 5).[57] Specific attention should be made to ensure there is adequate battery supply to powered systems, alarms are appropriate on the transport monitor, emergency medications are available, and that the oxygen cylinders for both the ventilator and ECMO circuit are full.[58] Given the known adverse impacts of atelectasis, volutrauma, and oxygen toxicity, continued use of the patient's ICU ventilator, maintaining baseline settings and sustained pressure, and V_T monitoring with audible alarms is advisable.[9,28,58] Although a transport ventilator is an alternative, they have inherent differences in performance from ICU ventilators, will require circuit disconnection and subsequent alveolar derecruitment, and introduce the possibility for an unintentional change in ventilator settings. The use of bag-mask ventilation during transportation provides no conceivable benefit to the patient and introduces risks of alveolar derecruitment, volutrauma, and barotrauma.

In cases of extreme patient instability, the bedside performance of emergent surgical procedures such as laparotomy may be required.[59] ECMO itself should not preclude transport the operating room, because interfacility transport of ECMO patients is increasingly frequent and has been demonstrated to be safe.[60,61] Transport decisions should take in to account patient factors, as well as system issues such as ECMO experience among hospital staff and surgical capabilities within the ICU and OR suites. After transport, a routine system check should include visual inspection for shifts in line position or kinks in tubing, because either can cause significant flow reductions, as well as assessment of the ECMO console to ensure blood flow and circuit pressures are stable.

Anesthetic Choice. Total intravenous anesthesia (TIVA) is the most practical method of anesthetizing patients requiring VV ECMO for multiple reasons (table 5). Delivery of volatile anesthetic is limited, but not impossible, due to the characteristically low V_T, significant dead space, and impaired gas exchange in patients on VV ECMO. The ECMO system can contribute to the elimination of volatile anesthetics; however, permeability across polymethylpentene membrane fibers is poor.[62]

TIVA allows for continuous delivery of anesthetic without a contribution from severely injured lungs and eliminates the need to transition the patient from the ICU ventilator to the anesthesia machine, fostering consistency in the ventilation strategy. A limitation to TIVA is the potential for drug adsorption onto the ECMO circuit, specifically lipophilic drugs such as propofol, fentanyl, and midazolam, making it imperative that medications are titrated to clinical effect. Electroencephalographic monitoring, such as utilization of bispectral index monitoring (Medtronic, USA), is a technique that will provide a quantification to depth of sedation and confirmation of drug delivery in patients who may have blunted hemodynamic responses to surgical stimuli.[63] Such monitoring may also help identify or quantify a preexisting state of deep sedation due to variable sedation practices among ICUs, particularly in patients receiving paralysis, especially as drug pharmacokinetics can be significantly altered in ECMO patients.[63–67]

Selection of Monitors and Personnel. All standard American Society of Anesthesiologist monitors should be employed in patients on ECMO and have only minimal limitations; even end-tidal carbon dioxide monitoring will be representative of $Paco_2$, albeit with a large gradient given lung pathology. An arterial line should be considered essential to all patients on VV ECMO for the assessment of respiratory gasses and blood pressure monitoring and may be used for pulse–contour analysis methods of CO measurement.[68] Although central venous pressure may be an unreliable measure of volume status in ECMO patients, central access for medication delivery should be present given the inherent severity of illness in ECMO patients.

Cardiac output has important implications as the ratio of ECMO blood flow to CO is a significant determinant of blood oxygen saturation. Pulmonary artery catheters, which utilize thermistor or thermodilution-based measurements of CO, are potentially unreliable in patients on ECMO due to the heat exchange occurring within the ECMO circuit. In addition, central venous oxygen saturation measurement will not represent $\dot{V}O_2$ or provide a surrogate for adequacy of DO_2 because sampling measures the oxygen saturation of post–ECMO blood in the pulmonary artery. Transesophageal and transthoracic echocardiography are perhaps the most reliable cardiac monitoring tools in patients on VV ECMO, because they can quantify ventricular function, assess volume status, identify cannula malposition, and calculate CO using Doppler measurements.[69] Utilization of intraoperative transesophageal echocardiogram should be considered to monitor cardiac function and volume status for procedures anticipated to result in significant hemodynamic or volume shifts. Multiple proprietary systems that measure CO using arterial line pulse wave analysis–based algorithms are approved for clinical use.[68] Because left heart function, and subsequently the arterial pressure waveform, are unaffected by VV ECMO, such CO measurements likely remain valid; however, the use of stroke volume variation to predict volume responsiveness has not been studied in patients on ECMO and is unreliable when V_T is low or pulmonary compliance is poor.[70] Pulse contour analysis should not be used in patients on VA ECMO, which generates nonpulsatile outflow. Given that ECMO performance is highly dependent on both preload and afterload and that significant

volume shifts can occur rapidly during operative procedures, a provider such as a perfusionist should be present throughout the surgery whenever possible and can be invaluable in recognizing and troubleshooting system complications during the management of these complex patients.

Volume Assessment. Volume assessment, in particular assessment of a patient's fluid responsiveness, is a particular challenge in patients on VV ECMO. Although VV ECMO is volume neutral, central venous pressure measurements are an unreliable marker of volume status in critically ill patients in general[71,72] and will be further confounded by the pressures generated by the ECMO cannulas (table 5). Accurate preload assessments are important given positive fluid balances in patients on VV ECMO have been associated with increased mortality, whereas hypovolemia can reduce ECMO flows.[73]

The impeller pump driving the ECMO system depends on uninterrupted blood flow to function and will be highly sensitive to reductions in "preload" to the pump, which are relative to pump speed, and may occur even when left ventricular end-diastolic volume is adequate. An early sign in which pump preload has decreased is an increasingly negative ECMO inflow pressure, representing a greater force requirement to maintain stable blood flow. Vibration or partial collapse of ECMO tubing ("chatter") may also occur and suggests insufficient blood flow to the pump for sustained function at the set speed and thus should trigger either volume administration or a reduction in pump RPMs when Sa_{O_2} is at an adequate level for the patient to tolerate reduced ECMO flow. With progressive volume loss, maximum ECMO blood flow will decrease, which results in hypoxemia. Echocardiographic assessment of the patient is warranted when volume status and cardiac function are unclear. Vigilance must be maintained throughout the operative course to closely track estimated blood loss and to observe for reversible changes in position or surgical maneuvers (such as retractor placement or abdominal insufflation), which can reduce preload to the ECMO circuit.

Management of Bleeding, Coagulopathy, and Anticoagulation. The perioperative management of anticoagulation in patients requiring VV ECMO will ultimately require balancing the risk of thrombosis against the patient and procedure-specific risk of perioperative bleeding (table 5). Risk factors for thrombotic complications include the occurrence of ongoing thrombotic events, especially when clot is adherent to the surface of ECMO cannulas, the presence of fibrin deposition or clot burden within the ECMO circuit or membrane lung (fig. 7), coexisting patient hypercoagulable state, and unrelated needs for anticoagulation such as a mechanical heart valve. Interruption of anticoagulation can also precipitate ongoing consumptive coagulopathy through platelet and clotting factor contact with the circuit. The benefits of withholding systemic anticoagulation will be facilitation of a "dry" surgical field and reduction of the risk of perioperative bleeding. Many centers will avoid ECMO flows less than 2 LPM or even increase flows when anticoagulation is interrupted to decrease the amount of time circulating blood dwells in the circuit, theoretically decreasing thromboembolic risk.

Unlike patients on VA ECMO, who are prone to left-sided clot formation due to stagnant blood flow in the left ventricle, the thromboembolic risk profile in VV ECMO is typically limited to right-sided events, with the notable exception of patients who have atrial or ventricular septal defects. In patients on VV ECMO, thrombus may occur around ECMO cannulas or within the circuit or oxygenators, with the most significant risks being pulmonary embolism and rarely the abrupt cessation of the ECMO function due to an obstructing thrombus in the circuit.

Considering a balance of risks and benefits, temporary cessation of anticoagulation in the immediate perioperative period is usually safe and feasible, and advisable, at least temporarily, for procedures at high risk of bleeding complications. Current guidelines suggest stopping heparin 4 to 6 h before elective surgery in patients from the general population admitted for bridging therapy.[74] It is, however, reasonable to consider a similar time period for patients undergoing nonemergent procedures which are categorized by a high bleeding risk, especially if there are no ongoing thrombotic complications. Reassuringly, a case report documents success of a VV ECMO patient off of anticoagulation for a period of 20 days while being treated for hypoxemic respiratory failure caused by alveolar hemorrhage.[75]

Evaluation of both the degree of anticoagulation and coagulopathy poses a challenge in patients on ECMO because no single lab value is without limitation in this population. For example, activated clotting time values are inconsistent at low levels of heparin, aPTT response to heparin is blunted when fibrinogen or factor VIII concentrations are elevated, and hepatic dysfunction can prolong prothrombin time (PT) due to reduction of factor VII despite compensatory elevations in factor VIII and fibrinogen.[76] Unlike activated partial thromboplastin time (aPTT), an anti-Xa level can be useful to quantify heparin effect independently of both elevations in acute phase reactants such as factor VIII or fibrinogen and factor deficiencies but remains dependent on endogenous anti-thrombin III activity.[77–80]

Although platelet count can be accurately measured, this value does not assess quality, which is significant as progressive platelet dysfunction occurs with increasing time on ECMO.[81] Viscoelastic tests (thromboelastography [Haemonetics Corporation, USA] or rotational thromboelastometry) have the potential to provide precise and timely identification of coagulopathy, can identify both hypo- and hypercoagulopathy, and have been correlated to predict bleeding complications in a small study of ECMO patients.[81–83] Viscoelastic tests, as well as anti-Xa levels, may have particular benefit in in identifying coagulopathy outside of heparin effect.[84] A low threshold for evaluation for disseminated intravascular coagulation, a relatively frequent phenomenon, should also be present in patients on VV ECMO.[76]

Specific thresholds to transfuse blood and blood products are highly controversial.[46,76,82] For example, ELSO guidelines support transfusion of fresh-frozen plasma to maintain international normalized ratio (INR) less than 1.5 to 2.0, platelet transfusion to maintain more than 100,000 cells/mm^3, and cryoprecipitate administration to maintain fibrinogen more than 100 to 150 mg/dl.[46] Meanwhile, in an international survey of ECMO centers that manage both adult and pediatric patients, transfusion thresholds in uncomplicated ECMO patients ranged from platelet counts of 20,000 to 100,000 cells/μl, fibrinogen levels of 50 to 200 mg/dl, and hematocrit thresholds of 20 to 40%.[18,82]

Aminocaproic acid has been demonstrated to significantly reduce surgical site bleeding due to fibrinolysis in a large series of pediatric ECMO patients[85] and can be considered in adult patients, especially those with thromboelastographic demonstration of fibrinolysis. Recombinant factor VIIa has been shown to be effective in management of intractable hemorrhage in VA and VV ECMO patients; however, both recombinant factor VIIa and prothrombin complex concentrates have been implicated in catastrophic thrombotic events in the ECMO population and must be used with caution.[86–88] Desmopressin may also have a role in the management of perioperative bleeding in ECMO patients, because a spectrum of acquired von Willenbrand factor deficiency is nearly ubiquitous in ECMO patients.[89] Cryoprecipitate that contains von Willenbrand factor can also be used for this condition. In bleeding patients, a combination of viscoelastic and traditional testing should be used to guide blood product and clotting factor utilization, while reserving prothrombin complex concentrates and recombinant factor VIIa for refractory bleeding combined with evidence of factor bleeding. Perioperative management of anticoagulation, like in other surgical procedures, must take into account risk *versus* benefit, because literature is limited to case reports.[90]

Procedure-specific Challenges in VV ECMO

Abrupt changes and extremes in positioning associated with surgical procedures may profoundly impact VV ECMO patients. Positions that lower the head may decrease a patient's already-impaired lung compliance; however, reductions in alveolar ventilation can be offset by increasing sweep gas flows. Conversely, reverse Trendelenburg positioning can cause a reduction in preload and lead to decreased ECMO flow.

Abdominal Surgery. Abdominal explorations and bowel resections are among the most common surgical procedures performed on ECMO patients, with 69 abdominal procedures performed in a series of 563 VA and VV ECMO patients.[14] Abdominal compartment syndrome, which is associated with high mortality, may be caused by resuscitative fluid shifts and/or pathophysiology related to the patient's underlying critical illness.[91,92] The condition is most common in pediatrics and neonates who are highly sensitive to the increased in circulating volume introduced by the ECMO circuit.[91,92] In addition to causing abdominal organ dysfunction and reducing pulmonary compliance, ECMO flows are often reduced in abdominal compartment syndrome due to the decrease in venous return, necessitating decompressive laparotomy.[91,92]

Laparoscopic surgery, which utilizes carbon dioxide to insufflate the abdomen, causes systemic absorption of the gas, which challenges the decarboxylation abilities of the membrane lung, resulting in refractory respiratory acidosis VV ECMO patients. Although laparoscopy is generally discouraged, preemptively increasing sweep gas flow is advisable to prevent an acute decrease in pH upon insufflation and to manage the increased dioxide load. Abdominal insufflation may also reduce venous return, decrease ECMO flow, and result in hypoxemia, requiring vigilant monitoring during the process. Although a fluid challenge may improve venous return, a low threshold to conversion to open procedure should be held. In patients who require high degrees of sweep or high V_T or P_{plat} to manage hypercarbic respiratory failure, safe management during laparoscopic procedures will be challenging, if not impossible.

Thoracic Surgery. Thoracic surgery may be required for management of conditions such as hemothorax, traumatic lung injuries, and empyema or for the purpose of open lung biopsy.[14,93–95] In a series of 589 mixed VA and VV ECMO patients, a total of 89 thoracic procedures were performed, with exploratory thoracotomy, video-assisted thoracic surgery (VATS), and lung biopsy being the most common procedures.[14] Reports of anticoagulant management in the immediate perioperative period are limited to case reports, with activated clotting time or aPTT goals being reduced in the days after the procedure, as well as one group completely holding anticoagulation for 6 h prior and 24 h after VATS.[93–95] One case reports the transfusion needs of 39 units of red blood cells and 25 units of platelets over a multiday period in which refractory bleeding from vessels to muscle beds and the chest well prompted a series of three VATs, as well as definitive thoracotomy, in the management of hemothorax after ECMO cannulation.[93]

During thoracic procedures, single-lung ventilation is often required, and decreases in minute ventilation and Sao_2 secondary to increased transpulmonary shunting can be offset by increasing the sweep gas flow and ECMO blood flow if hypercarbia or hypoxemia occur. Recent case reports demonstrate the utility of VV ECMO in the management of high-risk airway surgeries, as well as a means for gas exchange in high-risk lung resections.[96–99] Although heparin was administered during these procedures, the patient population differs substantially, because ECMO removal at the end of the procedure not only eliminates the need for anticoagulation but also allows for protamine administration.[99]

Tracheostomy. Tracheostomy is likely the most common procedure performed on VV ECMO patients. Cessation of mechanical ventilation during the procedure will eliminate

the patient's ability to decarboxylate and oxygenate blood and can be offset by increasing sweep gas flow and ECMO blood flow before the procedure. A report of two cases of fatal venous air embolism occurring in patients undergoing tracheostomy managed using a dual lumen catheter suggests that air entrainment through a thyroid vein is a potential complication of the procedure.[100]

Endoscopy. Endoscopy may be required in the evaluation and treatment of patients with gastrointestinal bleeding, which occurs in up to 5% of all ECMO patients, commonly due to stress gastritis.[101–103] Percutaneous endoscopic gastrostomy tube placement frequently accompanies tracheostomy. A series of four patients with prolonged ECMO courses (two VA and two VV) reports perioperative discontinuation of heparin without complications.[104] Often minimal additional sedation is required for these procedures, with the main anesthetic considerations being availability of blood and acquisition of venous access for patients with ongoing hemorrhage.

Perioperative ECMO Assessment and Management of Complications

The ability to troubleshoot common ECMO alarms and complications or the immediate availability of a practitioner capable of doing so is essential to safe perioperative management of the VV ECMO patient (table 6).

Line Chatter. Line chatter, or partial collapse of the ECMO drainage cannula, is a common occurrence in patients with relative hypovolemia and occurs in response to an insufficient availability of blood relative to the speed of the pump flow. The negative pressure generated by the impeller pump causes collapse of the cava or atrium in which the drainage cannula is positioned, immediately preceding collapse of the ECMO tubing. Management options will depend on the patient's DO_2, with oxygen saturation being the most commonly used surrogate. If oxygen saturation is adequate, the pump RPMs can be decreased, which will lower the impeller pump's demand for blood and stop line chugging. Alternatively, if DO_2 is inadequate, infusion of crystalloid solution or transfusion of blood will increase ECMO preload and allow the pump to function at higher RPMs and higher blood flows. In the perioperative setting, positioning changes can also trigger line chatter and should be reversed when practical.

Venous Air Embolism. Although VV ECMO is essentially a volume-neutral system, hypovolemia, resulting in increasingly subatmospheric pressures in the venous cannula, will increase the risk of air embolism during line placement.[105] Placement of lines during periods of line chatter should especially be avoided. In an experimental system, airflow through an open venous cannula was determined by pump flow and cannula diameter, exceeding 0.3 LPM through a 16-gauge cannula at a pump flow of 2.25 LPM, which can rapidly cause air-lock of the ECMO circuit.[106] Gas entrainment occurred in an all-or-nothing manner, meaning slight changes could result in a massive air embolism (for example, if a venous catheter tip migrated closer to the ECMO cannula).[106] Although the incidence of air embolism is unknown, preventative techniques can and should be utilized. Temporary reduction of pump flow rates during line placement, if tolerable, will decrease the negative pressure applied by the venous cannula and reduce airflow if embolism were to occur. Trendelenburg positioning will also help reduce the risk of air embolism by increasing venous return to patients undergoing internal jugular line placement. Even simple measures, such as ensuring caps are present on stopcocks, should be employed to prevent inadvertent air entrainment.

Medication Dosing in VV ECMO. VV ECMO patients will have altered pharmacokinetics due to the combination of critical illness, variable hepatic and renal function, and ECMO–specific changes including increase volumes of distribution (Vd), decreased drug clearance, and drug adsorption on the circuit tubing.[107] Prolonged release of drugs sequestered within the circuit may also occur (unpredictably), causing circulation of medications even after discontinuation of infusions.[107] Unfortunately, the majority of pharmacokinetic data is from neonates, who have different indications for ECMO, inherently different pharmacokinetics from adults, and, due to their size, will be much more sensitive to changes in Vd from the ECMO circuit.[107–109]

Sedative and Analgesic Dosing. Significant sequestration of drugs by the ECMO circuit (in *ex vivo* studies), which functionally results in an increased Vd, occurs with the lipophilic drugs such as fentanyl (where bioavailability is reduced by 65% or more) and midazolam.[110,111] Hydrophlic drugs such as morphine are less susceptible, with *ex vivo* studies demonstrating the reduction in bioavailability ranging from negligible to 43%.[110,111] A recent study of adult VV ECMO patients receiving sedation in the ICU, generally with a Richmond Agitation and Sedation Scale goal of 0 to −1, reported that patients required lower doses of opioids and benzodiazepines than suggested in previous reports.[64] Of 365 patients, 98.6% were managed with continuous opioids, with a mean of 4,800 μg fentanyl equivalents daily, and 64.7% received continuous benzodiazepines, with a mean dose of 22 mg midazolam equivalents daily.[64] The authors suggest that although changes in pharmacokinetics are present in VV ECMO patients, pediatric data do not fully extrapolate to adult patients, and clinical differences in drug requirements in ECMO patients likely also reflect differences in sedation practices.[64]

Propofol, which is lipophilic, is also highly sequestered by the ECMO circuit, leading to a reduction in drug concentration from expected levels, as decreased drug levels with infusions.[107,112] There is theoretical concern that lipemia resulting from propofol infusion may impair oxygenator function; however, the clinical effect of this is unclear. One small study actually found a reduction in the need for oxygenator exchanges in the patient cohort receiving propofol sedation, whereas an *ex vivo* cardiopulmonary bypass study found no impact on membrane gas exchange during propofol administration.[113,114] *In vitro* studies demonstrated

Table 6. Management and Troubleshooting of Hypoxemia, Hypercapnia, and ECMO Parameters

	ECMO Interventions	Patient Interventions
Hypoxemia	- Increase ECMO flow/RPMs	- Volume challenge if flows have acutely decreased - Increase F_{IO_2} during the perioperative period - Increase PEEP - Decrease patient demand (sedation, muscle relaxation, cooling)
Hypercarbia	- Increase sweep gas flow rate	- Decrease patient demand (sedation, muscle relaxation, cooling)
Decreased ECMO circuit blood flow (with signs of hypoxemia, hypercarbia, or new clinical instability)	- Increase pump RPMs - No intervention is necessary if patient condition is unchanged	- Assess for changes to patient position - Volume challenge - Consider line position change during transport
ECMO tubing vibration or partial collapse ("line chatter")	- Decrease pump RPMs	- Volume challenge - Reverse changes to patient position
Increasingly negative inflow pressure	- Decrease RPMs (if flows adequate for oxygenation)	- Volume challenge if progressive change from baseline - Reverse changes to patient position
High outflow line pressure	- Decrease RPMs (if flows adequate for oxygenation)	
Increased transmembrane pressure	- Assess for membrane clot; if severe consider replacement before OR - If acute, membrane change may be needed	- Consider using higher perioperative anticoagulation goals and restarting heparin earlier
High pre–ECMO Spo_2 (not available on all consoles)	- Consider a sign of possible recirculation: (1) Compare to systemic Spo_2 (should be lower), (2) assess for changes to cannula position, and (3) surgeon evaluation if likely requires cannula manipulation	- Can reflect improved cardiac output, improved lung function/oxygenation, or transfusion of blood
Low pre–ECMO Spo_2 (not available on all consoles)	- Consider this a sign of low $Scvo_2$ - Increase ECMO flows	- Increase cardiac output - Transfuse blood - Decrease patient oxygen demand

ECMO = extracorporeal membrane oxygenation; F_{IO_2} = inspired concentration of oxygen; OR = operating room; PEEP = positive end-expiratory pressure; RPM = revolutions per minute; $Scvo_2$ = oxygen saturation of central venous blood; Spo_2 = peripheral capillary oxygen saturation.

this phenomenon is far more prevalent in historically used polydimethylsiloxane than polypropylene membranes, which are similar to polymethylpente, which is used in modern oxygenators.[115]

Antibiotic Dosing. Like sedatives, antibiotic pharmacokinetics are altered in ECMO patients, whereas the drugs may become prone to sequestration. A study of meropenam dosing in ECMO patients, some of whom also required continuous renal replacement therapy, demonstrated an increased Vd but decreased clearance—pharmacokinetics that offset each other.[109] Meropenam has also been noted to be sequestered by the ECMO circuit itself.[110] Pediatric literature has demonstrated increased Vd and prolonged clearance times of vancomycin and the aminoglycosides gentamycin and tobramycin.[108] An infant study of the pharmacokinetics of cefotaxime demonstrated increased Vd with preserved drug clearance and highly variable drug concentrations among the patients.[116] Although a multicenter study designed to delineate to complex pharmacokinetics of antibiotics, sedatives, and analgesics in adult ECMO patients is ongoing, current best practice in the perioperative setting should remain focused on timely dosing of surgery-specific and ongoing antibiotics and utilization of drug levels to guide dosing whenever able.[117,118] Increased loading doses to offset increases in Vd should be considered, especially if the adverse effects of the selected antibiotic are low or minimally dose dependent.[107]

CPR on VV ECMO. Because VV ECMO does not provide circulatory support, advanced cardiac life support algorithms should be performed in response to cardiac arrest. Transesophageal echocardiography has been established as a useful tool to assist in the management of cardiac arrest in the OR and can also assess cannula positioning as a cause of arrest in ECMO patients.[55,119] Consideration of ECMO system failures as the etiology of arrest should occur, because hypercarbia and hypoxemia can rapidly result from a kink in the ECMO circuit or acute occlusion of the membrane lung (which would require an exchange). If system failure has been ruled out, VV ECMO patients can be transitioned to venovenous arterial (VVA) ECMO through the addition of a single arterial cannula to provide complete extracorporeal cardiopulmonary support.[120] As the potential outcomes benefits of VA ECMO deployment during in-hospital cardiac arrest are becoming increasingly apparent,[121,122] conversion to VVA ECMO should be considered in any VV ECMO patient who requires advanced cardiac life support.

Pulmonary Embolism (PE). Both VV and VA ECMO have been successfully used to support patients presenting with massive PE, including patients with resultant cardiac arrest.[123] In VV ECMO patients, PE may occur through either its typical pathophysiology, as a result of thrombus formation on the surface of an ECMO cannula, or thrombus formation within the return cannula. Thrombus adherent to cannula surfaces or within the right atrium, superior vena cava, or inferior vena cava can often be detected by Doppler sonography or echocardiography.[55,124,125] Depending on the type and degree of underlying lung disease necessitating ECMO therapy, the potential reduction in gas exchange caused by PE may be minimal. More concerning is the ability of PE to cause acute right heart failure, which can be initially treated with inotropic support and reduction of RV afterload; however, a low threshold should be present to transition the patient to VVA ECMO.[126,127] Surgical thrombectomy can also be considered, because these patients would categorically be considered unsuitable candidates for systemic or catheter directed fibrinolytic treatments.[126,127] In the general population, intraoperative PE is a rare event but portends a mortality of up to 68%.[128] Although surgery itself is unlikely to immediately cause PE in VV ECMO patients, given the potential for preexisting thrombus within the right atrium, superior vena cava, or inferior vena cava, especially in patients who are not anticoagulated, a high suspicion should exist for the presence of PE in the presence of acute heart failure or refractory hypotension.

Concurrent Myocardial Dysfunction

Right-sided heart failure is frequent in VV ECMO patients and may be attributable to the underlying etiology of respiratory failure such as influenza or sepsis or secondary insults such as stress cardiomyopathy or elevated pulmonary arterial pressures due to hypoxemia or hypercarbia.[129] VV ECMO has even been demonstrated to reduce pressor and inotrope requirement at 6 and 24 h in patients with hemodynamic instability (without severe ventricular dysfunction) at the time of deployment, potentially attributable to its ability to raise pH through decarboxylation.[130] Treatment of right heart failure on VV ECMO should focus on improving ventricular contractility with inotropes, decreasing afterload through inhaled pulmonary artery dilators such as nitric oxide or epoprostenol and, in refractory cases, conversion to VVA ECMO through the addition of an arterial cannula.

Left-sided heart failure management can begin with the optimization of preload and afterload and the introduction of inotropic agents, with consideration of insertion of an intraaortic balloon pump for more significant disease. Refractory myocardial dysfunction should prompt consideration of transition to VVA ECMO.

Circuit Failure. Circuit complications such as any mechanical complication, circuit clot, or tubing rupture have been described as occurring in up to 52% of 1,473 ECMO (78% VV) patients reviewed in the ESLO database.[101] Acute reduction in pump flows can be due to rapid blood loss, migration or kinking of ECMO lines, or changes in venous return due to repositioning. Obstruction downstream of the return cannula, such as by a pulmonary embolism, will increase pump afterload and can also reduce flow. Complete pump failure is typically caused by occlusion of the membrane lung or a cannula with thrombus and can only be managed by a circuit exchange. In experienced centers, a circuit or oxygenator exchange can occur in minutes or less, making recognition and timely intervention critically important. An understanding of the degree of the patient's underlying respiratory compromise will also dictate the urgency of intervention. Optimization of oxygenation and decarboxylation utilizing both the ECMO system and mechanical ventilator (through temporary, preemptive increases in ECMO sweep and blood flow as well as ventilator F_{IO_2}, PEEP, and V_E) can maximize the patient's reserve before interruption of ECMO flows. Some practitioners prophylactically administer anticholinergic agents, such as atropine, before circuit changes, because bradycardia and even cardiac arrest can be precipitated by hypercarbia or hypoxemia may occur, but neither efficacy or specific dosing ranges have been established. If administered, a dose of 0.02 mg/kg atropine, which was has been used as a pretreatment to prevent arrhythmias during induction of anesthesia in pediatrics,[131] would be reasonable.

Inadvertent decannulation or cannula migration can also lead to partial or complete circuit decannulation as well as massive hemorrhage. Blind manipulation of cannulas by an inexperienced provider can lead to patient injury (especially with dual-lumen cannulas that extend into the intrahepatic inferior vena cava) and should be considered a last resort in an unstable patient. In addition to requesting immediate surgeon presence, as well as additional help, concurrently acquiring fluoroscopy can be useful in the repositioning. Repositioning of a dual-luman cannula requires either fluoroscopy or transesophageal echocardiography guidance to properly align outflow with the tricuspid valve and to ensure the tip of the catheter is in the inferior vena cava as opposed to a hepatic vein. Obtaining hemostasis and the avoidance of air entrainment by the patient will be the first priority in the management of a patient with a complete cannula dislodgement. Blood loss within the circuit itself will also account for about 500 ml.

Circuit Disseminated Intravascular Coagulation (DIC). A concept of "circuit DIC" or a cascade of clot formation within the membrane lung is important to recognize perioperatively, because it can result in impaired membrane gas exchange, with progression to complete pump failure, while also exposing the patient to a risk of systemic bleeding due to fibrinolysis.[132] Elevations of D-dimer levels, especially acutely, are used to detect the condition, but are nonspecific; therefore, clinical suspicion is required for accurate diagnosis. The only definitive treatment for circuit DIC is replacement of the membrane lung.[132]

Need for Surgical Prone Positioning. Prone positioning has been studied only on a limited basis, but a systematic review of 49 patients, managed with a variety of cannulation strategies, from 7 articles demonstrated the feasibility of the positioning.[133] Cannula site bleeding was the most common complication, with 11 instances being reported in 74 prone positioning maneuvers done on 12 patients in a single study, as well as 1 other patient in the cohort.[133] Edema was reported in 12.2% of patients, 7 of 74 positioning events from one study resulted in more than 20% reduction in systolic blood pressure, and air entrainment and pneumothorax were both cited in a single patient each; however, there were no reports of cannula dislodgement.[133] In a series of five VV ECMO patients with right internal jugular–femoral (or right internal jugular–bifemoral) cannulation, who underwent 44 turns to prone position, there was only a single reduction in ECMO flow, which occurred in the supine position and resolved with cannula repositioning.[133,134] Although VV ECMO makes the process of prone positioning even more complex, multiple reports have demonstrated that it can be performed safely in patients with femoral, internal jugular, and dual-lumen cannulas. Although data cannot be directly extrapolated to lateral positioning, there is no evidence to support that the presence of ECMO should contraindicate specific surgical positioning.

Conclusions

The perioperative management of VV ECMO patients will likely be of increasing importance as the utilization of ECMO increases worldwide. In addition to the inherent critical illness of the patient, management must also focus on effective utilization of the ECMO system in response to perioperative fluid shifts and stressors, as well as the novel challenges it provides related to anesthetic delivery, hemodynamic monitoring, and hemostasis. Further studies specific to the perioperative period could provide immensely valuable in defining the optimal management of these patients.

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Competing Interests

The authors declare no competing interests.

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References

1. Schmidt M, Stewart C, Bailey M, Nieszkowska A, Kelly J, Murphy L, Pilcher D, Cooper DJ, Scheinkestel C, Pellegrino V, Forrest P, Combes A, Hodgson C: Mechanical ventilation management during extracorporeal membrane oxygenation for acute respiratory distress syndrome: A retrospective international multicenter study. Crit Care Med 2015; 43:654–64
2. Terragni PP, Del Sorbo L, Mascia L, Urbino R, Martin EL, Birocco A, Faggiano C, Quintel M, Gattinoni L, Ranieri VM: Tidal volume lower than 6 ml/kg enhances lung protection: Role of extracorporeal carbon dioxide removal. Anesthesiology 2009; 111:826–35
3. Karagiannidis C, Kampe KA, Sipmann FS, Larsson A, Hedenstierna G, Windisch W, Mueller T: Veno-venous extracorporeal CO2 removal for the treatment of severe respiratory acidosis: Pathophysiological and technical considerations. Crit Care 2014; 18:R124
4. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. JAMA 2012; 307:2526–33
5. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network: About the NHLBI ARDS Network. Available at: http://www.ardsnet.org. Accessed July 1, 2017
6. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network: Ventilator protocol card. Available at: http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf. Accessed July 1, 2017
7. Amato MB, Barbas CS, Medeiros DM, Schettino Gde P, Lorenzi Filho G, Kairalla RA, Deheinzelin D, Morais C, Fernandes Ede O, Takagaki TY: Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: A prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med 1995; 152:1835–46
8. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network: ARDSNet Predicted Body Weight Calculator. Available at: http://www.ardsnet.org/files/pbwtables_2005-02-02.pdf. Accessed July 1, 2017
9. Schmidt M, Pellegrino V, Combes A, Scheinkestel C, Cooper DJ, Hodgson C: Mechanical ventilation during extracorporeal membrane oxygenation. Crit Care 2014; 18:203
10. Sauer CM, Yuh DD, Bonde P: Extracorporeal membrane oxygenation use has increased by 433% in adults in the United States from 2006 to 2011. ASAIO J 2015; 61:31–6
11. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR Trial Collaboration: Efficacy and economic assessment of conventional ventilatory support *versus* extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. Lancet 2009; 374:1351–63
12. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, Forrest P, Gattas D, Granger E, Herkes R, Jackson A, McGuinness S, Nair P, Pellegrino V, Pettilä V, Plunkett B, Pye R, Torzillo P, Webb S, Wilson M, Ziegenfuss M; Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators: Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 2009; 302:1888–95
13. Aubron C, Cheng AC, Pilcher D, Leong T, Magrin G, Cooper DJ, Scheinkestel C, Pellegrino V: Factors associated with outcomes of patients on extracorporeal membrane oxygenation support: A 5-year cohort study. Crit Care 2013; 17:R73
14. Taghavi S, Jayarajan SN, Mangi AA, Hollenbach K, Dauer E, Sjoholm LO, Pathak A, Santora TA, Goldberg AJ, Rappold JF: Examining noncardiac surgical procedures in patients on extracorporeal membrane oxygenation. ASAIO J 2015; 61:520–5

15. Bosarge PL, Raff LA, McGwin G Jr, Carroll SL, Bellot SC, Diaz-Guzman E, Kerby JD: Early initiation of extracorporeal membrane oxygenation improves survival in adult trauma patients with severe adult respiratory distress syndrome. J Trauma Acute Care Surg 2016; 81:236–43
16. Guirand DM, Okoye OT, Schmidt BS, Mansfield NJ, Aden JK, Martin RS, Cestero RF, Hines MH, Pranikoff T, Inaba K, Cannon JW: Venovenous extracorporeal life support improves survival in adult trauma patients with acute hypoxemic respiratory failure: A multicenter retrospective cohort study. J Trauma Acute Care Surg 2014; 76:1275–81
17. Seo DJ, Yoo JS, Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW: Venovenous extracorporeal membrane oxygenation for postoperative acute respiratory distress syndrome. Korean J Thorac Cardiovasc Surg 2015; 48:180–6
18. Brodie D, Bacchetta M: Extracorporeal membrane oxygenation for ARDS in adults. N Engl J Med 2011; 365:1905–14
19. Tulman DB, Stawicki SP, Whitson BA, Gupta SC, Tripathi RS, Firstenberg MS, Hayes D Jr, Xu X, Papadimos TJ: Veno-venous ECMO: A synopsis of nine key potential challenges, considerations, and controversies. BMC Anesthesiol 2014; 14:65
20. Kuhl T, Michels G, Pfister R, Wendt S, Langebartels G, Wahlers T: Comparison of the Avalon dual-lumen cannula with conventional cannulation technique for venovenous extracorporeal membrane oxygenation. Thorac Cardiovasc Surg 2015; 63:653–62
21. Javidfar J, Brodie D, Wang D, Ibrahimiye AN, Yang J, Zwischenberger JB, Sonett J, Bacchetta M: Use of bicaval dual-lumen catheter for adult venovenous extracorporeal membrane oxygenation. Ann Thorac Surg 2011; 91:1763–8
22. Hirose H, Yamane K, Marhefka G, Cavarocchi N: Right ventricular rupture and tamponade caused by malposition of the Avalon cannula for venovenous extracorporeal membrane oxygenation. J Cardiothorac Surg 2012; 7:36
23. Javidfar J, Wang D, Zwischenberger JB, Costa J, Mongero L, Sonett J, Bacchetta M: Insertion of bicaval dual lumen extracorporeal membrane oxygenation catheter with image guidance. ASAIO J 2011; 57:203–5
24. Sidebotham D, McGeorge A, McGuinness S, Edwards M, Willcox T, Beca J: Extracorporeal membrane oxygenation for treating severe cardiac and respiratory failure in adults: Part 2. Technical considerations. J Cardiothorac Vasc Anesth 2010; 24:164–72
25. Rich PB, Awad SS, Crotti S, Hirschl RB, Bartlett RH, Schreiner RJ: A prospective comparison of atrio-femoral and femoro-atrial flow in adult venovenous extracorporeal life support. J Thorac Cardiovasc Surg 1998; 116:628–32
26. Bartlett RH: Physiology of gas exchange during ECMO for respiratory failure. J Intensive Care Med 2017; 32:243–8
27. Schmidt M, Tachon G, Devilliers C, Muller G, Hekimian G, Bréchot N, Merceron S, Luyt CE, Trouillet JL, Chastre J, Leprince P, Combes A: Blood oxygenation and decarboxylation determinants during venovenous ECMO for respiratory failure in adults. Intensive Care Med 2013; 39:838–46
28. Marhong JD, Munshi L, Detsky M, Telesnicki T, Fan E: Mechanical ventilation during extracorporeal life support (ECLS): A systematic review. Intensive Care Med 2015; 41:994–1003
29. Abrams D, Brodie D: Extracorporeal Life Support Organization (ELSO) identification and management of recirculation in venovenous ECMO. May 2015. Available at: https://www.elso.org/Portals/0/Files/ELSO_Recirculation_guideline_May2015.pdf. Accessed June 28, 2017
30. Nunes LB, Mendes PV, Hirota AS, Barbosa EV, Maciel AT, Schettino GP, Costa EL, Azevedo LC, Park M; ECMO Group: Severe hypoxemia during veno-venous extracorporeal membrane oxygenation: Exploring the limits of extracorporeal respiratory support. Clinics (Sao Paulo) 2014; 69:173–8
31. Kraut JA, Madias NE: Lactic acidosis. N Engl J Med 2014; 371:2309–19
32. van der Hoeven MA, Maertzdorf WJ, Blanco CE: Mixed venous oxygen saturation and biochemical parameters of hypoxia during progressive hypoxemia in 10- to 14-day-old piglets. Pediatr Res 1997; 42:878–84
33. Velissaris D, Pierrakos C, Scolletta S, De Backer D, Vincent JL: High mixed venous oxygen saturation levels do not exclude fluid responsiveness in critically ill septic patients. Crit Care 2011; 15:R177
34. De Backer D, Orbegozo Cortes D, Donadello K, Vincent JL: Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock. Virulence 2014; 5:73–9
35. Stapel SN, de Grooth HJ, Alimohamad H, Elbers PW, Girbes AR, Weijs PJ, Oudemans-van Straaten HM: Ventilator-derived carbon dioxide production to assess energy expenditure in critically ill patients: Proof of concept. Crit Care 2015; 19:370
36. Grocott MP, Martin DS, Levett DZ, McMorrow R, Windsor J, Montgomery HE; Caudwell Xtreme Everest Research Group: Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med 2009; 360:140–9
37. West JB, Boyer SJ, Graber DJ, Hackett PH, Maret KH, Milledge JS, Peters RM Jr, Pizzo CJ, Samaja M, Sarnquist FH: Maximal exercise at extreme altitudes on Mount Everest. J Appl Physiol Respir Environ Exerc Physiol 1983; 55:688–98
38. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D: Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994; 330:1717–22
39. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E; Canadian Critical Care Trials Group: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care: Transfusion requirements in critical care investigators. N Engl J Med 1999; 340:409–17
40. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC: Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2016; 10:CD002042
41. Agerstrand CL, Burkart KM, Abrams DC, Bacchetta MD, Brodie D: Blood conservation in extracorporeal membrane oxygenation for acute respiratory distress syndrome. Ann Thorac Surg 2015; 99:590–5
42. Combes A: Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA). March 21, 2017. Available at: http://clinicaltrials.gov/ct2/show/NCT01470703. Accessed June 28, 2017
43. Lequier L, Horton SB, McMullan DM, Bartlett RH: Extracorporeal membrane oxygenation circuitry. Pediatr Crit Care Med 2013; 14(suppl 1):S7–12
44. Lehle K, Philipp A, Gleich O, Holzamer A, Müller T, Bein T, Schmid C: Efficiency in extracorporeal membrane oxygenation-cellular deposits on polymethylpentene membranes increase resistance to blood flow and reduce gas exchange capacity. ASAIO J 2008; 54:612–7
45. Guarracino F, Zangrillo A, Ruggeri L, Pieri M, Calabrò MG, Landoni G, Stefani M, Doroni L, Pappalardo F: β-Blockers to optimize peripheral oxygenation during extracorporeal membrane oxygenation: A case series. J Cardiothorac Vasc Anesth 2012; 26:58–63
46. Extracorporeal Life Support Organization (ELSO) Anticoagulation Guideline. 2014. Available at: http://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf. Accessed June 28, 2017
47. Voelker MT, Busch T, Bercker S, Fichtner F, Kaisers UX, Laudi S: Restrictive transfusion practice during extracorporeal membrane oxygenation therapy for severe acute respiratory distress syndrome. Artif Organs 2015; 39:374–8
48. Gebistorf F, Karam O, Wetterslev J, Afshari A: Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev 2016: CD002787
49. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, Briegel J, Welte M, Peter K: Inhaled prostacyclin (PGI2) *versus* inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 1996; 154:1671–7

50. Torbic H, Szumita PM, Anger KE, Nuccio P, LaGambina S, Weinhouse G: Inhaled epoprostenol *vs.* inhaled nitric oxide for refractory hypoxemia in critically ill patients. J Crit Care 2013; 28:844–8
51. Fierro MA, Bartz RR: Management of sedation and paralysis. Clin Chest Med 2016; 37:723–39
52. Körver EP, Ganushchak YM, Simons AP, Donker DW, Maessen JG, Weerwind PW: Quantification of recirculation as an adjuvant to transthoracic echocardiography for optimization of dual-lumen extracorporeal life support. Intensive Care Med 2012; 38:906–9
53. Broman M, Frenckner B, Bjällmark A, Broomé M: Recirculation during veno-venous extra-corporeal membrane oxygenation: A simulation study. Int J Artif Organs 2015; 38:23–30
54. Zangrillo A, Landoni G, Biondi-Zoccai G, Greco M, Greco T, Frati G, Patroniti N, Antonelli M, Pesenti A, Pappalardo F: A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Crit Care Resusc 2013; 15:172–8
55. Douflé G, Roscoe A, Billia F, Fan E: Echocardiography for adult patients supported with extracorporeal membrane oxygenation. Crit Care 2015; 19:326
56. Fagnoul D, Pasquier P, Bodson L, Ortiz JA, Vincent JL, De Backer D: Myocardial dysfunction during H1N1 influenza infection. J Crit Care 2013; 28:321–7
57. Dirnberger D, Fiser R, Harvey C, Lunz D, Bacchetta M, Frenckner B, Conrad S, Müller T, Biscotti M: Extracorporeal Life Support Organization (ELSO) guidelines for ECMO transport. May 2014. http://www.elso.org/portals/0/files/elsoanticoagulationguideline8-2014-table-contents.pdf. Accessed June 28, 2017
58. Fanara B, Manzon C, Barbot O, Desmettre T, Capellier G: Recommendations for the intra-hospital transport of critically ill patients. Crit Care 2010; 14:R87
59. Schreiber J, Nierhaus A, Vettorazzi E, Braune SA, Frings DP, Vashist Y, Izbicki JR, Kluge S: Rescue bedside laparotomy in the intensive care unit in patients too unstable for transport to the operating room. Crit Care 2014; 18:R123
60. Lucchini A, De Felippis C, Elli S, Gariboldi R, Vimercati S, Tundo P, Bondi H, Costa MC: Mobile ECMO team for interhospital transportation of patients with ARDS: A retrospective case series. Heart Lung Vessel 2014; 6:262–73
61. Bryner B, Cooley E, Copenhaver W, Brierley K, Teman N, Landis D, Rycus P, Hemmila M, Napolitano LM, Haft J, Park PK, Bartlett RH: Two decades' experience with interfacility transport on extracorporeal membrane oxygenation. Ann Thorac Surg 2014; 98:1363–70
62. Wiesenack C, Wiesner G, Keyl C, Gruber M, Philipp A, Ritzka M, Prasser C, Taeger K: *In vivo* uptake and elimination of isoflurane by different membrane oxygenators during cardiopulmonary bypass. Anesthesiology 2002; 97:133–8
63. Wildschut ED, Ahsman MJ, Allegaert K, Mathot RA, Tibboel D: Determinants of drug absorption in different ECMO circuits. Intensive Care Med 2010; 36: 2109–16
64. DeGrado JR, Hohlfelder B, Ritchie BM, Anger KE, Reardon DP, Weinhouse GL: Evaluation of sedatives, analgesics, and neuromuscular blocking agents in adults receiving extracorporeal membrane oxygenation. J Crit Care 2017; 37:1–6
65. Lehr CJ, Zaas DW, Cheifetz IM, Turner DA: Ambulatory extracorporeal membrane oxygenation as a bridge to lung transplantation: Walking while waiting. Chest 2015; 147:1213–8
66. Floroff CK, Hassig TB, Cochran JB, Mazur JE: High-dose sedation and analgesia during extracorporeal membrane oxygenation: A focus on the adjunctive use of ketamine. J Pain Palliat Care Pharmacother 2016; 30:36–40
67. Odonkor PN, Stansbury L, Garcia JP, Rock P, Deshpande SP, Grigore AM: Perioperative management of adult surgical patients on extracorporeal membrane oxygenation support. J Cardiothorac Vasc Anesth 2013; 27:329–44
68. Hofer CK, Cecconi M, Marx G, della Rocca G: Minimally invasive haemodynamic monitoring. Eur J Anaesthesiol 2009; 26:996–1002
69. Peris A, Lazzeri C, Cianchi G, Bonizzoli M, Batacchi S, Bernardo P, Valente S, Gensini GF: Clinical significance of echocardiography in patients supported by venous-venous extracorporeal membrane oxygenation. J Artif Organs 2015; 18:99–105
70. Teboul JL, Monnet X: Pulse pressure variation and ARDS. Minerva Anestesiol 2013; 79:398–407
71. Stéphan F, Flahault A, Dieudonné N, Hollande J, Paillard F, Bonnet F: Clinical evaluation of circulating blood volume in critically ill patients: Contribution of a clinical scoring system. Br J Anaesth 2001; 86:754–62
72. Marik PE, Cavallazzi R: Does the central venous pressure predict fluid responsiveness?: An updated meta-analysis and a plea for some common sense. Crit Care Med 2013; 41:1774–81
73. Schmidt M, Bailey M, Kelly J, Hodgson C, Cooper DJ, Scheinkestel C, Pellegrino V, Bellomo R, Pilcher D: Impact of fluid balance on outcome of adult patients treated with extracorporeal membrane oxygenation. Intensive Care Med 2014; 40:1256–66
74. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R; American College of Chest Physicians: Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141: e326S–50S
75. Herbert DG, Buscher H, Nair P: Prolonged venovenous extracorporeal membrane oxygenation without anticoagulation: A case of Goodpasture syndrome–related pulmonary haemorrhage. Crit Care Resusc 2014; 16:69–72
76. Esper SA, Levy JH, Waters JH, Welsby IJ: Extracorporeal membrane oxygenation in the adult: A review of anticoagulation monitoring and transfusion. Anesth Analg 2014; 118:731–43
77. Guervil DJ, Rosenberg AF, Winterstein AG, Harris NS, Johns TE, Zumberg MS: Activated partial thromboplastin time *versus* antifactor Xa heparin assay in monitoring unfractionated heparin by continuous intravenous infusion. Ann Pharmacother 2011; 45:861–8
78. Frugé KS, Lee YR: Comparison of unfractionated heparin protocols using antifactor Xa monitoring or activated partial thrombin time monitoring. Am J Health Syst Pharm 2015; 72(suppl 2):S90–7
79. Lehman CM, Rettmann JA, Wilson LW, Markewitz BA: Comparative performance of three anti-factor Xa heparin assays in patients in a medical intensive care unit receiving intravenous, unfractionated heparin. Am J Clin Pathol 2006; 126:416–21
80. Vera-Aguilera J, Yousef H, Beltran-Melgarejo D, Teng TH, Jan R, Mok M, Vera-Aguilera C, Moreno-Aguilera E: Clinical scenarios for discordant anti-Xa. Adv Hematol 2016; 2016:4054806
81. Tauber H, Streif W, Fritz J, Ott H, Weigel G, Loacker L, Heinz A, Velik-Salchner C: Predicting transfusion requirements during extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth 2016; 30:692–701
82. Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P: Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: An international survey. Pediatr Crit Care Med 2013; 14:e77–84
83. Nair P, Hoechter DJ, Buscher H, Venkatesh K, Whittam S, Joseph J, Jansz P: Prospective observational study of hemostatic alterations during adult extracorporeal membrane oxygenation (ECMO) using point-of-care thromboelastometry and platelet aggregometry. J Cardiothorac Vasc Anesth 2015; 29:288–96

84. L'Acqua C, Passamonti SM, Spinelli E, Gattinoni L, Panigada M: Thromboelastography-guided thrombolysis during ECMO: A case report. Anaesth Intensive Care 2014; 42:807–9
85. Downard CD, Betit P, Chang RW, Garza JJ, Arnold JH, Wilson JM: Impact of AMICAR on hemorrhagic complications of ECMO: A ten-year review. J Pediatr Surg 2003; 38:1212–6
86. Bui JD, Despotis GD, Trulock EP, Patterson GA, Goodnough LT: Fatal thrombosis after administration of activated prothrombin complex concentrates in a patient supported by extracorporeal membrane oxygenation who had received activated recombinant factor VII. J Thorac Cardiovasc Surg 2002; 124:852–4
87. Repessé X, Au SM, Bréchot N, Trouillet JL, Leprince P, Chastre J, Combes A, Luyt CE: Recombinant factor VIIa for uncontrollable bleeding in patients with extracorporeal membrane oxygenation: Report on 15 cases and literature review. Crit Care 2013; 17:R55
88. Swaminathan M, Shaw AD, Greenfield RA, Grichnik KP: Fatal thrombosis after factor VII administration during extracorporeal membrane oxygenation. J Cardiothorac Vasc Anesth 2008; 22:259–60
89. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Benk C, Trummer G, Berchtold-Herz M, Schlensak C, Zieger B: Acquired von Willebrand syndrome in patients with extracorporeal life support (ECLS). Intensive Care Med 2012; 38:62–8
90. Schiff JH, Köninger J, Teschner J, Henn-Beilharz A, Rost M, Dubb R, Danassis M, Walther A: Veno-venous extracorporeal membrane oxygenation (ECMO) support during anaesthesia for oesophagectomy. Anaesthesia 2013; 68:527–30
91. Rollins MD, Deamorim-Filho J, Scaife ER, Hubbard A, Barnhart DC: Decompressive laparotomy for abdominal compartment syndrome in children on ECMO: Effect on support and survival. J Pediatr Surg 2013; 48:1509–13
92. Katsuhara K, Nakada TA, Yamada M, Fuse T, Idoguchi K, Matsuoka T: Veno-venous extracorporeal membrane oxygenation (ECMO) for acute respiratory failure caused by liver abscess. J Artif Organs 2015; 18:173–6
93. Lamb KM, Cowan SW, Evans N, Pitcher H, Moritz T, Lazar M, Hirose H, Cavarocchi NC: Successful management of bleeding complications in patients supported with extracorporeal membrane oxygenation with primary respiratory failure. Perfusion 2013; 28:125–31
94. Jotoku H, Sugimoto S, Usui A, Tanaka A, Makise H: Venovenous extracorporeal membrane oxygenation as an adjunct to surgery for empyema: Report of a case. Surg Today 2006; 36:76–8
95. Voelckel W, Wenzel V, Rieger M, Antretter H, Padosch S, Schobersberger W: Temporary extracorporeal membrane oxygenation in the treatment of acute traumatic lung injury. Can J Anaesth 1998; 45:1097–102
96. Heward E, Hayes T, Evison M, Booton R, Barnard J, Shah R: Extracorporeal membrane oxygenation assisted segmentectomy for metachronous lung cancer after pneumonectomy. Ann Thorac Surg 2016; 102:e187–9
97. Yuba T, Yamashita Y, Harada H, Tsubokawa N, Nagata H, Takasaki T, Kurita S, Fujii K: [Tracheal resection and primary anastomosis for adenoid cystic carcinoma using an extracorporeal membrane oxygenation]. Kyobu Geka 2016; 69:447–51
98. Redwan B, Ziegeler S, Freermann S, Nique L, Semik M, Lavae-Mokhtari M, Meemann T, Dickgreber N, Fischer S: Intraoperative veno-venous extracorporeal lung support in thoracic surgery: A single-centre experience. Interact Cardiovasc Thorac Surg 2015; 21:766–72
99. Smith IJ, Sidebotham DA, McGeorge AD, Dorman EB, Wilsher ML, Kolbe J: Use of extracorporeal membrane oxygenation during resection of tracheal papillomatosis. Anesthesiology 2009; 110:427–9
100. Lother A, Wengenmayer T, Benk C, Bode C, Staudacher DL: Fatal air embolism as complication of percutaneous dilatational tracheostomy on venovenous extracorporeal membrane oxygenation, two case reports. J Cardiothorac Surg 2016; 11:102
101. Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL: Extracorporeal membrane oxygenation in adults with severe respiratory failure: A multi-center database. Intensive Care Med 2009; 35:2105–14
102. Mazzeffi M, Kiefer J, Greenwood J, Tanaka K, Menaker J, Kon Z, Sanchez P, Pham S, Herr D: Epidemiology of gastrointestinal bleeding in adult patients on extracorporeal life support. Intensive Care Med 2015; 41:2015
103. Wu MY, Huang CC, Wu TI, Wang CL, Lin PJ: Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome in adults: Prognostic factors for outcomes. Medicine (Baltimore) 2016; 95:e2870
104. Cobb R, Jenoff JS, Cavarocchi NC, Hirose H: Percutaneous endoscopic gastrostomy tube placement in patients with extracorporeal membrane oxygenation. Mechanical Circulatory Support 2013; 4:1
105. Simons AP, Ganushchak YM, Teerenstra S, Bergmans DC, Maessen JG, Weerwind PW: Hypovolemia in extracorporeal life support can lead to arterial gaseous microemboli. Artif Organs 2013; 37:276–82
106. Høgetveit JO, Saatvedt K, Norum H, Kristiansen F, Elvebakk O, Dahle G, Geiran OR: Central venous catheters may be a potential source of massive air emboli during vascular procedures involving extracorporeal circulation: An experimental study. Perfusion 2011; 26:341–6
107. Shekar K, Fraser JF, Smith MT, Roberts JA: Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J Crit Care 2012; 27:741.e9–18
108. Buck ML: Pharmacokinetic changes during extracorporeal membrane oxygenation: Implications for drug therapy of neonates. Clin Pharmacokinet 2003; 42:403–17
109. Shekar K, Fraser JF, Taccone FS, Welch S, Wallis SC, Mullany DV, Lipman J, Roberts JA; ASAP ECMO Study Investigators: The combined effects of extracorporeal membrane oxygenation and renal replacement therapy on meropenem pharmacokinetics: A matched cohort study. Crit Care 2014; 18:565
110. Shekar K, Roberts JA, Mcdonald CI, Fisquet S, Barnett AG, Mullany DV, Ghassabian S, Wallis SC, Fung YL, Smith MT, Fraser JF: Sequestration of drugs in the circuit may lead to therapeutic failure during extracorporeal membrane oxygenation. Crit Care 2012; 16:R194
111. Preston TJ, Ratliff TM, Gomez D, Olshove VE Jr, Nicol KK, Sargel CL, Chicoine LG: Modified surface coatings and their effect on drug adsorption within the extracorporeal life support circuit. J Extra Corpor Technol 2010; 42:199–202
112. Lemaitre F, Hasni N, Leprince P, Corvol E, Belhabib G, Fillâtre P, Luyt CE, Leven C, Farinotti R, Fernandez C, Combes A: Propofol, midazolam, vancomycin and cyclosporine therapeutic drug monitoring in extracorporeal membrane oxygenation circuits primed with whole human blood. Crit Care 2015; 19:40
113. Hohlfelder B, Szumita PM, Lagambina S, Weinhouse G, Degrado JR: Safety of propofol for oxygenator exchange in extracorporeal membrane oxygenation. ASAIO J 2017; 63:179–84
114. Myers GJ, Voorhees C, Eke B, Johnstone R: The effect of Diprivan (propofol) on phosphorylcholine surfaces during cardiopulmonary bypass: An in vitro investigation. Perfusion 2009; 24:349–55
115. Rosen DA, Rosen KR, Silvasi DL: In vitro variability in fentanyl absorption by different membrane oxygenators. J Cardiothorac Anesth 1990; 4:332–5
116. Ahsman MJ, Wildschut ED, Tibboel D, Mathot RA: Pharmacokinetics of cefotaxime and desacetylcefotaxime

in infants during extracorporeal membrane oxygenation. Antimicrob Agents Chemother 2010; 54: 1734–41

117. Shekar K, Roberts JA, Welch S, Buscher H, Rudham S, Burrows F, Ghassabian S, Wallis SC, Levkovich B, Pellegrino V, McGuinness S, Parke R, Gilder E, Barnett AG, Walsham J, Mullany DV, Fung YL, Smith MT, Fraser JF: ASAP ECMO: Antibiotic, sedative and analgesic pharmacokinetics during extracorporeal membrane oxygenation: A multi-centre study to optimise drug therapy during ECMO. BMC Anesthesiol 2012; 12:29
118. Gonçalves-Pereira J, Oliveira B: Antibiotics and extracorporeal circulation: One size does not fit all. Crit Care 2014; 18:695
119. Memtsoudis SG, Rosenberger P, Loffler M, Eltzschig HK, Mizuguchi A, Shernan SK, Fox JA: The usefulness of transesophageal echocardiography during intraoperative cardiac arrest in noncardiac surgery. Anesth Analg 2006; 102:1653–7
120. Bacchetta M, Javidfar J, Sonett J, Kim H, Zwischenberger J, Wang D: Ease of conversion from venovenous extracorporeal membrane oxygenation to cardiopulmonary bypass and venoarterial extracorporeal membrane oxygenation with a bicaval dual lumen catheter. ASAIO J 2011; 57:283–5
121. Wang CH, Chou NK, Becker LB, Lin JW, Yu HY, Chi NH, Hunag SC, Ko WJ, Wang SS, Tseng LJ, Lin MH, Wu IH, Ma MH, Chen YS: Improved outcome of extracorporeal cardiopulmonary resuscitation for out-of-hospital cardiac arrest: A comparison with that for extracorporeal rescue for in-hospital cardiac arrest. Resuscitation 2014; 85:1219–24
122. Shin TG, Choi JH, Jo IJ, Sim MS, Song HG, Jeong YK, Song YB, Hahn JY, Choi SH, Gwon HC, Jeon ES, Sung K, Kim WS, Lee YT: Extracorporeal cardiopulmonary resuscitation in patients with in-hospital cardiac arrest: A comparison with conventional cardiopulmonary resuscitation. Crit Care Med 2011; 39:1–7
123. Yusuff HO, Zochios V, Vuylsteke A: Extracorporeal membrane oxygenation in acute massive pulmonary embolism: A systematic review. Perfusion 2015; 30:611–6
124. Riccabona M, Kuttnig-Haim M, Dacar D, Urlesberger B, Reiterer F, Maurer U, Zobel G: Venous thrombosis in and after extracorporeal membrane oxygenation: Detection and follow-up by color Doppler sonography. Eur Radiol 1997; 7:1383–6
125. Lee S, Chaturvedi A: Imaging adults on extracorporeal membrane oxygenation (ECMO). Insights Imaging 2014; 5:731–42
126. Lahm T, McCaslin CA, Wozniak TC, Ghumman W, Fadl YY, Obeidat OS, Schwab K, Meldrum DR: Medical and surgical treatment of acute right ventricular failure. J Am Coll Cardiol 2010; 56:1435–46
127. Cox JC, Jablons DM: Operative and perioperative pulmonary emboli. Thorac Surg Clin 2015; 25:289–99
128. Visnjevac O, Lee K, Bulatovic R, Pourafkari L, Porhomayon J, Nader ND: Outcomes-based systematic review for management of massive intra-cardiac or pulmonary thrombotic emboli during surgery. Heart Lung Vessel 2014; 6:24–32
129. Fierro MA, Bartz RR: Reducing the shock of acute respiratory distress syndrome: Is veno-venous ECMO a viable therapy in the hemodynamically unstable patient? Anesth Analg 2017; 124:716–8
130. Gutsche JT, Mikkelsen ME, McCarthy FH, Miano TA, Vernick WJ, Ramakrishna H, Patel PA, Augoustides Y, Szeto WY, Desai ND, Lane-Fall MB, Williams ML: Veno-venous extracorporeal life support in hemodynamically unstable patients with ARDS. Anesth Analg 2017; 124:846–8
131. Annila P, Rorarius M, Reinikainen P, Oikkonen M, Baer G: Effect of pre-treatment with intravenous atropine or glycopyrrolate on cardiac arrhythmias during halothane anaesthesia for adenoidectomy in children. Br J Anaesth 1998; 80:756–60
132. Dornia C, Philipp A, Bauer S, Stroszczynski C, Schreyer AG, Müller T, Koehl GE, Lehle K: D-dimers are a predictor of clot volume inside membrane oxygenators during extracorporeal membrane oxygenation. Artif Organs 2015; 39:782–7
133. Culbreth RE, Goodfellow LT: Complications of prone positioning during extracorporeal membrane oxygenation for respiratory failure: A systematic review. Respir Care 2016; 61:249–54
134. Goettler CE, Pryor JP, Hoey BA, Phillips JK, Balas MC, Shapiro MB: Prone positioning does not affect cannula function during extracorporeal membrane oxygenation or continuous renal replacement therapy. Crit Care 2002; 6:452–55