ARTÍCULO ORIGINAL

▶ EXTRACORPOREAL MEMBRANE OXYGENATION FOR ACUTE CARDIOPULMONARY FAILURE

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ABSTRACT

Extracorporeal membrane oxygenation represents an evolving therapeutic modality for the treatment of acute severe cardiac and respiratory failure in patients failing maximal medical therapy. Advances in technology, along with increasing worldwide clinical successes and broadening applications, have encouraged renewed interest in what was previously considered a salvage intervention associated with poor outcomes. With advances in technology, patient selection, management, and a better understanding of the pathophysiology of the long-term extracorporeal support, outcomes for both pulmonary and cardiac support have improved.

Key Words: Extra-corporeal membrane oxygenation. Cardiogenic shock. Respiratory failure. Cardiac surgery. Shock. Hypoxemia.

RESUMEN

OXIGENACIÓN CON MEMBRANA EXTRACORPÓREA PARA INSUFICIENCIA CARDIOPULMONAR AGUDA

La oxigenación con membrana extracorpórea representa una modalidad terapéutica en evolución para el tratamiento de la insuficiencia cardiopulmonar severa aguda en pacientes que han fracasado el tratamiento médico máximo. Los avances en la tecnología, junto con los

crecientes éxitos clínicos a nivel mundial y mayores aplicaciones, han reavivado el interés en lo que anteriormente se había considerado una intervención de rescate asociada a pobres resultados. Dados los avances en la tecnología, selección de pacientes y un mayor entendimiento de la patofisiología del soporte extracorpóreo a largo plazo, los resultados de la asistencia tanto pulmonar como cardíaca han mejorado.

Palabras claves: Oxigenación con membrana extracorpórea. Shock cardiogénico. Insuficiencia respiratoria. Cirugía cardíaca. Shock. Hipoxemia.

RESUMO

OXIGENAÇÃO COM MEMBRANA EXTRACORPÓREA PARA INSUFICIÊNCIA CARDIOPULMONAR AGUDA

A oxigenação com membrana extracorpórea representa uma modalidade terapêutica em evolução para o tratamento da insuficiência cardiopulmonar severa aguda em pacientes que fracassaram com o tratamento médico máximo. Os avanços da tecnologia, assim como os crescentes êxitos clínicos a nível mundial e maiores aplicações, renovaram o interesse no que anteriormente tinha sido considerado uma intervenção de resgate associada a pobres resultados. Devido aos avanços da tecnologia, seleção de pacientes e um maior entendimento da patofisiologia do suporte extracorpóreo a longo prazo, os resultados da assistência, tanto pulmonar quanto cardíaca, apresentam comprovada melhoria.

Palavras chave: Oxigenação com membrana extracorpórea. Choque cardiogênico. Insuficiência respiratória. Cirurgia cardíaca. Choque. Hipoxem.

Extracorporeal membrane oxygenation (ECMO), much like renal replacement therapy and hemodialysis, is a rapidly evolving technology for supporting the heart and/or lungs mechanically in cases of acute respiratory failure or cardiogenic shock (1-2). In theory, the concept is quite simple - venous blood is drawn from the body, oxygenated and cleared of carbon dioxide and actively pumped back into the body. In applications of acute respiratory failure, the oxygenated blood is returned back to the venous circulation, typically via a large bore cannula positioned near the right atrium. However for cardiac applications, the blood is returned into the arterial circulation either centrally, directly into the aorta, or peripherally into the femoral or axillary artery. While simple in concept, ECMO has been a challenge to implement clinically (3). Nevertheless, there is a growing experience and evidence to support the use of this therapy for not only salvage applications of cardiopulmonary failure but more and more as an acceptable option for patients failing conventional medical management for severe respiratory failure and/or cardiogenic shock (4-5).

Early attempts at utilizing cardiopulmonary bypass outside of the operating room resulted in poor outcomes that tempered enthusiasm for ECMO

considerably (6). Even though ECMO was initially developed in specialized major cardiovascular and respiratory care centers, management of these patients proved to be a challenge. There has been renewed interest in ECMO over recent years as the technology has improved along with a better understanding of the pathophysiology of extracorporeal support (1). Furthermore, clinical studies have assisted in developing indications, contraindications, and guidelines for therapy, all of which, has resulted in improved outcomes and increasing enthusiasm even outside of major cardiovascular centers(7-8).

Often termed extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS), ECMO is very similar to the cardiopulmonary bypass (CPB) technology that is used routinely for cardiovascular surgery. Large bore cannulas drain venous blood that is pumped through an oxygenator where it is cleared of carbon dioxide and oxygenated then actively pumped back into the body. While both ECMO and CPB use somewhat similar technologies in terms of cannulas, tubing for blood flow, and even oxygenators and pumps, the fundamental difference is that CPB incorporates a reservoir for adjusting real-time, total blood volume. In addition, the intra-operative use of CPB is to assist with short-term (i.e. hours) support of the cardio-pulmonary system thereby allowing for surgical management of cardiovascular pathology while the goal of ECMO is to support a patient's physiology for a prolonged period of time. Patients on ECMO can be supported for days or weeks (occasionally longer) to allow for pulmonary and/or cardiac recovery after an acute injury. Nevertheless, the principles of support between CPB and ECMO are similar (5).

Unlike intra-operative CPB that contains a blood reservoir that allows for the temporary and dynamic storage of blood that can be added or removed from the patient's circulation to assist maintaining hemodynamic stability, ECMO circuits do not contain this reservoir. Lack of this reservoir for the ECMO circuit permits lower levels of anticoagulation to which still minimizes clotting and embolizing of the ECMO circuit. However lack of this reservoir provides the disadvantage of requiring infusion of fluids via central or peripheral intravenous access when additional volume is needed. Similarly, while a reservoir could also drain or store extra volume, for patients on ECMO, volume overload is managed with diuresis, either medically (i.e. diuretics) or mechanically with renal replacement technology. Both ECMO and CPB circuits have heating and cooling systems in-line with the circuit to allow for active patient warming (for treating hypothermia) or cooling (for neuroprotection following cardiopulmonary arrest).

The major applications for ECMO are for either acute respiratory failure or for cardiogenic shock. Obviously, there can be significant overlap between these two catastrophic problems. Respiratory failure indications include primary etiologies such as pneumonias (bacterial, fungal, viral, aspiration), status asthmaticus, traumatic pulmonary contusions, or even pulmonary embolism, but also secondary causes such as Acute Respiratory Distress Syndrome (ARDS) from overwhelming sepsis or systemic inflammatory conditions. Applications for cardiogenic shock include the inability to wean from cardiopulmonary bypass following cardiac surgery, massive acute myocardial infarction, decompensated end-stage congestive heart failure, or acute cardiomyopathies (post-partum, viral). For a variety of technical reasons, support for respiratory failure is typically less complicated to implement and manage than for cardiac failure applications.

Support for only the lungs, or veno-veno ECMO (vv-ECMO), requires only venous access. Since many patients with profound respiratory failure also have associated hypotension, either from a severe acute respiratory acidosis with or without an

associated metabolic acidosis, the primary diagnosis can be unclear. Hence the decision to implement veno-veno support for isolated respiratory failure versus veno-arterial (for combined cardiac and respiratory failure) can be difficult. Like every other aspect of medical care, a good history and physical examination can assist in decision-making. It is the practice of these authors that if a patient presents with what appears to be an isolated respiratory failure with a history of "normal" cardiac function, then veno-veno support is attempted first whereby hemodynamic instability is managed by aggressively correcting acidosis with the ECMO circuit and supporting hypotension with vasoactive medications and fluids. It is important to remember that hypoxemia, hypercarbia, and acidosis are

very potent pulmonary vasoconstrictors and these patients often have evidence of acute right heart failure and pulmonary arterial hypertension. Addressing these issues with ECMO can often break the vicious and often fatal downward spiral of hypoxemia, hypercarbic (respiratory) acidosis, right heart failure, low cardiac output and a resulting metabolic acidosis from impaired oxygen availability at the cellular level. In fact, severe respiratory acidosis with hemodynamic instability requiring vasoactive support can be an indication for ECMO (9-10-11).

INITIATION OF THERAPY: VASCULAR ACCESS

PULMONARY (VENO-VENO) SUPPORT

Typically, venous access is peripheral and often percutaneous with options including the femoral vein(s), internal jugulars, and less commonly, the subclavian. The Seldinger technique is used to advance large-bore cannulas (15-25 French) into
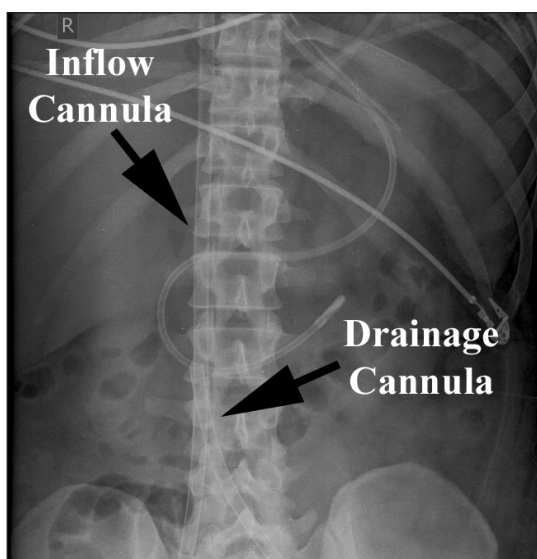

Figure 1: A KUB demonstrating the venous drainage cannula positioned in this distal inferior vena cava just above the iliac venous bifurcation. Likewise, the inflow cannula is also seen extending into the chest (see Figure 2). A feeding tube is also seen. The cannulas are typically wire reinforced, hence also being radiopaque, to minimize the potential for compression, kinking, or occlusion. The tips beyond the wire re-enforcements are typically not seen and extend for several more centimeters.
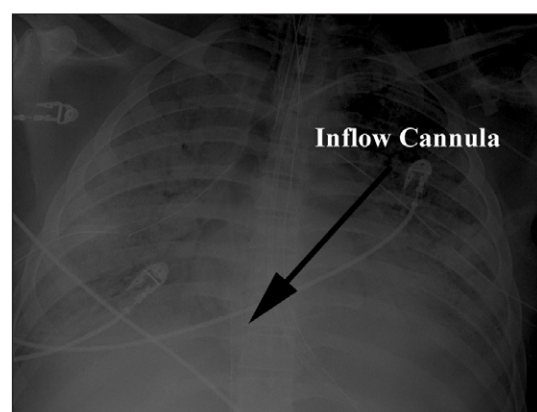

Figure 2: Chest x-ray of a patient with severe respiratory failure. The venous inflow cannula, inserted via the femoral vein, is positioned just at the left of the right atrium. The actual tip of the cannula extends an additional several centimeters beyond the radiopaque wire support as seen in the figure.

the venous system. Ultrasound guidance may be used to assist in cannula placement, particularly if the clinician is not comfortable or experienced with complex and emergent vascular access, but the use of an ultrasound probe is not necessary when cannula placement is associated with favorable anatomy and body habitus. Additionally, the site of access is often dictated not only by the needs of the patient, but also the clinical circumstances, degree of urgency, and, most importantly, the comfort of the clinician. At our institution, VV-ECMO is typically implemented via both femoral veins. A drainage or out- flow catheter is positioned just above the confluence of the iliac veins and the inferior vena cava with the umbilicus as a reasonable external anatomical landmark that can be used to guide placement until proper positioning can be confirmed radiographically (Figure 1). The inflow cannula is usually positioned into the right atrium with the nipple-line as a landmark until position can be confirmed with a chest x-ray (Figure 2). Using this configuration, venous blood is drained from the abdomen and both lower extremities, and oxygenated blood is returned directly to the right atrium where it then enters the heart, lungs, and ultimately pumped back into the systemic circulation. This is based upon the assumption that the patient has baseline normal cardiac function. As mentioned above, patients who are severely hypoxemic, hypercarbic, and/or acidotic may have pulmonary artery vasoconstriction with subsequent acute right heart dysfunction thereby potentiating a low cardiac output state despite normal left ventricular function (which might manifest as an underfilled hyperdynamic LV on echocardiography).

During the early phase of ECMO therapy, until the acid-base balance is restored, this can be managed medically with inotropes or inhaled vasodilators such as nitric oxide or epoprostenol (12). It is important to consider that supportive data and guidelines are lacking regarding the use of these agents acutely, or in combination.

If the venous drainage catheter is too low in the femoral or iliac vein (regardless of size), there may be significant shunting of the venous blood from the undrained leg into the native circulation. Some degree of shunting invariably occurs when the oxygenated blood is returned from the pump; it is often mixed with deoxygenated blood from the head and upper extremities. In addition, a common scenario in septic patients (a high cardiac output state) is that the limited flows of the ECMO circuit (6-7 liters/min max) may only oxygenate or clear the carbon dioxide of only part of the total blood flow. As such, even with maximal flows and circuit efficiency in conditions of very high metabolic rates and well-oxygenated states, the ability to achieve optimal saturations may be limited. Even with maximal ECMO flows, in such situations, the physiologic needs of the body might not be met. As long as the patient is not acidotic, suggestive of anaerobic metabolism from impaired oxygen delivery, then very low oxygenation saturations and PaO_2 can be tolerated. Again, while supporting evidence is lacking, patients can often survive neurologically intact with good end-organ function with prolonged periods of arterial saturations as low as 80% with the partial pressure of oxygen in the 40-50 mmHg range (13). From a technical aspect, if the outflow cannula is too high in the vena cava, such as at the level of the hepatic veins (and hence too close in distance to the drainage cannula), then recirculation and/or significant hemolysis may result. This means that freshly oxygenated blood that is being returned back into the patient might be overly 'sucked' back into the closely placed outflow cannula and thereby reducing the efficiency of the entire system (which may be indicated by a mixed venous sample of > 75%). Single cannula technology has been developed to assist in some of these limitations, but this also has potential problems (Figure 5 and 6) (14). The single cannula approach is considered more technically challenging to place and requires ultrasound guidance

(transesophageal echocardiography) or fluroscopy to insure the inflow jet is directed across the tricuspid valve. A concern about this cannula (and smaller cannulas in general) is that flow through the smaller lumen results in increased fluid pressures and this can increase the risk of hemolysis.

The cannula was designed to be placed percutenously via the right internal jugular and despite its simplicity, as with the placement of any large vascular cannula, catastrophic vascular injuries have been reported(15).

Cardiac (Veno-arterial) Support

Cardiac, with or without lung support using veno-arterial (VA-ECMO) is often more complex to implement and manage. Venous drainage is similar to VV-ECMO, however, the oxygenated blood is returned to the body directly into the arterial system. Peripheral cannulation is performed either using a surgical cut-down or by a percutaneous technique. Access can be peripheral or central (16). Central access is often performed at the time of cardiac surgery in patients who cannot successfully be weaned from cardio-pulmonary bypass. Sternotomy for ECMO cannulation is rarely indicated and should be discouraged, but may be required in rare situations in which peripheral access cannot be accomplished adequately or safely. Central arterial inflow is directly into the ascending aorta with techniques that are similar to conventional cannulation for CPB. If needed, existing cannulas used during cardiac surgery can often be used for ECMO by connecting them directly to the pump circuit. For long-term support additional tourniquets, skin sutures, or formal and sturdy fixation should be liberally used secure the cannulas to prevent leakage of blood over time and potential dislodgement during transport or routine bedside nursing care (Figure 3). Even though percutaneous cannulation is appealing, severe peripheral arterial

vasoconstriction secondary to cardiogenic shock (17) can make it technically difficult and increases the risk of a significant, and potentially fatal arterial injury. Similarly, overly aggressive venous access can result in potentially lethal venous or right atrial injuries. Femoral cannulation drains venous blood from the femoral vein, and after passing through the circuit, provides inflow of oxygenated blood in retrograde fashion up through the femoral artery into the aorta. Typically, this can be safely and quickly performed with a single cut-down at one site. Use of this manner of cannulation often requires placement of a distal perfusion cannula to provide adequate oxygenated blood flow to the leg. If distal flow is not restored promptly, then there is a significant risk for limb ischemia and/or loss (18). Adequate outflow to the lower extremity can be achieved with either with a small cannula (i.e. a 6 French introducer in the common femoral or superficial femoral artery) or a separate cut-down with cannulation directly into the tibial vessels (19). The clinical assessment of distal perfusion can be difficult since these patients might not have a pulse and require a good bedside exam looking at capillary refill, signs of a compartment syndrome, and tissue warmth (all signs of adequate arterial perfusion). A significant downside to femoral access is the mixing of the most oxygenated blood, which happens to be the furthest away from the heart, with the blood that is ejected from the heart (less oxygenated blood). In other words, if the heart is still ejecting, any residual undrained blood that passes through the cardiopulmonary tree is usually not well oxygenated and therefore mixed with the oxygenated inflow from the ECMO circuit. Clinically, this is a problem as deoxygenated blood being ejected from the heart may perfuse the brain and coronary arteries while oxygenated ECMO blood perfuses only the lower body. This phenomenon of an arterial admixture can be easily found at the bedside with "North-South syndrome" or "Blue-Head Red Toe syndrome" due to

the hypoxic blood delivered to the head and upper extremity and the oxygenated blood delivered to the lower. Monitoring pressures and blood gases from the upper extremities, specifically the right radial artery, in theory, might best correlate with the blood feeding the brain. An additional problem is that excessive ECMO inflow increases resistance (afterload) against the aortic valve thus impeding native cardiac function and can result in stagnation of blood within the heart thereby, even with full anti-coagulation, result in fatal intraventricular or even valvular and coronary thrombosis (20). For such reasons it is important to ensure ECMO flows be minimized to ensure some degree

of cardiac ejection as evidenced by a pulse pressure on an arterial waveform. Even with full ECMO support, inotropes, such as epinephrine, might be necessary to maintain some degree of cardiac ejection. In situations where the heart is "dead" and patients are awaiting transplant there might not be any native cardiac electrical or functional activity. Efforts to restore some contractility in a heart that has not been ejecting might result in a fatal
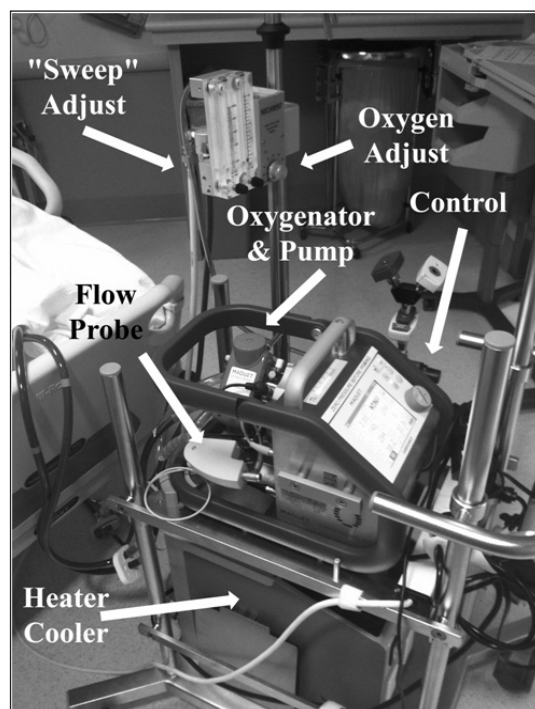

Figure 3: Central ECMO cannulation in a patient who was unable to be weaned from cardiopulmonary bypass. Existing cannulas for surgery were converted to an ECMO circuit and brought out through the top of the sternotomy incision. The chest was left open, but the skin was closed to minimize the risk for infection. The venous blood was drained from the right atrium and once oxygenated and cleared of carbon dioxide, it is pumped back directly into the ascending aorta. The hemostats are clamped around tourniquets that provide extra stability to the cannulas to minimize leakage of blood and risk of fatal dislodgement. This patient was weaned from ECMO 4 days post-op, his cannulas were removed, his chest was closed, and he was discharged home 14 days later.

Figure 4: Key components of a typical ECMO system. The Control panel contains the knob to adjust the speed and pump flow which is monitored via the flow probe. Key system parameters (i.e flow, speed, system monitoring) are displayed on the screen. Oxygen levels and gas sweep (see text) can also be adjusted to regulate oxygen concentration and carbon dioxide clearance. The disposable integrated oxygenator and pump connects to the back of the unit with tube coming from and going to the patient. A separate heater/cooler unit is position on the cart below the unit. The entire unit is designed to be hand-carried and portable for transport.

embolism and as such should be avoided. An additional concern is that VA-ECMO may lead to ventricular distention that will increase myocardial work and inherently compromise cardiac unloading, rest, and recovery. Direct ventricular cannulation for drainage might minimize the consequences of this (21). In patients with significant aortic vascular disease, high-pressure distal inflow from the ECMO inflow cannula may result in retrograde aortic dissections or systemic embolization - either being potentially acutely fatal.

The other major site of arterial cannulation is the axillary artery. Using a small incision inferior to the right (although the left can be used) clavicle, an 8-mm end-to-side side vascular graft is sewn onto the axillary artery as it passes under the subclavian vein and brachial plexus. Typically the graft is tunneled through a

separate incision in the skin and connected to the ECMO tubing circuit. Although this requires an OR environment and can be technically demanding, this approach, short of direct aortic cannulation returns maximally oxygenated blood as close as possible to the coronary arteries and the brain without requiring a sternotomy. Carotid artery access, a popular approach with neonates is rarely used in adults. While the practical reasons for this is somewhat unclear, but likely include concerns stroke, difficulties with access in urgent or emergent situations, and risk for local and technical complications.

PUMP AND OXYGENATOR TECHNOLOGY

The main components of the ECMO circuit are the oxygenator and the pump. As described above, blood is drained from the outflow cannula, enters the pump, is actively driven through the oxygenator,

Figure 5: Picture of an inflow cannula position in the right internal jugular vein returning oxygenated blood to the heart.
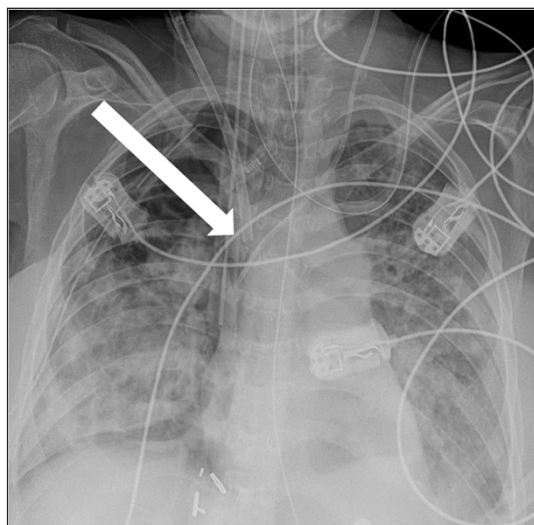

Figure 6: Chest x-ray of the same patient (Figure 5) showing the end of the cannula in the superior vena cava – right atrial junction (arrow). The cannula has a 3-4 cm radiolucent tip at the end extending into the right atrium for return of oxygenated blood.

and finally pumped via the inflow cannula back into the patient. This circuit has three primary modifiable settings that are 1) the pump speed, which determines the flow of blood through the circuit; 2) the gas "sweep" that determines the level of gas exchange with the blood and hence assists in carbon dioxide removal; and 3) oxygen setting, much like the ventilator, is the amount of oxygen supplementation to the blood passing through the circuit. Computer based monitoring systems are used to control flows and driveline pressures with gas regulators to adjust oxygen support and carbon dioxide removal (Figure 4). External heating and cooling systems can also be incorporated into the circuit for clinical situations requiring active warming or induced hypothermia (22). Similarly, if needed, a dialysis circuit can be incorporated in-line for renal replacement therapy.

Centrifugal pumps are currently the most popular type of pump technology used. There are several varieties of centrifugal pumps currently available. Much like propellers on an airplane or boat, some pumps are driven by external motors. As the motor spins, blood is actively pumped in a continuous non-pulsatile manner. Unfortunately, the heat generated from friction can lead to hemolysis and rarely, can melt the plastic housing of the centrifugal pump near the axis resulting in an acute pump failure or blood leak. More commonly, the other type of centrifugal pump is based upon magnetic levitation. As implied by the name, the rotors or fins within the pump housing are connected to a magnet that is suspended within a magnetic field. Since there is no direct contact of the fins with pump housing the amount of friction and heat generated is minimal. An important factor with all types of centrifugal pumps is that they are both preload and afterload sensitive. If there is a downstream occlusion of the pump circuit (afterload increase), the centrifugal pump will continue to spin but will not move blood volume forward. Likewise, if there

is a reduction in available drainage/inflow volume or any occlusion of the inflow cannula, the pump will suck down on the tubing and generate significant negative pressures that will result in hemolysis and, more importantly, cause an acute drop in blood flow. This event is typically referred to as "chugging" or "chatter" and can often be managed by reducing the pump flow/speed to decrease or eliminate the suction process and allow time to troubleshoot the cause. If necessary, volume should be given and the pump returned to previous settings. Increases of inflow or outflow line pressures independent of changes in pump speeds or blood flow can also be a sign of a cannula obstruction, either by a vessel wall or thrombus formation.

With the success and simplicity of centrifugal pumps, older systems using roller pumps (based upon early cardiopulmonary bypass technology) are used less commonly (23). For roller pumps, the tubing is laid in a semicircular track where two arms with rollers on the ends rotate at speeds that correlate with blood flow. As the rollers make contact with the tubing, they depress the tubing and push the blood forward. As one roller finishes moving through the semicircular raceway the next makes contact and starts the process over. Unfortunately, this technology is limited to short-term support, such as in the operating room, since prolonged and repeated compression of the tubing causes the tubing to weaken and lead to plastic particles being released into the blood stream. Tubing rupture can occur, leading to acute and massive blood loss. Roller pump technology is also more traumatic to the blood and associated with more hemolysis, cytokine activation, and evidence of systemic inflammation. In addition and a key factor with roller pumps is that they are not afterload dependent so an occlusion beyond the pump can result in a catastrophic tubing rupture unless limited by a pressure-alarm system and close bedside monitoring.

Ventilator Management

The fundamental principle behind VV-ECMO ventilator management is to "rest the lungs" until the underlying process is resolved and prevent ventilator-induced barotrauma to the lungs. Maintenance of low settings is important. Recruitment maneuvers should be avoided until the patient begins to recover their lung function (24). With an artificial membrane returning highly oxygenated, hyperventilated blood to the inferior vena cava, the settings on the mechanical ventilator can be adjusted to minimize the potential for ventilator induced lung injury (25). A common goal is to keep lung plateau pressures (P_{plat}) no higher than 25 cmH$_2$O while maximizing recruitment of the functional residual capacity while at the same time keeping the FiO$_2$ as low as possible (down to 30-50%) to prevent oxygen toxicity. A positive end expiratory pressure (PEEP) of 5-15 cm H$_2$O is acceptable. When using higher levels of PEEP the physician should be aware of the resultant increase in intrathoracic pressure may lead to a decrease in venous return with lower blood pressure thus affecting perfusion, especially to the brain, gut, and kidneys. It is essential to remember the there is much more oxygentated to deoxygenated blood circulated to right atrium (2-4:1). Thus, such a mixture will cause both PCO2 and PO2 to hover around 40 mm Hg, with an oxygen saturation of 80% in the pulmonary bed.

Our strategy for accomplishing this includes pressure-control ventilation with inverse ratio ventilation to maximize alveolar recruitment and low mandatory rates of breaths to minimize derecruitment, usually with airway pressure release ventilation (APRV) (26-27). However, an assist control/pressure control mode of ventilation is also acceptable. Alternatively, high frequency oscillatory ventilation (HFOV) can also achieve similar goals (28). Avoid any temptation to increase ventilator settings despite an abnormal peripheral arterial blood gas. During the acute injury phase of acute respiratory distress syndrome (ARDS), patients should have very low tidal volumes with essentially only dead-space ventilation due to minimal compliance and the need for a lung protective strategy (29). Although we encourage an open lung strategy, this approach has not been decisively proven to be the superior method over any other (30). As compliance and native lung function improve, clinicians may notice that changes in ventilator settings actually impact arterial blood gasses. A daily brief increase in ventilator FiO$_2$ can be used to test native lung function and indicate lung recovery (31). A true test of lung recovery can be performed by optimizing ventilator support, then turning down the gas source from the oxygenator membrane, and sampling an arterial blood gas 30-60 minutes later. This should be attempted only after the underlying process is perceived to be resolved and the pump speed and sweep flow through the oxygenator has been weaned to minimum settings. Spontaneously breathing is always an advantage for the patient. As recovery progresses such a strategy should be pursued usually through a combination of ventilator and pharmacologic strategies (weaning of narcotics, sedation, and any neuromuscular blockade).

In addition to the ventilator-based therapies of acute respiratory distress syndrome, the clinician should continue evidence-based pharmacologic therapies of ARDS (32-33). Standard therapy employed at our institution includes the use of nutritional therapy with enteral nutrition fortified with eicosapentaenoic acid and gamma-linolenic acid, in addition to formulas with low carbohydrate to protein ratios in those that are hypercarbic (34). Consideration is also given to the steroid therapy if the duration of acute lung injury is less than seven days and there is some evidence of the efficacy of short-term neuromuscular blockade therapy for patients with early ARDS in the first 48 hours (35-36-37). General critical care practices must also be vigilantly followed

to prevent venous thromboembolic disease and gastrointestinal bleeds.

Mechanical ventilator practices for VA-ECMO are also poorly understood with few, if any, guidelines. The primary goal is to achieve normal pulmonary vein saturation that will provide oxygenated blood flow to the coronary circulation without causing ventilator-induced lung injury. Normal lung function in a VA-ECMO patient makes this easily achieved. These patients can be placed on synchronous settings or even extubated to reduce the risk of ventilator-associated pneumonia. Blood going directly into the aortic vasculature has better oxygenation than blood supplied in a retrograde manner. In VA-ECMO the PaO2 will obviously be better in those patients whose cardiac insult is accompanied by normal lung function.

Patient Management

Other than ventilator management as described above, the management of patients on ECMO, either veno-veno or veno-arterial, is primarily supportive. Attention to detail, a cornerstone of ICU care, is even more important with patients on ECMO. A key goal is the management of the primary problem for which ECMO was indicated. For respiratory failure, culture-directed aggressive antimicrobial therapy is critical. Patients can often have polymicrobial infections and with rapidly developing resistance patterns and the development of superinfections; bronchoscopic evaluation of respiratory secretions should be performed frequently for both diagnostic and therapeutic indications. Routine treatment with prophylactic antibiotics while on ECMO due to the presence of indwelling cannulas should be avoided as there is no data to support its use and only results in drug resistance.

Similarly, as with any underlying pulmonary process, effusions and spontaneous pneumothoraces can develop and should also be treated aggressively.

Even a small effusion seen on a chest x-ray and be significant in patients with severe respiratory failure and drainage cannot only reduce the risk of developing an empyema or chronic consolidation, but may allow for improved lung expansion and facilitate the healing process.

Cardiac failure may be more problematic to treat. If the primary cause of cardiac failure has been addressed, either with definitive surgery or percutaneously, then hopefully recovery will occur as the ventricle is rested. Management of arrhythmias and electrolyte abnormalities should be a priority. Serial echocardiography with hemodynamic assessment and manipulation of flows can help monitor for cardiac recovery (38). For patients in whom cardiac recovery is not anticipated, then consideration for early transplant or implantation of a long-term ventricular assist device (VAD). While protocols for the patient selection and timing of bridging patients from ECMO to either a VAD or transplant vary from institution to institution and is out of the scope of this review, in general, patients should be neurologically intact, free of active infection, and ideally, with preserved renal and hepatic function (39).

Because blood contact with the extracorporeal tubing is highly thrombogenic, anticoagulation is necessary.

Most ECMO tubing circuits are heparin-bonded which can minimize this risk or provide some antithrombotic protection without systemic anticoagulation for short periods of the time. Typically the heparin bonding wears off after 1-2 days and this might be enough time to control surgical bleeding or reduce the risk of initial bleeding complications in high-risk patients (22). Typically heparin is used with conventional nomograms of dosing. While some clinical scenarios require customization of anticoagulation goals, our institution uses goal activated partial thromboplastin times (aPTT) ranges equivocal to an anti-Xa level of 0.3 - 0.5 units of heparin/mL. Although some centers

still use activated clotting times (ACT), a monitoring tool used in the operating room for CPB, such measurements have fallen out of favor in routine ECMO management due to variability in results and sensitivity of the ACT cartridges across a broad spectrum of anticoagulation (40). Thrombocytopenia is common with ECMO and is believed to be secondary to a consumptive process from the mechanical disruption of platelets as they pass through the circuit. Even with very low platelet counts, spontaneous bleeding is rare and empiric treatment with platelets should be discouraged as it might only contribute to more thrombus formation and unnecessary exposure to blood products. Heparin-induced thrombocytopenia (HIT) should always be considered, although surprising uncommon with patients on ECMO, and when suspected or encountered alternative means of anti-coagulation with direct thrombin inhibitors (i.e. bivalirudin or argatroban) should be used (41).

Additionally, plasma free hemoglobin and lactate dehydrogenase should be followed routinely to determine the degree of hemolysis. A large degree of hemolysis will expose the heme moiety to heme oxygenase enzymes and may allow the formation of unacceptable levels of carbon monoxide that could potentially be lethal independent of such known sequelae of hemolysis including renal failure(42-43).

An area that is poorly understood is the impact of ECMO, in particular the blood being in continuous contact with an extra-corporeal surface, and drug pharmacokinetics and pharmacodynamics in the context of drug dosing and response to therapy (44). The comorbidities of organ dysfunction in critical illness and ECMO often create a difficult challenge when it comes to optimizing pharmacotherapy to achieve the desired benefit and minimize risk of toxicity. Drug properties (particularly lipophilicity) must be taken into account in addition to the larger volume of distribution acquired by placement of ECMO (45). If available and indicated, drug levels should be monitored to optimize therapy.

The use of VV-ECMO needs to have fluid administration addressed, especially blood. In this mode of support the physician should always be cognizant of the equation for the oxygen content of arterial blood (O_2 content = 1.34 x hemoglobin x SaO_2) + PaO_2 x .003). In VV-ECMO ventilation is minimized and the hematocrit is kept at 40%; a SpO_2 of 80% and a PaO_2 of 40 mm Hg are acceptable. Thus, the O_2 delivery (cardiac output x oxygen content of arterial blood) will be ensured. However, there may be harm in transfusion and it

Variables:	0	1	2	3	4
PaO2/FIO2 (on 100% O2 for >20 minutes)	≥300	225-299	175-224	100-174	<100
PEEP	≤5	6-8	9-11	12-14	≥15
CXR (# of quadrants infiltrated)	0 (normal)	1	2	3	4
Compliance (ml/cmH2O)*	≥80	60-79	40-59	20-39	≤19

*The compliance may be calculated as follows: TV /(PIP-PEEP)

The Murray score is calculated by taking the score for each variable and an average score >3 can be an indication for VV-ECMO

Adapted from Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988 Sep;138(3):720-3.

Table 1: Indications for VV-ECMO for Respiratory Failure (Murray Score)

must be considered against the benefit of oxygenation (46-47). Additionally, if the blood is "old" it may increase the risk of death and attempts should be made to use blood without storage lesions (48). In contrast to this approach, Brodie et al recommend using the same transfusion thresholds as those used in the care of patients with ARDS who are not being treated with ECMO (1-49). Brodie *et al* state that, "If extracorporeal blood flow is compromised by depletion of intravascular volume, temporarily decreasing the output of the pump rather than administering intravenous fluid is our preferred approach when possible. This approach may require briefly increasing the FiO_2 from the ventilator to maintain oxygenation in the face of lower blood flows. These changes can be reversed once the intravascular volume is restored from the extravascular space" (20). The safety and efficacy of this approach needs to be studied. When volume is depleted or compromised (chugging/chattering of lines) in the ECMO patient the "normal/traditional" response has been to give fluid, or in the case of a hematocrit of less than 40%, to give blood. This approach leads to an accumulation of fluid that may be removed with diuresis or renal replacement therapy. An increase of 10% body weight secondary to fluid accumulation leads to increased mortality (50). It has been our practice to aggressively remove fluid even if low dose vasoactive medications are required to do so.

In patients undergoing surgical procedures or who are actively bleeding, anti-coagulation can be stopped for short periods of time. In such cases, the ECMO oxygenator needs to be monitored frequently for signs of thrombus formation and fibrin deposits. These can be sources of embolism and hemolysis and can decrease the efficiency of the oxygenator–.

INDICATIONS FOR ECMO

In general, the indications for VV-ECMO are respiratory failure with worsening hypoxemia and/or hypercarbia refractory to maximal medical and ventilator therapy due to a reversible cause. ECMO should not be considered in patients with severe or end-stage chronic lung disease. While indications are poorly defined, the Murray Score, a validated method of evaluating ARDS severity (51), was the method for enrolling patients in the CESAR trial comparing ECMO to ventilator management (table 1) (7-1-25-28). Unfortunately, because indications are based upon physiologic parameters rather than specific disease states, it is not until patients deteriorate hemodynamically that ECMO is considered. In addition, there are few criteria that consider the cause of respiratory failure or associated comorbidities when evaluating patients for ECMO. In general, regardless of the pathology, a key principle is that the respiratory failure must be secondary to a reversible cause and with appropriate therapy, recovery can occur with a reasonable quality and quantity of life (table 2) (52). While considered extremely high-risk and appropriate in selected patients, lung (or heart-lung) transplant might be an option for patients on ECMO for pulmonary failure. But successful outcomes are rare although it is a practice that is becoming more common (53). Successful cases are typically in patients with known end-stage lung disease, and who are often already listed for transplant and are currently mechanically ventilated, who deteriorate (54-55).

Similarly, indications for acute cardiac or cardiopulmonary failure are based upon specific clinical criteria (table 2). In general, VA-ECMO should be considered in patients with acute and potentially reversible actual cardiac injury in which myocardial recovery is a reasonable expectation. Indications are refractory cardiogenic shock as a consequence from a primary event, such as an acute myocardial infarction or acute

Respiratory Failure Indications:

Primary
        Pneumonia
                Bacterial
                Viral
                Fungal
                Aspiration
                Atypical
        Vasculitis
        BOOP (high risk)
        Pulmonary embolism
        Pulmonary hemorrhage
        Chemical pneumonitis
        Smoke inhalation
        Pulmonary contusion
        Alveolar proteinosis
Secondary
Post-Cardiac/Thoracic surgery
Sepsis/Septic Shock
Lung transplant (graft failure/rejection)
Trauma (Contusion)
Pancreatitis

Indications for Cardiac Failure:

        General Indications:
                NO surgically correctable cause
                Cardiac Index < 2.2 L/min/m2
                Systolic Blood Pressure < 90 mmHg
                Left Ventricular End-diastolic Pressure ("Wedge") > 20 mmHg
                >2 different high dose inotropes
                Cardiogenic shock despite intra-aortic balloon pump
                Unable to wean from cardiopulmonary bypass
        Specific Indications:
                Temporary support for high-risk percutaneous coronary interventions
                Cardiogenic shock from drug overdose
                Cardiogenic shock in the setting of septic shock
                Acute myocarditis
                Pulmonary embolism
                Anaphylactic shock
                Amniotic fluid embolism
                Post-heart transplant rejection

Table 2: Indications for ECMO (53)

myocarditis with evidence of end-organ dysfunction/failure. Unlike for pulmonary support, VA-ECMO can be a "bridge" to either long-term mechanical ventricular assist devices or heart transplantation. While ECMO might be an option for patients awaiting transplantation who acutely decompensate, this treatment algorithm requires significant clinical experience and judgment with regards to proper patient management and selection. More and more, ECMO is often considered as first-line therapy in patients with cardiogenic shock as a bridge to stabilization prior to implementing much more expensive, complex, and invasive cardiac support options (56-57).

CONTRAINDICATIONS

Contraindications for either VV-ECMO or VA-ECMO are similar (58). While difficult to clearly define, futility of care or inability to anticoagulate are strict contraindications. More commonly agreed upon contraindications include patients suffering from severe and often irreversible medical problems such as end-stage or metastatic cancers, advanced age, and prolonged or profound neurologic injury (59). Even selected patients with severe neurologic injuries may benefit from ECMO (60). Prolonged periods of cardiopulmonary arrest, in the absence of adequate documented CPR and/or adequate oxygenation (>15-20 minutes) or prolonged periods of end-organ damage prior to initiating therapy are often contra-indications. But giving patients the benefit of some time of support to watch for signs of neurologic improvement might be appropriate. In a small series, five days of mechanical ventilation was associated with 50% mortality, however this increased to 90% mortality at 12 days prior to initiating ECMO (61). Likewise, untreated or uncorrected surgical or anatomical problems contraindicate ECMO, unless such therapy can assist in

stabilizing a patient to allow for definitive management. Comorbidities associated with poor outcomes include chronic immunosuppression (particularly in the setting of a solid organ or bone marrow transplant), un-grafted burns, intracranial hemorrhage, and known hypercoagulable states (58). Morbid obesity may reflect a relative contraindication due to the challenges of caring for these patients (such as pressure ulcers, cannula compression/obstruction, uncertain medication dosing, etc.) rather than specifics issues related to extra-corporeal support (52). Many contraindications are relative and illustrate the importance of center experience and the need to evaluate each patient in the context of their specific co-morbidities.

OUTCOMES

Even though the first patient treated with ECMO over 30 years ago is still alive and doing well, ECMO has been associated with poor outcomes (6). With the developments and successes of cardiac surgery, there were attempts at supporting patients long-term with the bypass technology that was routinely used in the operating room. Anecdotal success stories prompted much enthusiasm for broader use and eventually prompted a large-scale study funded by the National Institutes of Health from 1974 to 1977 (6). Unfortunately, initial outcomes were poor with <15% survival rate, and the trial was stopped early. For years, ECMO was considered a failed therapy with little clinical value (62). However, these early failures only encouraged some researchers and clinicians to more aggressively better understand the limitations and barriers to success. Even today, ECMO is limited to only a handful of innovative and high-volume centers often with small Teams, advocating a therapy that they had witnessed in saving "unsalvageable" and "hopeless" cases.

In 1986, Mascheroni reported a 49% (21 patients) survival in patients treated with ECMO for primarily carbon dioxide

Pre-ECMO

> Age
>
> Low body weight
>
> Duration of ventilator support prior to ECMO
>
> Acidosis (pH<7.18)
>
> Hispanic/Asian race
>
> Hypercarbia (PaCO2 > 70 mmHg)

Complications during ECMO therapy

> Mechanical complications
>
>> Circuit/pump complications
>>
>> (rupture)
>
> Stroke
>
> Inotropic medications
>
> New infections
>
> Arrhythmias (esp ventricular)
>
> Seizures
>
> Gastrointestinal bleeding
>
>> Requiring transfusion or
>>
>> Discontinuing anticoagulation
>
> Pulmonary hemorrhage
>
> Use of or need for neuromuscular
>
> blockage
>
> pH<7.2 or pH>7.6
>
> CPR on ECMO*

*Interestingly, cardiac arrest prior to ECMO was not associated with a significantly worse outcome in the univariate model analysis (p=0.28)

Adapted from Brogan TV, et al. Intensive Care Med. 2009 Dec;35(12):2105-14)

Table 3: Predictors of Poor Outcomes of ECMO Support

removal. The University of Michigan, always a pioneering ECMO center, reported a 50% (for pneumonia) to 61% (ARDS) survival in 146 patients treated with VV-ECMO (63). Despite greater than ten years of experience, these outcomes still reflect the standard. A recent report by the Extracorporeal Life Support Organization (ELSO) reviewed the outcomes in 1473 patients supported with ECMO between 2002 and 2006 (57). In the patients supported with VV-ECMO (78% of all patients reported to the registry), survival to discharge was 50%. Predictors of poor outcomes and predictors of survival can be found in table 3.

More recently, Schmid *et al* reported outcomes in 176 patients treated with ECMO between January 2008 and December 2010. In their series, 102 patients were treated for acute lung failure in which 84% were weaned from ECMO and 57.8% survived to discharge. Outcomes were best in trauma patients (n=14) with 78.5% weaned and 71.4% discharged. Patients treated with ECMO for sepsis had the worse outcomes (n=43) with 62.7% weaned and only a 44.1% survived to discharge. Interestingly, outcomes when ECMO was initiated prior to transfer had better outcomes lending further support to the theory that patients treated earlier prior to the development of end-organ failure, in general, have better outcomes. In their experience, patients required 12.0 ± 90.0 days of ECMO support with 1 survivor treated for 67 days. Also, they did not find that pre-ECMO duration of ventilator support influenced outcome (range of pre-ECMO ventilation: 6.1 ± 10.2 days, max: 72 days), a topic that has always been controversial (64).

Outcomes for cardiac support have always been worse than outcomes for pulmonary support. Many of these patients sustained massive and irreversible cardiac failure. In such cases, the combined insults of cardiac and respiratory failure, and potentially associated surgical complications (bleeding, infection, neurologic dysfunction) present considerable obstacles to recovery. Bartlett and colleagues reported a 33% survival

in VA-ECMO supported patients (32). Rastan and colleagues recently reported in 517 adults supported on ECMO for post-cardiotomy shock (65). While 63% were successfully weaned from ECMO, only 25% were ultimately discharged from the hospital. In this group, complications on ECMO were common, and often severe (stroke, bleeding) and unresolved acidosis was a common variable associated with poor outcomes. When used as a bridge to either long-term mechanical support or heart transplantation, the Cleveland Clinic reported a 38% short term (66) and 24% five year survival (67), suggesting that patients who survived their initial hospitalization have an acceptable long-term prognosis.

In a more recent experience of 77 patients supported on peripheral VA-ECMO for post-cardiac surgery cardiogenic shock (mean age 60 ± 13 years), 62% were weaned from ECMO. Overall, 30 day survival was only 30%, but for those patients weaned from ECMO, there was a 48% 30 day survival (68). Chung reported similar outcomes and colleagues in 132 patients with profound cardiogenic shock (regardless of etiology) were supported with ECMO. In their hetergenous population of patients requiring cardiopulmonary resuscitation as an indication for ECMO, 50.7% were weaned from ECMO with 42.5% survival to discharge. The most significant pre-ECMO predictor of survival was the APACHE II score (69). Clearly this recent data demonstrates a need to strive for better outcomes.

For non-cardiac surgery patients, ECMO has also demonstrated value in supporting high-risk percutaneous coronary interventions, particularly in patients experiencing acute myocardial infarctions. Experiences with this indication are limited to small series (70), however a single center series reported a 2-fold increase in survival in patients presenting with severe cardiogenic shock and acute myocardial. Sheu argued that ECMO allowed for a more complete revascularization and prevention of acute

end-organ damage (71). However, this study was not performed in a Ventricular Assist Device/Transplant center and predictors of poor outcomes included post-ECMO heart failure suggesting an ability to improve on their results if they had access to long-term cardiac support therapies.

While the survival to discharge rates can always be better, what is encouraging is that those patients who do survive, either after VA or VV ECMO, can have a good quality of life. Most patients treated for respiratory failure have good pulmonary function (72-7). However, survival after cardiac failure is defined by the magnitude of the heart failure.

While there continue to be isolated reports and cases series building on these experiences, it is clear that there is still much to learn and understand in the pursuit of better short and long-term outcomes.

FUTURE DIRECTIONS

The widespread and successful use of ECMO for severe respiratory failure secondary to Pandemic Influenza 2009 H1N1 demonstrated the effectiveness for acute respiratory and cardiac failure (73-74). Simultaneously to reports of ECMO for H1N1 flu, the CESAR Trial results –a randomized trial of patients with severe respiratory failure comparing ECMO to conventional ventilator management– was published in The Lancet (7). The primary endpoints demonstrated a trend towards improved survival, neurologic outcomes and lower costs in patients supported with ECMO versus conventional ventilator management. These mainstream and high-profile publications emphasized the potential clinical role for ECMO. However, these publications also highlighted some of the shortcomings, particularly in the context of challenges with patient selection protocols and outcomes that are perceived to still be less than ideal. The recent development of a portable completely self-

contained and easy to use ECMO system designed, and FDA-approved, for short-term circulatory support has contributed to a renewed interest in offering ECMO support (Figure 6). Initial experience with this system has been encouraging as it may allow for earlier, easier, and safer implementation of therapy –all factors historically associated with improved outcomes–. Such technology can even be used in centers without ECMO experience and care teams who can stabilize a sick patient prior to transfer to a specialized center (75-76). Even though ECMO is currently only offered at a limited number major specialized centers, hopefully such portable technology will allow for implementation of therapy in smaller programs who can then stabilize patients and transfer them to reference centers with broader experience in complex, and often salvage, interventions (76). Despite these advances, there is still considerable room for improvement and research in this rapidly expanding field.

CONCLUSIONS

ECMO is proving to be a life-saving tool for the support of acute and severe respiratory or cardiac failure. Allowing the heart and/or lungs to recover after an acute physiologic insult is the cornerstone to success. While simple in theory, optimal selection of potentially salvageable patients, clinical management, and the science, technology, and physiology of long-term extra-corporeal support is complex. As outcomes and experience improve, hopefully with renewed optimism, the role of early intervention with ECMO therapy will also expand.

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All authors have contributed significantly to the preparation of this manuscript and have approved the final version.

Many of the applications described reflect areas of research and currently no device or system has been approved by the FDA (United States Food and Drug Administration) for long-term (>6 hrs) clinical support.

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