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ECMO: Technique, Patient Care and Role in Brain Death

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ECMO Extracorporeal Membrane Oxygenation (**ECMO**) also known as Extracorporeal Life Support (**ECLS**) is a system similar to a cardiopulmonary bypass machine used during cardiothoracic surgical procedures. The machine provides prolonged patient support, substituting the function of either the heart and/or the lungs, in cases where a severe but essentially reversible injury has occurred to these organs and the organs need to be "rested" so that they can recover.

HISTORY

Initially developed in 1970's, ECMO was employed for adults suffering from respiratory distress. It quickly lost the interest of researchers, after a multicenter trial failed to show any reduction in mortality [1]. The study met severe criticism, due to the lack of ECMO experience in some centers, blood loss during the procedure and lack of "lung rest" ventilator settings among ECMO treated patients [2].

It emerged again as a therapeutic modality in 1990's when some trials showed success in mortality reduction in neonates and children [3,4]. CESAR (Conventional versus ECMO Support in Adult Respiratory Failure) was a significant landmark, where statistically significant improved outcomes of about 31% were reported [5]. The trials showed that the success of ECMO depends on identifying the right patient population, transfer of patients to institutions equipped to handle ECMO and early initiation of therapy.

ECMO CIRCUIT

The ECMO circuit consists of a cannula, an oxygenator, a blood pump and tubing.

Oxygenator-used for oxygenation and ventilation. Oxygenation is determined by flow rate; while ventilation is controlled by adjusting the rate of the countercurrent gas flow through the oxygenator. They are classified according to structure and the type of membrane used. The structure can be a hollow fiber or flat sheet. The membrane can be either microporous or non-microporous. The non-microporous hollow fiber oxygenators are preferred nowadays as they have longer life and provide efficient gas exchange.

Blood pumps have two varieties roller and centrifugal. Centrifugal pumps are preferred as they are smaller, and have a low volume. They also offer less hemolysis.

Cannula - For most patients, a drainage cannula of 23F to 25 F and a return cannula of 17F to 21F is preferred.

Tubing - The diameter of tubing is usually 3/8 of an inch and is made of polyvinylchloride.

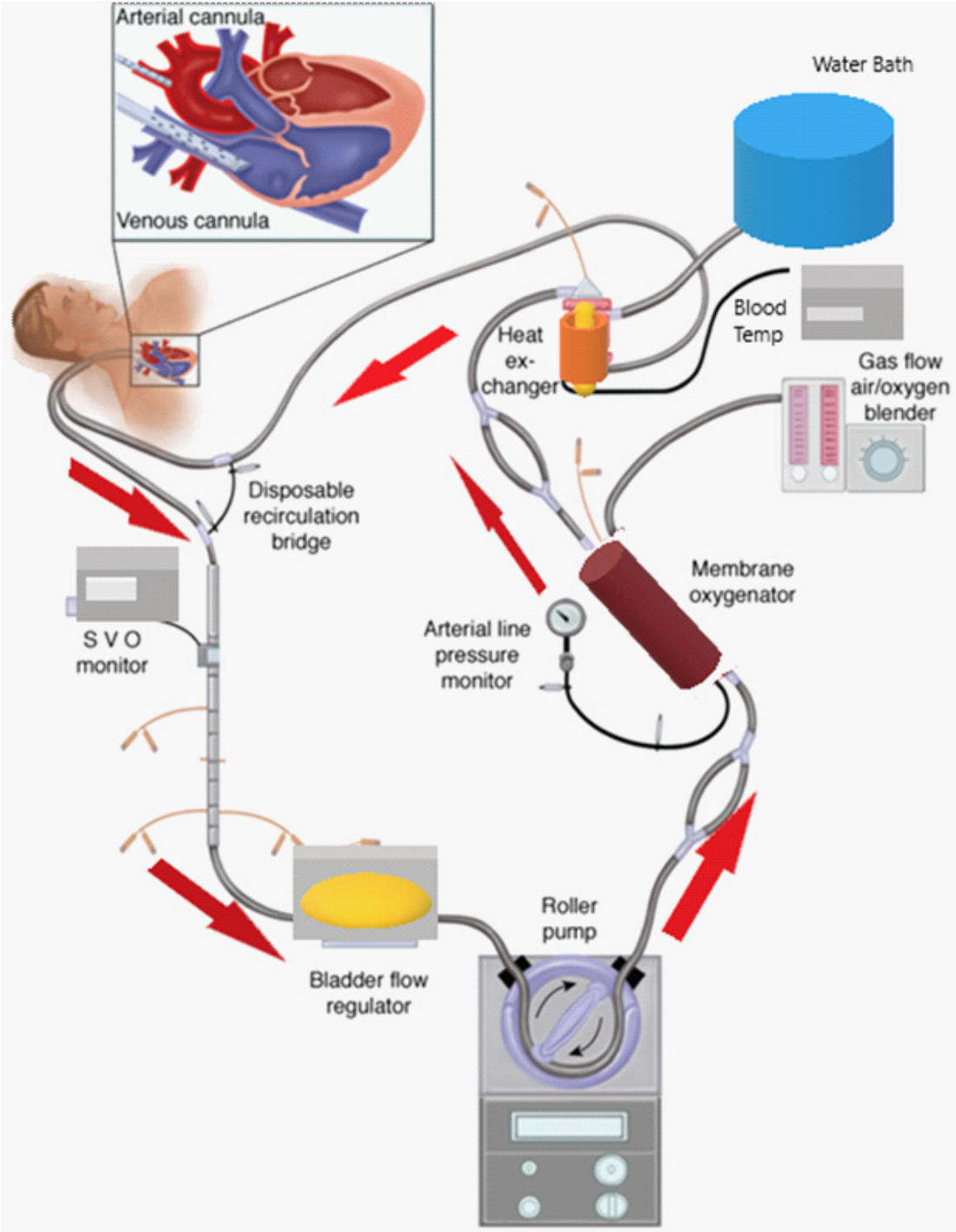

Figure 1: ECMO circuit.

TECHNIQUE

While utilizing the ECMO device, the blood from a patient's body is diverted, partially or completely, to anapparatus that replaces heart and/or lungs to provide oxygenation. Ventilation and circulatory support to the body; mainly using an oxygenator and a mechanical blood pump.

There are two basic types of ECMO which are currently being used:

VENOVENOUS VS VENOARTERIAL CIRCUIT

The Venovenous circuit is connected in series to the heart and lung. Single cannulation technique uses blood taken from the vena cava or right atrium, returned to the venous drainage. Double cannulation technique drains blood from the right femoral vein, returning it to the left femoral vein or internal jugular vein used for respiratory support only.

The venoarterial circuit is connected in parallel to the heart and lungs. It provides respiratory and hemodynamic support to the body. It results in lower PaO2 and higher perfusion rates. In the venoarterial circuit, drainage is taken from the Vena cava or right atrium and after passing through the circuit, the blood is transfused to the femoral, axillary, carotid artery or to the ascending aorta. Usually the femoral artery route is used in a peripheral cannulation circuit and the ascending aorta in a central cannulation circuit (specially after cardiopulmonary bypass surgery).

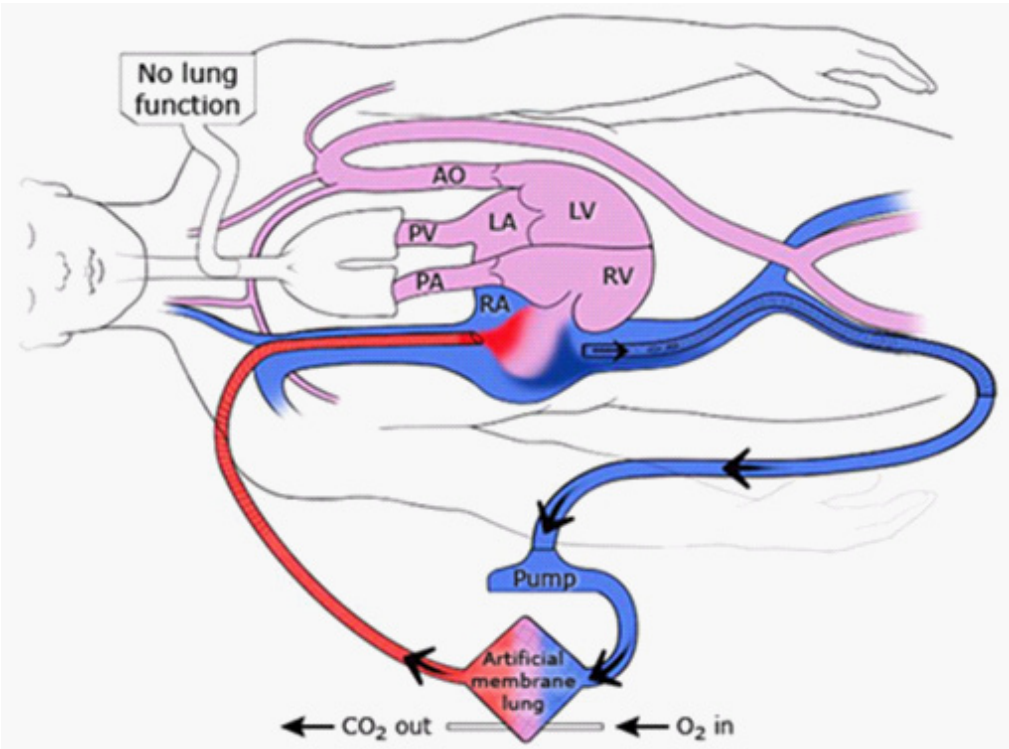

Figure 2: Venovenous (**VV**) ECMO for isolated respiratory failure.

Diagram of venovenous ECMO for respiratory failure. When there is no native lung function the arterial saturation will be 75 to 85 percent. VV access: Blood is withdrawn from the IVC, circulated through the artificial membrane and returned via the SVC to the RA.

ECMO: Extracorporeal Membrane Oxygenation; AO: Aorta; PV: Pulmonary vein; PA: Pulmonary artery; LA: Left atrium; LV: Left ventricle; RA: Right atrium; RV: Right ventricle; VV: Venovenous; IVC: Inferior vena cava; SVC: Superior vena cava.

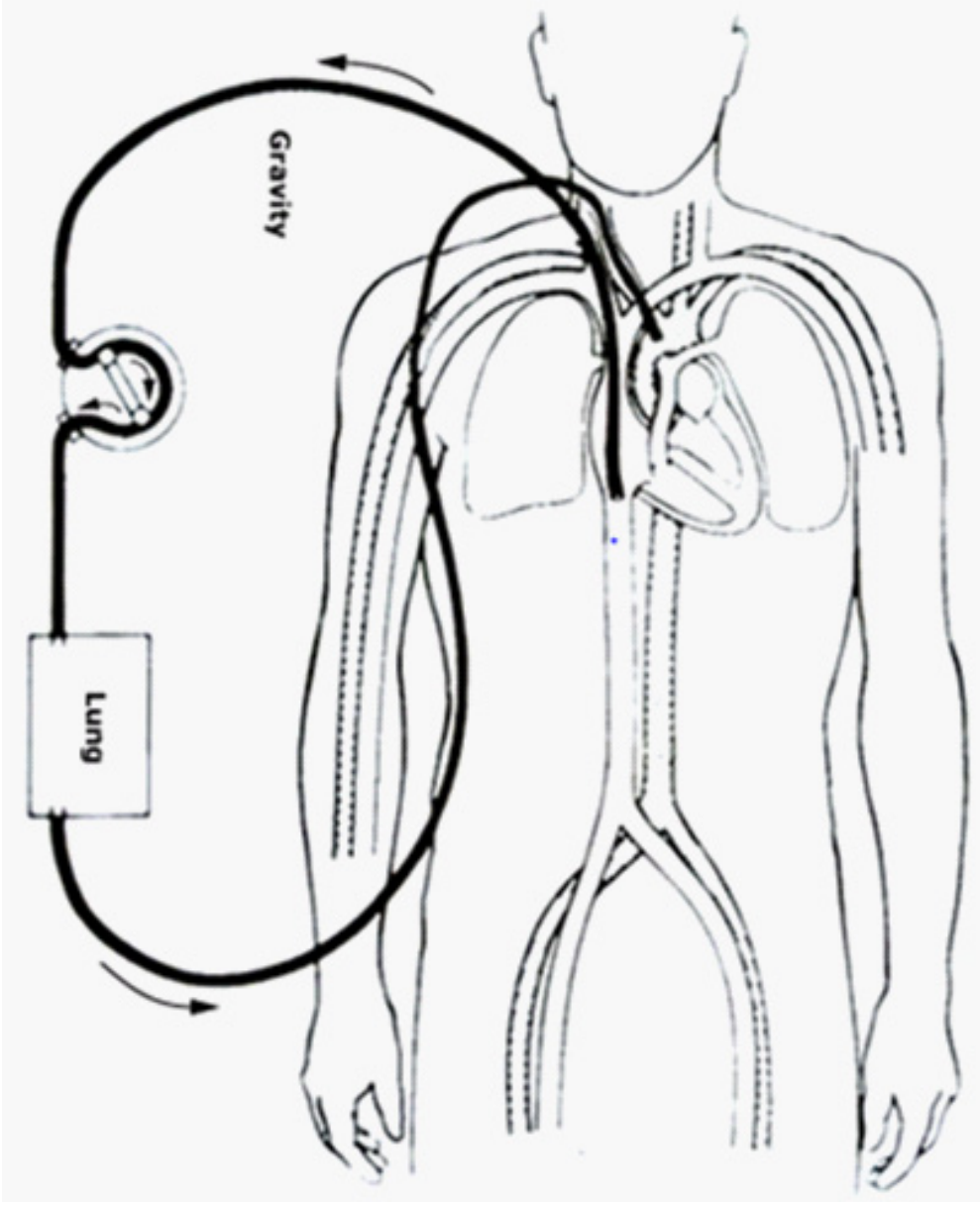

Figure 3: Veno-arterial (**VA**) ECMO for cardiac and/or respiratory failure.

Demonstrated here with right internal jugular vein drainage and right carotid artery infusion.

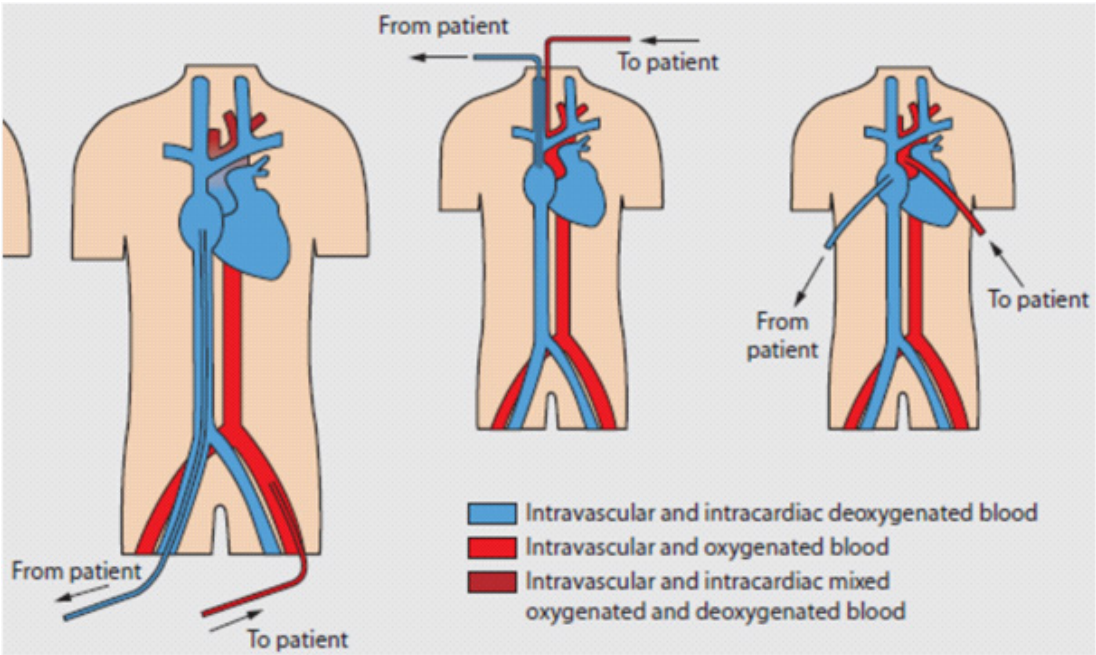

Figure 4: VA, ECMO, showing femoral, cervical and central cannulation.

The blood flow, after cannulation is increased to achieve desired respiratory and hemodynamic parameters. Usual targets are:

- Arterial oxyhemoglobin saturation of > 90 percent for VA ECMO or > 75 percent for VV ECMO
- Venous oxyhemoglobin saturation 20-25 percent lower than arterial saturation
- Adequate tissue perfusion, determined by arterial blood pressure, venous oxygen saturation and blood lactate level

Maintenance - once the targets are achieved, flow is maintained at that rate. Monitoring is done by continuous venous oximetry. If it falls below target, flow, volume or hemoglobin concentration is increased.

The maintenance of the circuit needs anticoagulation with un fractionated heparin or direct thrombin inhibitors to prevent the circuit from clotting. A target activated clotting time of 180 to 210 seconds or a PTT of 1.5 times the normal is used. Platelet destruction occurs as they come in contact with a foreign membrane. A concentration of 50,000/micro liter should be maintained, for which platelets are transfused as needed. Patients may also need diuresis as they become fluid overloaded; ultrafiltration is a reasonable option if patients have renal failure and fail to produce adequate urine.

This involves managing two main parts; The Patient and The ECMO circuit.

THE ECMO CIRCUIT

Transport of an ECMO patient around the hospital premises needs to be preplanned. Furthermore, transporters must be educated to economize battery life by switching off the water bath.

After connecting the ECMO circuit to the patient, blood flow gradually increases until a maximum flow is attained and monitored. Using the blood flow settings, the flow is decreased to suit the optimum and minimum requirement of the patient. Other parameters regulated include, venous saturation, arterial saturation and mean arterial pressure.

Carbon dioxide clearance in the ECMO circuit is controlled by the sweep gas. Sudden changes in partial pressure of carbon dioxide can lead to changes in cerebral perfusion pressure, leading to a raised intracranial pressure.

Fibrinogen levels are decreased by heparin. They are measured daily and kept constant at 250-300 mg/dL by FFP or Fibrinogen concentrates when needed. Fibrin split products can be found the blood if fibrinolysis occurs due to the clots in the ECMO circuit. If so, antifibrinolytics can be used to stop the bleeding [6]. Clots are discovered in the cannula tubing by vigilant examination with a flashlight. One should use heparin with them, to decrease the chances of clots but it is currently possible to manage ECMO without Heparin, as a last resort [7].

400mm Hg is the highest safe level of perfusion pressure. It can increase in case the patient has high blood pressure or if there is resistance anywhere in the tubing. In case the High blood pressure an alarm goes off stopping the pump.

If air is discovered in the circuit, the lines are immediately clamped near the patient, the patient placed on support settings and the cause determined hurriedly. Plasma Hb levels should be checked often to ensure they are <10mg dL.

THE PATIENT

Sedation

It is important to sedate the patient for at least the first 12-24 hours to decrease the metabolic rate, to prevent an air embolism [8] that might occur if the patient died tried to breathe simultaneously.

Blood Volume

When the ECMO circuit is connected to the patient, extra fluid volume is added to the patient s existing blood volume. This volume is in the form of a priming crystalloid solution. The aim of blood volume management here is to ensure that once ECMO stops, the patient is returned to his normal Hematocrit. Normal ECF to ICF ratios are resumed. The problem arises if this ECF fluid leads to pulmonary and cardiogenic edema, which will further exacerbate the baseline issue.

Temperature

The temperature of the system should be maintained at 37C. If the patient was admitted under conditions of ischemic brain injury, then it is acceptable to keep the patient slightly hypothermic at 32 to 34C for 24 to 72 hours.

Hemodynamics

Hemodynamic management varies during VV procedures versus during VA procedures. During a VV support a person is dependent on his own hemodynamic physiology while during VA procedures the patient s hemodynamics are a combination of his own physiology and the blood flow pump s set parameters. The mean systemic arterial pressure should be 50-70 mm Hg for a child or adult & 40-70 mm Hg for a neonate. Pressors and other drugs can be titrated as needed. To check for adequate perfusion keep a check on the patients urine output. The best test of systemic perfusion pressure is the venous blood oxygen content. Ensure that that the venous return is at 75% oxygenation.

Bleeding

Since a patient on ECMO is on artificial anticoagulation, care must be taken to ensure that he has adequate platelet counts, low Clotting time and specifically normal AT3 levels.

Bleeding can occur from several local areas such as the cannulation area, the site of a recent operation, mucous membranes, uterus, GIT, head or brain. Bleeding within the intracranial cavity is the most dangerous and can be fatal. When coming off the ECMO circuit in this situation ensure that high flow ventilator and inotrope settings are used.

Ventilator Management

In the beginning phases when the patient has just been converted onto ECLS, the lungs are in an acute inflammatory state because of which the ventilator settings have to be kept low [9]. The initial low settings means a low respiratory state, long inspiratory time, low plateau inspiratory pressure (<25cm H2O), low FiO2 (< 30%) and the Positive end expiratory pressure (**PEEP**) can be set at any level but usually at 5-15cm H2O. If the PEEP is too high it decreases the venous return.

Weaning - Weaning can be initiated once conditions improve clinically and objectively. Frequent trial should be performed prior to discontinuing the ECMO circuit. Trial for VV ECMO is done by stopping the countercurrent gas flow through oxygenator. VA ECMO can be temporarily disconnected by clamping the cannulas.

USE OF ECMO IN BRAIN DEAD POTENTIAL ORGAN DONORS

According to the American Academy of Neurology brain death involves, coma (with a known cause) absence of brain stem reflexes and apnea. ECMO technology is substantial in the management of brain-dead organ donors. Organ availability and procurement is of vital importance for

transplant procedures. The demand for organs is in excess of availability from diseased donors. Currently, the greatest number of potential organ donors are brain-dead individuals. However, complex pathophysiological disturbances that follow brain death lead to hemodynamic instability, tissue hypo-perfusion and ischemia of potentially transplantable organs. This results in failure of usefulness of those organs for the purpose of procurement and transplantation. ECMO can play a useful role in the process of determining the occurrence of brain death and play a vital role in the management of brain-dead individuals who are potentially subject to organ donation [9].

The main goal of managing critically ill patients is to maximize oxygen delivery and perfusion of vital organs to maintain them in a state of homeostasis. Once brain death is confirmed, it is pertinent to consider continuing efforts towards a slightly different goal to now maintain the viability of potentially transplantable organs in such a patient.

Strategies for the management of organ donors consist of the normalization of donor physiology. After the declaration of brain death, treatment of the potential organ donors should aim to curtail progressive somatic deterioration and sustain specific transplantable organ function. Conserving optimal donor physiology and stability preserves organ quality, viability, and eventually organ function in the recipient. For this purpose, organ perfusion must be optimized, endocrine homeostasis stabilized, and weaker organs safeguarded.

Maintaining hemodynamic sufficiency and stability in brain dead patients until organ procurement is paramount to organ viability. The progression of intracranial hypertension after brain stem infarction causes death of the vasomotor centers (loss of blood pressure auto regulation) and a loss of sympathetic tone with a massive reduction of systemic vascular resistance and profound vasodilation. Subsequently, severe relative hypovolemia (venous blood pooling) and hypotension occur, sometimes leading to multi factorial cardiac dysfunction [10].

The goals of management for the donor's hemodynamic status are to achieve normovolemia by volume expansion, maintenance of blood pressure, and optimization of cardiac output so as to reach perfusion pressure and blood flow gradients that promote organ function with the least support of vasoactive drugs.

Although not always evident, brain death is associated with a massive increase in catecholamine levels (the sympathetic/autonomic storm) sometimes resulting in increased heart rate, blood pressure, cardiac output, and systemic vascular resistance. The consequences of autonomic storm are an imbalance between myocardial oxygen demand and supply, which triggers metabolic functional alterations and sometimes anatomical heart damage (myocytolysis and micronecrosis).

The effects of brain death on the hypothalamic-hypophyseal axis are profound. The most frequent and almost immediate manifestation is diabetes insipidus due to loss of antidiuretic hormone incretion secondary to supraventricular and paraventricular hypothalamic nuclei ischemia. The kidneys are unable to concentrate urine and excrete large amounts (4 mL/kg/h) of dilute urine (specific gravity: <1 005 and urine osmolality: <200 mosm/L). Polyuria may lead

to hypernatraemia (>145 mEq/mL, which is common and sometimes severe and progessively worsening), associated with rising serum osmolality and hypovolemia. Undetectable levels of ADH have been noted in 75% of brain dead donors and are associated with hemodynamic instability and compromised transplantable organ function [11].

Anterior pituitary function (blood supply via hypophyseal extradural arteries) is usually preserved, but variable deficiency of hormones regulated by the anterior pituitary including (**T3**), thyroxine (**T4**), adrenocorticotropic hormone, thyroid stimulating hormone, and growth hormone have been described. Several detrimental metabolic effects follow acute adrenopituitary insufficiency. These include shifts in the myocardial energy supply from aerobic to anaerobic, as shown in animal brain death models, and depletion of myocardial high energy phosphates that is accompanied by an increase in lactate production [9,12].

Recent guidelines advocate the addition of a standardized hormonal resuscitation package (a three drug "hormone resuscitation" or "combined hormonal therapy") to the standard management protocol consisting of methylprednisolone (15 mg/kg in a single intravenous bolus) or low dose hydrocortisone (50 mg e.v. q6h), a triiodothyronine (4 μg bolus intravenously followed by infusion of 3 μg/h), and arginine vasopressin (1 U bolus infusion at 0.5 to 4 U/h) [13].

Extracorporeal membrane oxygenation (**ECMO**) is a technique that was developed as a bridge to support cardio respiratory functions in patients with severe heart or lung dysfunction or non-function and later used in patients with refractory cardiac arrest and it is considered one of the technique potentially useful to expand the organ donation pool [14,15]. Overall, the implementation of ECMO technique depends on several factors ranging from national/regional guidelines, experience with this technique in the single center, prompt decisions of the intensive care team and definite local protocols.

While in a Beating-Heart donor, abdominal and intra-thoracic organs are perfused, in a non beating heart donor (NHBD, or DCD (donor after Cardio-circulatory death), perfusion should be maintained, after confirmation of death, by means of ECMO and inflation of intra-aortic balloon according to the localization of the organs that should be transplanted. In this setting, ECMO allows selective perfusion of the organs which should be transplanted ("compartmental ECMO"). DCD produces organs that have experienced warm ischemia, which compromises their early function and ECMO offers the possibility of minimizing this inevitable damage and extending the range of organs that can be harvested.

BACKGROUND OF USE OF ECMO IN ORGAN TRANSPLANT PROCESS

Although initially the technique was used in combination with hypothermia to maintain organ perfusion with various solutions, over time the concept of norm thermic perfusion evolved demonstrating the benefits of norm thermic reperfusion with donor's blood using ECMO technology.

Hsieh et al. [16] reported that during the 9-year period from January 2001 to March 2010, their organ donation unit evaluated 179 patients; however, only 35 patients were donors. Ten families of the 144 patients signed the consent forms, but the donations failed because five potential donors were unable to reach the determination of brain death, three were medically unsuitable, and two were declared dead after the first determination of brain death. Six patients in this study were placed on ECMO support before the heart stopped beating, seeking to sustain the hemodynamics and gas exchange as well as to maintain the mean arterial pressure above 50 to 60 mm Hg and the SaO2 within 98% to 100% to avoid warm ischemia-related complications. As a result, eight kidneys, two livers, and one liver-kidney simultaneous transplantations were successfully performed on 11 recipients. Overall existing evidence strongly support the notion that ECMO implementation, in centers widely experienced in this technique, is associated with an increase in potential organ pool.

The aim of organ preservation is to maintain the organ in a viable state from the time of retrieval until transplantation since ischemic injury increases the risks of primary graft failure, delayed graft function, and other ischemic complications (e.g. biliary structures) [17,18]. Three different approaches have been proposed for organ preservation [19]. The first approach is called "cold in-situ perfusion ISP", that is cooling the organs in situ as quickly as possible, using a double-balloon triple-lumen catheter, inserted in the femoral artery to infuse a cold preservation solution at the abdominal level [18]. ECMO closed circuit can be used to performed the two other approaches (using donor's blood): 1) to lower the temperature to reduce cellular metabolism and the requirement for oxygen (core cooling or total body cooling -TBC); to maintain normothermic temperature (ANOR-abdominal normothermic oxygenated recirculation) [19]. Though the preliminary findings are very promising (both experimentally and clinically) in lung transplantation, liver transplantation and kidney transplantation, the clinical studies are still few, all retrospective, with small cohorts and not always comparative [20]. ECMO assisted DCD works on the principle of providing a Physiologic milieu in terms of Po2 maintained at 100%, Paco2 at 30-50mm Hg, infusion of sodium bicarbonate to maintain a PH of > 7.1, and heparin infusion to maintain the activated clotting time >500 seconds to the Organ to be harvested for the future organ transplantation during the delay of cardiac arrest and procurement of the organ. ECMO assisted DCD has shown very promising results in the past by increasing the potential donor organs pool by 35%, decreasing the incidence of non-functioning by 6-35%, and decreasing the DFG by 38-85%.

Centers with ECMO facilities should implement local programs for donation after cardiac death (both in the emergency department and intensive care unit) using ECMO taking into account that this technique has been proven to increase donor pool. The potential advantages of ECMO perfusion are as follows: a) time and temperature can be regulated to optimal conditions; b) organ function can be assessed before procurement, c) procurement is semi-elective. Ultimately, these advantages may translate into a decrease in the rate of Donor graft failure.

COST OF ECMO

The worldwide demand for ECMO has grown after the H1N1 pandemic in 2009. (For patients with severe hypoxemic respiratory failure, the publication of the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (**CESAR**) trial and several reports of improved survival in patients with acute respiratory distress syndrome (**ARDS**) treated with ECMO during the H1N1 influenza pandemic have led to a significant expansion of ECMO use). Its provision remains limited due to several factors (high cost, complicated technology, lack of expertise) that increase healthcare cost. It is an expensive procedure with significant complications, but with a high survival rate justifying its increasing use in the western world.

ECMO patients are more resource demanding than other regular intensive care patients. The cost analysis approach for each ECMO procedure mentioned in different research article includes different variables. In one such study, these costs include resources such as physicians, perfusionists, anesthesiologists, respiratory physiotherapists, and other special staff members who are not the part of regular ICU staff. Costs generated by their contribution (additional ECMO costs) were consequently added to the basic ICU costs to obtain the total ICU costs during the ECMO procedure. In order to calculate the total hospital costs, resources related to pre- and post-ECMO stays were included. Some patients had longer hospital stay prior to and after the ECMO procedure and underwent other procedures during their hospital stay that contributed to higher total hospital costs.

The average duration of the ECMO was 9.5 days (range: 4-23 days), of which almost all days were ICU days. The mean length of stay at the hospital was 51.5 days (range: 6-123 days). The ICU stay constituted the main part of the total length of hospital stays, with an average of 32.8 days (range: 0-88 days).

Table 1: [a] Patients 4 and 6 received all or most ECMO outside the ICU.

ECMO #	Days on ECMO	Days in ICU	Total length of stay
1	4	20	24
2	7	14	83
3	4	22	87
4[a]	5	0	6
5	14	57	95
6[a]	18	1	31
7	23	45	45
8	6	83	56
9	23	45	77
10	5	88	123
11	6	19	19
12	5	5	6
13	5	15	18
14	9	30	37
15	8	48	65
Mean	9,5	32,8	51,5
Range	4-23	0-88	6-123

The mean and median values for total hospital costs, including pre- and post-ECMO stays and procedures, were 210,142 USD (SD 12,265) and 191,436 USD (range: 59,871-405,497), respectively. The mean and median costs for the ECMO procedure were 73,122 USD (SD 34,786) and 62,545 USD (range: 34,121-154,817 USD). Further analysis showed that the ECMO procedure accounted for additional cost in the ICU (average 67,000 USD), majority of the additional costs being related to personnel such as physicians, perfusionists, anesthesiologists, physiotherapists and ICU nurses. A break up of cost drivers shows that, of the total hospital costs, staff constituted 82%, blood products 7%, lab and radiology 2.5%, disposable items 3% and drugs 1.5%.

While the worldwide demand for ECMO support was growing during the era of H1N1 pandemic, there were a few setbacks (high cost, complicated technology and lack of expertise) to its application in the tertiary care centers. In the milieu of this dilemma, there was a major progress made in the year of 2010 in the form of a multidisciplinary advanced ICU approach called intensive care unit (**ICU**) run ECMO model. The sole reason of this approach was to decrease the cost of ECMO by reducing the cost of continuous bedside perfusion support without a change in outcomes. Within the first two years of implementation of this approach, there was a significant decrease around 61% noted in the overall hospital cost of ECMO without affecting the differences in outcome related to ICU safety events.

The current literature shows that a large variation exists in the in-hospital cost estimates for ECMO. Further research is needed to understand how the diagnosis, setting and other factors relate to this variation in the cost of this technology. Reliable costing methodologies and cost information will be critical to inform policymakers and stakeholders wishing to maximize the value of advanced medical technologies such as ECMO.

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